SECTION 1

Section Overview

The COVID-19 classification and evolution through its multiple mutations have increased its transmissibility rate up to 70% or more globally, threatening to undermine the promise of a number of emerging medications and vaccines that primarily focus on the immune detection of the Spike trimer.

Mutations have been long considered as random events, or mistakes during the viral RNA replication. Usually, what can go wrong will go wrong; therefore, repeated transformations lead to the extinction of a virus. On the contrary, the aggregate result of over 300,000 COVID-19 variants have expanded its transmissibility and infectiousness. COVID-19 mutations do not degrade the virus; they empower and facilitate its disguise to evade detection. Unlike other coronaviruses, COVID-19 amino acid switches do not reflect the random unfolding of errors that eventually eradicate the disease. COVID-19 appears to use mutations adaptively in the service of its survival and expansion.

One of the COVID-19 primary strategies is to inhibit the production of interferon type (INF) that is involved in recognizing the virus. The deleterious consequences of the cytokine storm where the $CD8^+$ killer cells injure the vital organs of the host may well be collateral damage, as the blind immune system struggles to annihilate the unidentified COVID-19. It is probable that evolution has programmed COVID-19 with an adeptness designed to debilitate key systemic defences to secure its subsistence. To date the infectiousness of the COVID-19 pandemic is exponentially increasing, denoting the possibility of an even more dangerously elusive, inconspicuous, and sophisticated version of the disease.

CHAPTER A: CORONA VIRUS EVOLUTION

Corona Virus Structure & Mutations

The corona virus is a positive RNA virus enveloped by a membrane that was first identified in Wuhan in 2019 (SARS-CoV2 or COVID-19). It is classified under the Beta coronaviruses category along with SARS-CoV (Severe Acute Respiratory Syndrome) and MERS CoV (Middle East Respiratory Syndrome). There are other beta type of human coronaviruses that cause enteric and upper respiratory tract infections, experienced during the common cold, such as the HCoV-OC43 and HCoV-HKU1. On the other hand, HCov-229D and HCoV-NL63 come under the Alpha classification. Feline (FCoVs) and canine corona viruses (CCoVs) are also sorted under the alpha group. The remaining coronaviruses fall under the genera of Gamma and Delta categories that primarily affect poultry, wildlife and other birds, although rather sparce information is available regarding the delta division [1, 2]. The Delta section of coronaviruses should not be confused with the Delta COVID-19 variant, or B.1.167.2, that has demonstrated the highest transmissibility rate so far, and which was first detected in India towards the end of 2020. Very different types of viruses such as the Bafinivirus infects fish, while the Arterivirus is limited to specific species including mice, monkeys, horses and pigs [3]. Adenovirus infects the lining of the eyes (pink eye), the intestine, resulting in gastrointestinal disturbances, the urinary track, the lungs and respiratory system, and the nervous system. It primarily infects children, however, it often infects adults as well. The Tiki Monkey Adenovirus (TMAdV) is currently used in the Astra Zeneca vaccine after its genome has been modified. TMAdV that can cause life threatening respiratory disturbances in monkeys, has been also known to infect in humans. Figure 1 graphically represents the different types of viruses and the categories they belong to. (All categories are in grey colour. All subcategories in white).

According to the latest live updates on worldmeter, the COVID-19 pandemic resulted in 192,974,202 cases and 4,145,502 deaths globally until July, 22 2021. Its lethal consequences have motivated a large body of evolving scientific research that often broadcasts contradictory results giving rise to personal opinions, misunderstandings and misinformation. That further obscures data interpretation, and obstructs the formation of a united front that would entail everyone in the world working together to combat the virus.

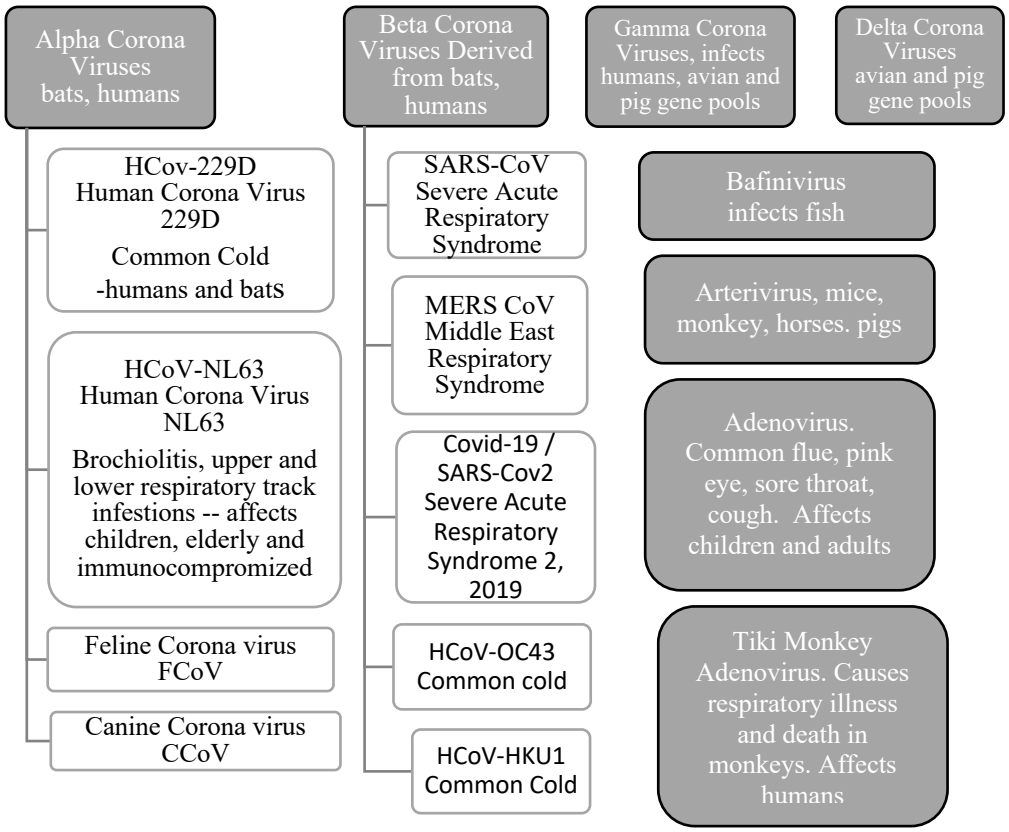

Figure 1. Corona virus classifications: Alpha, Beta, Gamma and Delta. Other viruses: Bafinivirus, Arterivirus, Adenovirus, Tiki Monkey Adenovirus.

Unlike the MERS-CoV that uses adenosine deaminase complexing protein 2, also known as Dipeptidyl peptidase-4 (CD26), as its primary receptor, both SARS-CoV and COVID-19 (SARS-CoV2) target and fuse with the angiotensin-converting enzyme 2 (ACE2) that serves as the viral portal into the cell. During their multiplication process, all viruses strive to outlive the immune counterattack. Since mutations are randomly adopted without foresightedness, they lead to an accumulation of errors that eventually eradicate the virus. Interestingly, the COVID-19 variants appear to enhance its

effectiveness and transmissibility, in contrast to other types of coronaviruses which are adversely affected by amino acid transpositions that define a new mutation, eventually decaying into annihilation.

Coronavirus Composition

The genome of corona viruses is composed by sequences of around 26,000-32,000 variations of the ribonucleic acid (RNA) nitrogenous bases: adenosine, cytosine, guanine, and uracil. It harbours 6-11 open reading frames (ORFs), 67% of which encode 16 non-structural proteins (nsps) that direct virus assembly, transcription and replication in connection with the host, and the rest encode the accessory and structural proteins. Structural proteins include the main surface trimeric Spike glycoprotein (S) that binds and fuses with the ACE2 receptor, a key-to-lock process that releases the viral RNA into the cells; the smaller surface proteins are the envelope (E) protein, the membrane (M), while the nucleocapsid (N) defensively surrounds the genome. The N protein offers protection and signature sequences, equipping the virus with adaptation skills that enable it to survive the adversities of the host's environment. A graphical representation of COVID-19 structure is given in Figure 2.

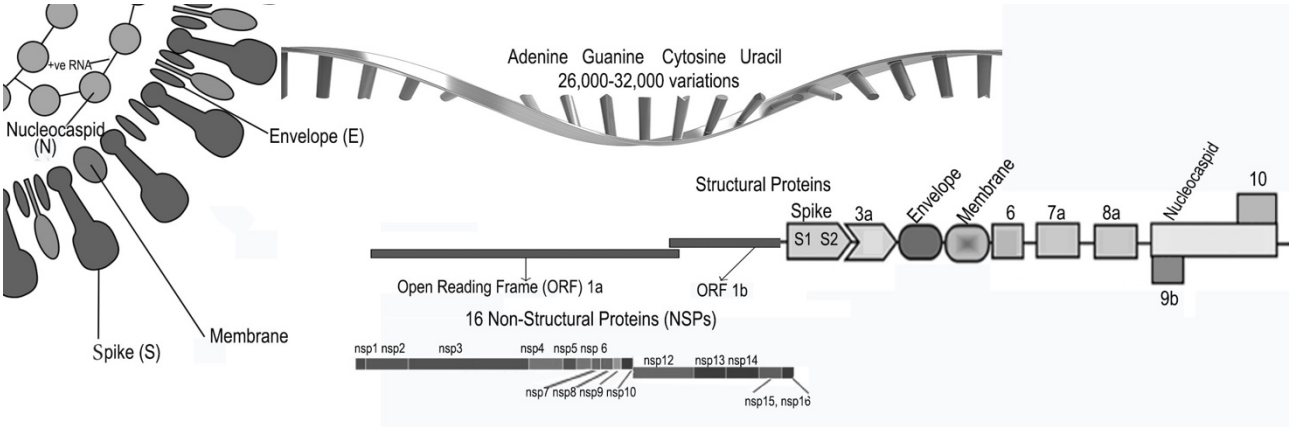

Figure 2. COVID-19 Composition

The immune defence assembled against the antigen is composed by:

A/ The innate immune response during which antibodies prophylactically obstruct the Spike's contact and fusion with the human cells.

B/ The adaptive immune response comprised by a number of cells including cytotoxic T-killer cells or $CD8^+$ that clasp onto the infected cells' antigens, and obliterate them by releasing perforin and granzyme that is absorbed through the cellular pores [4, 5].

The Difference between SARS-CoV and COVID-19

The SARS-CoV and COVID-19 genomes are similar, however, they have significant structural differences that amount to 380 amino acid substitutions [6, 7]. Despite their kinship, the two viral configurations, SARS-CoV and COVID-19 are packed with different messages that are bound to have important implications pertaining to their pathogenetic effects. There are important dissimilarities that may hinder upon the COVID-19 rate of infectiousness and virulence. We mention only some:

1. COVID-19 is missing the 8a accessory protein that is present in SARS-CoV.
2. The COVID-19 8b accessory protein has 37 more amino acids than SARS-CoV.
3. the SARS-CoV 3b has 132 more amino acids than COVID-19.
4. There are 102 variations in its amino acid sequence of non-structural nsp3 protein of the two COVID-19 and SARS-Cov.
5. There are 61 amino acid conversions in the nsp2 of the two viral versions.
6. The COVID-19 Spike protein has 27 different amino acids than SARS-CoV.
7. COVID-19 and SARS-CoV have significant differences between the open reading frames ORF3a, ORF6, and ORF8, with homology rates of only 72%, 68%, and 40% respectively.
8. The ORF7a appears of COVID-19 when compared to SARS-CoV appears to have the highest similarity rate, approaching 85%

MERS-CoV, SARS-CoV and COVID-19

1. The S gene that encodes the Spike protein in COVID-19 is approximately 24% different from the S gene in SARS-CoV, and 65% different from the S gene in MERS-CoV.

2. The N gene that encodes the nucleocapsid protein has around 90% homology between SARS-CoV and COVID-19, but only 48% between MERS-CoV and COVID-19.
3. The E and M proteins' genes of COVID-19 have a 94% and 90% similarity with the SARS-CoV E and M genes respectively. Moreover, a comparison between [8, 9, 10].

Spike Conformations if COVID-19 and SARS-CoV

The trimeric spike (S) protein undergoes a structural transformation while binding with the ACE2 receptor. As a result, the S1 subunit sheds, allowing the S2 subunit to fuse with the receptor. This process is common in both SARS-CoV and COVID-19. The structural transformation of the S1 subunit consists of two conformation states, the up that exposes and makes the viral receptor available and the down that closes off the receptor. However, in SARS-CoV the down conformation of the receptor binding domain clicks into the N-terminal domain of the trimeric Spike (S) protein, while in the COVID-19, the down receptor fits into the central cavity of the trimer. [11, 12]. This may be of significance under the assumption that the N-terminal domain remains available, in light of recent findings that certain human antibodies bind with the N-terminal domain (NTD). NTD targeting human antibodies can be added to those binding with the receptor binding domain (RBD) for greater therapeutic efficiency [13, 14]. Table 1 displays a summary of the similarities and differences between COVID-19 and its predecessor SARS-CoV.

The Kinship between SARS-CoV and COVID-19

	SARS-CoV	**SARS-CoV2 / COVID-19**		**SARS-CoV**	**SARS-CoV2 / COVID-19**
	SIMILARITIES			**DIFFERENCES**	
Spike Gene	76%		**Structural**	380 different amino acid substitutions than COVID-19	
Nucleocapsid Gene	90%		**8a Accessory Protein**	present	absent
Envelope Protein	94%		**8b Accessory protein**		37 more amino acids
Membrane Protein	90%		**3b Accessory protein**	132 more amino acids	

Open Reading Frame 3a	72%	**Nsp3 differences**		102 different more amino acid variations
Open Reading Frame 6	68%	**Nsp2 differences**		61 different amino acid variations
Open Reading Frame 8	40%	**Spike Protein**		27 different amino acid variations
Open Reading Frame 8a	85%	**Spike Protein Conformation**	down conformation clicks into the N-terminal domain	down conformation fits into the central cavity of the trimer

Table 1: Similarities and differences between COVID-19 and its predecessor SARS-CoV.

Methods of COVID-19 Transmission

1. Droplet transmission as a result of infected individuals coughing, sneezing, talking, singing, etc.
2. Transmission via touch from contaminated surfaces where the virus may survive for hours outside the body of a host. Poor hygiene increases the probability of contracting COVID-19 via touch.
3. Defective sewage system containing toxic sewage where the virus can sustain itself for days [15]
4. Flushing waste water that may contain viral particles from COVID-19 patients' faeces. Infected faeces could increase COVID-19 escalation in countries like India where the "night soil," as it is historically referred to faeces and other human excretions, is widely utilized as a fertilizer.
5. Airborne dust transporting the virus along with environmental pollution that undermines and compromises immunity
6. Evidence regarding vertical transmission is inconclusive. Some research has reported neonates testing positive to COVID19, while others manifested increased IgM and IgG levels, while testing negative to COVID19. These results are juxtaposed against research demonstrating no evidence of COVID19 in neonates of placentas of mothers infected by the virus [16. 17. 18. 19].
7. Transmission via saliva that generally appears to contain high concentrations of COVID-19 [20].

8. Reports of COVID-19 in semen present contradictory evidence, depending on whether testing was completed during the acute phase of the disease or during recovery [21, 22]
9. Ocular route of transmission is rather controversial, with some studies evidencing pronounced ocular defects in several COVID-19 patients, and others reporting little or no ocular manifestations of COVID-19 [23, 24].

Once COVID-19 has entered the body via any of the routes enumerated above, its Spike protein connects and fuses with the ACE2 (Angiotensin converting enzyme 2) receptors of the vital organs to release the COVID-19 into the human cells, where the virus is duplicated, inevitably spreading and overwhelming the body. This process will be described in more detail in later chapters.

In June 14, 2021, over 11,700 cases of mucormycosis, or as commonly termed "black fungus," have been reported in diabetics and COVID-19 patients in India and a few are currently evident in Oman. Mucormycosis is an aggressive fungal infection with an overall mortality rate of 50% that affects the ocular system, often resulting in the removal of the eye. It also affects the sinuses, the lungs, and the brain, causing facial paralysis. It may be a side effect of steroids used in COVID-19 patients to reduce inflammation. Mucormycosis is typically related to mucor mould exposure in the soil from putrefied fruit and vegetables. Therefore, hygiene appears to be a central issue in contracting mucormycosis [25]. In conclusion, compromised sanitation, environmental toxicity can speed up COVID-19 transmission with high mortality rates among immunosuppressed individuals.

COVID-19 Neutralizing Antibodies

COVID-19 neutralizing antibodies are Y shaped proteins that can recognize the S1 RBD and fit into the viral antigens like a key to a lock. This prohibits the virus from binding with the ACE2 cellular receptor, thus preventing viral entry. Other antibodies can neutralize the heptad repeat 2 (HR2) domain to impede S2 fusion with the ACE2

receptor, so even if the Spike protein can bind with the ACE2 receptor, the second step of antigen/receptor fusion is compromised, disallowing COVID-19 entry into the cells, without which the virus can neither replicate, nor spread inside the body [26].

A recent study experimented on a powerful monoclonal antibody, LY-CoV555, that binds with the COVID-19 spike protein obstructing it from fusing with the cells' ACE2 receptors. The results of 309 patients who received the LY-CoV555 antibody treatment were compared to 148 patients who received placebo. Eighty percent of all 452 participating patients had mild COVID-19 symptomatology. By the 11^{th} day of clinical observation both experimental and placebo group had a significantly reduced viral load, with the treated patients exhibiting a modest advantage. The experimental group patients who received a 2800mg antibody dose had a -0.53 difference from the placebo group ($p=0.02$ / $p<0.05$), which is a statistically significant result. Neither a lower dose of 700mgs ($p=0.38$) nor a higher dose of 7000mgs ($p=0.7$) were statistically significant. Importantly, however, when the rate of hospitalizations was examined on the 29^{th} day, the percentage of the viral load in the experimental group that was treated with LY-CoV555, was 1.6%, contrasted with the significantly higher viral load of the placebo / control group that was 6.3%. Further analysis focusing on high risk aged (>65) and obese (BMI>35) individuals denoted a diminished hospitalization rate of 4.2% for those receiving LY-CoV555, when compared to 14.6% of non-treated patients [27].

Defensive Immune Memory. Are CE8+ T cells the only ones that Remember?

Immune memory that develops from milder forms of coronaviruses such as the HCoV variants (229E, NL63, OC43, HKU1) which cause the common cold, may be a significant factor contributing to the activation of immune defences to obstruct the virus, and/or reduce the viral load that diminishes contagion [28, 29]. Immune memory pertains to antibodies that are secreted by B cells, the adaptive immune system killer-T cells ($CD8^+$) that obliterate infected cells, and helper T cells ($CD4^+$) that are in charge of activating cytokines. Neutralizing antibodies that people develop after being infected with the common cold do not appear to prevent COVID-19 pathogenesis [30]. However the cytotoxic $CD8^+$ T cells demonstrate a lasting SARS-CoV viral

recognition. In this experimental study $CD8^+$ T cells were reminiscent in 60.9% of SARS-CoV recovered patients for at least six years, whereas these patients' B cells specific memory, that is crucial in generating antibodies, appeared to be negligible or absent [31].

The purpose of vaccination is to enhance inherent immune memory by presenting the Spike protein that informs the immune system of the enemy's malevolence, thus prohibiting future binding and fusion between the trimer and the ACE2 receptors. This type of innate immune "education," designed to obstruct viral entry altogether, is particularly useful in the elderly, whose adaptive immune response is compromised due to aging, and who will be inherently more vulnerable in combating the antigen via the adaptive immune defences, once COVID-19 has invaded human cells and has started replicating [32].

Robust $CD4^+$ T and $CD8^+$ T cells Memory

A recent study has identified $CD4^+$ T cells which appeared to be reactive to COVID-19 Spike (S) glycoprotein of 83% of COVID-19 patients, targeting epitomes in both the N and C terminals of S, as well as in 34% of healthy controls, although that the target was limited to the C terminal. These investigators entertained the possibility that the $CD4^+$ T cells found in healthy controls that were reactive to COVID-19 S protein, may be the result of previous exposure to the common cold variant virus under the HCoV umbrella [33]. Another recent study revealed that COVID-19 patients have 70% of reactive $CD8^+$ cytotoxic cells and 100% of $CD4^+$ helper cells, which appeared to recognize the Spike, Membrane and Nucleocapsid proteins, as well as certain non-structural proteins (nsp3, nsp4) and open reading frames (ORF3a and ORF8). Additionally, they identified 50% of CD4+ T helper cells and 20% of CD8+ T cytotoxic cells reacting to the Spike, Membrane, and non-structural proteins in individuals that had tested negative to COVID-19, again suggesting that these cytotoxic and helper T cells' reactivity was obtained from previous exposures to milder coronavirus forms such as HCoV-OC43 and HCoVNL63 which, as previously noted,

are responsible for the “common cold.” The CD4+ and CD8+ cells' reactivity to open reading frames (ORFs) is significant, considering that ORFs encode both non-structural and structural proteins as well as assembly ones [34].

Antibodies: The Safest Avenue to Restrict Viral Entry

The immune memory of CD4+ and CD8+ T cells is an encouraging finding. However, allowing COVID-19 to enter the system which will occur in the absence of antibodies, may be already too late, especially in elderly, or immunosuppressed individuals. The optimum method of fighting COVID-19 is focusing on antibodies that can block viral invasion in the first place. This is important for two reasons:

1/ Preventing viral entry into the cells is the safest option. Once Covid19 enters the cells, the $CD8^+$ cells must exterminate the infected cells, a necessary intervention, but a casualty nevertheless, that can often injure the host.

2/ There is evidence that coronavirus inhibits the interferon type I production and therefore, it suppresses the ability of the adaptive immune system to recognize the virus, possibly leading to the destruction of healthy cells. This is illustrated by the cytokine storm that indiscriminately attacks and rampages the host’s vital organs [35, 36, 37]. During the cytokine storm the adaptive immune system is informed about the lethal danger, but has difficulty identifying the enemy that is evasive and imperceptible due to insufficient availability of Interferon I. As a result, immune counterattack is persistently fierce yet, undifferentiating, with deleterious consequences for the human body. The inhibition of the interferon type I production that compromises adaptive efficiency can be particularly detrimental to aged individuals with compromised immunity, who are faced by viral influx, and rely on the adaptive immune system for protection. This is why neutralizing antibody treatments have become so promising in the treatment of older COVID-19 patients.

COVID-19 Mutations

COVID-19 mutations appear to increase its contagiousness as if these evolving transformations occur as a result of predetermined calculations rather than merely

representing random events. Viruses have a propensity to change in an effort to adjust and survive within their hosts. However, according to the second law of thermodynamics systemic changes from one state into another decrease energy and increase entropy, eventually driving a virus into extinction; There are millions of incorrect combinations and only one correct solution, therefore, during amino acid transpositions what can go wrong will go wrong. Inevitable extinction has been the inexorable fate of all previous life threatening viruses. But COVID-19 stands alone. It defies the laws of physics to secure its sustenance, while increasing its transmissibility. Interestingly, unfolding mutations do not make COVID-19 more lethal, because that would be against the virus' interests, since it depends on its host for survival. Its evolving variants are more contagious, serving the virus' main purpose to proliferate and establish its ascendancy over the world.

The COVID-19 Sophisticated Modus Operandi

COVID-19 Spike protein binds with the ACE2 receptor in a manner that is 10 times more secure and steadfast than the juncture formed between the SARS-CoV Spike with the ACE2 receptor. COVID-19 is endowed to form more stable connections with the host's cellular receptors. This explains the speed with which COVID-19 has spread globally [38]. Since it first appeared in Wuhan, COVID-19 has mutated from 614D to 614G, basically exchanging the amino acid Aspartate (D) with the amino acid Glycine (G) in the genome's 614 position [39]. Korber et al. (2020) looked at single amino acid changes in 28,576 sequences of the trimeric spike (S) protein that included both the subdomain Spike 1 (S1), which mediates the binding with the ACE2 receptor, and the Spike 2 (S2) subdomain that accomplishes the membrane fusion, ultimately resulting in the release of viral contents into the cell. These investigators found that the Spike variant D614G that exchanges Aspartate with Glycine had a significantly higher rate of transmissibility globally, when compared to its predecessor 614D. Several countries were affected including Europe, the USA, Canada and Australia. This new mutation D614G varied only 0.3% from the original 614D COVID-19 sequence that was identified in Wuhan. Yet, this elementary, single substitution of the amino acid

Aspartate (D) by the amino acid Glycine (G) in Spike's 614th amino acid position, resulted in an increase of at least 20% in the viral infectiousness rate [40]. The elegant simplicity and speed of deploying the exact specific amino acid transformation that will increase a viral transmissibility by 20%, is astounding. 614D involves one conformation, while D614G exhibits two to three Spike protein conformations. Again, it is remarkable how such a minor change can invigorate such a substantial difference! [41]

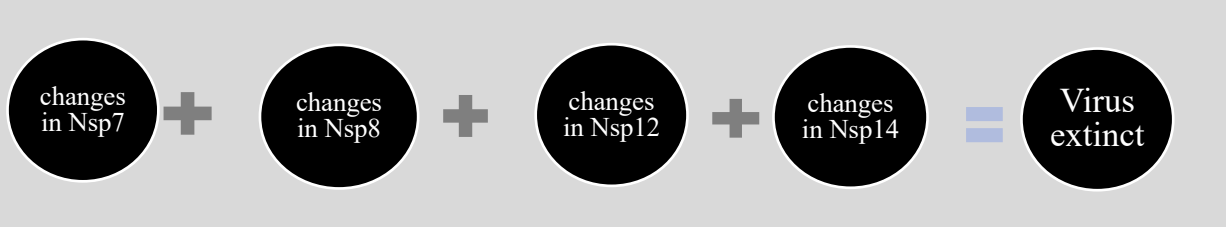

Figure 3. *Coronaviruses (other than COVID-19) Nsp transformations may have deleterious effect for the virus leading to its extinction.*

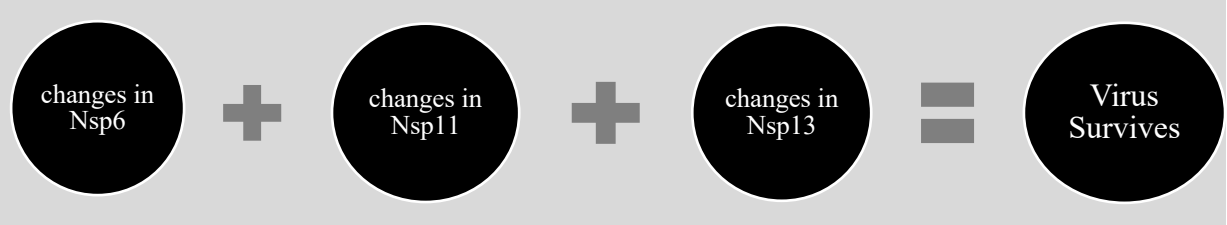

Figure 4. *COVID-19 nsps transformations are adaptive, leading to the survival of the virus.*

Since it first appeared in Wuhan, COVID-19 genome has undergone several mutations, usually based on one or two amino acid substitutions that reflect the virus' adaptation to each host's diverse biological apparatus to maximize viral survival and transmissibility. Some of these changes may not be as important as others. Van Dorp et al (2020) reported changes in the non-structural proteins Nsp6, Nsp11, Nsp13 as well as the trimeric spike [42]. However, if instead of the Nsp6, Nsp11 and Nsp13, the non-structural proteins Nsp7, Nsp8, and Nsp12 in association with Nsp14 were involved, the antigen's capacity to replicate long viral RNA would have been compromised. Research on previous versions of the antigen indicated that the mutation of the nsp8 residues P183 and R190 that are involved in the interphase between nsp8 and nsp12 as well as K58 had deleterious effects for the virus [43]. *Figure 3* and *Figure*

4 illustrate the maladaptive transformations of other coronaviruses that lead to their extinction, juxtaposed against the adaptive variations of COVID-19 which sustain and perpetuate the viral contagion.

At that time, D614G was manifested in around 86.5% of COVID-19 infections, while other mutants, such as the A222V, were relatively less frequent. A222V substitutes Alanine with Valine on the 222nd position. It was primarily linked to infections identified in Italy and Spain, where it appeared to represent about 11.2% of the genetic sequences collected from COVID-19 patients between June and October 2020. This mutant primarily occurred in the S protein segment that binds with the ACE2 receptor [44, 45]. D614G has been often present along with A222V, as well as other common mutations such as the S477N that exchanged Serine (S) with Asparagine (N) at the 477th position and L5F that involved the transformation of Leucine (L) into Phenylalanine (F) in the fifth position. Several other mutations have been identified such as the L18F reflecting a Leucine (L) exchange with Phenylalanine (F), the A262S involving a switch between Alanine (A) and Serine (S) and other far less frequent ones such as the T632N (Threonine to Asparagine), V3G (Valine to Glycine), D574Y (Aspartate to Tyrosine), P272L (Proline to Leucine), D1163Y (Aspartate to Tyrosine), and others. The S protein contains around 98,699 amino acid sequences, each consisting of around 1273 amino acids. Around 3,205 of these amino acid sequences that compose the Spike protein are unique, suggesting that COVID-19 has progressively developed a substantial genetic diversity from previous versions of coronavirus [46].

The Alpha Variant: B.1.1.7 – 70% more contagious

A highly contagious new mutant, the B.1.1.7 appeared in the UK in September 2020. Three months later, it accounted for around two thirds of the UK cases. B.1.1.7 is approximately 70% more transmissible than previous manifestations of COVID-19. It may have emerged as the virus multiplied within an infected immunocompromised patient [47]. Presumably, this specific immunosuppressed organism precipitated a

progressive evolution of COVID-19 transformations that ultimately increased its transmissibility. It almost seemed as if while fighting for its survival within the hostile environment of this immunosuppressed host, COVID-19 was trained in new combat techniques designed to escalate its virulence. B.1.1.7 combines around 23 mutants, primarily affecting the Spike protein, that include substitutions of amino acid Asparagine (N) with Tyrosine (Y) at the 501 position forming the mutant N501Y; amino acid Alanine (A) with Aspartate (D) at the 570 position, composing A570D; the D614G variant discussed above that involves replacement of Aspartate (D) with Glycine (G) at the 614 position; P681H entailing an interchange of Proline (P) with Histidine (H) at the 681 position; T716I reflecting a switch of Threonine (T) with Isoleucine (I) at the 716 position; the S982A featuring an exchange between Serine (S) and Alanine (A) at position 982; D1118H representing a commutation between Aspartate (D) with Histidine (H) at position 1118, etc [48]. Seventeen out of these 23 alterations appear to have occurred simultaneously, and appeared to be coordinated with the purpose to disguise viral proteins to compromise the efficacy of various antibodies against infection (see *Figure 3*). The mutation N501Y modifies the structure of the S protein. It camouflages it from immune detection and threatens to eventually render ineffective several vaccines that target the S protein. What is remarkable is that after undergoing around 300,000 mutations, COVID-19 mutants have evolved into being more effective and contagious rather than disintegrating into extinction, which is what would be expected if such accumulated mutations were random. As if there is some calculated programming within COVID-19 that systematizes mutations to enhance viral contagiousness – something that does not appear to be common among naturally occurring coronaviruses [49].

How Variants are Formed. From Alpha to Beta Variant

The 501.V2 or, as otherwise termed B.1.351, B.1.351.2, B.1.351.3 or Beta variant, or otherwise termed 501Y.V2, was first identified in the Eastern Cape province of South Africa. It is at least as dangerously transmissible as the UK B.1.1.7 and is spreading globally at the same time as B.1.1.7. The Beta Variant or 501.V2 is known to have

three main substitutions of amino acid Lysine (K) into Asparagine (N) at the 417 position (K417N); the variant E484K that involves Glutamate (E) being switched into Lysine (K) at position 484; and the mutant N501Y where Asparagine (N) is replaced by Tyrosine (Y) at the 501 position of the genetic sequence. The N501Y that is shared by both the B.1.1.7 and the 501.V2, and which enhances the affinity between the Spike protein and the ACE2 receptor appears to be compromised by the K417N and E484K substitutions, possibly rendering the African mutation less infectious than the British one. The deleterious effects of these two transformations are due to the action of E484K and K417N. The salt bridges, originally build by E484 and K417, are disrupted after E484 and K417 are transformed into 484K and 417N. 484K along with BD23 R108 / H11013 R52 and 417N along with C105 E96/E99 do not support salt bridges [50].

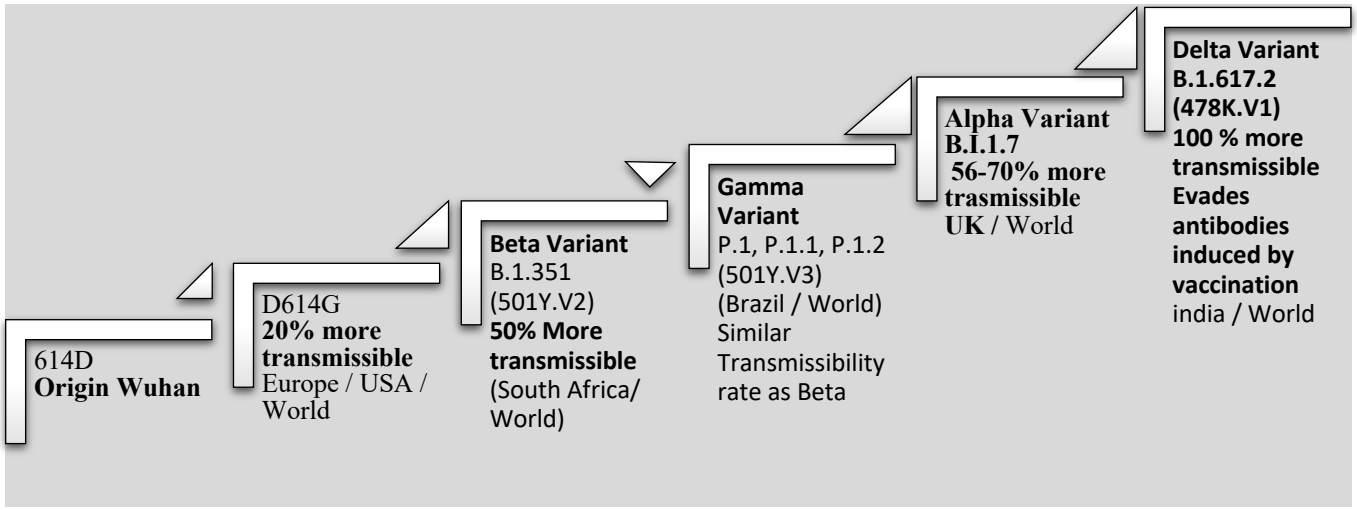

Figure 3. COVID-19 evolution of transformations has significantly enhanced the COVID-19 transmissibility rate as demonstrated by the 70% more contagious B.1.1.7 or variant and the 100% more transmissible Delta Variant. This distinguishes COVID-19 from previous coronaviruses that became extinct as a result of repeated mutations.

COVID-19 From Beta to Gamma Variant

The Beta variant B.1.351, B.1.351.2, B.1.351.3 of 501Y.V2 shares a lot of the amino acid transformations composing B.1.1.7, as well as the newly reported Gamma variant, otherwise termed as P.1, P.1.1 and P.1.2 or P1/501YV3 which emerged in Brazil and involves amino acid changes that include N501Y (Asparagine being replaced by Tyrosine in the 501st position), E484K (Glutamate being replaced by Lysine in the

484th position) and K417N (Lysine being exchanged by Asparagine in the 417th position). The 501Y.V2 or B.1.351 includes 19 mutations, with ten of them located in the Spike protein including the exact same mutations enumerated in the Brazilian P1 and P2: N501Y (Asparagine being replaced by Tyrosine), the E484K (Glutamate being replaced by Lysine) and K417N (Lysine being exchanged by Asparagine). Additionally, it lodges mutations on the N-terminal domain, including L18F - replacing Leucine (L) with Phenylalanine (F) in the 18th position, D80A – transposing Aspartate (D) with Alanine (A) at the 80th position, and D215F that substitutes Aspartate (D) by Phenylalanine (F) at the 215 position.

COVID-19 Gamma Variant / P1, B.1.1.28.1 and P2

The Brazilian P.1, or otherwise called the Gamma variant, or 501Y.V3, the UK B.1.1.7 and the South African B.1.351 or 501Y.V2 , all harbour the N501Y mutation that enhances the contact affinity between the Spike protein and the ACE2 receptor, rendering the variant significantly more contagious [51]. The California variant in the USA B.1.429 or CAL20C involved around three mutations in the spike protein: L452R – replacement of Leucine (L) with Arginine (R) on the 452nd position; S13I- replacement of Serine (S) with Isoleucine (I) in the 13th position; and W152C- replacement of Tryptophan(W) by Cysteine (C) in the 152nd position. There is no evidence of increased transmissibility with either the P1 from Brazil or the B.1.429 from California.

COVID-19 Delta Double Mutant

The lineage B.1.617 first identified in India combines two mutations E484Q (transposing Glutamic Acid with Glutamine in the 484th position) and L452R (transforming Leucine into Arginine in the 452nd position) that have only been observed separately in other variants, rendering this variant as a “double mutant” [52]. The B.1.617 consists of the Kappa or B.1.617.1, and the Delta or B.1.617.2 and B.1.617.3. By July 2021, the Delta variant, B.1.617.2 has manifested a transmissibility rate that is often estimated to 100% with the lowest neutralization so far. Recent

research has reported that the B.1.617.2 appears to be moderately resistant against both vaccinated and previously infected individuals, especially with regard to the antibody Bamblanivimab that is used to treat COVID-19 patients [53].

Delta Enhanced Structural Stability, Stronger Affinity for ACE2 Receptors

Additional research has indicated that the Delta B.1.617.2 COVID-19 mutations (India), demonstrates a higher structural stability of the Spike protein and a stronger affinity of the Spike with the human ACE2 receptor. In the Delta variant, B.1.617.2, the average energy of Arginine (R) in the 452nd position is much higher than that evidenced by Leucine (L). Additionally, the energy of Glutamine (Q) in the 484th position is significantly higher than that of Glutamic Acid (E). And the energy of Arginine (R) in the 681 position is higher than that of Proline (P). In contrast to the Delta variant, the transformations of the Alpha and Beta variants were different. For example, in the Alpha B.1.1.7 variant, the energy of Asparagine (N) in the 501st position was higher than that of Tyrosine (Y). All these energy modifications increase the variants' binding affinity, signifying a remarkably higher transmissibility rate [54]. The World Health Organization has also reported other COVID-19 variants that may be of interest. These include:

1. The Eta variant B.1.525 or 484K.42 that is currently infecting the world.
2. The Iota variant, B.1.526 or 253G.V1 primarily identified in the USA.
3. The Kappa variant or B.1.617.1 or 453R.V3 that is mostly found in India.
4. The Lambda C.37 or 452Q.V1 which emerged in Peru.

Other mutations currently monitored are:

1. B.1.427 and B.1.419 in the USA.
2. The Zeta or P.2 in Brazil.
3. The Theta of P3 in the Philippines.
4. The B.1.446.2 in Indonesia
5. The B.1.621 in Colombia.
6. The R.1, R.2, B.1.1.519, C.36.3, C36.3.1, B.1.1.523, B1.619, B.1.214.2 and B.1.620 that are currently transmissible in multiple countries [55].

It seems as if this virus is international with an immense capacity to adjust within any group of individuals irrespective of discrepancies in their physique and biology or their cultural genetics, the nature and nurture interactions specific to different countries. Therefore, each country appears to develops its own variant, which however, is most often not contained within it place of origin but spreads worldwide.

COVID-19 Striking back with a Vengeance

In July 2021, when the infection rates started going down in the USA and Europe as a result of vaccinations, COVID-19 stormed into the world with its Delta variant that defies the potency of several vaccines and significantly reduces the effectiveness of others. Currently, the Delta mutation has spread in over 90 countries and has become the prevailing type of infection among the USA COVID-19 cases. Vaccine efficiency data is changing daily and most of it lacks figures. The consensus is that vaccines can avoid mortality, however, being protected against infection has become increasingly questionable with a variety of conflicting percentages reported from different countries regarding the Delta variant, versus the previously identified ones; Alpha, Beta and Gamma. Johnson and Johnson, Janssen DNA vaccine have been the only ones claiming higher efficiency with the Delta variant, however a recent study on 10 individuals contradicted this statement. No data has been released on the Janssen vaccine that led Johnson and Johnson to their conclusion. Without data the internal and external validity of their findings cannot be evaluated. Moderna showed a significant reduction in the effectiveness of their mRNA vaccine on the Delta variant when compared to Alpha, Beta and Delta. Chinese scientists have postulated that the Sinovac vaccine is three times less effective in preventing infection with the Delta variant, but again without releasing any specific data. United Kingdom researchers reported that the effectiveness of the AstraZeneca DNA vaccine and the Pfizer/BioNTech or Comirnaty mRNA vaccines in protecting against infection was reduced down to 88% and 60% respectively with the Delta variant. More recently, however, Scottish scientists revised Pfizer/BioNTech or Comirnaty 88% figure to 79%. Clinical trials in Israel further reduced this percentage to 64%. Apparently, the Spike protein mutations, L452R

(Arginine (R) replacing Leucine (L) at the 452 position) and P681R (Arginine (R) replacing Proline (P) at the 681 position) significantly increases the transmissibility rate [56]. More information about the different vaccines will be found in the next chapter addressing this issue.

The Remarkable Capacity of COVID-19 Adaptation and Survival Within the Human Host

The COVID-19 evolution has demonstrated progressively more successful mutations that increase its infectiousness and transmissibility unlike its predecessors, SARS-CoV and MERS-CoV that were eventually driven to extinction. Despite their close kinship, SARS-CoV and COVID-19 display significant structural differences, including 380 amino acid substitutions, and variable homology between certain open reading frames that are bound to diversify the pathogenesis and virulence of the two viral compounds. However, when it comes to COVID-19, a single amino acid substitution such as replacing Aspartate (D) with Glycine (G) composes the D614G mutation that is around 20% more infectious than its predecessor 614D. The B.1.1.7 variant, that exhibits a 70% transmissibility rate, harbours 23 mutants, each reflecting one amino acid exchange. The Delta variant has increased its transmissibility rate to almost 100%. Globally spreading mutations and their sublineages appear to enhance viral contagion despite the inevitable decline predicted by the second law or thermodynamics, or even in defiance of expected entropy. With COVID-19, what can go wrong does not go wrong as is the case with previous coronaviruses. With COVID-19 what can go wrong, goes alarmingly right, strengthening rather than weakening the virus. Unlike previous versions of coronavirus, where random mutations eventually precipitate extinction, the multiplicity of over 300,000 mutations appears to have rendered COVID-19 more contagious, facilitating its ability to evade detection, thus challenging the effectiveness of a large variety of emerging vaccines. Vaccination enhances immune memory and intelligence to combat or obstruct viral entry by generating antibodies that will prohibit the cellular binding and fusion with the Spike protein, ultimately debilitating the virus from releasing its contents into the cell. Developing antibodies during the innate

response, appears to be the most compelling solution in light of the hypothesis that COVID-19 inhibits the production of Interferon type I, compromising adaptive efficiency to recognize the virus, consequently provoking a cytokine storm that injures vital organs. With respect to that perspective, the safety and effectiveness of different vaccines is evaluated and compared, including the Spike protein mRNA version, the Adenovirus DNA, Spike protein subunits, the deactivated virus genres, or, finally, the live attenuated coronavirus which is not currently in the market since it may encompass a relatively higher risk.

CHAPTER B
VACCINES: THE LIGHT AT THE END OF THE TUNNEL

mRNA Vaccines

COVID-19 messenger ribonucleic acid (mRNA) based vaccines, like the two-dose Pfizer/BioNTech and Moderna vaccines, that have now received emergency use authorization from the FDA, are developed by first sequencing the gene of the S protein, they develop a transcription of its mRNA, they encapsulate the nucleotide-modified messenger in a lipid nanoparticle that is subsequently delivered within a sterile saline solution, acting as a dilutant, into the muscles of the host's upper arm. mRNA is a single stranded molecular sequence that can be read by the host's ribosomes. The intention is to introduce the immune system to the configuration of the Spike protein, provoking it to produce the specific antibodies that can defensively wrap around the Spike protein to prohibit viral binding, fusion and entry into the human cells [57]. The vaccine encodes the COVID-19 S1 subunit of the trimer that binds with the ACE2 receptors, as well as the S2 one that fuses with the ACE2 receptors, releasing the viral RNA into the cells. For additional safety, the S2 subunit is stabilized by substituting two amino acids at two consecutive positions, 986 and 987, by prolines which are secondary amines that do not contain the amino-group -NH, often used in the biosynthesis of proteins.

Although the Pfizer/BioNTech vaccine was recently approved for children over the age of 12, its effect on children under the age of 12, pregnant women and individuals with certain specific pre-existing conditions is currently unclear, since the above mentioned populations were mostly excluded from the clinical studies. Additional unknowns involve the vaccine's interaction with a wide range of medications; the durability of immune protection against viral infection; and the vaccine efficiency against new viral mutations [58].

DNA Vaccines

Two other vaccines are produced by inserting the Adenovirus' DNA the AstraZeneca which uses the Adenovirus found in chimpanzees, and the Johnson and Johnson Janssen vaccine that uses an Adenovirus derived from humans. Adenovirus is a group of common viruses infecting the lungs, intestine, urinary tract and nervous system. They primarily infect children more often than adults manifesting symptomatology that ranges from runny nose, fever and cough to gastrointestinal tract infections. Both AstraZeneca and Janssen vaccines are made by deleting part of the Adenovirus genetic sequence and inserting the genetic code of the Spike protein of COVID-19. The method of delivery is similar to the mRNA vaccines, with the exclusion that the Spike Protein mRNA is synthesized out of the genetic material of the Spike DNA that was previously inserted into the DNA of the Adenovirus. Theoretically, deleting part of the DNA sequence of the Adenovirus and altering it by inserting the genetic information of the Spike protein, renders the Adenovirus unable to duplicate. The genetic material of COVID-19 is not even available, expect for the Spike protein that accounts for only one out of its 29 proteins. Besides the COVID-19 Spike genetic material is incorporated within a completely different virus, the Adenovirus. Therefore, Covid-!9 replication is impossible. Once the Spike mRNA serves as a template to compose the Spike protein in the cytoplasm, the process is the same as with the mRNA vaccines, where the mRNA is translated by the ribosomes to form Spike proteins which activate the production of antibodies and T-cells to efficiently defend against COVID-19 infection [59].

Protein Subunit Vaccines

Other vaccine research companies like the Novavax and Sanofi-GlaxoSmithKline produce the spike protein vaccines in insect cells out of recombinant baculovirus [46]. Protein subunit vaccines utilise an isolated protein, in this case the Spike protein, which is purified from any viral infectious components to establish safety. The problem arises when the isolated protein becomes denatured, losing its quaternary, tertiary or

secondary structure as well as its functionality, thus failing to stimulate the immune production of the necessary antibodies that can ultimately protect the system against COVID-19. Therefore, its high safety may be undermined by its potentially compromised efficiency [60].

Deactivated Virus Vaccines

An alternative method is vaccination with a COVID-19 virus that has been deactivated and therefore, it is unable to replicate. This type of vaccine research has obtained different COVID-19 strains from hospitalized patients around the world including China, Italy, Switzerland, United Kingdom and Spain, and has chemically inactivated the hazardous viral features, leaving a purified, disarmed COVID-19 version that can no longer assail the body. Introducing the sight of the inactivated virus in terms of the new PiCoVacc, or otherwise known as Sinovac vaccine, prepares the body to anticipate future viral invasion and encompass immune defences by eliciting potent antibodies, which have so far demonstrated an ability to neutralize at least 10 viral mutations in mice, rats and nonhuman primates. The PiCoVacc was formed by deactivating the CN2 strain and testing it against CN3, CN5 and OS6, as well as the CN1 and OS1, which are closely related to the COVID-19 mutations observed in Wuhan that evinced severe clinical symptoms. These investigators report that the purified inactivated virus exhibited genetic stability, despite multiple passages. The comparison of the different purification stages unveiled minor amino acid substitutions in the Envelope protein - residue 32, which replaced Alanine (A) with Aspartate (D). It also presented an interchange between Threonine (T) with Isoleucine (I) in the non-structural protein nsp10 - residue 49. Genetic stability persisting despite inactivation, signified that the immune system should be able to recognize and create antibodies to potentially protect the cells from future mutations. Immune recognition should occur despite future alternations of the Spike protein, designed to disguise it, so that it eludes antibodies, inconspicuously succeeding in infecting the cells [61, 62]. The PicoVacc is currently better known as the Sinovac or Coronavac.

	Pfizer/BioN Tech BioNTech / BNT162b2	Moderna	Astra Zeneca	Johnson & Johnson	Sinovac / Coronavac/ PiCoVacc
Type of Vaccine	mRNA of Spike protein embedded in lipid nanoparticle	mRNA of Spike protein embedded in lipid nanoparticle	Part of the monkey Adenovirus genetic sequence deleted to insert the Spike DNA (non-replicating)	Part of the human Adenovirus genetic sequence deleted to insert the Spike DNA (non-replicating)	Purified inactivated virus with genetic stability, to allow immune recognition (non-replicating)
Safety	Benefits outweigh the risks	Benefits outweigh the risks	Benefits outweigh the risks	Benefits outweigh the risks	Benefits outweigh the risks
Additional Safety	Two amino acid substitution in positions 986 & 987 by prolines	Two amino acid substitution in positions 986 & 987 by prolines			Several purification stages
Two-dosage effectiveness	93-95%	93-95%	66.7- 70%	66.7-70%	50.7-56.5%
One-dosage effectiveness	52-83%	52-83%	58.9%	58.9%	3-27%
Adverse Reactions (AE)	pain at the injection site (65-80%), fatigue, (35-60%) headache (25-50%), fever (10-15%)	pain at the injection site (65-80%), fatigue, (35-60%) headache (25-50%), fever (10-15%)	pain at the injection site (40-70%), fatigue, headache, fever (15-20%) Rare blood clots 10 cases in 100,000	pain at the injection site (40-70%), fatigue, headache and fever (15-20%) Rare blood clots 10 cases in 100,000	pain at the injection site (60%), fatigue (15%), headache (35%), fever (<1%)

Approved Age	12 and over most countries	16 and over most countries	18 and over most countries	18 and over most countries	18 and over most countries
Two-dosage against B.1.1.7 (UK) P1 (Brazil)	93%	93%	65%	65%	50.7-56.5%
Two-dosage against B.1.1.7 (UK) P1 (Brazil)	51.1%	51.1%	51.1%	51.1%	3-27%
Two Dosage B.1.351 (South Africa)	90% Mostly susceptible within 14 days after 2nd dose but not after that	90%	65%	65%	Undetermined
Two-dosage against B.1.617.1 B.1.617.2 (India)	88% England 76% Scotland 64% Israel	88% USA 65% Canada	59.8% England 60% Scotland	59.8%	21% (no valid data)
One-dosage against B.1.617.1 B.1.617.2 (India)	33% England 37% Scotland Canada 58%	33% England 37% Scotland 65% Canada	70% Canada	33%	undetermined

Table 2. Comparison of Vaccines' efficacy and safety. It should be noted that new research continuously revises the percentages presented in this table. Therefore these are only estimated percentages offering contradictory evidence.

Live Attenuated Virus Vaccines

Live attenuated virus vaccines are based on whole viruses that have been modified and hence weakened. A single dosage can stimulate immune responses against a wide

variety of viral proteins, without infecting the body with the disease. However, a mutation in live attenuated viral compounds could potentially reinstate their harmful potency; or they may have deleterious consequences in individuals with compromised immunity. Moreover, in light that COVID-19 is excreted in the faeces, there is a risk of transmitting the attenuated viral compound to healthy individuals. Lastly, there is the potential of COVID-19 fusion with alternative wild-type versions of coronavirus [63]

Vaccines' Comparison on Safety and Effectiveness

All vaccines appear to demonstrate both safety and effectiveness, which, however, varies from vaccine to vaccine. The two dosage Pfizer / BioNTech / Comirnaty mRNA (messenger Ribonucleic Acid) vaccine has been 100% effective in preventing critical illness and death as a result of contracting COVID-19 on the basis of the US Centres for Disease Control and Prevention. It is 95.3% effective in preventing severe infection according to the standards of the US Food and Drug Administration. Recent evidence elucidated that two dosages of the Pfizer / BioNTech The Spike mRNA are 94% effective for adults over 65. The vaccine effectiveness is based on two applications, while only one application significantly reduces this percentage to 64% according to research findings on a multi ethnic sample of adults with a median age of 73 [64]. A large body of research has confirmed that overall, Pfizer / BioNTech / Comirnaty mRNA vaccine is effective around 52 - 83% after the first dose ascending to an optimal 95% after the second dosage. However Pfizer opposed the idea of only administering one dose on the basis that vaccine efficacy cannot be guaranteed with a single dose [65, 66]. The Pfizer / BioNTech / Comirnaty vaccine consists of the nucleotide-modified messenger RNA of the Spike protein embedded in a lipid nanoparticle within a saline solution that is injected into the recipient's muscle. The messenger RNA represents a transcript recorded by the RNA polymerase that normally carries the DNA genetic information from the cell's nucleus into the cytoplasm, where it is translated by the ribosomes into functional proteins. The Pfizer/BioNTech mRNA vaccine that is injected into the human muscle, is limited to carrying only the genetic information of

the Spike protein, which is one out of around 29 primary proteins that compose COVID-19. The virus cannot replicate when only one of its proteins is available, the way it is impossible to copy a book when only one of its pages is available. After the ribosomes have translated the genetic information carried by the mRNA that serves as a template for the synthesis of the Spike protein, the mRNA is either stored for future translation or discarded. The presence of the Spike (S) protein activates naïve or memory B cells which produce spike protein-specific antibodies designed to defensively bind to the COVID-19 S protein disallowing the virus from releasing its contents into the cells. B cells are associated with receptors in the plasma membrane that stimulate intracellular signalling pathways in case antibodies fail to prevent the virus from binding to the ACE2 cellular receptors. B cells can proliferate and become differentiated into lymphocytes, phagocytes and other effector cells that can eventually obliterate any remaining pathogens that have managed to enter the system [67].

Common Side Effects of Vaccination

Vaccination results in temporary adverse effects, lasting from 3-7 days, that mostly include pain at the injection site, fatigue, headache and fever with serious adverse effects like facial paralysis noted in less than 1% of the studied population. The experience of mild or moderate transient symptoms following vaccination signifies the laborious activity of the immune production of antibodies which are later transformed into other defensive mechanisms that consume large amounts of biological energy to prepare and defend the body from future viral invasion. Therefore, side effects is a necessary part of vaccination that denotes vaccine efficacy. Lack of any adverse reactions may either indicate greater tolerance or, in certain cases, that the vaccine is ineffective. A new variant that was first detected in India is now spreading around the world, diminishing the effectiveness of the Pfizer/BioNTech Comirnaty from 93% to 88% (or 64% according to more recent studies); and the AstraZeneca vaccine from 66% to 60%.

The DNA vaccine has had some rare life threatening side effects of blood clots that

occur around 10-11 times per 100,000 vaccination. Other than that, it involves very similar symptomatology of temporary adverse reactions as the mRNA vaccines. Vaccine efficacy appears to be around 66.7-70% on the average, based on a number of different studies with moderately lower vaccine effectiveness following the first dose which is around 58.9% [68].

Vaccine Effectiveness. What can Go Wrong?

The DNA vaccine is not even based on the COVID-19 virus. It is based on the Adenovirus after its genetic sequence has been altered to disable reproduction within the cell. As a result of the vaccination, the B cells can produce antibodies for the particular S protein configuration presented, thus obstructing the COVID-19 spike protein from targeting and fusing with human cells. However, any formation of immune memory resulting from this process can be rendered ineffective by a viral mutation that substantially disguises the S protein to be unrecognizable by the immune system.

The genetic stability of inactivated vaccines could perhaps offer protection against several mutated strains; however, it is unclear whether accurately examining and mapping certain current strains can extend to future emerging ones. Additionally, it is unclear how many vaccine dosages will be warranted with the inactivated virus vaccines; and what will be their final level of effectiveness and durability [69]. Until today, July 22 2021, Sinovac offers two doses.

Both mRNA and DNA vaccines have been proven to be effective against the UK/Kent variant, also known as B.1.1.7. However, the Delta mutation that is more transmissible than B.1.1.7, has been found to mildly compromise the effectiveness of the Pfizer/BioNTech and AstraZeneca vaccines from 93% to 88% and from 66% to 59.8% respectively. However, one dose of both vaccines appears to reduce the vaccine effectiveness on B.1.617 down to 33%. These findings strongly urge for a two-dose administration of both vaccines to secure a higher protection against COVID-19,

against the B.1.617.2 new variant [70].

The Sinovac or Coronavac vaccine has attained the lowest efficacy rate when compared against both its mRNA and DNA alternatives. The University of Chile study reported that Sinovac was effective around 56.5% after two weeks administration of the second dose and only 3% effective after only one dose that exponentially increased to 27% within two weeks. Brazilian researchers have found that the Sinovac only has 50.7% overall efficacy that did not seem to be compromised by the Brazilian P1 variant, while Turkish studies reported an 83% efficacy [71]. The Sinovac has not released data regarding its effectiveness against the Delta variant.

Overall, around 2.12 billion people have been vaccinated around the world by June 2021 with very rare serious adverse effects, leading to the conclusion that the benefits of any vaccine available today are greater than the risks involved in contracting the COVID-19 [72].

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CHAPTER 2

COVID-19 Affinity for ACE2 receptors in Adipose Tissue and Testes.

Summary:

The imminent danger of the COVID-19 pandemic has accelerated research in pharmaceuticals that either target the fusion of the Spike protein with ACE2 receptors, or the infectious RNA replication that often overwhelms immune defences. The scope of this review was to elucidate the main human vulnerabilities to COVID-19, including the accumulation of ACE2 receptors in testes, adipose tissue, thyroid, heart and kidneys that escalate viral affinity in males, the aged, and certain medical conditions, including diabetes, CVD, and pulmonary diseases. Pre-existing inflammation inherent in obesity may exacerbate the "cytokine storm," a rampaging immune reaction during the course of COVID-19 that is deleterious to the host. A number of new therapeutics have emerged in the pharmaceutical market along with alternative techniques that include hormone replacement procedures and mesenchymal stem cells. None of them appear to offer a conclusive solution which leaves only preventive and protective interventions designed to enhance immunity. The current perspective explores the primary components of dysregulated health predisposing individuals to COVID-19, including hormonal imbalance, increased lipids and lipoproteins, thyroid dysfunction, degraded fitness, age-related testosterone decline and cortisol increase that provokes stress eating behaviours and weight accumulation. Obesity facilitates COVID-19 proliferation in human cells due to the abundance of ACE2 receptors in adipose tissue. ACE2 receptors are sparce in muscle cells, therefore, physical activity, regular exercise or any alternative to exercise may restrict COVID-19 escalation, by exchanging fat with muscle mass.

The COVID-19 Affinity for ACE2 Receptors

The COVID-19 two main genes ORF1a and ORF1b encode sixteen non-structural proteins, and four structural proteins: the spike (S), divided into S1 / S2 subtypes,

membrane (M) and envelope (E) proteins on the viral surface, and the nucleocapsid (N) protein, associated with the viral RNA. The S glycoproteins reflect the characteristic viral morphology surrounded by "coronas" the Greek word for crowns. S1 subunit recognizes and binds to angiotensin-converting enzyme 2 (ACE2) receptors, and S2 releases the fusion peptide to secure the connection to prelude the insertion of the viral contents into the cell [2, 3]. ACE2 is a membrane-bound enzyme. A Disintegrin And Metalloprotease 17 (ADAM17) is able to cleave ACE2 and cast it into the blood and body fluids, rendering the S1 /ACE2 fusion less likely [4].

The S/ACE2 affinity has been documented for over 15 years since the emergence of SARS-CoV [5, 6, 7]. The M and E proteins are in charge of the viral assembly and encapsulation of genetic material respectively [8, 9]. The N protein is intertwined with the viral genome and is involved in replicating and transcribing the viral RNA, eventually overwhelming the human biomolecular network. Due to the imminent threat of the pandemic most research has focused on therapeutics rather than prevention.

Therapeutics

A series of studies postulate that theophylline and pyrimidone can prevent the replicating ability of the N protein, by blocking contact of the protein's N-terminus with RNA, thus inhibiting viral multiplication [10]. COVID-19 does not respond to most nucleotide analogues (NA), designed to interfere with viral replication, due to the COVID-19 inherent Exonuclease (ExoN) domain that compromises NAs; however, it appears to be responsive to the new NA drug Remdesivir, that features the active metabolite, GS441524 [11]. Another therapeutic research target is drugs intended to obstruct the COVID-19 entry into the human system associated with TMPRSS2 (Transmembrane protease, serine 2) inhibitors, such as camostat mesylate [12]. TMPRSS2 is an enzyme encoded by the androgen regulated gene. TMPRSS2 serves to prime the ACE2 receptor, facilitating its fusion with the Spike protein of COVID-19. Multiple interventions involve ACE2 receptor blockers, or calmodulin antagonists [13].

ACE Inhibitors

ACE inhibitors (ACEI) commonly used for hypertension and Diabetes, prevent the conversion of Angiotensin I into Angiotensin II, a peptide in the renin-angiotensin system (RAS) that increases blood pressure. However, there is evidence that ACEIs increase COVID-19 vulnerability. ACEIs do not block the ACE2 receptors, because ACE and ACE2 are different entities. The function of ACE2 is to degrade the production of Angiotensin II, thus hindering ADAM17 (A disintegrin and metalloprotease 17). ADAM 17 cleaves ACE2 from the cellular membrane, shedding it into body fluids. Since ACEIs suppress ADAM17 via suppressing Angiotensin II, the ADAM 17 sheddase activity is restricted. This may be interpreted to mean that in the absence of ADAM17, the cellular ACE2 receptors are not cleaved and therefore remain as open doors inviting COVID-19 fusion.

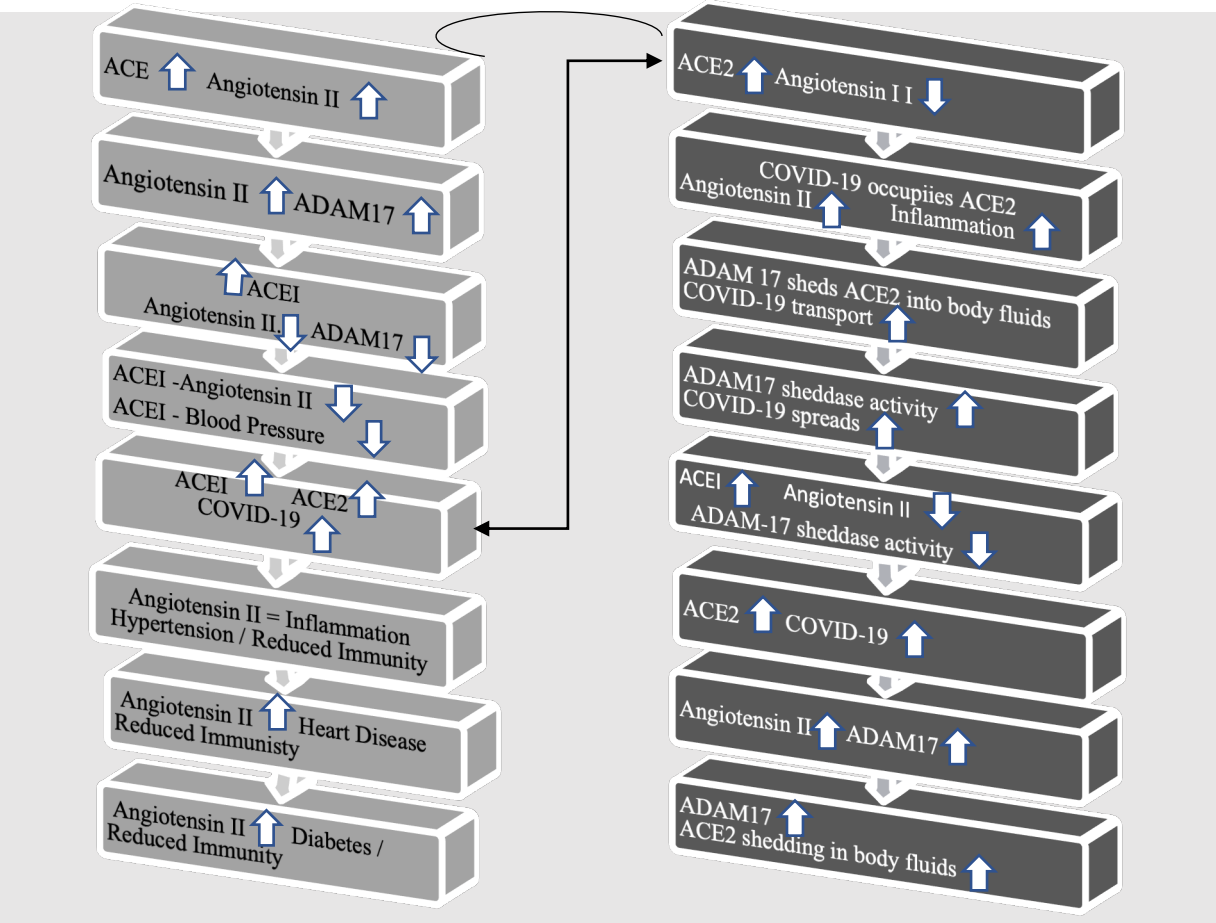

Figure 1. The COVID-19 vicious circle dilemma of ACE & ACE2 receptors, angiotensin I & II and ADAM17.

The alternative explanation is also possible. As COVID-19 receptors are possessed by COVID-19, their regular function of Angiotensin II degradation is compromised. Therefore, Angiotensin II increases, leading to both inflammation and expression of ADAM 17 that is prone to cleaving the COVID-19 portals, the ACE2 receptors, shedding them into body fluids, that could potentially facilitate the transport of COVID-19 [14, 15]. ACEIs decrease Angiotensin II and the ADAM 17 activity, basically again allowing whatever ACE2 receptors are not seized by COVID-19, available for fusion. It is a checkmate situation where COVID-19 will win irrespective of what move the body chooses to make. ACEI which are necessary to lower inflammation and blood pressure may not be the safest treatment in preventing COVID-19 from overwhelming the body because they restrict the ADAM17 activity and increase the number of ACE2 portals available to bind with COVID-19. This interaction is graphically presented in Figure 1.

ACE2 Receptors: The answer to why Males are more Vulnerable to COVID-19

Research has repeatedly confirmed that COVID-19 exhibits a greater affinity for males. ACE2 receptors are protagonists in elucidating the increased fatalities observed among men rather than women [16, 17]. The reason lies in the high incidence of ACE2 receptors in male tissues [18]. ACE2 is largely expressed in spermatogonia in human testes. The androgen producing Leydig cells and Sertoli cells are involved in the nourishment of spermatozoa in humas testes; this ACE2 / male tissues bond exposes the male reproductive system to possible malfunction following COVID-19 infection [19, 20]. Liu et al, (2020) analysed both embryonic primordial germ cells (PGCs) and adult Sertoli cells and postulated that all testes cells are enriched in ACE2 expression starting from the embryonic stage all the way to adulthood [21]. There is an additional process increasing the probability of infection in males. The androgen receptor (AR) that is largely expressed in male tissues, promotes the expression of type II transmembrane serine protease (TMPRSS2) which acts as a catalyst priming both the viral S glycoprotein and the various vital organs' ACE2 receptors, thus accelerating

the fusion of the Spike (S) with ACE2 receptors, inevitably infecting the body with COVID-19 [22, 23, 24].

Cathepsin L1 Protein and COVID-19

Although ACE2 receptors, prepared by proteases like TMPRSS2 may be the main point of viral entry, autopsies of COVID-19 patients reveal a higher incidence of the cathepsin L1 protein (CTSL) rather than ACE2 receptors in the lungs. These investigators found a dysfunctional biological landscape characterized by deteriorated protein translation and lipid metabolism as well as substantially damaged lungs, kidneys, spleen, liver, heart, thyroid, and testes featuring a reduced number of Leydig cells [25]. Although their results may have been affected by the lethal aftereffects of COVID-19, they strongly suggest that CTSL is another protease facilitating the entry of COVID-19 into the body [26]. Cathepsin L1 (CTSL) serving as an additional portal of COVID-1, increases the probabilities of viral infection, and hinders the immune system's ability to counteract the invasion after it has been overwhelmed. Li et al. (2020) examined 31 different human tissues and found that ACE2 expression in the lungs was in fact moderate [27], suggesting the possibility that the increased CTSL in the lungs found post-mortem may reflect the virus exploiting CTSL to increase its transmissibility within the human system.

Viruses commonly exploit various cell structures to interfere with the host's cellular mechanisms in the service of their survival. RNA viruses have been traditionally more successful in rewiring within their hosts to avoid extinction. Protein interactions controlled by viruses can mislead host proteins, inhibiting necessary biological functions or activating molecular responses that are damaging to the host. Viruses act like disguised adversaries, pretending to be part of the genetic configuration. Therefore, exploiting both ACE2 receptors and the cathepsin L1 protein (CTSL) as an alternative viral portal may appear as nothing new or alarming. However, when such details are noted from the larger perspective of the remarkably sophisticated mutations of COVID-19 discussed in Chapter 1, they may leave a sense of uneasiness. In the

following chapters as the landscape of the COVID-19 pandemic is further investigated this dark premonition will start shaping itself into reality.

The Importance of ACE2 Receptors in Human Tissues

Li et al. (2020) found that ACE2 receptors were more abundant in testes, adipose tissue, heart, thyroid and kidneys with a minimum expression in the muscles, blood and blood vessels. The minimum expression of ACE2 receptors in the muscles, immediately brings to mind the concept of fitness, raising the possibility that fitness may serve as a solution to decrease COVID-19 vulnerability. If fat is exchanged with muscle, as it happens after long term intense workouts, then, the muscle increase will reduce the number of ACE2 receptors and restrict the available entry points that can be exploited by COVID-19. Obviously, muscle cannot possibly offer full protection against COVID-19. However, fitness leads to health enhancement and reinforced immunity so, at least it may prevent severe symptomatology and decrease mortality rates.

Li et al found, that although ACE2 receptors in most vital organs were equivalent in males, females, old, young, Asian and non-Asian populations, the immune responses widely varied in the four groups delineating greater vulnerability among the male and older groups. This point will be discussed in greater detail in later chapters.

The increased incidence of ACE2 in male tissues explains the younger men susceptibility to COVID-19. The dimension of immunity, including evidence that age-related testosterone decline affects the activity of respiratory muscles, elucidates the COVID-19 susceptibility of older males who manifest an age-related testosterone decline [28, 29]. From the fitness standpoint, aging results in greater adipose tissue accumulation, and less opportunities for fitness, due to weight gain and bodily fragility that make exercising cumbersome. Overall, an unfit body is correlated with testosterone below the normal range and therefore a weakness in the respiratory muscles. Added upon that, is the abundance of ACE2 receptors on male tissues,

multiplying the entry portals of the virus. Hence, the ease with which an unfit body can readily become prey to COVID-19.

The Double-Edged Effects of Testosterone on COVID-19

It should be noted that both abnormally high and low testosterone are associated with increased COVID-19 vulnerability. Declined levels of testosterone have been correlated with increased inflammatory markers and a poor prognosis of male COVID-19 patients [30]. Several studies report that testosterone increases ACE2 expression, while androgen upregulates TMPRSS2. During COVID-19 invasion, ACE2 receptors are primed by TMPRSS2, tailoring them into forming a steadier connection with the Spike protein, which at that point is not recognized by the immune system as a harmful antigen. TMPTSS2 assists COVID-19 to penetrate the cells, which may explain why children who are low on androgen before puberty as well as females are less vulnerable to COVID-19 infection than adult males. ACE2 receptors are involved in generating Angiotensin 1-7, a vasodilator that decreases blood pressure and protects both the heart and the lungs from serious injury [31].

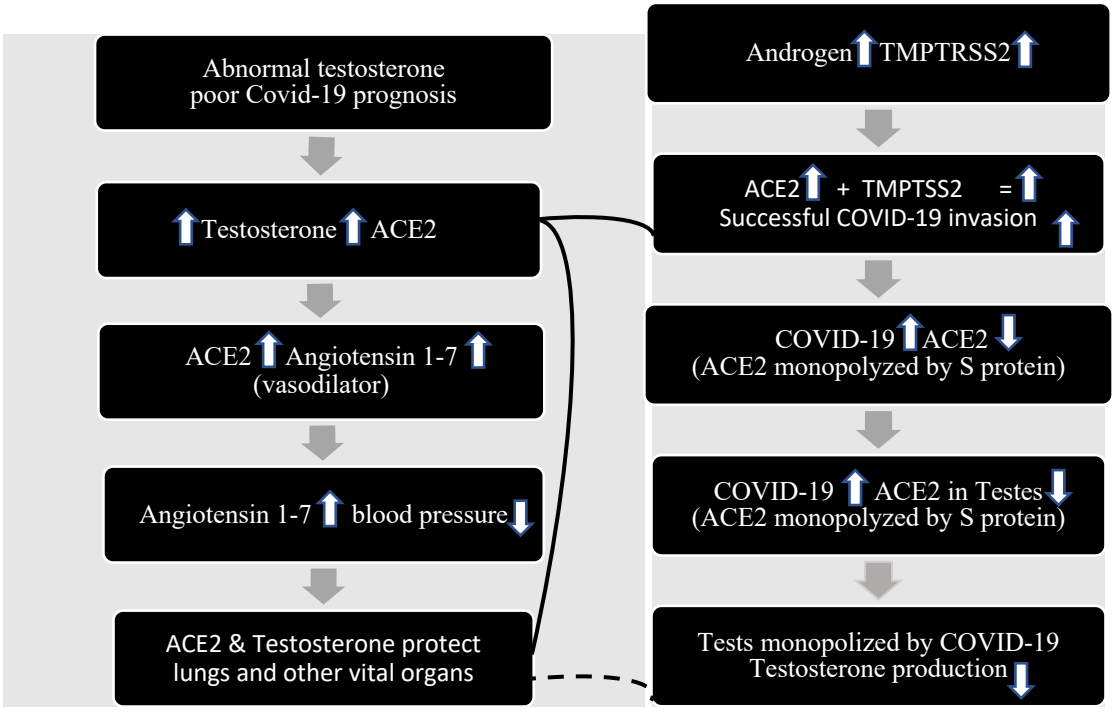

Figure 2. The Testosterone Double-Edged Dilemma.

The Spike protein fusion with ACE2 receptors renders them unavailable to moderate the Angiotensin 1-7 production, compromising their ability to safeguard vital organs. COVID-19 exploits the biological advantage of testosterone by first upregulating ACE2 receptors, with which it subsequently binds, debilitating them from offering pulmonary protection. Basically, testosterone simultaneously manifests the advantage of increasing vital organs' defence, and the disadvantage of increasing entry points to COVID-19 via promoting a higher ACE2 receptors' expression. The multiplicity of ACE2 receptors in the Leydig cells of the testes, that produce testosterone, also serve as Spike's gateway into the system and once they are monopolized by the virus, testosterone secretion is jeopardised and with it, the beneficial effects of testosterone on the lungs. This is depicted in Figure 2.

High testosterone leads to Thrombosis which is deleterious to COVID-19 patients, a fact that testosterone hormone replacement treatments should consider. Thromboembolism or blood clots in the veins or erythrocytosis, a condition where your body makes too many erythrocytes which can subsequently lead to thromboembolism, are very serious medical conditions and in certain cases, life threatening [32, 33].

In conclusion, too much is as bad as too little. The golden standard here is hormonal balance, again, pointing towards to the necessity for fitness and a healthy lifestyle possibly offering the safest precautionary mechanism against the ravaging consequences of COVID-19.

The Thyroid Connection

One aspect of hormonal imbalance, delineated by the thyroid disorder, has been directly connected to COVID-19, indicating a malfunction in transforming free thyroxine (T4) to free triiodothyronine level (Free T3) [34, 35]. Research has demonstrated that ACE2 receptors have a higher expression in the thyroid than in the lungs, as will be discussed in later chapters, and thyroid dysregulation affects disorders

presenting the highest incidence of COVID-19 mortality rates, such as Diabetes and CVD [36, 37, 38 39]. Diabetes is one of the most prevalent premorbid conditions preceding COVID-19 symptomatology and hypothyroidism appears to be a central dysfunction in Diabetes.

Diabetes and Hypothyroidism

Experimental evidence links Type 1 Diabetes (T1B) with hypothyroidism by showing that subclinical hypothyroid adolescents demonstrate a higher incidence of hypoglycaemic symptomatology [40]. A series of animal model studies report a pharmaceutically induced diabetic and a hypothyroidic status by administering streptozotocin and propylthiouracil respectively. These investigators observed an increased sense pre-mRNA of the b gene that is associated with a lower contraction rate of the myosin heavy chain, consistent with the simultaneous presence of diabetes and hypothyroidism, thus connecting the two. This finding was complemented by the observation that the sense RNA of the a gene that regulates a faster level of muscle contraction in normalcy, was substantially decreased [41]. A study on 1112 diabetics found a connection between Type 2 Diabetes (T2D) and hypothyroidism, especially in individuals over 65 [42]. An earlier investigation of the records of 922 T2D patients unveiled a high correlation between T2D and hypothyroidism, with a prevalence in white subjects [43]. Research has denoted that diabetes is underlaid by a defective mechanism that fails to generate Triiodothyronine (T3) from thyroxine (T4), the 4-iodine atoms hormone produced in the thyroid gland, resulting in systemically insufficient levels of T3 in diabetics [44].

The Importance of Optimal T3 Levels in the Treatment of Diabetes

In an animal study, cellular apoptosis was induced experimentally by streptozotocin injections, administered to artificially precipitate diabetes. The deleterious effects of the streptozotocin injections were partly reversed by T3. This finding indicated that increasing T3 to normal levels could potentially improve the diabetic condition, possibly placing diabetics to a path towards recovery. T3 protects B cells through

activating the PI3K-Akt (Ak strain transforming) signalling pathway that generally promotes cellular survival and growth. There is a connection between defective proliferation or apoptosis of B cells, and hyperglycaemia, the cornerstone of both Type I and Type II Diabetes. This fact brings centre stage the beneficial effects of T3 on the cellular integrity of B cells. T3 injections appear to act as an "anti-diabetic" intervention counteracting the diabetic deterioration following streptozotocin injections. This has been shown experimentally, by a documented reinstatement of insulin responsiveness as well as the euglycemic range of serum glucose levels [45, 46, 47, 48, 49].

Adrenals and COVID-19

Adrenals have a moderate ACE2 expression, yet, research reveals that increased levels of the stress hormone, cortisol, decreases COVID-19 survival chances. High cortisol concentrations have been linked to diabetes and heart disease [50, 51, 52]. Cortisol has been reported to be higher in hospitalized COVID-19 individuals possibly due to physiological stress. Cortisol levels in COVID-19 patients are even higher than patients undergoing surgery. Cortisol increase under stressful situations is both normal and important for survival and environmental adaptation, because it activates metabolic and immune changes that can prepare the body to confront a given adversity. However, doubling cortisol levels as it has been reported by research with COVID-19 patients, appears to be maladaptive since it results to a 42% increase in COVID-19 mortality rates. In a clinical study COVID-19 patients with cortisol levels higher that 744 nmol/L could only survive for around 15 days, versus patients with cortisol levels under 744 nmol/L who were able to survive for over twice as many days with a median range of 36 days [53].

The Effects of Oestradiol on COVID-19 Infection and Mortality Rates

A number of investigators driven by the lower number of female fatalities following COVID-19 infection, have highlighted the anti-inflammatory effects of oestradiol [54]. There is evidence from animal models that oestradiol is associated with a twofold

decrease of ACE2 receptors in the female kidney [55]. ACE2 is normally upregulated in the kidneys, therefore, the oestradiol suppression of ACE2 receptors in the female kidneys may be partly responsible for their lower mortality rates. However, other studies have reported a higher rate of infections among premenopausal women, but not deaths, juxtaposed by higher mortality rates in men. A recent review presented evidence that the anti-inflammatory effects of steroids 17b-oestradiol (E2) and progesterone (P4) may counteract the deleterious effects of the hyperinflammatory state associated with the cytokine storm, where white blood cells indiscriminately attack both the virus and the vital organs that contain it [56]. A study of 68,466 COVID-19 cases found that premenopausal females had a 15% higher incidence of infection than males yet, men demonstrated 50% higher mortality rates. Postmenopausal women evidenced an equivalent susceptibility to men but lower mortality rates. In other words, the premenopausal women that were slightly more susceptible to COVID-19 infection than men, were able to overcome it more efficiently than the males who demonstrated higher mortality rates. This finding may appear in contradiction with research evidencing that oestradiol suppresses the ACE2 receptors in the kidneys, decreasing the female COVID-19 infection susceptibility, at least as related to that vital organ. Obviously it is not a contradiction since kidneys is only one of the vital organs that can be affected by COVID-19. Additionally, these results may be sample specific, because Li et al's research cited earlier, found that ACE2 receptors in most vital organs were equivalent in males and females, young and old, Asian and non-Asian populations; however, there was a notable variability in the males' vs females' immune responses that pointed towards males being more vulnerable. Obviously the immune responses of the young are more efficient than those of the old, so the vulnerability of the aged is indisputable.

Some clinical studies have demonstrated that COVID-19 fatality risk is reduced by 50% in postmenopausal women treated with oestradiol. However, oestradiol treatment has no effect on premenopausal women who manifest optimal oestradiol levels in their systems [57]. This finding signifies the importance of hormonal balance where both

too much or too little may increase not only COVID-19 susceptibility, but vulnerability to several other medical disorders. Therefore, indiscriminately administering oestradiol to all women may not have the expected desirable effects with regards to COVID-19.

The Adverse Effects of CRP on COVID-19

The evidence of increased susceptibility risk among premenopausal women should be examined in greater detail. This higher susceptibility may be due to the C-reactive protein (CRP) being higher in females than males, as a survey on 22,000 individuals indicated [58]. CRP is one of the most reliable markers of inflammation. Predictably, the higher the initial inflammatory state, the higher the possibility of the hyperinflammatory state observed in severe COVID-19 cases. In this study, oestradiol and cyproterone acetate (CPA) hormone therapy on postmenopausal women had no effects on CRP. What was worse, oestradiol plus norethindrone acetate and levonorgestrel significantly increased CRP unlike the no-treatment control group that displayed no CRP changes [59]. These results suggest caution with hormonal replacement therapy cocktails (HRT) can potentially result in hormonal imbalance, and possibly trigger unwanted processes increasing inflammation which will reinforce the hyperinflammatory state and inflame the cytokine storm.

Hormonal Replacement Therapy (HRT) and Other Inflammatory Markers

Silvestri et al (2003) reported that although HRT raises CRP, it actually appears to decrease other inflammatory markers such as interleukin-6 (IL-6), soluble thrombomodulin (TM) plasma levels, and E-selectin concentrations [60]. TM is often associated with organ failure [61] and the risk of haemorrhage [62]. It should be noted that IL-6 can act as a pro-inflammatory cytokine as well as an anti-inflammatory myokine. It is unclear why and how HRT decreases other inflammatory markers while raising CRP that has been traditionally featured as a consistently reliable marker of inflammation [63]. The conflicting evidence on the effects of HRT on inflammation should signify the necessity to consider age, health status, and the possibility of

inducing hormonal imbalance or initiating undesirable processes leading to inflammation.

The Effect of Mesenchymal Stem Cells (MSC) on COVID-19

A recent study postulated that human umbilical cord mesenchymal stem cells (MSC) had a positive effect on one COVID-19 patient [64]. Additional research reported a significant decline in CRP, TNF-a and lymphocytes, followed by an absence of the immune cells CXCR3+CD4+, CXCR3+CD8+, and CXCR3+ that are associated with the cytokine storm, after injecting seven COVID-19 patients with MSC [65]. Although these results are promising, the samples in these particular studies were too small to serve as valid and conclusive evidence that MSC can be clinically useful in the treatment of COVID-19. More clinical research with a larger number of subjects is necessary to further investigate the possibility that MSC can consistently reduce inflammation.

Inflammation, a Common Denominator of Adipose Tissue, Aging and COVID-19

The primary expression of ACE2 receptors in adipose tissue, heart and thyroid is consistent with research evidencing higher COVID-19 fatality rates among obese individuals, and patients suffering from cardiovascular disease (CVD), hypertension, and diabetes [66, 67, 68, 69, 70]. The relatively lower ACE2 expression in muscle tissues renders physical activity, and exercise alternatives as optimal protective methods to safeguard health [71, 72].

The need for exercise or an equivalent alternative become prominent in light of evidence that body mass index (BMI) over 25 is associated with a fatality rate increase of 88% after contracting COVID-19 [73]. Visceral adiposity has been associated with inflammatory markers like C-reactive protein (CRP), tumour necrosis factor-a (TFN-a) and interleukin-6 (IL-6) that have been prominently featured in COVID-19 patients [74, 75, 76, 77]. Age is positively correlated both with visceral adipose tissue increase and inflammation as measured by CRP, TFN-a and IL-6 [78]. Therefore, adipose

tissue, aging, and COVID-19 disease severity with poor prognosis are all closely associated with elevated inflammatory markers including interleukins (IL-2, IL-6, IL-8), CRP and TNF-a [79]. Interleukins, tumour necrosis factors, and interferons are involved in the "cytokine storm syndrome" (CSS), an overzealous immune defensive activity that spirals out of control damaging the vital organs of the host [80, 81, 82]. The higher the initial level of inflammation, due to obesity or other factors, the greater the chance of the lethal effects of the cytokine storm. The fusion of the S COVID-19 glycoprotein with the ACE-2 receptors that are abundant in adipose tissue, trigger a chain of events, such as overproduction of Angiotensin II, a proinflammatory cytokine, that promotes A Disintegrin And Metalloproteinase 17 (ADAM17). ADAM17 is instrumental in the ACE2 shedding process in body fluids which further transport the virus throughout the body. As angiotensin II increases ADAM17, it ultimately activates TNF-a, and amplifies IL-6 along with other parameters, rapidly progressing to a hyperinflammatory state that precipitates multi-organ injury or failure [83 84, 85].

In conclusion, COVID-19 is a complex medical 'double edged-sword' posing major pharmaceutical dilemmas, progressing globally with infections and fatalities despite the diagnostic and drug research it has accumulated. None of the pharmaceuticals currently in the market guaranteed a complete cure. Hence, the necessity of gearing some of COVID-19 research towards prevention. An obvious target is weight management to reduce obesity that is featured as one of the major factors increasing global COVID-19 susceptibility and mortality rates.

Radiofrequency Techniques for Weight Loss

A number of radiofrequency (RF) technologies claim virtually instant subcutaneous lipolysis, however, they offer no clear data on long term results, and do not control for weight rebound. Additionally, they present no evidence supporting increased muscle mass or detoxification caused by the actual technology rather than relying on exercise, or the efficiency of the body to perform these functions [86, 87, 88, 89, 90, 91]. Despite the success stories cited by clinicians, research studies, often present statistically

insignificant results and no follow up to evaluate the long term effects of the RF treatment. A clinical study that combined RF and cryolipolysis on the reduction of subcutaneous fat, reported improvement in 73.46% of the patients, a statistically non-significant result. 22.44% of these patients experienced no change, and 4.08% of them disclosed that RF had deleterious effects on their appearance [92].

Another, even more crucial issue is that RF lipolysis studies primarily address the subcutaneous fat area. The visceral fat that accumulates with aging and is very difficult to remove can still become a COVID-19 target, even if the subcutaneous fat is successfully reduced. The proximity of the visceral fat to vital organs substantially increases the danger of mortality. Visceral fat does not only surround the vital organs, but it invades them. It gives, in a matter of speech, the keys to COVID-19 to enter the liver, the heart, the kidneys, etc and destroy them. There is one study published in the Cairo University Bulletin, which is not a peer reviewed journal, that claims visceral fat reduction. However, there is no specific measurement or evidence that the RF treatment reduced visceral fat or any method to distinguish between visceral and subcutaneous fat in the reduction of the "overall fat" reduction reported. Basically, the "overall fat" decrease presented in this study could merely pertain to subcutaneous fat [93].

Radiofrequency and Inflammation

Reports on the medical uses of RF present evidence of increased inflammation. A study on 130 patients delineated a significant increase in the inflammatory marker CRP at the level of $p<0.01$ statistical significance following radiofrequency procedures [94]. Research exploring RF medical interventions revealed an increase in both oxidative stress and inflammation biomarkers [95]. Another study on ninety patients undergoing RF treatments documented elevated C-reactive protein (CRP), creatine kinase suggesting muscle damage, Troponin-P, indicating heart injury or the possibility that a heart attack has occurred, and increased fibrinogen, a glycoprotein complex associated with the formation of blood clots [96]. This data is not directly connected

to COVID-19 patients, but it cautions against the application of RF technologies on this population due to the estimated muscle damage, escalated inflammation, possibility of thrombosis, embolism or heart disease. Overall, the RF induced increase of inflammation and prothrombotic markers could undermine immune defences and reinforce the hyperinflammatory state of the cytokine storm that often ravages vital organs and patients' lives. Even without the COVID-19 threat, inflammation can be deleterious to the overall health status.

In conclusion, what would be the purpose of an inflammatory procedure implemented for weight loss during a pandemic that capitalizes on inflammation to overpower and subdue immunity? RF multiple adverse effects reported by a number of investigators render RF procedures at best counterproductive, and at worst detrimental to optimal health.

Laser Lipolysis

Laser technology has also claimed subcutaneous lipolysis [96, 97, 98, 99, 100, 101, 102, 103, 104]. A review evaluating laser induced complications on 537 cases found only one case of skin infection, and four skin burns, rendering laser weight loss procedures relatively safe [105, 106]. A more detailed review, however, has compiled a number of side effects following laser treatments, including skin burns, dysesthesia, superficial thrombophlebitis, hematoma, nerve injury, and some rare incidences of pulmonary embolism [107].

Lasers and Inflammation

A number of investigators make claims about the anti-inflammatory effects of low level laser therapy (LLLT) and present cases of pain analgesia, reduced oedema, and improvement of some pulmonary diseases [108, 109, 110, 111, 112, 113, 114]. A recent LLLT review proposes that this type of therapy should be used to counteract the cytokine storm of COVID-19. However, the entire review appears to be hypothetical

because these investigators fail to present clinical studies involving COVID-19 patients (115).

Some investigators have reported visceral fat reduction after combining LLLT and exercise; yet, it is not clear whether the effects on visceral fat were due to the laser rather than the exercise. Moreover, a replication of this study by the same investigators revealed no visceral fat reduction, contradicting the findings of the first study. The discrepancy between the two studies questions the external validity of initial reported finding that LLLT reduces visceral fat [116, 117]. Another concern is which layer of visceral fat does a laser treatment target? Even if LLLT or other laser technology could indeed reduce superficial visceral fat, how could that help the visceral adipose tissue layers wrapped around vital organs that pose a major health concern? Importantly how could laser technologies for lipolysis address visceral fat that invades and becomes integrated with vital organs precipitating severe medical conditions such as non-alcoholic steatosis or fatty liver, for example? How can LLLT, or any other laser type for that matter, target fatty liver without causing hepatic damage?

Exercise as a Protective Method against COVID-19 Fatalities.

Physical fitness safeguards health and reinforcing immunity protecting the body during the initial stages of the disease to avoid deterioration [118, 119, 120, 121, 122]. There is evidence that engaging in moderate intensity gymnastics reduces the risk of respiratory symptoms [123, 124, 125]. Influenza research that explored the immunity status of 24,658 adults demonstrated that sedentary lifestyles with infrequent exercise were associated with 5.8% - 8.5% mortality rates, while low to moderate exercise reduced the risk level down to 4.2% - 6.4% [126].

On the down side, exploration of visceral fat reduction via exercise has demonstrated modest findings. One study found a statistically insignificant decrease of visceral fat and fatty liver, which, however, was not accompanied by overall weight reduction [127, 128]. Research on 160 healthy Korean adults used computed tomographic scanning to

test the results of exercise on inflammation and visceral fat. They found that visceral fat was the best predictor of inflammation as measured by CRP levels and insulin resistance. These investigators reported significantly lower visceral fat, yet in the absence of BMI changes or any improvement in physical fitness [129]. The absence of muscle increase in this study may signify the need for longer periods of exercise or combinations of different types of physical activity.

The Problem with Commitment and Long-Term Effort

Unless, an individual has led a healthy lifestyle that involves sports and frequent visits to the gym throughout life, it is not easy to lose weight or build muscle in a short time. Enhanced immunity via physical activity is attainable, because it replaces fat with muscle, thus reducing the ACE2 receptors that are abundant in fat but sparce in muscle. Regular exercise can be a protective method that ultimately limits the number of COVID-19 fatalities. However, exercise demands extensive commitment and long term effort to reach optimal results. In other words, physical fitness can safeguard against developing severe COVID-19 symptomatology, provided that one has the discipline and dedication required. Nevertheless, the habit of an inactive lifestyle is difficult to break, due to the resistance of replacing inertia with action.

Adverse Effects of Exercise

There is some evidence that exercise may trigger asthma. Strenuous exercise is connected to increased cortisol, which as noted previously, is associated with diabetes, heart disease and increased COVID-19 mortality rates [130, 131]. Strenuous gymnastics result in an inverse cortisol/testosterone relationship, where both cortisol increase and testosterone decrease are bound to elevate stress, fatigue, and hunger which ultimately undermines the advantages of exercise [132, 133].

Cortisol induced stress-eating behaviours can be reinforced by the decrease of the anorexic hormone, leptin, that is compromised by strenuous activity [134, 135].

Table 1. T-Tests Statistical Significance Results on Blood Tests and Measurement Variables of a totals of 95 overweight individuals with an average BMI>25, after 12 treatments with a new, health enhancing methodology. Abbreviations: WNR: Within Normal Range / CRP: C-Reactive Protein / HA: Healthy Adults / PMD: Patients with Medical Disorder. VLDL: Very-Low Density Lipoprotein / HDL: High Density Lipoprotein / VAT: Visceral Adipose Tissue / BMI: Body Mass Index / BMR: Basal Metabolic Rate / SMM: Skeletal Muscle Mass / PP: Postprandial / IGF-1: Insulin Growth Factor-1 / D: Diabetics / PD Prediabetics

	Mean	*S^2 =SS/df*	*T Value*	*p Value*	*Probability*	*Comments*
VLDL 25 HA / 20 PMD	-1.19	0.31	-9.35	<0.00001	P<0.00001	VLDL was Reduced by -41.59%
Triglycerides 25 HA / 40 PMD	-1.25	0.61	-6.94	<0.00001	P<0.00001	Triglycerides were reduced by -31.96
HDL 30 PMD	9.34	23.66	10.52	<0.00001	P<0.00001	HDL was increased by +19%
Free T-3 45 HA / 10 PMD	0.93	0.13	11.62	<0.00001	P<0.00001	Free T3 was increased by +41.07% WNR
Leptin 10 HA / 10 PMD	1.82	2.68	4.98	0.00004	P<0.0001	Leptin increased by +13.41% WNR
Ghrelin 10 HA / 10 PMD	-43.55	962.79	-6.28	<0.00001	P<0.00001	Ghrelin decreased by -8.28% WNR
Bilirubin 10 PMD	-0.08	0.12	-7.26	0.00002	P<0.0001	Bilirubin decreased by -69.23% WNR
Creatinine 10 PMD	-0.24	0.04	-4.06	0.00143	P<0.01	Creatinine decreased by -19.67% WNR
CRP 10 PMD	-0.59	0.16	-4.72	0.00055	P<0.001	CRP decreased by -36.87% WNR
Cortisol 35 HA	-18.26	142.98	-6.66	<0.00001	P<0.00001	Cortisol decreased by -13.08% WNR
Testosterone 35 HA	2.9	4.6	6.05	<0.00001	P<0.00001	Testosterone increased by +43% WNR
VAT 35 HA / 60 PMD	-4.68	7.12	-13.6	<0.00001	P<0.00001	VAT decreased by -21.95%
Overall Fat 50 PMD	-4.98	6.43	-13.88	<0.00001	P<0.00001	Overall Fat decreased by -13.42%
BMI 60 PMD	-2.3	1.28	-15.73	<0.00001	P<0.00001	BMI decreased by -10%
BMR 10 HA	91.6	3782.04	4.71	0.00055	**P<0.001**	BMR increased by +91.60%
SMM 35 HA / 15 PMD	+4.3	0.45	+13.49	<0.00001	P<0.00001	SMM increased by +40.7%
IGF-1 35 HA				<0.00001	P<0.00001	IGF-1 increased by +19.68
Blood Glucose Fasting 15 D	-61.88	7675.12	-8.11	<0.00001	P<0.00001	50% normal after 12 treatments
Blood Glucose PP 15 D	-63.07	7353.79	-845	<0.00001	P<0.00001	33% normal after 12 treatments
Insulin Fasting 20 PD	-30.71	5961.47	−2.97	0.01031	P < 0.01	100% normal after 12 treatments

Insulin PP 20 PD	−129.43	18065.62	−7.20	0.00009	P < 0.0001	100% normal after 12 treatments
Weight Loss 10 HA / 50 PMD	-6.49	9.34	-11.63	<0.00001	P<0.00001	Average Weight loss -7.22 kilograms
Above Umbilicus Measurement 50 PMD	-8.04	9.54	18.22	<0.00001	P<0.00001	Average cm loss -9.375 cm
Umbilicus Measurement 50 PMD	-8.93	12.31	-17.81	<0.00001	P<0.00001	Average cm loss -9.1 cm
Below Umbilicus Measurement 50 PMD	-9.33	20.1	-14.56	<0.00001	P<0.00001	Average cm loss -9.635 cm

Additionally, interleukin-6 appears to increase following excessive exercise that is often necessary to reduce visceral fat [136, 137], a problematic event, since an initial high inflammatory state may reinforce the occurrence of the COVID-19 induced cytokine storm after infection.

Exercise Alternatives

A series of recent studies report statistically significant decreases in lipids, visceral fat and the absence of hepatic steatosis in patients previously diagnosed with fatty liver. Specifically, the clinical trials delineate a statistically significant decrease in the very-low density lipoprotein (VLDL) and triglycerides, juxtaposed by an increase in the high-density lipoprotein (HDL). Additionally, they demonstrate increased fitness and normalized levels of Insulin Growth Factor-1 (IGF-1), the metabolic hormone Triiodothyronine (Free T3), Insulin, Testosterone, Cortisol, the anorexic hormone Leptin and the orexigenic one, Ghrelin, after 10-12 treatments with an alternative to exercise, originally invented in London University. Some of these studies rely on small samples demonstrating reduced inflammation and oxidative damage as measured by wound healing, neuropathic pain analgesia, as well as statistically significant decreases in CRP, creatinine, and bilirubin. In a metanalysis of the raw data derived from 95 subjects, 73 females and 22 males with an average BMI of 30.9, revealed the statistical significance values depicted on Table 1. Thirty-five out of the 95 subjects were healthy adults. The remaining sixty patients suffered by at least one or more medical disorder:

Fifteen were diagnosed with diabetes, twenty with prediabetes; eleven had hypertension, ten presented hyperphagia, fifteen had hepatic steatosis and twenty-one had hypothyroidism. One of the clinical trials on twenty diabetic and prediabetic patients presented evidence of a significant reduction in both fasting and postprandial glucose and insulin. Seven patients with hepatic steatosis who underwent sonography manifested no evidence of fatty liver after twelve treatments with this London University technology. Ten of the subjects diagnosed with hyperphagia, reported normal appetite after 12 treatments [138, 139, 140, 141, 142, 143, 144, 145, 146].

Conclusion

COVID-19 is a global lethal pandemic that has stirred an enormous body of clinical trials including both therapeutic methods and protective / preventive interventions. Research primarily targets the COVID-19 point of entry via the fusion of the S glycoprotein with ACE2 receptors, or the involvement of the N protein in the RNA viral replication. The abundance of ACE2 receptors in adipose tissue and the testes renders obese males highly susceptible to the decease. The heart, liver, and thyroid are also enriched with ACE2 expression, precipitating increased mortality rates among CVD and diabetic patients, as well as overweight individuals with excess visceral fat that often results in non-alcoholic hepatic steatosis. The diminished incidence of ACE2 receptors in muscle tissue spotlights physical activity or its effortless exercise alternative as a protective shield against the virus, due to the body's propensity to utilize fat as an energy source to build muscle. However, strenuous activity can be detrimental by increasing inflammation and escalating the stress hormone, cortisol, while decreasing testosterone and the anorexic hormone leptin leading to increased food consumption, and eventual fat accumulation. This process is exacerbated by age-related testosterone decline. The anti-inflammatory properties of oestradiol are highlighted within the moderation of hormonal balance. Overall, adiposity is featured as the epicentre of inflammation, which increases the probability of the cytokine storm rampaging the body, following COVID-19 infection. This lethal

process is facilitated and accelerated by the plenitude of ACE2 receptors in adipose tissue.

There are several weight management techniques, including different versions of lasers and RF, some of which may exacerbate inflammatory conditions, and none of which contributes to decreased visceral fat or increased fitness. A metanalysis of recently published clinical trials that used a novel London University effortless exercise invention, demonstrated a statistically significant decrease of adiposity that was validated by the absence of fatty liver post treatment, increase muscle mass and overall hormonal balance. None of these clinical trials involved COVID-19 patients or claimed to address a COVID-19 therapeutic intervention. The purpose was defined as investigating effective methods to reinforce health and fitness which could enhance immunity and protect against the detrimental consequences of COVID-19 .

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SECTION 3

The Importance of Hormonal Balance in Safeguarding Health

Viral Checkmate

The previous chapter discussed in some detail how the angiotensin enzyme 2 (ACE2) receptors serve as entry portals of COVID-19. ACE-2 converts angiotensin II, that is involved in tissue injury and inflammation, into angiotensin 1-7 which acts on the MAS receptor to counteract the deleterious effects of Angiotensin II thus reducing inflammation and tissue fibrosis [1]. MAS is an abbreviation of the last name (Massey) of the human tumour donner from which the MAS oncogene was derived.

By seizing ACE2 receptors to fuse and release its contents into the cells, COVID-19 neutralizes the body's main anti-inflammatory and anti-fibrotic defences that can control cytokine release, eventually leading to the hyperinflammatory state during which white blood cells indiscriminately attack vital organs, otherwise known as cytokine storm. Importantly, COVID-19 affinity for the ACE2 receptors that are involved in monitoring both inflammation and fibrosis, sets the system on "check" from the first move, with checkmate lurking in the horizon.

Obesity: The Epicentre of all Disease

Optimal health appears to be the best defence against all disease including viral infections. Excess adiposity, elevated lipids, and hormonal imbalance instigate systemic disintegration, stemming from accumulated inflammation, dyslipidaemia, metabolic dysfunction, and insulin resistance. Obesity is associated with diabetes and respiratory problems which contribute significantly to the burden of respiratory diseases [2, 3]. There is a high correlation between visceral adiposity and cardiovascular disease [4, 5]. Body mass index (BMI) that correlates with obesity (BMI>29.9) often provokes myocardial infarction, particularly in the presence of abnormally high triglycerides [6]. Obesity or being overweight (BMI>25) is

multiracial contributor to the prevalence of diabetes 2, characterized by excess very-low density lipoproteins (VLDL) among other factors [7, 8, 9]. Corona virus (COVID-19) morbidity rates have gone up to 88.1% among patients with a BMI>25 [10]. A possible explanation for this adiposity/COVID-19 relationship is the virus' binding preference to angiotensin-converting enzyme 2 (ACE2) receptors of adipose tissue. The ACE2 expression in fat tissue is higher than in other organs, therefore, overweight individuals have a multiplicity of ACE2 expressing cells that may foster an inviting affinity to spreading the virus within the human body, escalating infection. ACE2 expression increases with hypertension and diabetes, which explains the vulnerability to COVID-19 infection and eventual fatality among these patients [11, 12].

Thyroid Hormones

Thyroid hormones modulate every component of the cardiovascular system necessary for normal cardiovascular development and function, highlighting a correlation between Free T3 abnormalities and cardiovascular disease CVD [13]. Diabetes mellitus (DM) and Thyroid dysfunction influence each other, dysregulating metabolism, and interfering with Free T3 secretion [14, 15].

Triglycerides and VLDL

Overabundance of triglycerides, transported by very low-density lipoprotein (VLDL), narrows the arteries by hardened plaque, and prompts an upsurge of blood pressure which accelerates the risk of CVD, aneurysms, dementia, metabolic syndrome, etc. [16] A 15-year multi-provincial cohort study found that high VLDL cholesterol was a prominent contributor of coronary heart disease [17]. Upraised VLDL and triglyceride concentrations have been confirmed in both Type 1 and Type 2 diabetes mellitus [18].

Cortisol

Cortisol abnormalities are linked to both heart disease, and diabetic complications [19] [20]. Cushing's syndrome, defined by excess cortisol, is one of the leading determinants of CVD fatality rates [21]. Cortisol increase is associated with

hyperphagia and dyslipidemia [22]. Table 1 gives a list of medical disorders and conditions that increase the deleterious consequences of COVID-19 symptomatology.

COVID-19 Susceptibility Factors	Medical Disorders Susceptible to COVID-19						Age	Gender
	Diabetes	CVD	Hypertension	Cushing's Syndrome	Respiratory Disorders	Metabolic Syndrome	Old Age	Males
COVID-19	✓	✓	✓	✓	✓	✓	✓	✓
BMI >25	✓	✓	✓	✓	✓	✓	✓	✓
Thyroid Dysfunction	✓	✓	✓	✓	✓	✓	✓	✓
Elevated VLDL	✓	✓	✓	✓	✓	✓	✓	
Elevated Triglycerides	✓	✓	✓	✓	✓	✓	✓	
Hyperleptinemia / Leptin Resistance	✓	✓	✓	✓	✓	✓	✓	
Elevated Ghrelin	✓	✓	✓	✓	✓	✓	✓	
Hyperglycaemia	✓	✓	✓	✓	✓	✓	✓	
Elevated Cortisol	✓	✓	✓	✓	✓	✓	✓	
Dyslipidaemia	✓	✓	✓	✓	✓	✓	✓	
Elevated CRP	✓	✓	✓	✓	✓	✓	✓	
Inflammation	✓	✓	✓	✓	✓	✓	✓	
Oxidative Stress	✓	✓	✓	✓	✓	✓	✓	
Systemic Toxicity	✓	✓	✓	✓	✓	✓	✓	
Suppressed oestrogen	✓	✓	✓	✓	✓	✓	✓	✓
ATP energy depletion / Immune Exhaustion	✓	✓	✓	✓	✓	✓	✓	
Suppressed oestrogen	✓	✓	✓	✓	✓	✓	✓	✓
T3 Deficiency	✓	✓	✓	✓	✓	✓		

Suppressed Testosterone	✓	✓	✓	✓	✓	✓	✓	✓
Low plasma Leptin	✓	✓	✓	✓	✓	✓		
High Insulin / High Glucose/ Insulin Resistance	✓					✓		
High Glucose	✓							
Tobacco		✓	✓				✓	✓

Table 1. COVID-19 Susceptibility Factors and Medical Disorders vulnerable to COVID-19

The Chaos Induced by Toxicity

Toxicity is inherent in visceral adiposity. It overloads hepatic detoxification systems, and promotes insulin and leptin resistance that overstate the action of ghrelin, one of the central stimulators of appetite, ultimately promoting increased caloric intake [23]. Ghrelin, is an orexigenic hormone that stimulates appetite. Research has shown that ghrelin-producing cells seem to be more abundant in pathologically obese patients [24]. A minor increase in leptin reduces appetite, downsizing overall fat mass. However, escalated levels of the anorexic hormone are often associated with leptin resistance, a condition linked to weight gain [25]. This reflects a defect in intracellular communications, compromising the transport of leptin signals across the blood–brain barrier (BBB). Simply put, leptin overabundance is ineffective unless the body can receive and utilize its signals [26]. Both leptin resistance derived from excess, and its opposite, low plasma leptin, increase appetite, leading to obesity which exacerbates vulnerability to disease.

Inhibited Leptin Signalling, Obesity and Disease.

Cardiovascular mortality is often associated with low plasma leptin, while obesity, one of the causes of CVD, is usually correlated with unutilized leptin overabundance, or leptin resistance [27]. In other words the system has masses of leptin that it cannot use because the leptin signalling or communicating capacity has been compromised.

Viral infections cause elevated cytokine-3 signalling expression which inhibits leptin signalling. This signalling interference promotes overeating, precipitating visceral adiposity, which, as previously stated, has an inviting affinity to the virus binding preference to ACE2 that is abundant in adipose tissue [28].

Leptin is involved in glucose metabolism, and the regulation of cholesteryl esters that are crucial in energy modulation [29, 30, 31]. Diabetic insulin resistance allows for high glucose concentrations in the blood; this is exploited by the virus' tendency to increase glucose metabolism leading to hyperinflammation and immune exhaustion [32].

ATP and COVID-19

Depleted cellular energy provokes immune dysfunction, inevitably promoting T-cells apoptosis, and overall cellular degradation [32]. Earlier research has indicated that SARS-CoV morbidity relies on disabling systemic alarms, and depleting ATP (Adenosine triphosphate) by provoking a "cytokine storm" over-secretion of proinflammatory cytokines. Interestingly, COVID-19 inhibits the production of interferon type 1 (IFN-1) [33, 34]. Interferons are a type of cytokine barrier that protect non-infected cells from viral contamination. Doctors on the ground report that the COVID-19 induced lung immunopathology is not triggered by the "viral load," but hyperinflammation that turns out to be lethal for the patient, as rapid multiplication of cytokines mobilize overdriven white blood cells (WBC) to uncontrollably attack internal organs [35].

Some investigators have hypothesized that ATP replenishment will rectify the adverse effects of hyperinflammation, by providing the energy necessary for systemic repair [36]. This premise is supported by several research findings. COVID-19 inhibits the IFN-1 "alarm" response; this can be reversed by restoring ATP [37]. Energy depletion in the elderly evidences the highest COVID-19 fatality rate of 14.8% [38]. Aging instigates immune failure in secreting IFN-1 which may be related to ATP

insufficiency [39, 40].

Muscle Stimulators Deplete ATP

Electrical stimulation that exceeds 1.5 milliamps (1.5/1000 of an ampere). significantly decreases adenosine triphosphate (ATP). Experimentation on human type II fibres from vastus lateralis muscle has indicated a mean decrease of ATP to 14.8 and a lactate increase to 128.9 $mmol\ kg^{-1}$. This does not apply to microcurrents that range from 10 microamp (10/1,000,000 of an ampere) to 1000 microamp (1000/1,000,000 of an ampere) which actually increase ATP concentrations and promote amino acid integration activating protein synthesis [41, 42]. Such devices are also termed micro-TENS (transcutaneous electrical nerve stimulation involving microcurrent (1/1000,000 of an ampere). If any intensity above 1.5 milliamps depletes ATP , then cellular apoptosis is to be expected from regular TENS devices applied in the field of pain management, as well as other popular electrical stimulators used for muscle building that emit at least 10 milliamp minimum and up to over 120 milliamps during treatment. Reduced ATP compromises the functioning of cells with aftereffects that are even more deleterious as a result of a phenomenon called “secondary injury” a process that promotes cellular apoptosis of both injured and surrounding healthy cells, an event termed “bystander damage” [43]. ATP insufficiency is associated to a compromised production of IFN-1, the guardian agent protecting healthy cells from infection. Apart from acting as an energy supply, ATP is also involved in autocrine and paracrine signalling [44]. Clinical research indicates that Adenosine triphosphate (ATP) and its metabolite adenosine (Ado) play an important multifaceted role in both immunity and inflammation, shifting from immunostimulatory to immunoregulatory functions depending on extracellular concentrations, the complexity of purinergic receptors that participate in synaptic process, and the membrane proteins ectoenzymes, many of which are found in leucocytes [45]. Therefore, biological shortage of ATP may be deleterious in a pandemic and electrical stimulators that use over 1.5 milliamp may not be the best avenue towards health enhancement.

How ATP Interacts with COVID-19

Regular Exercise can increase ATP reinstating mitochondrial functioning [46]. Tobacco smokers are more susceptible to COVID-19 infection, possibly due to mitochondria decay inhibiting ATP output [47, 48]. Men have higher morbidity rates than women, potentially due to females' higher levels of oestrogens which stabilize ATP production during inflammation and oxidative stress [49]. It should be noted, however, that as it was previously explained oestrogen may not be the best predictor of COVID-19 risk level, due to evidence that oestrogen appears to elevate C reactive protein (CRP) one of the most pronounced markers of inflammation.

Immune Panic, Misapplied ATD and Hyperinflammation

With regards to ATP, a complementary interpretation to the above hypotheses places the focus on the need to stabilize a system in disarray; this delineates the significance of balance which is the theoretical perspective founding the current clinical trial. From this frame of reference, it can be argued that hyperinflammation is sustained by misapplied ATP during an immune panic reaction to overpower incoming danger. ATP replenishment in an disturbed system, dysregulated by disease, could potentially exaggerate the overabundance of interferons, interleukins, and overall biological activity that eventually ravages the host. Current research on 150 COVID-19 patients confirms that mortality is due to virally driven hyperinflammation provoked by elevated ferritin, interleukin-6 (IL-6), and interferon-γ inducible protein 10. The interferons trigger cascades of antiviral activity. Eventually, they shut down host protein synthesis inducing cell death [50]. All these processes including the white blood cells attaching the host are powered by cellular energy; therefore, it may be the systemic panic blindly lashing its defences against itself that devastates the body, and wasting biological energy until it is depleted.

	COVID-19 Exploitation	**Result**
ACE2 Receptors	COVID-19 Entry: fuses / occupies / neutralizes anti-inflammatory functions of ACE2 receptors	Hyperinflammation
Insulin Resistance / high plasma glucose	Increases glucose metabolism	Hyperinflammation Immune exhaustion

Leptin Dysfunction	Inhibits Leptin Signalling	Increases food consumption / exacerbates obesity
Leptin Dysfunction	Compromises Glucose metabolism / energy modulation	Immune exhaustion
Elevated Ghrelin - more abundant in obesity	COVID-19 affinity for Adipose tissue ACE2 Receptors	Increases overeating
High Cortisol	COVID-19 invasion biological stress	Increases overeating
High Cortisol	COVID-19 invasion biological stress	Systemic panic / body blindly lashes defences against itself
Inflammation	Further elevates ferritin, interleukin-6 (IL-6), and interferon-γ inducible protein 10	Hyperinflammation
Elevated interferons	Shut down host protein synthesis	T-cells apoptosis / Cellular degradation
Low Energy (e.g. obese, elderly)	COVID-19 interference further depletes cellular energy (highest COVID-19 fatality rate)	Immune dysfunction
IFN-1 "alarm" response	COVID-19 inhibits the IFN-1 "alarm" response	Disabled systemic alarms
cytokines	Mobilize overdriven WBC	Cytokine storm
Elevated ALT and IL-6	Lymphopenia / Leucocytosis	WBC damage vital organs

Table 2. Biological Factors Exploited by COVID-19

Inflammation: The Enemy Within

An examination of the clinical course, and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, found that mortality rate was higher in aged patients with diabetes, or coronary heart disease, as a result of increased inflammation, toxicity, and immune dysregulation. Inflammation was demonstrated by the elevated alanine aminotransferase (ALT), and interleukin 6 protein (IL-6). A dysfunctional immune system was identified by the evidence of lymphopenia, the abnormally low level of lymphocytes in the blood, and leucocytosis that reflects a higher leukocyte count of white cells, the cells that end up lashing against the body during the hyperinflammatory state [51].

In conclusion, obesity, diabetes, CVD, respiratory disorders and COVID-19 appear to be interconnected by hyperinflammation, excess lipids, lipoproteins, and hormonal irregularities including metabolic disturbances, and disproportionate variances in leptin, ghrelin, and cortisol. Testosterone deficiency is also correlated with CVD and diabetes [52]. Clinical research has shown that a raise in inflammatory markers was accompanied by both free and total testosterone suppression, suggesting that perhaps

the older males' higher mortality rates from COVID-19 may have been due to testosterone decline with age [53]. Tables 1 offers a summary of the COVID-19 Susceptibility Factors and some of the Medical Disorders susceptible to COVID-19, and Table 2 displays the biological factors exploited by COVID-19. Table 1 makes evident how systemic imbalances result in a number of medical conditions which are interrelated to overeating, signalling deficiencies, age and obesity and which enhance the prevalence of COVID-19.

Effortless Exercise Pilot Study

We conducted a pilot clinical study that focused on some of the common denominators that appear to bridge life-threatening medical conditions that have manifested the highest COVID-19 vulnerability. Overeating, obesity and inflammation are the starting point of a process eventually evolving into hormonal and appetite dysregulations, complemented by excess lipids, and lipoproteins that prelude the emergence of diabetes, CVD and respiratory disease. All these conditions are known to ultimately increase COVID-19 mortality rates [54]. We used an alternative to exercise to explore visceral adiposity, skeletal muscle mass (SMM) increase, insulin growth factor-1 (IGF-1) levels, VLDL, Triglycerides, Free T3, Testosterone, Cortisol, and the appetite controlling hormones leptin and ghrelin. The rationale and necessity of a method that bypasses physical activity is multidetermined:

1) Extensive quarantine imposed to restrict the rapid spread of COVID-19 leads to reduced physical activity that is necessary to maintain an adequate health status.

2) Realistically, most overweight individuals avoid gym workouts due to body image concerns, or the subjectively herculean effort and energy expenditure required, along with the months-long persistence and patience necessary before being rewarded by a visible body transformation.

3) The fact that physical training promotes cardiorespiratory fitness (CRF) is verified by a number of studies and the statistically significant inverse relationship between CRF and all-cause mortality ($p<0.05$). There is also evidence that exercise improves immunity [55, 56, 57, 58]. However, excessive exercise is perceived by the body as a

form of stress, and stimulates the release of cortisol that may cause tissue breakdown with overtraining.

4) Cortisol is involved in the conversion of protein to glucose, potentially predisposing older individuals to type II diabetes [59].

5) Strenuous exercise, necessary to reduce visceral adipose tissue, is associated with a negative relationship between cortisol and testosterone. As cortisol increases, testosterone decreases provoking stress eating behaviours, and accumulated adiposity, that offset the benefits of exercise [60].

6) During overtraining muscle-derived IL-6 is released into the circulation in high amounts leading to increased inflammation [61].

7) Recent research using this alternative to exercise procedure has shown a decrease in visceral fat, VLDL, and triglycerides, juxtaposed by an increase of Free T3, and skeletal muscle mass [62, 63].

8) Goldspink et al [64], used an earlier modified version of this method exploring gene expression in fast and slow muscle fibre phenotypes. The stimulation method resulted in rapid hypertrophy of adult skeletal muscle that reflected an increase of up to 250% in RNA content, associated with the repression of the fast, and the activation of the slow myosin heavy chain genes.

Methodology

We utilized an apparatus originally built in London University 2008 by Gerald Pollock, an electronics engineer who was also involved in the invention of the first pacemaker in the UK, based on his combined research with Donald Gilbert on motor nerve signalling. Patents of four out of the eight hand-made boards were obtained during the early 80s when the empirical studies commenced. The apparatus consists is purely voltage driven with a signalling output based on multiple connections between the eight boards that are made by hand to synthesize and regulate the unlimited resolution complex waveforms that are composed out of four thousand frequencies, each having a specific resultant frequency that ranges from 55Hz to 888Hz. At a resistance of 500 Ω the maximus voltage is 15V, increasing to 25V at 2000 Ω, and 50V at 10K Ω. Any

current generated by the voltage, based on Ohm's law, is minuscule and cannot be directly measured. The technology is classified as IEC class I according to IEC60601-1 standard, and it is used with 3-pin din and 4-pin din IEC 60601-1 compliant cables and silver threaded self-adhesive pads that have been awarded their own FDA clearance. The technology has a CE marketing directive of Class I, with electromagnetic compatibility regulations applied standards EN50081-1, and EN50082-1. It complies with the EEC UK directive of electrical equipment safety applied standard EN 60601-1. The general design of this technology has had no known side effects, in the past 20 years that it has been used in clinical practice by over 5,430 physicians, aesthetic practitioners and private users. The only contraindication, according to the FDA, is having an implanted device like a pacemaker. The main caution is pregnancy. All major medical and mental disorders require clearance by the patient's physician. Adverse reactions are limited to temporary skin redness from the gel pads, that occurs sporadically and usually dissipates within a few hours. Earlier versions of this technology based on the same electronic design have FDA clearance numbers K132158 and K132179. Additional measuring instruments included a conductance scale that calculated BMI, visceral adipose tissue and skeletal muscle mass and a blood test that investigated VLDL, triglycerides, cortisol, testosterone, Free T3, leptin and ghrelin.

Procedure

Nine adults, five females and four males, ages 35–49 years, with an average BMI of 32.23, participated and completed this fifteen treatments clinical trial that took place over a period of five weeks. Subjects were randomly selected out of a list of 14 eligible candidates, offered by five different clinics. The inclusion criteria were determined on the basis of a comprehensive health questionnaire completed by 18 subjects that agreed to undertake the treatment. Four subjects did not fulfil the inclusion criteria and were excluded: Inclusion criteria were:

1) Overweight or obese.

2) BMI over 28.

3) No experience with the technology.

4) Sedentary lifestyle of at least five years.

5) Had previously received laser and radiofrequency treatments with modest outcome and rebound results.

6) Not currently following a particular diet plan.

7) No operation or child birth for at least four months.

Exclusion criteria were:

1) Pacemaker, or other implanted device.

2) Pregnancy, or trying to get pregnant.

3) Operation, or childbirth within the past four months.

4) Any medical or mental disorder, or condition other than obesity.

5) Prior experience with the technology – this term was important, to exclude subjects that could guess the study's hypotheses.

6) Engaging in regular exercise – this intended to control the study outcome, so that results were not influenced by the subjects' active lifestyle.

7) Following a strict diet with a dietician – this exclusion criterion was adopted to eliminate the possibility that results were scewed by the subjects' diet.

Every precaution was taken to protect the subjects' privacy and the confidentiality of their personal information. Subjects were informed that they had the right to refuse participation at any time. All subjects were presented with the consent form, which they had to read thoroughly, and sign after confirming that they had clearly understood its contents. The subjects were not in a dependent relationship with the technology operators, the lab and measurement technicians, or the author. The subjects did not receive a specific diet, or instructions regarding changes in their lifestyles. There was no subject attrition.

The individuals appointed as clinical operators were given basic training on how to operate the technology, without disclosing the experimental hypotheses. None of the

operators had a dependent relationship with the author. None of them had any known bias or any personal interest in the direction of the results.

Each participating clinic selected their own lab; therefore, five independent laboratories were assigned to take blood samples, before, and two weeks after completion of the fifteen one-hour treatments, that took place three times a week, for five weeks.

Subjects' sessions were arranged on different days, to avoid subjects' interaction. The clinical operators were prohibited from discussing their observations or opinions with each other. In case a subject had a side effect or adverse reaction, the clinical operators were instructed to contact the clinic's physician immediately. None of the subjects had any adverse reactions or reported side effects.

The scale measurements were performed in a separate room, by the independent technician who had no experience in the technology or conflicts of interests. They were done before the first treatment, and two weeks after the last treatment. The subjects did not receive any other procedure during the two weeks after their last treatment and until the measurements and blood tests were performed.

Following the initial blood tests and measurements, each subject went to their private treatment room, and lay on the massage bed, while the gel pads and cables from the 16 channels of the technology were attached onto his / her body by the clinical operator. The cables from ten of the channels were attached onto the gel pads of the waist and abdomen, and the cables from the six remaining channels were connected to the gel pads placed along the lymphatic system pathways of the legs and arms, to enhance detoxification during treatment.

All subjects gave a detailed report of their subjective experience immediately after all treatments were completed and two weeks later**.** The procedure was performed in

accordance with the ethical standards and principles for medical research involving human subjects and was approved by the ethical boards of each clinic that supplied the study participants.

Results

The data was analysed with the Analysis of Variance for repeated measures and T-tests for two dependent means. Table 1 shows the testosterone and cortisol fluctuations for each subject before and after treatments. Testosterone increase was statistically significant with a T=3.101333, a p value of p=0.00732 and a significance level of $p<0.01$. For cortisol decrease the T value was T=-5.98; p value was p=0.00017. Cortisol significantly decreased at the $p<0.001$ level.

Insulin growth factor-1 (IGF-1), skeletal muscle mass (SMM) leptin, and Free T3 significantly increased at a high statistical probability level. Visceral Adipose tissue, ghrelin, very-low-density lipoprotein(VLDL), and triglycerides showed a statistically significant decrease. Importantly, all hormonal fluctuations were within the normal range.

Gender	**Age**	**Testosterone Pre nmol/l**	**Testosterone post nmol/l**	**Normal range nmol/l**	**Testosterone % increase**	**Cortisol pre nmol/l**	**Cortisol post nmol/l**	**Normal range nmol/l**	Cortisol% decrease
M	36	14.75	17.3	8.64-29	**17.28%**	158	121	80-477.3	-23.42%
M	39	11.34	13.96	8.64-29	**23.1%**	182	144	80-477.3	-20.87%
M	43	12.38	14.6	8.64-29	**17.92%**	219	198	80-477.3	-9.6%
M	35	15.41	18.65	8.64-29	**21.02%**	143	138	80-477.3	-3.49%
F	42	0.5	0.92	0.29-1.6	**84%**	185	162	80-477.3	-12.43%
F	45	0.3	0.63	0.29-1.6	**110%**	198	183	80-477.3	-7.6%
F	49	0.72	1.01	0.29-1.6	**52.77%**	129	112	80-477.3	-13.18%
F	38	0.63	0.78	0.29-1.6	**23.8%**	173	129	80-477.3	-25.43%
F	37	0.53	0.69	0.29-1.6	**30.18%**	256	231	80-477.3	-49.76%

Mean Average Testosterone % Increase	**+42.23%**	Mean Average Cortisol % Decrease	**-18.42%**

Table 1. Both testosterone increase and cortisol decrease remained within the normal range. Testosterone overall increase was +42.23%. Testosterone showed a mean average increase of +20.15% increase for males and a mean average of +60.15% for females. Cortisol showed a mean average decrease of -18.42%. (n=10. Tx= 15)

Gender	**Age**	**BMI Pre**	BMI Post	**IGF-1 Pre (nmol/l)**	**IGF-1 Post (nmol/l)**	**Normal range (nmol/l)**	IGF-1 % increase	**SMM Pre**	**SMM Post**	SMM % increase
Male	36	29.7	-25.7	22.93	24.75	15.08-32.5	**7.93%**	27.65	30.87	**11.64%**
Male	39	33.3	-26.9	27.16	30.06	15.08-32.5	**10.67%**	33.30	39.60	**18.91%**
Male	43	34.2	-27.3	29.97	31.96	15.08-32.5	**6.63%**	36.40	39.80	**9.34%**
Male	35	32.8	-26.4	24.33	26.75	15.08-32.5	**9.04%**	27.13	31.95	**17.75%**
Female	42	29.6	-25.9	18.55	24.37	11.25-28.8	**23.88%**	17.57	23.32	**32.72%**
Female	45	35.2	-27.4	23.76	27.94	11.25-28.8	**17.59%**	20.16	24.53	**21.67%**
Female	49	33.8	-26.1	15.86	21.08	11.25-28.8	**23.83%**	16.89	22.85	**35.28%**
Female	38	32.6	-27.8	19.12	22.99	11.25-28.8	**20.24%**	20.73	25.52	**23.11%**
Female	37	28.9	-24.5	14.28	18.83	11.25-28.8	**24.16%**	16.83	23.18	**37.73%**

Average BMI Before	**32.23**	Average BMI After **26.44**	**BMI Reduced by an average of -5.79**	**Mean Average IGF-1 % Increase**	**+16.00%**	**Mean Average % Increase for SMM**	**+23.13%**

Table 2. BMI mean average decrease was -5.79. Mean average percentage increase of IGF-1 was +16%. Mean average percentage increase for skeletal muscle mass was +23.13%. (n=10. Tx= 15)

Table 2 reflects a body mass index (BMI) decrease of -5.79 and a highly statistically significant t= -10.94 with a value of $p<0.00001$. Table 2 also denotes a 16% increase of IGF-1, a statistically significant outcome with t=7.607811, a value of p=0.00003 and a significance level of $p<0.0001$. There was also an average 23.13% increase of

SMM, with value of t=12.66705 and the value of p<0.00001 raising the statistical significance level to p<0.00001.

G	A	Triglycerides Pre mmol/L	Triglycerides Post mmol/L	Normal range mmol/L	Triglycerides % decrease mmol/L	VLDL Pre mmol/L	VLDL Post mmol/L	Normal range mmol/L	VLDL % decrease mmol/L
M	36	3.87	1.56	<1.7	**-59.68%**	3.18	1.24	<1.6	**-61%**
M	39	3.96	1.24	<1.7	**-68.68%**	3.79	1.64	<1.6	**-56.72%**
M	43	3.98	1.59	<1.7	**-60%**	2.98	1.39	<1.6	**-53.35%**
M	35	2.88	1.12	<1.7	**-61.11%**	2.43	1.12	<1.6	**-53.90%**
F	42	2.64	0.98	<1.7	**-62.87%**	3.21	1.45	<1.6	**-54.82%**
F	45	3.23	1.64	<1.7	**-49.22%**	2.86	1.16	<1.6	**-59.44%**
F	49	2.45	0.93	<1.7	**-62%**	2.61	1.52	<1.6	**-41.76%**
F	38	3.10	1.44	<1.7	**-53.54%**	3.22	1.87	<1.6	**-41.92%**
F	37	2.99	1.64	<1.7	**-45.15%**	2.94	0.93	<1.6	**-68.36%**

Mean Average Triglycerides Decrease	**-58.03%**	**Mean Average VLDL Decrease**	**-54.59%**

Table 3. The average triglycerides and VLDL decreases were consistently analogous with values of -58.03% and -54.59% respectively. (n=10. Tx= 15)

Table 3 displays a notable decrease in both VLDL and triglycerides that was significantly more robust than the results of most other variables both in terms of percentage and statistical significance level (Table 6). Triglycerides t=-12.065904 and value of p<0.00001 with a significance level of p<0.00001. VLDL t=-14.042083 with a value of p<0.00001 and a significance level of p<0.00001.

Table 4. Results on Visceral Adipose Tissue and Blood Plasma Results on Free T3 for each subject ***(n=10)****.*

Gender	**Age**	**Ethnicity**	**Visceral Fat Pre**	**Visceral Fat Post**	**Visceral Fat % Decrease**	**Free T3 Pre (pmol/L)**	**Free T3 Post (pmol/L)**	**Normal Range (pmol/L)**	**Free T3 % Increase (pmol/L)**
Male	36	Asian	128.97	113.14	-12.27%	2.56	4.29	2.63-5.7	**67.5%**
Male	39	Caucasian	131.20	98.53	-24.9%	2.69	4.65	2.63-5.7	**72.86%**
Male	43	Caucasian	119.67	96.62	-19.26%	2.81	4.16	2.63-5.7	**48.%**
Male	35	Asian	99.56	79.34	-20.22%	3.56	5.31	2.63-5.7	**49.15%**
Female	42	Asian	121.68	104.29	-14.29%	2.15	3.86	2.63-5.7	**79.53%**

Female	45	Indian	129.73	109.28	-15.76%	2.29	4.12	2.63-5.7	**79.9%**
Female	49	Caucasian	109.63	95.85	-12.56%	2.96	4.87	2.63-5.7	**64.52%**
Female	38	Caucasian	122.66	87.85	-28.38%	2.54	4.20	2.63-5.7	**65.35%**
Female	37	Asian	134.64	112.80	-16.22%	1.99	3.83	2.63-5.7	**92.46%**

Mean Average Visceral Fat % Decrease	**-18.21%**	**Mean Average Free T3 % increase**	**+68.81%**

Table 4. Average percentage decrease of visceral adipose tissue was -18.21% Average percentage decrease of Free T3 was +68.81%. (n=10. Tx= 15)

A close inspection of Table 5 indicates that around 55% of the subjects were hypothyroid. This was not evident during their medical interview and, apparently the subjects were not aware of having a hypothyroid conditions which could be suggestive of prediabetes. We did not test for blood glucose or insulin, therefore we could not confirm such a hypothesis. However, we recommended that these subjects check their glucose and insulin levels with their primary physicians. The subjects that indicated a hypothyroid condition by their Free T3 being below the normal range, evidenced the greatest increase of Free T3, which however did not spike above normality. Visceral fat decrease had a t=-9.302125 and a value of $p<0.00001$ which brought the statistical significance to $p<0.00001$. The Free T3 t=29.428273 with a value of $p<0.00001$ and a statistical significance level at $p<0.00001$. Table 6 displays the leptin and ghrelin fluctuations for each subject before and after the treatments. Leptin consistently increased, while ghrelin decreased after the fifteen treatments, for all subjects. Mean average leptin increase was +10.82% and mean average ghrelin decrease was -7.35.

Gender	**Age**	**Leptin pre ng/mL**	**Leptin post ng/mL**	**Normal range ng/mL**	**Leptin % increase ng/mL**	**Post prandial Ghrelin pre pg/mL**	**Post prandial Ghrelin post pg/mL**	**Normal range pg/mL**	**Ghrelin % decrease pg/mL**
Male	36	3.69	3.98	**1.2-9.5**	**7.86%**	687	602	520-700	**-12.37%**
Male	39	4.43	4.98	**1.2-9.5**	**9.78%**	695	634	520-700	**-8.77%**
Male	43	5.62	6.22	**1.2-9.5**	**10.68%**	598	552	520-700	**-7.69%**
Male	35	6.15	6.83	**1.2-9.5**	**11.05%**	629	587	520-700	**-6.68%**
Female	42	9.16	9.74	**4.1-25.0**	**6.33%**	577	542	520-700	**-6.06%**

Female	45	5.23	6.09	**4.1-25.0**	**16.44%**	659	613	520-700	**-6.99%**
Female	49	7.22	8.17	**4.1-25.0**	**13.15%**	644	617	520-700	**-4.19%**
Female	38	12.34	13.22	**4.1-25.0**	**7.13%**	569	536	520-700	**-5.79%**
Female	37	11.38	13.08	**4.1-25.0**	**14.93%**	499	461	520-700	**-7.62%**

Mean Average Leptin Increase	**10.82%**	**Mean Average Ghrelin Decrease**	**-7.35%**

Table 5. There was an inverse relationship between leptin and ghrelin where leptin significantly increased and ghrelin significantly decreased within the normal range. Mean average percentage leptin increase was +10.82% and ghrelin decrease was -7.35%. (n=10. Tx= 15)

Table 4 displays the results of the T-tests on all the variables tested.

Table 6. T-Tests Statistical Significance Results on Blood Plasma and Measurement Variables (n=10. Tx= 15)

	Mean	S^2 =SS/df	$S^2_M = S^2/N$	SM= √S2M	T Value	p Value	Probability
Free T-3 INCREASE	1.75	0.03	0.00	0.06	29.43	<0.00001	**P<0.00001**
Leptin INCREASE	0.78	0.16	0.02	0.13	5.93	0.00018	**P<0.001**
Testosterone INCREASE	1.33	1.66	0.18	0.43	3.1	0.00732	**P<0.01**
IGF-1 INCREASE	3.64	2.06	0.23	0.48	7.61	0.00003	**P<0.0001**
SMM INCREASE	5	1.4	0.16	0.39	12.67	<0.00001	**P<0.00001**
VLDL DECREASE	-1.66	0.13	0.01	0.12	-14.04	<0.00001	**P<0.00001**
Triglycerides DECREASE	-1.88	0.22	0.02	0.16	-12.07	<0.00001	**P<0.00001**
Ghrelin DECREASE	-45.89	309.61	34.4	5.87	-7.82	0.00003	**P<0.0001**
Cortisol DECREASE	-25	157.25	17.47	4.18	-5.98	0.00017	**P<0.001**
BMI DECREASE	-5.79	2.52	0.28	0.53	-10.94	<0.00001	**P<0.00001**

Visceral Adipose Tissue DECREASE	-22.23	51.38	5.71	2.39	-9.3	<0.00001	**P<0.00001**

The Analysis of Variance (Table 7) yielded statistically significant results for all variables. All hormones' values were significant but without spiking outside the normal range.

Table 7. Analysis of Variance Statistical Significance Results on All Variables.
Abbreviations: BT: Between Treatments / WT: Within Treatments / E: Error. (n=10. Tx= 15)

	SS	df	MS	F-Ratio Value	p-Value	Significance Level
Testosterone Cortisol	BT: 242251.2736 WT: 25503.9549 E: 14196.1284	BT:3 WT:32 E:24	BT: 80750.4245 WT: 796.9986 E: 591.5053	F= 136.51681	<0.00001	P<0.00001
IGF-1 / SMM	BT: 251.7344 WT: 1167.9813 E: 123.2835	BT:3 WT:32 E:24	BT: 83.9115 WT: 36.4994 E: 5.1368	F= 16.33532	<0.00001	P<0.00001
VLDL /Triglycerides	BT: 28.34943 WT: 5.2282 E: 2.7888	BT:3 WT:32 E:24	BT: 9.4648 WT: 0.16434 E: 0.1162	F= 81.45242	<0.00001	P<0.00001
Visceral Fat Free T3	BT: 105989.285 WT: 2064.6557 E: 1202.9437	BT:3 WT:32 E:24	BT: 35328.4283 WT: 64.5205 E: 50.1227	F= 704.83951	<0.00001	P<0.00001
Leptin Ghrelin	BT: 3100114.916 WT: 55563.1985 E: 30926.4581	BT:3 WT:32 E:24	BT:1036371.6387 WT: 1736.35 E: 1288.6024	F= 804.2602	<0.00001	P<0.00001

All subjects experienced the procedures as a series of strenuous, yet, effortless exercises. They stated that the technology took control of their bodies, vigorously contracting their entire musculature, then shaking and twisting their muscles in circular coordinated motions, as if they were performing gymnastics, but without the muscle aches and tiredness following an intense workout. They also reported reduced cravings for chocolate, snacks, fried foods and carbohydrates, and were excited by the idea of buying new, smaller size clothes. In both of their interviews, after the last treatment, and two weeks later, the subjects consistently reported enhanced fitness and energy.

Systemic Balance & BMI

The primary goal of this randomized double blind clinical trial was to bring attention

to the systemic balance perspective of health maintenance. Deterioration into illness is gradual. It evolves out of minor dysregulations, inconspicuously disintegrating the structure of wellness. Hormonal levels within the normal range are widely accepted as optimum, without examining the actual ranking position that enables each variable defend or undermine health. Cortisol rising towards the peak of the normal range can easily spiral out of control, and Free T3 close to the bottom may signify the insidious onset of hypothyroidism. A preventive perspective focuses on the rate of differentiation, observing the degrees of minor imbalances within normalcy, before they are exacerbated into a medical disorder. This is necessary to safeguard a biological network in flux. Variations within the normal range can be utilized to estimate both health improvement and the probability of illness vulnerability.

BMI and Visceral Adiposity Decrease, plus Hormonal Balance

An equally important objective was to examine whether an alternative to exercise can reduce BMI, and improve the health of overweight individuals, possibly decreasing their susceptibility to medical disorders or viral infections. All subjects indicated a BMI decrease after the fifteen treatments. There was evidence that visceral adiposity, VLDL and triglycerides were reduced, accompanied by increased metabolism, and an optimal leptin/ghrelin inverse relationship, indicating that this method can serve as a proactive/preventive and possibly corrective measure to counteract the adverse effects of obesity. The substantial IGF-1 and skeletal muscle mass enhancement implied enhanced fitness. Using this method as an alternative to exercise can be both practical and convenient at a time when an active lifestyle is limited due to the COVID-19 pandemic. But even without the COVID-19 confinement and social distancing, an alternative to exercise can be beneficial in maintaining wellness. Usually, work responsibilities and socioeconomic demands take precedence over engaging in sports. Physical activity becomes more laborious and cumbersome with age, hence the accumulation of visceral fat along with its inherent inflammation, lipids and lipoproteins, and the greater vulnerability to decease during aging. Offering a fast

solution that can produce a visible physique change, and improve health within five weeks, has significant implications in safeguarding immunity.

Optimal Inverse Testosterone/ Cortisol Relationship

Although physical training is necessary for cardiovascular health, strenuous exercise increases cortisol, reinforcing stress eating behaviours, while reducing testosterone that is clinically associated with a number of medical and mental conditions. Low testosterone levels are prominent in diabetics, and they are correlated with a prolonged depressive disorder in elderly males, often expressed in terms of low energy, anhedonia, appetite disturbances, hopelessness and sexual dysfunction. Our sample evidenced the opposite: an optimal inverse testosterone/cortisol relationship, where testosterone climbed towards the peak of the normal range and cortisol decreased but without dipping into abnormality. Our subjects reported reduced cravings for sugar and fatty foods, yet, normal appetite, possibly signifying a combination of optimal cortisol levels, combined with adequate modulation of central inhibitors and stimulators of appetite such as leptin and ghrelin respectively.

Methodological limitations

Firstly, the small sample size, and the absence of imaging techniques that were beyond our research budget, since we received no financial aid from an outside source. We assessed visceral fat and skeletal muscle mass on the basis of a conductance scale, the results of which are not widely recognized as reliable, despite their common use by a large body of research. We did not compare our sample to a control exercise group, or a placebo group. In previous research, discussed earlier, eight weeks of regular exercise showed a modest reduction of visceral fat, but without a clinically significant weight loss. Another computer tomographic scanning study found no differences in BMI or physical fitness following regular physical activity [65, 66]. The alternative to exercise adopted in this clinical trial, showed a statistically significant decrease in BMI and an increase in skeletal muscle mass after only five weeks of treatment. Subjects were only followed for two weeks, during which time they maintained the results they achieved

without rebound. However, a longitudinal study is necessary to confirm results durability, and establish that the health enhancement observed with this diverse population is effective in eventually preventing the likelihood of disease or a viral infection. Lastly, we did not include other important weight variables such as basal metabolic rate (BMR), cm loss and kgs, as a result of inconsistency of these measurements in the data collected from the five clinics.

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Conflict of Interest

The author declares no conflict of interest since the study was conducted by independent clinics. No funding was received by a third party or institution.

Ethical Standards

Statement of Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of

1. Ethical Principles for Medical Research involving Human Subjects*
2. American Psychological Association (APA)
3. IELLIOS Research department for Development and invention of Innovative Technology

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SECTION 4

Biological "Weak Links" – How COVID19 Checkmates the Body

Adipose Tissue: The Proprietrix of Inflammation

Health is undermined by inflammation. Common soil of inflammation is visceral adipose tissue and excess VLDL, cholesterol, and triglycerides, which are viewed as key components of arterial plaques, obstructing blood flow and detoxification. Inflammation is associated with reactive oxygen species and overall toxicity, inducing hormonal imbalance defined by disturbances in free T3, growth hormones and cortisol that is associated with stress-eating behaviours. Eventual dysregulation of the orexigenic hormone ghrelin and anorexic hormone leptin that are part of a reciprocal network regulating inflammation, leads to increased food consumption, and the vicious circle of excess adipose tissue elevating toxicity and inflammation, provoking obesity, oxidative stress, immune cell dysregulation, hormonal imbalance, aging and disease [1]. Subcutaneous adipose tissue secretes pro-inflammatory cytokines interleukin-6 (IL-6) in vivo, and is closely associated to C reactive protein (CRP), one of the most prominent markers of inflammation [2]. Visceral adipose tissue (VAT) is one of core sources of inflammation due to its secretion of pro-inflammatory cytokines and free fatty acids [3]. Compared to men, premenopausal females have higher concentrations of the CRP inflammatory markers, presumably as a result of oestrogens enhancing CRP concentrations [4]. This hypothesis is supported by oestrogen hormone replacement interventions that evidently increase CRP levels in healthy women [5].

Adiposity, Atherosclerosis, Hyperlipidemia and Steatohepatitis

Excess adipose tissue appears to play a critical role in atherosclerosis a vascular site-specific chronic inflammation, leading to disturbed blood flow as a result of abnormal elevations in triglycerides [6, 7]. Triglycerides have been closely associated with low grade inflammation [8], while hyperlipidemia, caused by the very-low density lipoprotein (VLDL) that mainly carries triglycerides, is one of the best predictors of atherosclerosis [9]. Lipids mainly accumulate in the liver often causing lipotoxicity

and insulin resistance [10]. Non-alcoholic (NA) steatosis or fatty liver, one of the consequences of visceral adiposity, is the result of an imbalance between intrahepatic triglycerides' production and export. It often progresses to steatohepatitis, fibrosis and cirrhosis that has major health consequences [11, 12]. Overall, lipotoxicity and inflammation inherent in both subcutaneous and visceral fat compromise health along with excess of VLDL and triglycerides that represent the key components of arterial plaques.

The Moderation Principle

In moderation, all body mechanisms are useful and purposeful. VLDL represents one of the main transport mechanisms, carrying triglycerides that are released as an energy source. Adipose tissue stores and regulates metabolic energy playing a crucial role in body homeostasis. It consists of white, beige and brown adipose tissue, where white and brown adipocytes have different ontogenetic origin and the beige adipose tissue has properties of both white and brown adipocytes. White adipocytes serve as an energy bank, while brown and beige adipocytes are thermogenic cells involved in energy expenditure in the form of heat [13]. Oxidation of brown fatty acids is regulated by thyroid hormones, specifically T3, the active metabolite of the prohormone thyroxine or T4, which is a major thyroid hormone in the thyroid gland and the circulation. T3 also regulates gene transcription throughout the body, accelerates resting energy expenditure and is involved in lipolysis [14]. Leptin that is secreted by adipocytes regulates conversion of T4 to T3.

Leptin and T4/T3

Leptin is derived from the Greek term "leptos" that means thin, and is considered to be a circulating anorexic hormone associated with weight loss [15]. Research has postulated leptin decrease in animals infused with high T4 and T3 doses, while leptin levels remain elevated in controls infused with placebo [16]. It should be noted that the methodology of these experiments entailed the injection of hormones on animals to

stage an artificial T3 / leptin interaction based on hormonal imbalance. Therefore it may not accurately reflect the mechanics of a healthy balanced human body.

Systemic Balance

Systemic balance may be a key concept in explaining the relationship between leptin and thyroid hormones. A clinical trial on 21 women with thyrotoxicosis which is characterized by abnormally elevated activity of thyroid hormones, and 14 women with hypothyroidism revealed that previously suppressed leptin concentrations tended to increase after both groups received treatment that restored their euthyroid state [17]. In other words, optimal leptin levels were restored when the excess of thyroid hormones in the bloodstream of the 21 thyrotoxic women was reduced to be within the normal range, and when the thyroid hormones of the 14 hypothyroid women ascended into normalcy. Additional research confirms the deleterious effects of hormonal imbalance by demonstrating significantly inhibited levels of leptin in 50 hyperthyroid woman aged from 30-58 years as compared to 30 healthy controls of the same age [18].

In Vitro versus in Vivo Research

Research examining the T3 / Leptin relationship in vitro and in vivo found that in vitro, high levels of T3 inhibited basal leptin production by 42%, and simulated leptin mRNA expression by 47% in human adipose tissue. However, artificially increasing T3 by 195% in vivo, decreased thyrotropin and increased energy expenditure with no effects on serum leptin [19]. These results are consistent with other research indicating that short-term artificially induced hyperthyroidism had no effects on leptin levels on 22 men [20]. It seems that in vitro, transformations and permutations developed much faster than in vivo. Is there a reason to justify the transfigurations often seen in vitro that are not observed in vivo research?

The Propensity of Molecular Mechanisms for Time Reversal

Experimental differences between in vivo and in vitro research may have another very interesting origin. In vivo research may be affected by the versatility and reversibility

tendency of molecular mechanisms. A free radical is a deleterious agent for the human body. Yet, merely replenishing and repairing its missing electrons it turns the free radical back into a stable molecule that can be useful in the overall systemic functioning. There are so many examples. The Adenosine Triphosphate has three transformational states depending on how many phosphates are involved. With one phosphate it becomes AMP (monophosphate). With two phosphates it turns into its future format of ADP (diphosphate). One more phosphate to complete the process into the one of the prominent sources of energy, ATP (triphosphate). Only to be broken down into its past becoming ADP and then back to its original state, AMP. It routinely transverses past, present, and future. The ATP circular metamorphosis by the addition or subtraction of a phosphate is a molecular process that goes forward and backwards in time, in a manner that would be impossible for a human body. Whole objects have limited reversibility stabilized by homeostasis that offers stability and relative permanence progressively increasing systemic resistance to change. Microscopic mechanisms are governed by different principles that do not apply to the wholes they compose. The synthesis of molecular elements into a whole inevitably coalesce into a new entity, a Gestalt, defined as more than the sum of its parts, because it displays idiosyncratic characteristics absent in the parts that compose it and a tendency to persist despite altering or deleting some of its components [21]. The more durable the Gestalt the less its capacity for reversibility.

The Hyperleptinemia Paradox

As different principles govern molecular mechanism and whole objects, deficiency, excess, moderation and balance play are crucial in the regulation of health. Hence the research findings that at first sight appears counterintuitive. For example, more leptin in the system should result in a greater anorexic effect. Indeed, a minor increase in leptin concentrations has been found to reduce appetite, inducing weight loss [22]. However, obese patients have excess leptin in their systems, and yet leptin does not exert an anorexigenic effect in these individuals, because of their evident leptin resistance [23]. Leptin resistance implies a surplus of leptin that remains

unutilized. In other words, it is a matter of leptin signalling, irregularities irrespective of quantity, that result in subsequent decreases in leptin intracellular signalling across the blood–brain barrier (BBB). Leptin and slimming do not delineate a linear relationship where more leptin always leads to greater weight loss [24, 25]. Defective communications between leptin and the brain may promote weight gain despite the leptin surge in the system. In common forms of obesity hyperphagia, hyperinsulinemia and hyperleptinemia coexist [26, 27].

Pro-inflammatory Leptin and Anti-inflammatory Ghrelin

The anorexic hormone, Leptin, is the antagonist of Ghrelin, the orexigenic hormone that stimulates appetite. Research has shown that ghrelin-producing cells seem to be more abundant in morbidly obese patients [28]. Ghrelin is secreted in the stomach and is inhibited by the satiety-effects of leptin that functions as a feedback signalling mechanism mediated by the hypothalamus [29]. Again, from an intuitive point of view, decreasing ghrelin and increasing leptin may be the apparent target of weight loss methods. However, there is a fine line between artificially altering leptin / ghrelin concentrations and hormonal imbalance that is often closely associated with weight gain. Unwarrantable ghrelin decrease and leptin increase may also impose a health risk. Leptin has been found to exert pro-inflammatory effects in mice [30] and an increase in the pro-inflammatory cytokine interleukin-6 (IL-6) in humans [31]. Ghrelin is expressed in human T lymphocytes and monocytes to inhibit the expression of proinflammatory anorectic inflammatory cytokines such as IL-1β and IL-6 [32]. Anorexia is a very common symptom of illness, injury, or inflammation. Ghrelin is warranted to counterbalance and reverse the anorexic inflammatory state provoked by leptin [33].

IL-1β, IL-6 have been implicated with chronic low-grade inflammation and aging, therefore, more leptin can enhance inflammation and speed up aging [34]. Regulation of inflammatory cytokines by normal levels of ghrelin has important implications in preventing inflammation. In short, both excessive leptin and shortage of ghrelin can be

deleterious to an organism. Excess of leptin is associated with inflammation. Shortage of Ghrelin will deprive the system from Ghrelin's anti-inflammatory action contributing to more inflammation and subsequently to aging and disease.

The Importance of treating the System not the Symptom

Health is hormonal balance-contingent, therefore, optimum levels of ghrelin are necessary to regulate persistent inflammation. Weight loss-targeting interventions, either for health or aesthetic purposes, cannot not be merely based on the restricted perspective of symptom elimination but an enriched frame of reference centred around overall physical health. Symptom targeted weight loss that imbalances hormones, increases oxidative damage, toxicity and inflammation is not only a health risk but pointless, since inflammation and hormonal imbalance will negate all attained benefits leading to weight gain rebound.

Oxidative Damage and Inflammation

Oxidative damage and inflammation are at the core of most pathological conditions including diabetes, cardiovascular disease (CVC) and even COVID-19. Both oxidative damage and inflammation are a fundamental property of excess weight. Recent reports suggest that a high percentage of the population who will contract COVID-19 will also have a BMI over 25, while 73.4% of COVID-19 patients in intensive care are classified as overweight [35] [36]. Increased adiposity, VLDL and triglycerides, metabolic dysfunction, dysregulated appetite controlling hormones, leptin and ghrelin, are the common denominators of inflammation-compromised health. COVID-19 is not lethal. Hyperinflammation driven by the patient's immune system is the cause of death. During hyperinflammation, interferons trigger cascades of antiviral activity, however, in the process they shut down host protein synthesis inducing cell death. The system attacks the virus with a cytokine storm, injuring itself in the process [37] [38]. The importance of a balanced system with processes functioning in moderation, never spiking outside the normal range appears to be crucial in safeguarding health.

Weight Loss Solutions

Laser Studies on Visceral Fat Reduction

What is the solution for those that have already accumulated excess visceral adiposity along with its inherent inflammatory toxicity and hormonal imbalance? Very few laser clinical trials report visceral fat reduction, and usually they are combined with exercise. Low-level laser therapy (LLLT) was offered for 16 minutes to women aged 20-40 years old with BMI ≥ 30 kg/m^2, every time after they were trained with aerobic and resistance exercises for 1 hour three times weekly for 16 weeks. Results revealed a statistically significant reduction in neck and waist circumferences which do not represent the main sites of visceral adipose tissue concentrations. These investigators report visceral fat decrease on the basis of a conductance instrument, as well as leptin decrease after the 16 combined treatments [39]. Leptin decrease may be a normal effect of exercise, since energy spent requires replenishment of nourishment. Importantly, it is not clear whether the outcome was the result of LLLT or whether young healthy subjects selected for the study would have the exact same results with exercise alone and without the laser treatment. A similar clinical trial with women aged 20-40 years old, and BMI or 30-40 kg/m^2, treated with a combination of LLLT and exercise three times a week for four months, reportedly yielded a reduction in IL-6 and an increase in WNT5 signalling. However, no differences in visceral fat, VLDL, low-density lipoprotein (LDL), lean mass, or triglycerides were demonstrated between the experimental and control groups [40]. Noticeably, this second study contradicted the results of the first study on visceral fat reduction, posing serious concerns about external validity. Once again, it is uncertain whether it was the LLLT or the exercise that produced the benefits of IL-6 reduction and increase in WNT5 signalling. Instead of comparing an only LLLT group with an only exercise group, both experiments were designed to offer a combination of LLLT and exercise, a choice that resembles contamination, a threat to internal validity. Perhaps their intention was to support a clinical recommendation that LLLT should be always accompanied by exercise. However, by lumping two different treatments together they ended up with an amalgam of results that is impossible to interpret.

Radiofrequency Studies on Visceral Fat Reduction

Radiofrequency studies reducing visceral fat are very sparse or non-existent and mostly suffer from poor methodology. Visceral fat measurements rely on battery operated conductance devices that are highly unreliable in identifying visceral adiposity; there is no measurement of VLDL, inflammatory markers like C reactive protein (CRP) or treatment effects on fatty liver.

The Cairo University clinical trial published in the Bulleting of Cairo University [41] used cavitation ultrasound therapy (CUT) on 50 perimenopausal women aged between 37-39 years with a BMI of 31.5-40.04 kg/m^2. The experimental group that received CUT treatments plus a low-calorie diet for three months was compared to a control group that was only given the low-calorie diet for the same period of time. Both groups evidenced pre and post differences in weight, waist and hip circumferences, BMI, Triglycerides, LDL and high-density lipoprotein (HDL) with the CUT experimental group showing an advantage in overall body fat reduction, triglycerides and LDL, but no difference in HLD, percent of lean weight, and basal metabolic rate. These investigators report a decrease of visceral fat on the basis of the CUT group advantage in reducing overall fat. However, they present no proof that these subjects actually lost adipose fat rather than subcutaneous fat. Upon examinations of the two samples, the CUT plus diet group and the only diet group, the means and standard deviations of the t-test results conducted, indicated that the reported advantage of the experimental group was limited to a very small percentage that could be due to chance or other confounding variables. Additionally, visceral fat is more prominent in the lower abdominal area, which was never measured, and not the waist or hip circumferences where the measurements of this clinical study were taken.

Exercise and Visceral Fat Reduction

There is limited randomized placebo controlled data on whether exercise reduces visceral adipose tissue and liver fat. Recent research looked at liver fat spectroscopy

and magnetic resonance imaging of visceral adipose tissue before and after three modes of 8 weeks exercise performed by inactive overweight adults. This well designed study using highly reliable measures found no significant difference between dose or intensity of exercise. There was a small reduction in visceral adipose tissue and fatty liver, without a clinically significant weight loss [42]. Another well designed study on 160 healthy Korean adults, 38 men and 122 women explored the results of exercise on visceral adiposity and C-reactive protein (CRP) one of the most prominent markers of inflammation. Abdominal fat area was measured by computed tomographic scanning. They also looked at blood levels of glucose, lipids, and leptin among other variables. Visceral fat was the best predictor of inflammation as measured by CRP along with insulin resistance and endothelial dysfunction-related factors. Exercise participants had significantly lower visceral fat. However, there was no significant difference in BMI or physical fitness, suggesting that even in the absence of visible results, exercise can still act as a protective measure in safeguarding health [43].

The Adverse Effects of Physical Exercise

Excessive exercise is perceived by the body as a form of stress. Physical strain stimulates the release of cortisol that may cause tissue breakdown and increase food consumption [44]. Cortisol is involved in the conversion of protein to glucose potentially predisposing older individuals to type II diabetes [45]. Strenuous exercise, necessary to reduce visceral adipose tissue, is associated with a negative relationship between cortisol and testosterone. As cortisol increases, testosterone decreases. Both low testosterone and high cortisol lead to weight gain and other complications that inevitably offset the benefits of exercise, [46] [47]. Importantly, during overtraining muscle-derived IL-6 is released into the circulation in high amounts resulting in increased inflammation [48]. The outcome of exercise appears to range from decreasing to increasing inflammation depending on the intensity and duration of physical activity.

Prolonged exercise decreases leptin concentrations by 32% and increases free fatty

acids as expected by the understanding that free fatty acids act as an energy replenishment mechanism after energy expenditure [49]. Leptin reduction will reinforce increased food consumption after exercise again, undermining the weight loss benefits [50].

Effortless Exercise Solutions

In search of solutions that can proactively protect and enhance health, the current research focused on levels of visceral adipose tissue, skeletal muscle mass and IGF-1, as well as plasma levels of VLDL cholesterol, triglycerides, leptin, ghrelin, T3 and cortisol, increases in which are associated with obesity and its inherent inflammation and toxicity. The effortless exercise method used was similar to the device used in previous studies on chapters 2 and 3. It was invented and build in London University after 27 years of research. London University professor Goldspink et al. (1991) [51], used an earlier much less sophisticated version of this method exploring gene expression in fast and slow muscle fibre phenotypes. The stimulation method resulted in rapid hypertrophy of adult skeletal muscle that reflected an increase of up to 250% in RNA content associated with the repression of the fast and the activation of the slow myosin heavy chain genes.

Methodology

The device used was completed in 2019 on the basis of a London University invention that was later modified at the EU funded Business Innovations Centre to treat muscle wasting conditions and multiple sclerosis. It has twenty four waveforms, each composed by up to 4,000 intertwined sine frequencies that when combined they form a square complex waveform. The various 24 waveforms are operated manually to offer a large variety of whole body contractions as in regular exercise during a multilevel gym workout . The technology has inbuild safety mechanisms and is classified as IEC class I according to the IEC60601-1 standard. It is used with 3-pin din and 4-pin din IEC 60601-1 compliant cables. It has a CE marketing directive of Class I with electromagnetic compatibility regulations applied standards EN50081-1 and

EN50082-1. Additionally, it complies with the EEC UK directive of electrical equipment safety applied standard EN 60601-1. The technology has had no known side effects. The only contraindication, according to the FDA, is having an implanted device like a pacemaker. The main caution is pregnancy. Adverse reactions are limited to temporary skin redness from the pads that occurs sporadically and usually dissipates within an hour. Earlier versions of this technology with the same hardware design have been cleared by the FDA in 2012 (K132158) and 2013 (K123157). FDA clearance is specific to the indication of muscle conditioning.

Additional measuring instruments included a conductance scale that calculated visceral adipose tissue and skeletal muscle mass and a blood test administered before and after the completion of the treatments that measured, T3, Leptin, Ghrelin, Testosterone, Cortisol, IGF-1, the Very Low Density Lipoprotein (VLDL) and Triglycerides.

Procedure

10 subjects ages 35–45 years with an average BMI of 26, participated and completed the twelve treatments clinical trial. Subjects were randomly selected out of a list of 18 eligible candidates. All subjects fulfilled the inclusion and exclusion criterial which were:

Inclusion:

1. Healthy adults.
2. No pregnancy.
3. No pacemaker.
4. Non-smoker.
5. No known medical or mental illness.

Exclusion:

1. Surgery within the past year.
2. Received treatment with another modality in the past year (e.g. laser or radiofrequency).
3. Exercises at least once a week.
4. Physically active.

5. An implanted device like a cardiac pacemaker.
6. Pregnant or trying to get pregnant.

The inclusion exclusion criteria were assessed on the basis of a comprehensive health questionnaire completed by all subjects. Every precaution was taken to protect the subjects' privacy and the confidentiality of their personal information. Subjects were informed that they had the right to refuse participation at any time. None of the subjects was in a dependent relationship with the technology operators, the lab and measurement technicians or the author. The subjects did not receive a specific diet or instructions regarding changes in their lifestyles.

All data was collected after the subjects had completed their treatments, at which point they were presented with the consent form that would allow them to participate in the study. Therefore, neither the subjects nor the technology operators were aware that they would be eventually part of a clinical study. Two independent labs were assigned to take blood samples from all subjects before and after twelve one-hour treatments that took place three times a week, for four weeks.

Subjects were asked to fast for twelve hours before getting their blood tests that were obtained prior to the first treatment and ten days after the last treatment. The scale measurements were performed before the first treatment in a separate room by an independent technician with no prior experience in the technology or conflicts of interest, and ten days after the last treatment. Following blood tests and measurements each subject went to their private treatment room and lay on the massage bed while the gel pads and cables from the 16 channels of the device were being attached onto his / her body by the technology operator. The cables from ten of the channels were attached onto the gel pads of the waist and abdomen, and the cables from the six remaining channels were attached onto the gel pads placed along the lymphatic system pathways of the legs and arms, to enhance lymphatic drainage during treatment.

All subjects gave a detailed report of their subjective experience during, ten days after and a month after the last treatment. The procedure was performed in accordance with the ethical standards and principles for medical research involving human subjects.

Results

This was a within subjects design. The data was analysed with the Analysis of Variance for repeated measures and T-tests for two dependent means. Results indicated an inverse testosterone/cortisol relationship where testosterone increased while cortisol decreased (*Table 1*). Importantly testosterone increase and cortisol decrease were within the normal range. (*Table 1*). These findings were in contrast with observations following strenuous exercise where cortisol increase is accompanied by testosterone decrease. Testosterone increase reflected a p value of $p=0.00157$ and a significance level of $p<0.01$. For cortisol decrease the p value was $p=0.00041$. Cortisol significantly decreased at the $p<0.001$ level *(Table 6)*.

All variables' statistical significance values are displayed on *Table 6*. IGF-1, skeletal muscle mass (SMM) and Free T3 significantly increased at a high probability level. Visceral adipose tissue, VLDL and triglycerides showed a statistically significant decrease.

Table 1. Blood Plasma Subjects' Results on Testosterone and Cortisol for each subject. (n=10. Tx=12) Cortisol Normal Range nmol/L: 80-477 nmol/L

G	Testosterone Free Pre nmol/L	Testosterone Free Post nmol/L	Testosterone Free Normal Range nmol/L	Testosterone % Increase nmol/L	Cortisol Pre nmol/L	Cortisol Post nmol/L	Cortisol % Increase nmol/L
M	10.92	14.6	8.64-29	33.6%	198	181	-8.5%
M	12.16	15.43	8.64-29	26.9%	177	163	-6.8%
F	0.3	0.71	0.29-1.6	136.6%	135	128	-5.2%
F	0.4	0.9	0.29-1.6	125%	168	153	-8.9%
M	15.38	21.6	8.64-29	40.4%	229	198	13.5%
M	13.41	19.92	8.64-29	48.5%	160	149	-6.9%
F	0.64	0.92	0.29-1.6	43.7%	116	109	-6.0%

F	0.4	0.71	0.29-1.6	77.5%	87	82	-6.7%
M	11.3	14.4	8.64-29	27.4%	221	214	-3.16%
F	0.43	0.72	0.29-1.6	67.4%	197	189	-4.0%

Mean Average Testosterone % Increase	62.18%	Mean Average Cortisol % Decrease	-4.27%

Both testosterone increase and cortisol decrease remained within the normal range. Testosterone showed a mean average of 62.18% that was comprised from a 35.36% in males and a mean average of 90.04% in females. Cortisol showed a mean average decrease of -4.27%.

Table 2 displays an average percentage increase in IGF-1 of 25.8% after the 12 treatments which was elevated towards the peak of the normal range. As expected skeletal muscle mass (SMM) also increased significantly by an average percentage of 36.45%.

Table 2. Blood Plasma Subjects' Results on IGF-1 and Scale Results on SMM. (n=10. Tx=12)

G	IGF-1 Pre nmol/L	IGF-1 Pre nmol/L	IGF-1 Normal Range nmol/L	IGF-1 % Increase nmol/L	Skeletal Muscle Mass (SMM) Pre	Skeletal Muscle Mass (SMM) Post	SMM% Increase
M	25.97	30.35	15.08-32.5	16.86%	36.40	43.80	20.3%
M	23.98	31.12	15.08-32.5	29.77%	30.30	38.60	27.39%
F	16.33	20.75	11.25-28.8	27.06%	18.40	27.00	46.79%
F	15.14	19.21	11.25-28.8	26.88%	17.00	26.80	57.64%
M	22.27	28.11	15.08-32.5	26.22%	37.80	44.80	18.5%
M	26.98	30.52	15.08-32.5	11.80%	29.40	38.30	30.27%
F	15.86	21.08	11.25-28.8	32.91%	17.20	26.80	55.81%
F	18.55	23.50	11.25-28.8	26.68%	19.80	28.80	45.45%
M	24.56	31.34	15.08-32.5	27.60%	29.80	37.22	25.89%
F	19.34	25.66	11.25-28.8	32.67%	17.95	26.63	48.35%

Mean Average IGF-1 % Increase	25.85%	Mean Average % Increase for SMM	36.45%

Mean average percentage increase of IGF-1 was 25.85%. IGF-1, remained within the normal range. Mean average percentage increase for Skeletal muscle mass was 36.45%.

Table 3 displays an average of 40.7% decrease in Triglycerides. The average percentage decrease of VLDL was particularly robust at 71.88%.

Table 3. Blood Plasma Results Triglycerides and VLDL for each subject. (n=10. Tx= 12)

G	Triglycerides Pre- mmol/L	Triglycerides Post- mmol/L	Triglycerides Normal Range mmol/L	Triglycerides % Decrease mmol/L	VLDL PRE mmol/L	VLDL POST mmol/L	Normal Range mmol/L	VLDL % Decrease mmol/L
M	2.90	1.23	<1.7	-55%	1.48	0.24	<1.6	-83.78%
M	2.34	0.94	<1.7	-59.8%	1.55	0.64	<1.6	-58.7%
F	2.50	1.50	<1.7	-40%	0.80	0.20	<1.6	-75%
F	2.00	1.44	<1.7	-28%	0.86	0.27	<1.6	-68.6%
M	0.80	0.53	<1.7	-33%	0.52	0.04	<1.6	-92.3%
M	0.90	0.64	<1.7	-41.1%	1.36	0.24	<1.6	-82.35%
F	1.00	0.60	<1.7	-40%	0.68	0.05	<1.6	-92.64%
F	0.90	0.58	<1.7	-35%	0.53	0.26	<1.6	-50.9%
M	1.32	0.92	<1.7	-30%	1.53	0.67	<1.6	-56.20%
F	0.98	0.54	<1.7	-44.9%	1.75	0.73	<1.6	-58.28%
Mean Average Triglycerides Decrease				-40.7%	Mean Average VLDL Decrease			-71.88%

The Analysis of Variance showed statistically significant results for both Triglycerides and VLDL at p<0.01.Mean average percentage decrease of Triglycerides was 40.7%. Mean average percentage decrease of VLDL was 71.88%.

Table 4 displays an average of 30.34% decrease in visceral adipose tissue and an average of 25.8% increase of Free T-3 after the 12 treatments which was elevated towards the peak of the normal range.

Table 4. Results on Visceral Adipose Tissue and Blood Plasma Results on Free T3 for each subject (n=10. Tx= 12).

G	Visceral Fat Pre	Visceral Fat Post	Visceral Fat% Decrease	Free T3 Pre pmol/L	Free T3 Post pmol/L	Normal Range pmol/L	FREE T3 Decrease pmol/L
M	139.30	93.80	32.66%	2.98	4.22	2.63-5.7	41%
M	102.20	69.30	32.19%	3.69	4.98	2.63-5.7	34.95%
F	93.50	58.30	37.64%	4.77	5.37	2.63-5.7	12.5%
F	85.50	61.40	28.30%	4.56	5.31	2.63-5.7	16.44%
M	76.40	48.80	36.12%	4.15	5.47	2.63-5.7	31.80%
M	118.60	89.30	24.70%	3.29	4.86	2.63-5.7	47.7%
F	98.80	70.60	28.54%	4.36	5.64	2.63-5.7	29.35%
F	102.70	77.30	24.73%	3.66	4.79	2.63-5.7	30.87%
M	145.30	104.34	28.18%	3.19	4.12	2.63-5.7	29.15%
F	109.80	74.67	31.99%	4.09	5.12	2.63-5.7	25.18%

Mean Average Visceral Fat % Decrease	30.34%	Mean Average Free T3 % increase	30%

The Analysis of Variance showed statistically significant results for both Visceral Adipose Tissue and Free T3 at p<0.01. Average percentage decrease of visceral adipose tissue was 30.5% Average percentage decrease of Free T3 was 30%

Table 5 depicts an average percentage of 32.23% in Leptin increase that mounted towards the peak of the normal range and an average percentage of 14.57% in Ghrelin decrease that descended towards the bottom of the normal range.

Table 5. Blood Plasma Results on Leptin and Ghrelin for each subject. (n=10. Tx= 12)

G	Leptin Pre ng/mL	Leptin Post ng/mL	Normal range ng/mL	Leptin % increase - ng/mL	Postprandial Ghrelin pre pg/mL	Postprandial Ghrelin post pg/mL	Normal range pg/mL	Postprandial Ghrelin % decrease pg/mL
M	1.38	1.84	1.63-2.54	33.5%	634	531	520-700	-16.24%
M	1.25	2.03	1.63-2.54	62.4%	647	584	520-700	-9.73%
F	5.43	7.22	5.69-7.26	32.96%	679	524	520-700	-22.82%
F	5.98	7.09	5.69-7.26	20.73%	663	543	520-700	-18.09%
M	1.53	1.94	1.63-2.54	26.79%	590	532	520-700	-9.83%
M	1.22	1.97	1.63-2.54	61.47%	603	544	520-700	-9.78%
F	4.87	5.84	5.69-7.26	19.9%	687	522	520-700	-24.01%
F	5.89	6.54	5.69-7.26	11.03%	693	565	520-700	-18.47%
M	1.47	2.01	1.63-2.54	36.73%	689	532	520-700	-22.76%
F	4.99	5.83	5.69-7.26	16.83%	634	523	520-700	-17.50%

Mean Average Leptin Increase	32.23%	Mean Average Ghrelin Decrease	-16.92%

There was an inverse relationship between leptin and ghrelin where leptin significantly increased and ghrelin significantly decreased. Mean average percentage leptin increase was 32.23% and ghrelin decrease was 14.57%. Importantly, leptin and ghrelin values increased and decreased respectively within the normal range.

Table 6. T-Tests Statistical Significance Results on Blood Plasma and Measurement Variables. (n=10. Tx=12)

	Mean	**S^2 =SS/df**	**$S^2_M = S^2/N$**	**SM= √S2M**	**T Value**	**p Value**	**Probability**
VLDL DECREASE	-0.77	0.09	0.01	0.1	-7.95	0.00001	P<0.0001

Triglycerides DECREASE	-0.67	0.26	0.03	0.26	-4.2	0.00115	P<0.01
Visceral Adipose Tissue DECREASE	-32.43	47.62	4.76	2.18	-14.86	0.00001	P<0.0001
Cortisol DECREASE	-12.2	59.96	6	2.45	-498	0.00038	P<0.001
Ghrelin DECREASE	-0.86	0.16	0.02	0.12	-6.92	0.00003	P<0.0001
Leptin INCREASE	0.83	0.16	0.02	0.13	6.52	0.00005	P<0.0001
Testosterone INCREASE	2.46	6.14	0.61	0.78	3.14	0.006	P<0.01
Free T-3 INCREASE	1.11	0.08	0.01	0.09	12.1	0.00001	P<0.0001
SMM INCREASE	8.47	0.89	0.09	0.3	28.39	0.00001	P<0.0001
IGF-1 INCREASE	5.27	1.47	0.15	0.38	13.72	0.00001	P<0.0001

The Analysis of Variance (*Table 7*) yielded statistically significant results for all variables. All hormones' values were significant but without spiking outside the normal range.

Table 7. Analysis of Variance Statistical Significance Results on Blood Plasma and Measurement Variables
(n=10. Tx=12)

	F-Ratio Value	p-Value	Significance Level
Testosterone / Cortisol	F= 154.22073	0.00001	P<0.0001
IGF-1 / SMM	F= 37.86392	0.00001	P<0.0001
VLDL / Triglycerides	F= 14.02706	0.000011	P<0.0001
Visceral Fat / Free T3	F= 191.86419	0.00001	P<0.0001
Leptin / Ghrelin	F= 7.9841	0.000573	p<0.001

After their last treatment, the subjects reported that they experienced a large variety of 8-secs long vigorous contractions some of them resembling resistance exercises, others like body twists or aerobics. Contractions were involuntary and painless involving the entire body's musculature contracting in a coordinated fashion. In all three

of their interviews, after the last treatment, ten days after their last treatments and a month later, the subjects consistently reported a sustainable weight reduction, enhanced fitness and an inhibition of cravings for sweets and fatty foods.

Purpose of the Study

The purpose of this randomised double-blind pilot study was to explore exercise alternatives that can safely demonstrate visceral fat reduction and optimal hormonal balance. The goal was to increase individual choices in becoming healthy, especially during COVIE-19 lockdowns that restrict physical activity. The sample that was included in the study was composed of healthy adults with a BMI of 26 that was lower than that of individuals included in previous studies. Yet, the resistance to physical activity was equally pervasive. All subjects initially expressed a reluctance to exercise, offering a number of excuses that ranged from time restraints to work and personal obligations. However, after the twelve treatments, they reported that they were willing to continue with some form of exercise to maintain the fitness level attained. Basically, this method had changed their original leisure driven attitude and had set the foundation for a more active lifestyle.

This was a pilot clinical trial confined to a small sample of subjects. However, results were robust with no apparent rebound. 100% of the subjects consistently validated the experimental hypothesis by demonstrating a reduction in visceral adipose tissue, cortisol, VLDL and triglycerides, while displaying optimal regulation by 'normal range' increases and decreases of leptin and ghrelin respectively.

As previously stated, cortisol increases during strenuous physical exercise results in lactic acid production and oxidative damage. Excessive physical activity provokes leptin decrease and inflammation increase. This new exercise method bypasses exercise-induced negative asymmetries by increasing testosterone and decreasing cortisol. In addition, three of four months of exercise does not appear to produce visible results. Yet, four weeks of treatment with this new method

appeared to rebalance the body while offering speedy fitness as shown by the increased IGF-1 and skeletal muscle mass, without any side effects. Obviously, this method should not be seen as a permanent solution that replaces exercise; but as a technique that can achieve visceral fat reduction while increasing fitness and health. It can help reduce weight, increase muscle mass, and build up self-confidence while introducing the benefits of an active lifestyle. In later chapters we will focus on the COVID-19 affinity for ACE2 receptors in adipose tissue, as contracted by its conspicuous indifference for muscle mass that contains much less ACE2 receptors. Increased muscle mass, along with hormonal balance can be seen as the shield of health against COVID-19. Therefore any method that results in the exchange of fat with muscle may be significantly useful in protecting against severe or life threatening infection.

Additional Bonus: Absence of Stress

Another interesting benefit of this effortless exercise method is the absence of stress. This clinical trial demonstrated a testosterone increase juxtaposed by cortisol decrease, but without spiking outside the normal range, in contrast to the adverse cortisol/testosterone inverse relationship observed after strenuous exercise that undermines fitness by increasing food consumption. All subjects reported reduced cravings for sugar and fatty foods, yet, normal appetite, possibly signifying a combination of optimal cortisol levels combined with a decrease in systemic toxins, hence enhancing optimum function of the hypothalamic satiety modulation mechanisms of central inhibitors and stimulators of appetite.

Methodology Limitations

1. Lack of inflammatory markers such as CRP or IL-6, or markers of oxidative damage.
2. Visceral fat and skeletal muscle mass measurements were based on a conductance scale rather than more conclusive diagnostic instruments such as magnetic resonance imaging or sonography that could explore the possibility of liver fat reduction.
4. Lack of a placebo group and a sham control group receiving twelve regular exercise

sessions to be compared to the experimental group.

5. Sample size was still small, begging for further exploration of this method with more subjects and additional variables reflecting inflammation and oxidative damage markers.

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Conflict of Interest

The author declares that she has no conflict of interest since the study was conducted by independent. No funding was received by a third party or institution.

Ethical Standards

Statement of Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of

4 Ethical Principles for Medical Research involving Human Subjects*
5 American Psychological Association (APA)
6 IELLIOS Research department for Development and invention of Innovative Technology

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SECTION 4
Adverse Effects of Sedentary Lifestyles

Section Summary

Sedentary lifestyles promote adipose tissue accumulation that generates systemic inflammation and oxidative damage. Physical activity induces cardiovascular fitness, increases muscle mass, and healthy blood glucose regulation, while reducing visceral fat, triglycerides and low-density lipoproteins. It is theoretically possible to develop a long-term multi-exercise regimen for health management and enhancement. Pragmatically, time and career restraints, individual choices, genetic factors or demoralization due to the draconian commitment involved in weight loss, have rendered over a billion of individuals obese, or overweight, burdened by excess lipids, insulin resistance, elevated glucose levels, and inflammation, that foster a number of medical conditions including diabetes. Strenuous overtraining has ensued adverse effects, including an upsurge of proinflammatory cytokines, and hyperglycaemia. We implemented an one-month long innovative method with 20 diabetic and prediabetic patients. Results demonstrated a statistically significant reduction of both fasting and PP blood glucose. Fasting and PP insulin reached optimal levels. There was a substantial decline in dyslipidaemia, reflecting a reverse relationship of elevated HDL and decreased triglycerides. Both variables were either within or close to the normal range. The notable visceral fat reduction was validated by sonography reports that indicated no evidence of fatty liver in seven patients previously diagnosed with hepatic steatosis. These findings have important implications in improving the health status of obese diabetic and prediabetic individuals, by helping them jumpstart an active lifestyle, or by serving as an exercise alternative to reduce lipids, blood glucose levels and insulin resistance.

The Multiple Advantages of Exercise

Regular exercise increases cardiovascular health, and leads to optimal blood glucose regulation while positively impacting on lipids, high-density lipoprotein (HDL) and

low-density lipoprotein (LDL) [1]. Resistance training lowers LDL and optimally elevates HDL, a multi-protein particle that modulates vascular health by removing excess cholesterol from peripheral tissues and reverse-transporting them to the liver [2, 3]. Prolonged exercise decreases triglycerides in both endurance athletes and untrained men [4]. Excess triglycerides are the mecca of inflammation and metabolic syndrome, escalating the risk for heart attack, stroke and diabetes.

Health Deteriorates with Physical Inactivity

Lack of physical activity due to work load and time restraints and the popularity of cheap, energy-dense food has resulted in a global alarming increase of obese and overweight individuals to over 1.7 billion [5]. Excess body weight, combined with physical inactivity, promotes insulin resistance, and increases blood glucose which induces tissue injury due to DNA disintegration. Additionally, it causes abnormal increases in caspase-3, the executioner of apoptosis. Caspase-3 is in charge of eliminating DNA fragments, and decomposed cytoskeletal proteins [6, 7]. Diabetic nephropathy, and non-alcoholic fatty liver are some examples of the adverse consequences of degraded systemic controls regulating blood glucose [8].

The Liver Plays a Critical Role in ATP Production

The liver is crucial for glucose metabolism which, in turn, is necessary for the synthesis of adenosine triphosphate (ATP), the primary source of biological energy. High concentrations of glucose are a biological trigger for liver damage, due to an overstimulation of metabolic oxidation that transforms molecules into unpaired-electron ions, termed free radicals [9]. Even mild increases in glucose provoke an overproduction of reactive oxygen species (ROS), inevitably causing oxidative stress, partial depletion of ATP, and neuronal apoptosis [10]. Oxidative stress emanates from an imbalance between the generation of excess free radicals, and the electron-donation process by anti-oxidants that replenish and rebalance the ROS unpaired electrons [11]. ROS are released by phagocyte cells to eliminate invading pathogens or harmful bacteria; therefore, in moderation, they serve as an immune system defence. [12].

Visceral Fat as a Vessel for Inflammation and Oxidative Stress

Oxidative stress, as measured by urinary 8-epi-prostaglandin F2 alpha (8-epiPGF2a) concentration, is specifically implicated in visceral fat accumulation [13]. Systemic inflammation is the result of visceral adipose tissue secreting inflammatory adipokines, such as interleukin-6 (IL-6), into the portal veins of the blood circulatory system. This was demonstrated by research looking at inflammatory markers such as C-reactive protein (CRP), and interleukin-6 (IL-6) that were 50% greater in the portal vein blood samples, rather than the radial artery blood samples of 25 obese patients [14]. Intraabdominal adiposity is also characterized by a reduced production of adiponectin, a hormone involved in regulating glucose fatty acids breakdown. Adiponectin has anti-diabetic, anti-inflammatory and anti-oncogenic properties, and it is inversely correlated with visceral fat [15]. Accumulated adiposity is accompanied by elevated apolipoprotein B (apoB), the primary component of low-density lipoproteins (VLDL, IDL, LDL), and dyslipidaemia, defined as a combination of high triglycerides / low HDL [16]. It is also associated with an over-secretion of tumour necrosis factor-alpha (TNF-α) that induces insulin resistance [17]. In conclusion, visceral adipose tissue as evidenced by imaging techniques is associated with hyperinsulinemia, glucose intolerance, hypertriglyceridemia, dyslipidaemia, inhibited HDL, oxidative stress, and inflammation marked by increases in IL-6, CRP and TNF- α.

Obesity, Insulin Resistance and Hyperglycaemia

Obesity or being overweight combined with insulin resistance promotes the pathogenesis of type 2 diabetes and hypertension, the major predisposing factors of cardiovascular disease (CVD) that kills about 18 million individuals yearly [18]. Diabetes and CVD have been connected to a higher mortality rate following COVID-19 infection. According to a recent report a high prevalence of COVID 19 patients are classified as overweight [19].

Obesity is defined as the excess accumulation of adipose tissue predisposing the body to unmanageable oxidative stress and inflammation. The elevated production of free radicals during hyperglycaemia disrupt both insulin signalling, and insulin secretion by pancreatic B cells, escalating and promoting diabetes [20].

Diabetes Definition

Diabetes encompasses a variety of metabolic disorders primarily related to either an insulin deficit which defines the primary cause of Type 1 diabetes (T1D), or an insulin resistance commonly found in Type 2 diabetes (T2D) [21]. Autoimmune diabetes falls under the T1D category. T1D ordinarily emanates out of defective immunity characterized by an insufficient amount of B-cells whose primary function is to develop antibodies against invasive antigens. T1D is distinguished by usually normal weight and is primarily diagnosed in children, adolescents, and young adults who exhibit symptomatology such as polyuria, polydipsia and fatigue [22]. T2D is a cluster of diseases associated with both hyperglycaemia and the metabolic syndrome, typically represented by obesity. It involves excessive visceral fat deposits, low grade inflammation and increased mortality rates. T2D is associated with an inverse relationship between triglycerides and high density lipoproteins (HDL), where increased levels of triglycerides are accompanied by abnormally low HDL; additionally it is linked to hypertension that often leads to enhanced risk of coronary heart disease (CRD) or strokes. The severity of T2D progresses over a dimension that ranges from reduced insulin secretion to persisting insulin resistance induced by deficient insulin production [23]. Diabetes has been connected to a number of other disorders that include Cushing Syndrome, defined by hypercortisolism [24]; pancreatitis, propagated by pancreatic inflammation [25]; acromegaly, distinguishable by an enlargement on the hands and feet due to an excess of growth hormone (GH) [26]; cystic fibrosis that affects the lungs, liver, kidneys and intestine and is expressed in difficulty breathing or coughing [27]; hemochromatosis delineated by an iron overload [28]; and pheochromocytoma that involves a benign tumour in the adrenal gland. There's clinical evidence that diabetes may develop as a result of pharmaceutical

treatments with atypical neuroleptics often prescribed to treat schizophrenia [29], glucocorticoids [30], or alpha-interferons [31].

Diabetes, VLDL, Triglycerides, LDL and HDL

The very low density protein (VLDL) that is normally composed in the liver, transports triglycerides (esters comprised out of glycerol and three fatty acids), that represent the main source of energy storage in tissues, otherwise known as overall body fat. Increased levels of triglycerides carried by VLDL are the hallmark of dyslipidaemia that is commonly accompanied by inhibited levels of the high density lipoprotein (HDL). HDL absorbs both low density and very low density lipoproteins transferring them back to the liver, thus relieving the arteries of potential plaque build ups, and reducing the risk of both atherosclerosis and heart decease. Dyslipidaemia is intrinsically linked both to insulin resistance and T2D [32]. Liu et al [33] tested the null hypothesis that ischemic strokes and heart decease may not be directly related to a high ratio of triglycerides reciprocated by low HDL. These investigators examined the health statues of 30,378 individuals over a period of fifteen years. Failing to falsify a hypothesis is the most experimentally scientific method of proving a premise. Liu's results confirmed the strong connection between a pathological lipid profile of high triglycerides predicting coronary heart decease, and low HDL being associated with ischemic stroke, with a high prevalence of Diabetes and high low density lipoproteins (LDL) being present in patients with coronary heart decease [34].

Triglycerides and Diabetic Neuropathy

Recent studies have associated T2D Neuropathy to dyslipidaemia defined by an abnormally high triglycerides / low HDL profile [35]. Diabetic neuropathy is characterized by chronic pain, anomalous sensations and malfunctioning nerve conduction velocities (NVCs) underlaid by deficient sural nerve myelinated fibber densities (MFDs). Wiggin et al [36] followed patients with high triglycerides and abnormalities in motor nerve conducting velocities for one year. Their study unveiled a significant correlation between dyslipidaemia and deficient motor nerve conduction

velocities that are the foundation of diabetic neuropathy. A recent research project focused on symptomatology relief and pain analgesia from chronic diabetic neuropathy with patients who had a history of multiple hospitalizations, followed by an accumulation of medical expenses, and a poor prognosis that involved the imminent threat of a lower limp amputation as the best case scenario to avoid further deterioration. [37]. A second study that reviewed different therapeutic modalities on diabetic wound healing with lasers and ultra-low microcurrents, demonstrated fast irreversible improvement of diabetic lesions following treatment with a novel nanotechnology using nano-energies [38].

Sedentary Lifestyles Increase Oxidative Stress and Inflammation

Hyperglycaemia disrupts both insulin signalling, and insulin secretion by pancreatic B cells, provoking an inevitable deterioration of the diabetic condition [39]. Clinical research has demonstrated that increased hyperglycaemia elevates oxidative stress and suppresses antioxidant production that could potentially donate electrons to reinstate symmetry in the otherwise disequilibrium state of the radical oxygen species (ROS). In vitro studies on the mitochondria of obese type 2 diabetics have evidenced a significant increase of ROS [40]. For the average individual, the absence of exercise renders detoxification insufficient. An individuals that does not regularly engage in physical activities is unable to establish the necessary balance between production and elimination of free radical species, routinely formed by normal aerobic metabolism via oxygen while breathing. Oxidative damage leads to toxicity that erodes the boundaries between health and illness, being exacerbated by the growing immune limitations during aging. Inadequate detoxification results in accumulated oxidative damage that adversely affects the diabetic condition instigating glucotoxicity, lipotoxicity, and cardiac dysfunction. Hence the therapeutic intervention provided by antioxidants and exercise which are highly recommended to both T1D and T2D. Antioxidants will reduce free radicals by electron donation and exercise will promote detoxification along with other benefits that will improve the health status of diabetics [41].

The Miracle of Exercise

Therapeutic recommendations given to obese and diabetic individuals consist of both exercise, defined by a coordinated set of repetitive movements at different speeds and resistances, as well as physical activity, interpreted as representing a regular pattern of increased everyday motion. Both have been long advocated by a number of national guidelines including the American Diabetes Association that has disclosed clinical evidence of reducing the prevalence of T2D by 58% as a result of an active lifestyle. [42, 43, 44].

The Convergence of Oxidative Stress and Inflammation

Oxidative stress has been intricately related to C-Reactive protein, the hepatic origin inflammation marker that is linked to proinflammatory cytokines, and which has been consistently associated with both diabetes and cardiac dysfunction [45, 46, 47]. An experimental study on 529 subjects established a statistically significant correlation between CRP and mononuclear cells' oxidative stress, as well as demonstrating that ROS in polymorphonuclear leucocytes and mononuclear cells were prevalent in both diabetes and hypertension [48]. Diabetes is aggravated by obesity that is defined by low grade inflammation and an excess of CRP, identified in the white adipose tissue (WAT). WAT is primarily used for energy storage, in contrast to the brown adipose tissue (BAT) that is predominantly involved in energy production [49]. Overall, visceral adipose tissue (VAT) is associated with diabetic hyperinsulinemia, glucose intolerance, hypertriglyceridemia, dyslipidaemia, defined by a combination of high triglycerides and inhibited HDL, oxidative stress and inflammation as marked by CRP [50, 51].

Hyperglycaemia Elevates Oxidative Stress

As previously noted, there is evidence that hyperglycaemia elevates oxidative stress, while significantly compromising systemic antioxidant defences. In vitro, the mitochondria of obese type 2 diabetics produce significantly more ROS, with a notable decrease of the antioxidant enzymes glutathione (GSH) peroxidase, and superoxide

dismutase [53]. Moreover, diabetics' erythrocytes present reduced levels of GSH, juxtaposed by high levels of glutathione disulfide (GSSG), which is the oxidized form of GSH [54]. Diabetics manifest abnormal glucose levels despite fasting glucose treatments, due to a combination of glucose toxicity and lipotoxicity, provoked by the metabolic oxidation of elevated lipid levels in the blood. According to this view, both hyperglycaemia and hyperlipidemia eventuate a dysfunctional B-cell activity [55].

Excess Triglycerides: the Pit of Malaise

Both obesity and type 2 diabetes are associated with an increase in inflammatory markers including TNF-α and IL-6 that presumably inhibit insulin signalling, leading to a dysfunctional glucose insulin regulatory system [56]. Triglycerides, one of the common denominators underlying both conditions. Triglycerides are implicated in low-grade inflammation and represent one of the best predictors of atherosclerosis [57] [58]. Excess lipids in the blood accumulate in the liver, often causing lipotoxicity and insulin resistance [59]. Non-alcoholic (NA) steatosis or fatty liver, one of the consequences of visceral adiposity, is the result of an imbalance between intrahepatic triglycerides' production and export. It often progresses to steatohepatitis, fibrosis, and cirrhosis. Overall, lipotoxicity, inflammation, and visceral fat are associated with excess triglycerides that represent the core components of arterial plaques [60]. On the other hand, high-density lipoprotein (HDL) has been correlated with cardiovascular health. Optimum HDL levels are anti-inflammatory, plus they inhibit oxidized phospholipids and low-density lipoproteins [61]. However, in systemic inflammatory states like atherosclerosis, HDL loses its protective properties and becomes pro-inflammatory [62]. This apparent contradiction is the outcome of systemic imbalance. In moderation, all biological mechanisms are purposeful and necessary. Optimal levels of triglycerides serve as an energy source. In excess, however, triglycerides pose a significant health risk.

Descending to the Point of No Return

Obesity and diabetic or pre-diabetic conditions characterized by visceral fat

accumulation, are very difficult to treat due to multiple complications including inflammation, insulin resistance, and high-blood glucose which provokes oxidative stress. The necessity of reducing visceral adipose tissue is evident. Laser and radiofrequency studies primarily target subcutaneous fat reduction. Those reporting visceral fat reduction are sparce and suffer from methodological issues, or lack of clarity regarding their measuring variables [63]. Sixteen minutes of Low-level laser therapy (LLLT), combined with one hour of aerobic and resistance exercise, reported visceral fat reduction as measured by a conductance scale. A follow up study by the same investigators demonstrated no visceral fat differences between the experimental and control groups, debating the external validity [64, 65]. A radiofrequency study, published in Cairo University Bulletin, showed an overall fat loss in the experimental group; however, there was no clear indication of visceral adipose tissue decrease [66]. In conclusion, most laser and radiofrequency studies report results on overall fat reduction, without specifically addressing visceral adiposity. Other modes of combating obesity is diet that is excruciatingly difficult for most individuals, accompanied by a complete lifestyle change that demands an overturn of habitual patterns, an endeavour that is theoretically possible to accomplish, yet rather unlikely to achieve by the average person.

The Treatment of Diabetes Demands Lifestyle Changes

A literature search on the multidimensional spectrum of diabetic treatments usually reiterates the same recommendation, pertaining to lifestyle changes and exercise [67, 68, 69, 70]. Randomized placebo-controlled data demonstrated some modest reduction of visceral adipose tissue, and fatty liver improvement following eight weeks of aerobic exercise [71]. Resistance training resulted in significantly lower levels of the low-density lipoprotein (LDL), and an improvement in muscular strength, but no differences in BMI, in obese postmenopausal women who usually manifest a greater prevalence of visceral fat [72, 73]. Exercise was effective in both reducing visceral fat, and inflammation, as measured by the inflammatory marker CRP; however, there were no visible results in terms of reduced BMI or enhanced physical fitness [74]. Although

short-term exercise appears to be moderately effective in reducing visceral fat, long-term physical activity seems necessary to sustain, and further reduce visceral adipose tissue. Intense interval running is efficient in improving cardiorespiratory fitness and glucose tolerance; but it has no effect on total bone mass or muscle mass, unlike strength training interventions. Prolonged training is necessary to treat hyperlipidemia and obesity [75]. Low-volume intense exercise reduced hyperglycaemia in type 2 diabetic patients [76]; yet, a single session of this type of physical activity demonstrated a non-significant reduction of blood glucose ($p=0.16$) [77].

The Double-Edged Sword of Exercise.

There are concerns associated with certain types of exercise, which increase blood glucose levels and, in certain subjects, result in abnormal hypoglycaemia [78]. Clinical studies on dynamic exercise have demonstrated hyperglycaemia and hyperinsulinemia in diabetics, persisting for at least one hour after physical training [79]. Additional research has delineated a disproportionate increase of seven to eightfold glucose production as a result of intensified catecholamine signalling, accompanied by a deficient glucose utilization, limited to only three to fourfold [80]. Diabetics and individuals with other medical disorders need exercise because sedentary lifestyles increase the incidence of diabetes and coronary heart decease by 30-50% [80, 81]. Physical activity spends glucose derived energy that could theoretically help the diabetic hyperglycaemia, however, the long term effects of exercise on the diabetes' dysregulated metabolic profile remain inconclusive [82].

Few Follow the Recommendation to Exercise

A 2006 survey revealed that exercise was recommended to 73% of diabetes patients as opposed to only 31% of non-diabetic adults, however very few of these patients increased their physical activity [83]. Exercise appears to decrease diabetic symptomatology, hence being beneficial to those with both T1D and T2D who can use exercise as a protective, therapeutic method against further deterioration. However,

patients with advanced diabetes, complicated by obesity, or neuropathic pain, will be obviously less willing or capable of exercising. [84].

Effortless Exercise: An Alternative Solution

A number of clinical studies on a novel effortless fitness technology from London University, have delineated a reduction in both visceral and overall fat, demonstrating improved hormonal regulation, and a reversal of the diabetic status into either the realm of prediabetes or normalcy [85, 86, 87, 88]. A more recent clinical study on diabetics with hyperphagia reports hunger suppression as a result of an optimal inverse relationship of leptin increase and ghrelin decrease [89]. The current research examined levels of pre and post T3 and C-reactive Protein (CRP), as well as pre and post fasting and postprandial (PP) insulin and glucose levels in the blood samples of forty one diabetic and prediabetic subjects. The study also measured the potential of the treatment attaining an optimal inverse relationship between triglycerides and HDL. The goal of the study was to offer diabetics the benefit of enhanced fitness and weight control while overcoming the general resistance to exercise.

Methodology:

We adopted the same London University invention described in previous chapters that was developed over a period of 27 years. The technology boards were patented in the early 80s when the empirical studies started. The output is based on the proprietary formula that synthesizes, and regulates the complex waveforms which generate the sensation of a multi-exercise regimen, experienced as fast paced or slow/resistance physical training. The voltage driven apparatus consists of multiple connections between the eight boards that are made by hand to synthesize and regulate the unlimited resolution complex waveforms that are composed out of four thousand frequencies, which together form square waveforms each having a specific resultant frequency that ranges from 55Hz to 888Hz. At a resistance of 500 Ω the maximus voltage is 15V, increasing to 25V at 2000 Ω, and 50V at 10K Ω. Any current generated by the voltage, based on Ohm's law, is minuscule and cannot be directly measured. The technology

is classified as IEC class I according to IEC60601-1 standard, and it is used with 3-pin din and 4-pin din IEC 60601-1 compliant cables and silver threaded self-adhesive pads that have been awarded their own FDA clearance. The technology has a CE marketing directive of Class I, with electromagnetic compatibility regulations applied standards EN50081-1, and EN50082-1. It complies with the EEC UK directive of electrical equipment safety applied standard EN 60601-1. The general design of this technology has had no known side effects since 1994 when different versions of this technology were first adopted in furthering research or to be utilized in various clinical practices. The only contraindication, according to the FDA, is having an implanted device like a pacemaker. The main caution is pregnancy. All major medical and mental disorders require clearance by the patient's physician. Adverse reactions are limited to temporary skin redness from the gel pads, that occurs sporadically and usually dissipates within a few hours. Earlier versions of this technology based on the same electronic design have FDA clearance numbers K132158 and K132179.

Measuring instruments included: 1) a blood test that measured Free T3, CRP, triglycerides, HDL, fasting and PP glucose and insulin levels; 2) a conductance scale that calculated weight, BMI, overall fat, visceral fat, and skeletal muscle mass (SMM). 3) Sonography reports of 11 diabetic subjects diagnosed with non-alcoholic steatosis. 4) Tape measurements of the upper and lower abdomen, and the umbilicus.

Procedure

A total of 21 Diabetic and 20 Prediabetic obese individuals (total 41 subjects), 15-82 years of age, with an average BMI of 36.9 consented to release their records. These included eleven diabetic females, ten diabetic males, ten prediabetic females and ten diabetic males. Eleven diabetic subjects, nine females and two males were also diagnosed with fatty liver on their sonography reports. All subjects had completed 20 treatments with the London University technology before the study commenced. Since the study was based on the chart results of all participants, there was no subject attrition. The current research project fulfils the double blind standards, since neither the subjects nor the operators of the technology knew at the time of the treatments' administration that these results were going to be used in a clinical trial. The subjects

were made aware of this clinical research only after they had competed all 20 treatments and were asked to sign a consent form. Subjects were randomly selected out of four different clinics on the basis of the following inclusion and exclusion criteria: Inclusion:

1) Overweight or obese;
2) BMI > 29;
3) Age above 12 years old;
4) At least three months after a surgery procedure;
5) At least three months after childbirth;
6) Diabetes;
7) Prediabetes;
8) Had completed 20 treatments with the London University Technology;
9) Had received the treatment at least twice or three times weekly.

Exclusion:

1) Pregnancy or trying to get pregnant;
2) An implanted device like a cardiac pacemaker;
3) Severe medical condition other than Diabetes or Prediabetes;
4) Hepatic cirrhosis;
5) Renal failure;
6) Surgery or childbirth less than three months prior to treatment;
7) Cancer;
8) Hernia;
9) Other severe medical or mental condition;
10) Had not received any additional treatments with lasers, radiofrequency, any other slimming devices or electrical muscle stimulators.

Inclusion and exclusion criteria were verified by a certified physician in each of the four clinics. As part of each clinic's general policy, a physician was routinely available during the entire duration of the twenty treatment packages, to ensure the

comfort and safety of the participants. All subjects reportedly underwent the treatment with no adverse reactions or side effects.

Every precaution was taken to protect the subjects' privacy and the confidentiality of their personal information. Subjects were informed that they had the right to discontinue treatment at any time. Subjects were not in a dependent relationship with the technology operators, the lab and measurement technicians, or the authors. The subjects were given some general diet instructions like increasing their vegetables, lean protein, and fruit intake, while reducing sugar and oily foods. However, there was no structured measure of calculating daily caloric intake or the veracity of their statements regarding their eating habits. Subjects were instructed to continue taking their prescribed medications and follow the guidance and recommendations of the physician in charge of their medical status. Subjects were specifically told that the treatment they were receiving was intended as a weight loss/ fitness enhancement to potentially jump start a healthier lifestyle, and it was not meant to replace exercise or treat their diabetic condition. None of the subjects had a history of exercising or an active lifestyle, or was engaged in a regular exercise regimen.

Four independent labs with no personal interest in the direction of the results, one from each of the four participating clinics, were assigned to take blood samples before and after the completion of twenty, one-hour treatments that took place two to three times weekly, for a total of seven to eight weeks. Subjects were asked to fast for twelve hours prior to their blood tests. The conductance scale measurements were performed by technicians who obtained a printout of the results which were included in the chart and were subsequently used in the study. Eleven subjects offered their sonography results before and after the twenty treatments, but without releasing the full sonography report. Only 27 out of the 41 subjects had measurements from the same conductance scale for BMI, Overall Fat, Visceral Adipose Tissue (VAT) and Skeletal Muscle Mass (SMM). Only twenty of the subjects offered measurements on their Free T3 and CRP levels, ten of which subjects were diabetics and 10 prediabetics.

Following blood tests and measurements, each subject went to a private treatment room, and lay on a massage table, where the self-adhesive silver-threaded gel pads and silver plated microphone cables from the 16 channels of the electronic apparatus were attached onto his / her body by the operator. The cables from ten of the channels were attached onto the gel pads of the buttocks and the abdomen, and the cables from the six remaining channels were attached onto the gel pads placed along the lymphatic system pathways of the legs and arms. According to each clinics policy, the technology operator constantly checked if the subject was comfortable during the entire procedure. We only retrieved data form 30 subjects' tape measurements which were taken after before the first treatment and after the 12th treatment. No measurements were consistently obtained by the clinics after the 12th treatment. Therefore the number of subjects reported for this variable are 30 and the number of centimetres lost is after 12 treatments and not 20 treatments.

All subjects gave a detailed report of their subjective experience during and after the treatments, when their overall health status was reassessed. The procedure was in accordance with the ethical standards and principles for medical research involving human subjects.

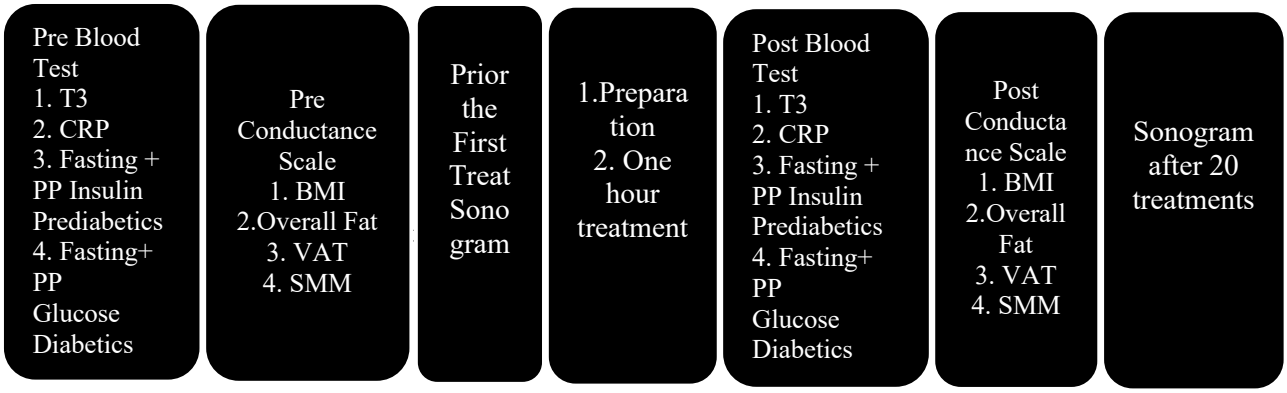

Figure 1. A graphic representations of the pre and post treatment variables and procedure before and after 20 treatments.

Results:

Statistical analysis was based on a repeated measures design where subjects' after treatment results were compared to their baseline. Table 1 displays the results of the twenty one diabetic subjects on pre and post treatment fasting glucose and postprandial

(PP) blood glucose levels. Both fasting and postprandial glucose levels decreased in 100% of the subjects in an average percentage that reached -38.44% decrease for fasting glucose, and -39.1% for postprandial glucose.

Table 2 displays the results of the twenty prediabetic subjects on pre and post treatment fasting insulin and postprandial (PP) insulin levels. Both fasting and postprandial insulin levels decreased in 100% of the subjects in an average percentage decrease that reached -54.53% for fasting insulin, and -44.7% for postprandial insulin.

Table 1. TYPE 2 DIABETICS (N=21; Tx=20)
Pre and Post Treatment Results on Blood Glucose (Fasting and PP)

Fasting Blood Glucose: Normal <100 mg/dL; Prediabetes = 100 - 125 mg/dL; Diabetes >126 mg/dL
Blood Glucose Postprandial (PP): Normal < 140 mg/dL; Prediabetes = 140 - 199 mg/dL; Diabetes > 199 mg/dL

S	G	A	Medical Diagnosis Post Tx	Blood Glucose Fasting mg./dL Pre Tx	Blood Glucose Fasting mg/dL Post Tx	Blood Glucose Normal <100 mg/dL Post Tx	Blood Glucose PP mg/dL Pre Tx	Blood Glucose PP mg/dL Post Tx	Blood Glucose PP Normal < 140 mg/dL Post Tx
1	F	45	Diabetes Fatty liver	178	104	Prediabetic	260	185	Prediabetic
2	M	69	Diabetes	209	108	Prediabetic	230	125	Normal
3	M	46	Diabetes	131.7	99.15	Normal	290	183.2	Prediabetic
4	F	50	Diabetes	177	106	Prediabetic	221	176	Prediabetic
5	F	49	Diabetes Fatty Liver	192	102	Prediabetic	248	175	Prediabetic
6	F	48	Diabetes Fatty Liver	189	115	Prediabetic	224	163	Prediabetic
7	M	44	Diabetes Fatty Liver	178	109	Prediabetic	196	162	Prediabetic
8	F	45	Diabetes Fatty Liver	186	117	Prediabetic	197	126	Normal
9	F	47	Diabetes Fatty Liver	169	102	Prediabetic	243	178	Prediabetic
10	M	45	Diabetes	135	92	Normal	218	156	Prediabetic
11	M	82	Diabetes	136	87	Normal	191	142	Prediabetic
12	M	46	Diabetes	134	97	Normal	216.3	139	Normal
13	M	59	Diabetes	106.8	82	Normal	199.9	133	Normal
14	F	45	Diabetes Fatty Liver	186	117	Prediabetic	207.5	123	Normal
15	M	59	Diabetes	188	119	Prediabetic	202	133	Prediabetic
16	M	49	Diabetes	141	99	Normal	125.6	144	Prediabetic
17	F	69	Diabetes Fatty Liver	136	87	Normal	231.4	131	Normal
18	F	53	Diabetes	190	108.5	Prediabetic	212	118	Normal
19	F	68	Diabetes Fatty Liver	176	92	Normal	209.8	98	Normal
20	F	61	Diabetes Fatty Liver	157.5	98.5	Normal	204	103	Normal
21	M	55	Diabetes Fatty Liver	194	107	Prediabetic	231	138	Normal
			Total	3490	2148..15		4557.5	3031.2	
			Average	166.19	**102.29**	**Normal**	237.02	**144.34**	**Normal**

Percentage Of Blood Glucose Decrease	Blood Fasting Glucose % Decrease	-38.44%	Blood PP Glucose % Decrease -39.1%

Table 1. 57% of Diabetics reached Prediabetic levels on Blood Fasting Glucose. 43% of them reached normal levels on Blood Fasting Glucose. 52% of Diabetics reached Prediabetic levels on Blood PP Glucose. 48% of them reached normal levels on Blood PP Glucose.

Table 3 offers the results of the and pre and post sonography reports on the eleven diabetic subjects' fatty liver that indicates no fatty liver after the 20 treatments.

Table 2 PREDIABETICS (N=20; Tx=20)
Pre and Post Treatment Results on Insulin (Fasting and PP)

Insulin Fasting: Normal < 25 mIU/ml Insulin Postprandial (PP): Normal <75

S	G	A	Medical Diagnosis Pre Tx	Insulin Fasting mIU/ml Pre Tx	Insulin Fasting mIU/ml Post Tx	Insulin Fasting Normal < 25 mIU/ml Post Tx	Insulin PP mIU/ml Pre Tx	Insulin PP mIU/ml Post Tx	Insulin PP Normal <75 mIU/ml Post Tx
1	F	43	Prediabetes	72	15.7	Normal	174.3	73.9	Normal
2	F	27	Prediabetes	25.8	8.7	Normal	136	74	Normal
3	F	63	Prediabetes	105	12.27	Normal	150	76.2	Normal
4	F	24	Prediabetes	34	21	Normal	139.9	71.8	Normal
5	F	30	Prediabetes	27.4	18.5	Normal	241	24.6	Normal
6	M	15	Prediabetes	29	10.9	Normal	136.6	74.8	Normal
7	M	58	Prediabetes	50.4	24	Normal	246	68.4	Normal
8	M	46	Prediabetes	25.56	12.56	Normal	68.8	23.5	Normal
9	F	39	Prediabetes	48	24.9	Normal	69.7	72	Normal
10	M	40	Prediabetes	22.2	11.8	Normal	127.2	73.4	Normal
11	M	53	Prediabetes	23.8	14.6	Normal	102.8	96.8	Prediabetes
12	M	39	Prediabetes	19.5	14.6	Normal	103.9	68.8	Normal
13	M	31	Prediabetes	43.5	22.8	Normal	116.3	73.4	Normal
14	F	33	Prediabetes	41.9	18.6	Normal	109.3	68.4	Normal
15	M	49	Prediabetes	53.7	24.8	Normal	126.4	73.8	Normal
16	M	69	Prediabetes	35.8	27.4	Prediabetic	112.4	83.74	Prediabetic
17	M	53	Prediabetes	42.7	23.12	Normal	93.4	71.6	Normal
18	F	68	Prediabetes	53.6	28.9	Prediabetic	77.2	70.65	Normal
19	F	49	Prediabetes	42.8	23.4	Normal	81.4	72.5	Normal
20	F	52	Prediabetes	39.8	21.7	Normal	76.8	64.3	Normal
			Total	836.46	380.25		2489.4	1376.59	
			Average	**41.823**	**19.02**	**Normal**	**124.47**	**68.83**	**Normal**
			Percentage Of Insulin Decrease	Fasting Insulin % Decrease	**-54.52%**		Insulin PP % Decrease	**-44.7%**	

Table 2. 90% of Prediabetics reached normal levels on Blood Fasting Insulin. 10% of them improved but remained within the prediabetic statues. 90% of prediabetics reached normal levels on Blood PP Insulin. 10% of them improved but remained within the prediabetic level.

Additionally, table 3 displays the results on the triglycerides and HDL levels of all twenty one diabetic subjects. All diabetic subjects (100% of diabetics) evidenced an average of -28.56% decrease in triglycerides and an average of +49.12% increase in

HDL. Table 4 depicts the results on the triglycerides and HDL levels of the twenty prediabetic subjects. All prediabetic subjects' triglycerides (100% of the prediabetics) indicated a reduction in triglycerides at an average of -22.88% from what it used to be previously, and an average increase of +30.34% in blood plasma HDL.

Table 3. Diabetes: Pre and Post Treatment Results on Fatty Liver Sonography Reports, Triglycerides and High Density Lipoprotein (HDL) ((N=21; Tx=20)

Triglycerides Normal Range: > 150 mg/dL;
High-Density Lipoprotein (HDL) Normal Range: Men >60 mg/dL; Women >60 mg/dL
High-Density Lipoprotein (HDL) At Risk: Men: < 40 mg/dL; Women < 50 mg/dL

G	A	Medical Diagnosis Pre Tx Fatty Liver Sonography Report Pre Tx	Sonography Report Post Post Tx	Triglycerides mg/dL Pre Tx	Triglycerides mg/dL Post Tx	Triglycerides mg/dL Decrease Post Tx	HDL mg/dL Pre Tx	HDL mg/dL Post Tx	(HDL) mg/d Increase Post Tx
F	45	Diabetes Fatty liver	No fatty liver	203	158	Improved	32	39	Improved
F	46	Diabetes Fatty Liver	No fatty liver	287	176	Improved	32	39	Improved
F	48	Diabetes Fatty Liver	No fatty liver	266	147	Normal	29	41	Improved
M	44	Diabetes Fatty Liver	No fatty liver	283	189	Improved	30	35	Improved
F	45	Diabetes Fatty Liver	No fatty liver	225	179	Improved	33	40	Improved
F	47	Diabetes Fatty Liver	No fatty liver	237	188	Improved	31	41	Improved
F	45	Diabetes Fatty Liver	No fatty liver	228	134	Normal	34	58	Normal
F	45	Diabetes Fatty Liver	No fatty liver	214	138	Normal	28	51	Normal
F	68	Diabetes Fatty Liver	No fatty liver	198	122	Normal	31	59	Normal
F	61	Diabetes Fatty Liver	No fatty liver	219	112	Normal	28	52	Normal
M	55	Diabetes Fatty Liver	No fatty liver	223	106	Normal	24	66	Normal
M	69	Diabetes		215	158	Normal	35	47	Improved
M	46	Diabetes		230	176	Improved	28	37	Improved
F	52	Diabetes		196.7	147	Normal	47.6	53	Normal
F	49	Diabetes		193	189	Normal	34.5	38	Improved
M	45	Diabetes		212	179	Normal	41	45	Improved
M	72	Diabetes		197	188	Normal	26	38	Improved
M	59	Diabetes		202	134	Normal	31	62	Normal
M	49	Diabetes		197	138	Normal	44	71	Normal
M	57	Diabetes		192	122	Normal	37	61	Normal
M	55	Diabetes		199	112	Normal	42	68	Normal
			Total	4616.7	3298		698.1	1041	
			Average	219.84	157.04	Improved	33.24	49.57	Improved
				% Of Triglycerides Decrease	-28.56%		% of HDL Increase	49.12%	

Table 3. 100% of the diabetic subjects with fatty liver prior to the 20 treatments, showed no fatty liver on sonography reports post treatments. 71% of diabetics indicated normal level of triglycerides after

20 treatments. 29% of diabetics manifested a decrease in triglycerides which remained in the abnormal range. 45% of diabetics indicated normal levels of HDL. 55% of diabetics manifested an increase in HDL which, however, remained within the 'at risk' range.

Table 5 gives the results of the pre and post blood levels of Free T3 and C Reactive Protein of ten diabetic and 10 prediabetic subjects. All diabetic and prediabetic subjects (100% of diabetics and 100% of prediabetics) demonstrated an average increase of 40.78% in Free T3 levels, and an average decrease of -37.88% in blood CRP.

Table 4. Prediabetics: Pre and Post Treatment Results on Triglycerides, High-Density Protein (HDL) (N=20; Tx=20)

Triglycerides Normal Range: > 150 mg/dL;
High-Density Lipoprotein (HDL) Normal Range: Men >60 mg/dL; Women >60 mg/dL
High-Density Lipoprotein (HDL) At Risk: Men: < 40 mg/dL; Women < 50 mg/dL

S	G	Age	Medical Diagnosis Pre Tx	Triglycerides mg/dL Pre Tx	Triglycerides mg/dL Post Tx	Triglycerides mg/dL decrease After 20 Tx Treatments	HDL mg/dL Pre	HDL mg/dL Post	HDL mg/dL Increase After 20 Tx
1	F	43	Prediabetes	294	197	Improved	36	42	At risk
2	F	27	Prediabetes	192	126	Normal	36	48	At risk
3	F	63	Prediabetes	155	117	Normal	45	47	At risk
4	F	24	Prediabetes	88	86	Normal	45	52	Normal
5	F	30	Prediabetes	156	124	Normal	37	46	At risk
6	M	15	Prediabetes	187	132	Normal	36	42	Normal
7	M	58	Prediabetes	141	136	Normal	39.1	46.8	Normal
8	M	46	Prediabetes	262	158	Improved	34.3	56	Normal
9	F	24	Prediabetes	186	148	Normal	41	58	Normal
10	M	40	Prediabetes	178	137.6	Normal	34.8	45.4	Normal
11	M	50	Prediabetes	169	142.8	Normal	34.7	43.0	Normal
12	M	39	Prediabetes	172	139.2	Normal	29.6	48.8	Normal
13	M	31	Prediabetes	159	122.4	Normal	26.6	53.4	Normal
14	F	33	Prediabetes	163.6	134.8	Normal	39.3	67.2	Normal
15	M	49	Prediabetes	158.9	128.3	Normal	34.7	53.1	Normal
16	M	69	Prediabetes	184.6	148.9	Normal	29.4	54	Normal
17	M	53	Prediabetes	176	146.8	Normal	39.2	51.6	Normal
18	F	68	Prediabetes	154.7	129.6	Normal	47.2	58.5	Normal
19	F	49	Prediabetes	154.6	121.7	Normal	47.4	52.5	Normal
20	F	52	Prediabetes	189	138.5	Normal	46.2	57.9	Normal
			Total	3520.4	2714.6		785.5	1023.2	
			Average	176.02 High	135.73 Normal		39.25 Low	51.16 Normal	
			Average Decrease In Triglycerides		-22.88	Average Increase In HDL		30.34	

Table 4. 90% of prediabetics indicated normal level of triglycerides after 20 treatments. 10% of prediabetics manifested a decrease in triglycerides which however remained within the abnormal range. 80% of prediabetics indicated normal levels of HDL after 20 treatments. 20% of prediabetics manifested an increase in HDL which however, remained within the 'at risk' range.

Table 6 gives the results on the pre and post BMI, overall fat, visceral fat and skeletal muscle mass (SMM) of twenty seven out of the 41 subjects that were measured with the same conductance scale.

Table 5. Free T3 (triiodothyronine) and CRP (C-Reactive Protein) (N=18; 20Tx)									
Free T3 Normal Range: 2:30-4.20 pg/mL. CRP Normal Range <1 mg/dL (G: Gender; A: Age**)**									
Subject # Table 1 Diabetes	G	A	Medical Condition Pre Tx	Free T3 Pre Tx pg/mL	Free T3 Post Tx pg/mL	Free T3 Normal Range pg/mL	CRP Pre Tx mg/dL	CRP Post Tx mg/dL	Normal Range mg/dL
12	M	46	Diabetes	1.99	2.69	2.30-4.20	1.45	1.05	<1.00
13	M	59	Diabetes	1.92	2.78	2.30-4.20	1.29	1.08	<1.00
14	F	45	Diabetes Fatty Liver	2.12	2.55	2.30-4.20	2.51	1.25	<1.00
15	M	59	Diabetes	1.97	2.62	2.30-4.20	1.83	0.96	<1.00
16	M	49	Diabetes	1.18	2.29	2.30-4.20	1.13	0.91	<1.00
17	F	69	Diabetes Fatty Liver	1.43	2.42	2.30-4.20	1.67	1.01	<1.00
18	F	53	Diabetes	1.63	2.15	2.30-4.20	1.09	0.86	<1.00
19	F	68	Diabetes Fatty Liver	1.93	2.88	2.30-4.20	1.18	0.84	<1.00
20	F	61	Diabetes Fatty Liver	2.23	2.37	2.30-4.20	1.94	0.95	<1.00
21	M	55	Diabetes	1.47	2.26	2.30-4.20	2.23	1.03	<1.00
Subject # from Table 2 Prediabetes									
14	F	33	Prediabetes	2.25	2.77	2.30-4.20	1.09	0.76	<1.00
15	M	49	Prediabetes	2.22	2.58	2.30-4.20	1.59	1.05	<1.00
16	M	69	Prediabetes	1.68	2.51	2.30-4.20	1.19	1.02	<1.00
17	M	53	Prediabetes	1.99	2.89	2.30-4.20	2.42	1.25	<1.00
18	F	68	Prediabetes	1.28	2.25	2.30-4.20	1.98	0.99	<1.00
19	F	49	Prediabetes	1.43	2.36	2.30-4.20	1.52	1.14	<1.00
20	F	52	Prediabetes	1.53	2.14	2.30-4.20	1.75	1.03	<1.00
14	F	33	Prediabetes	1.97	2.78	2.30-4.20	1.08	0.89	<1.00
				32.22	45.29		28.94	18.07	
Average Free T3 Pre & Post				**1.79** Pre Tx **Below Normal**	**2.52** Post Tx **Normal Post Tx**	**Average CRP Pre & Post Tx**	**1.61 BELOW Normal PreTx**	**1.00**	
Free T3 Percentage Increase					**+40.78%**	**Average CRP Percentage Decrease**		**-37.88%**	

Table 5. 84% of diabetic and prediabetic subjects with previously abnormal levels of T3, demonstrated an optimum <u>increase</u> of T3 levels within the normal range. 16% of diabetic and prediabetic subjects with previously abnormal levels of T3, demonstrated an optimum <u>increase</u> of T3 levels which however, did not reach the normal range. 45% of diabetic and prediabetic subjects with previously abnormal levels of CRP, demonstrated an optimum <u>decrease</u> of CRP levels within the normal rang. 55% of diabetic and prediabetic subjects with previously abnormal levels of CRP,

demonstrated an optimum decrease of CRP levels, which however did not ascend into the normal range.

Table 7 depicts the measurement results on the upper and lower abdomen and the umbilicus in centimetres (cm), before and after the 12 treatments. Subjects lost an average of 9.65cm off the upper abdomen, 10.2 cm off the umbilicus, and 11.5 cm off the lower abdomen.

Table 6 Pre and Post Treatment Results on BMI, Overall Fat, Visceral Fat, and Skeletal Muscle Mass (SMM)

S #	G	A	Medical Condition	BMI Pre Tx	BMI Post Tx	Overall Fat Pre Tx	Overall Fat Post Tx	Visceral Fat Pre Tx	Visceral Fat Post Tx	SMM Pre Tx	SMM Post Tx
1	F	46	Diabetes Fatty Liver	39.2	36.2	44.6	36.8	35	24.8	22.1	29.4
2	F	48	Diabetes Fatty Liver	41.2	38.5	42.9	33.5	33	29	23.8	29.7
3	M	44	Diabetes Fatty Liver	42.6	38.2	34.9	24.6	29	26	34.5	47.3
4	F	48	Diabetes Fatty Liver	32.0	30.1	42.9	33.5	29	24	23.8	31.8
5	F	45	Diabetes Fatty Liver	29.1	25.1	34	28.7	31	27	20.7	26.3
6	F	24	Prediabetes	29.3	25.0	34.7	33	9.5	5	21.8	24.2
7	M	40	Prediabetes	33.7	25.1	33.0	13.4	21	13.4	28.8	31.2
8	M	39	Prediabetes	36.2	32.0	41.1	37.4	18	14.5	36	38.9
9	M	31	Prediabetes	43.8	39.1	37.6	34.6	30	25	25.2	27.4
10	M	46	Diabetes	39.2	24.6	42.3	25.6	24.7	10.8	28.9	39.4
11	M	59	Diabetes	36.5	28.9	37.9	31.6	32.3	16.4	26	41
12	F	45	Diabetes Fatty Liver	41.3	27.4	43.8	22.7	39.5	19.4	23.8	38.5
13	M	59	Diabetes	34.2	24.8	36.9	25.8	35.4	22.8	28.9	41.2
14	M	49	Diabetes	37.4	29.5	41.3	22.5	29.3	18.3	35.7	42.6
15	F	69	Diabetes Fatty Liver	42.6	36.8	44.2	37.9	34.6	31.7	27.9	33.2
16	F	53	Diabetes	33.5	25.1	30.1	25.7	38.2	30.1	32.4	39.9
17	F	68	Diabetes Fatty Liver	40.7	30.1	42.3	39.8	37.4	33.8	30.2	39.7
18	F	61	Diabetes Fatty Liver	34.2	25.3	36.7	33.2	38	36.1	23.8	28.6
19	M	55	Diabetes	36.7	26.4	38.7	29.6	33.5	23.2	27.9	39.4
20	F	33	Prediabetes	36.8	22.5	39.2	21.3	25.3	9.4	32.5	43.2
21	M	49	Prediabetes	35.9	24.6	39.4	18.4	24.3	8.5	35.4	48.3
22	M	69	Prediabetes	38.2	33.7	39.6	31.5	28.3	24.6	31.4	37.8
23	M	53	Prediabetes	37.2	30.3	40.2	29.3	36.2	30.6	29.3	36.7
24	F	68	Prediabetes	35.7	29.4	33.6	31.4	37.3	32.9	30.8	34.2
25	F	49	Prediabetes	35.3	24.5	37.4	21.5	27.6	10.8	38.9	47.2
26	F	52	Prediabetes	36.1	29.6	36.5	28.3	29.7	25.3	37.5	41.3
27	F	37	Prediabetes	39.2	23.9	47.3	24.1	28.4	12.3	24.6	42.8
28	M	46	Diabetes	40.2	24.4	51.3	29.3	32.1	16.3	23.1	40.8
29	M	59	Diabetes	43.2	24.7	56.2	33.4	37.4	21.9	25.4	52.5
30	F	45	Diabetes Fatty Liver	31.8	21.3	45.3	23.4	33.2	15.4	27.4	53.1
31	M	59	Diabetes	34.5	22.9	38.4	19.3	36.2	20.2	28.9	55.4
32	M	49	Diabetes	32.6	21.9	36.7	20.3	29.8	24.3	24.5	39.4

33	F	69	Diabetes Fatty Liver	35.4	27.3	38.5	30.2	38.6	29.8	19.4	34.2
34	F	53	Diabetes	32.1	24.3	35.2	22.6	36.7	23.9	24.8	42.9
35	F	68	Diabetes Fatty Liver	29.4	24.7	29.6	25.3	32.8	22.1	26.3	45.2
36	F	61	Diabetes Fatty Liver	28.4	23.5	29.2	22.8	38.2	23.4	27.5	46.1
37	M	55	Diabetes	29.7	22.9	32.6	24.8	34.9	21.8	29.9	55.1
38	F	33	Prediabetes	34.1	17.3	36.2	19.6	29.4	15.3	31.9	62.3
39	M	49	Prediabetes	33.6	19.7	37.4	20.4	31.7	21.1	29.6	52.9
40	M	69	Prediabetes	27.6	21.9	28.3	23.5	34.2	23.8	28.8	49.9
41	M	53	Prediabetes	31.8	24.9	31.5	25.8	36.2	26.9	31.9	51.6
Total				1423	1116	1573.4	1106.9	1293.53	888.85	1168.4	1694.3
Mean Average				35.58	27.08	38.5	27.22	301.63	28.34	28.98	41.03
Mean Overall BMI Decrease: -23.46%					Mean Average Overall Fat Decrease % -23.8%		Mean Visceral Fat Decrease % -29.3%		Mean SMM % Increase 41.6%		

Table 6. Overall mean average decrease of BMI was -23%. Mean average decrease of Overall Fat was -23.8%. Mean average decrease of Visceral Fat was -29.3%. Mean average Skeletal Muss increase (SMM) was 41.6%. Age appeared to be a significant variable affecting both visceral and overall fat loss and fitness enhancement as noted by skeletal muscle increase. Younger individuals consistently demonstrated far greater fat loss and muscle building results than older individuals

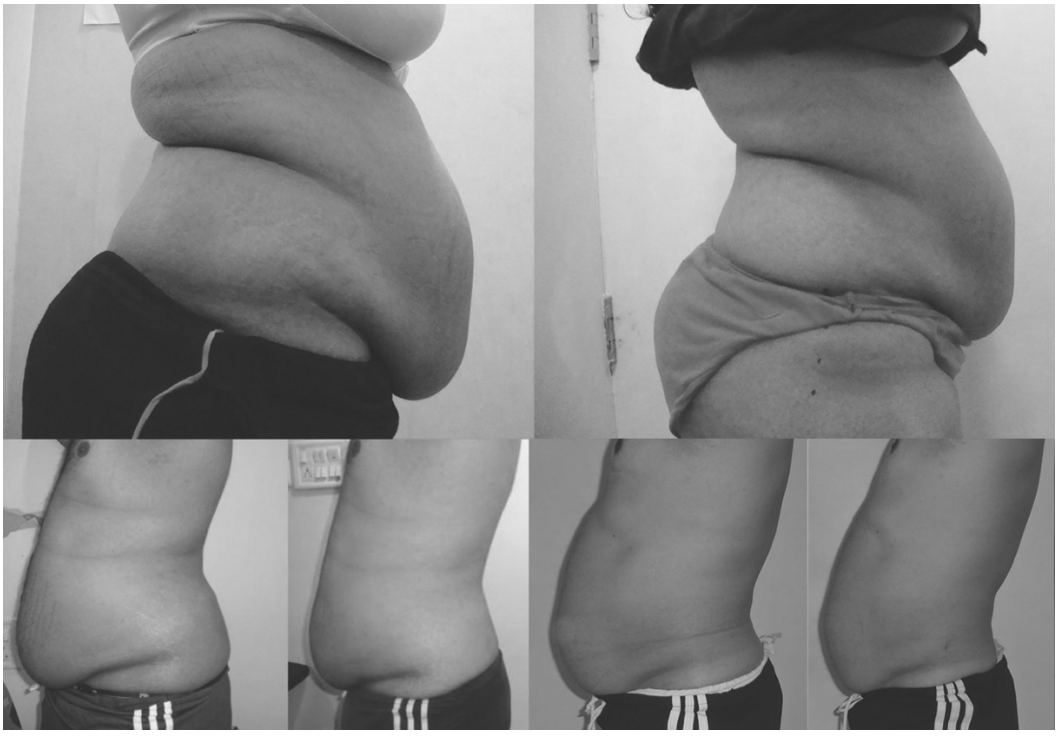

Figure 2. Before (left) and after (right) of three subjects who consented to release their photos.

The cm loss around the lower abdomen that usually accumulates visceral adipose tissue appears consistent with the visceral fat reduction results. The cm loss was disproportionally higher than the kgs lost (Table 2), suggesting that overall fat may

have been replaced by skeletal muscle mass; a hypothesis supported by the results of the significantly increased skeletal muscle mass (SMM) on Table 1. The results of the upper and lower abdomen reduction in cm were analysed by the one-way ANOVA for repeated measures, and were highly statistically significant with a standard deviation of 18.43043, an F value of F= 43.37643, and a p-value of p< 0.00001. The results of the umbilicus reduction in cm and weight loss in kgs were also analysed by the one-way ANOVA for repeated measures, and were highly statistically significant with a standard deviation of 22.4058, an F value of F=108.22199, and a p-value of p< 0.00001.

Table 7. Tape Measurements in cm. Upper (upper abdomen); Middle (umbilicus); Lower (lower abdomen) (N=30; Tx=12)

G	A	Medical Condition	Upper cm Pre Tx	Upper cm Post Tx	Total cm lost	Middle cm Pre Tx	Middle cm Post Tx	Total cm lost	Lower cm Pre Tx	Lower cm Post Tx	Total cm lost
F	45	Diabetes	108	98	10	111	100	11	115	100	15
M	69	Diabetes	100	94	6	105	98	7	107	100	7
M	46	Diabetes	130	120	10	134	124	10	130	120	10
F	50	Diabetes	109	100	9	118	111	7	128	120	8
F	49	Diabetes	125	112	13	137	123	14	145	129	16
F	46	Diabetes	134	122	12	138	118	20	152	127	25
F	48	Diabetes	137	128	9	136	128	8	138	129	9
M	44	Diabetes	126	120	6	128	121	7	131	124	7
F	45	Diabetes	76	65	11	69	65	4	78	66	12
F	47	Diabetes	81	74	7	69	58	11	77	63	14
M	45	Diabetes	95	88	7	98	90	8	100	92	8
M	82	Diabetes	118	106	12	119	113	6	117	114	3
F	43	Prediabetes	97	82	15	100	88	12	105	94	11
F	27	Prediabetes	96	87	9	103	91	12	114	101	13
F	63	Prediabetes	118	108	10	122	110	12	125	114	11
F	24	Prediabetes	108	90	18	119.5	101	18.5	126	107	19
F	30	Prediabetes	122	109	13	125	113	12	128	112	16
M	15	Prediabetes	114	109	5	117	113	4	116	112	4
M	58	Prediabetes	118	105	13	120	106	14	120	104	16
M	46	Prediabetes	104	96	8	107	98	9	104	98	6
F	24	Prediabetes	95	83	12	98	89	9	105	97	8

M	40	Prediabetes	112	104	8	118	105	13	120	106	14
F	53	Diabetes	91	84	7	92	88	4	97	89	8
M	72	Prediabetes	100	94	6	104	96	8	102	96	6
F	66	Prediabetes	90	84	6	107	97	10	105	101	4
M	50	Prediabetes	103	96	7	101	95	6	99	93	6
M	39	Prediabetes	110	105	5	115	109	6	120	113	7
M	31	Prediabetes	125	108	17	138	115	23	140	123	17
F	65	Prediabetes	118	108	10	122	110	12	125	114	11
F	46	Prediabetes	116	105	11	119	108	9	122	112	10
		Upper Abdomen Average cm loss. Post Tx			9.73cm	Umbilicus Average cm loss Post Tx		10.21cm	Lower Abdomen cm loss. Post Tx		10.7cm

Table 7. The average cm loss from the upper abdomen was 9.65cm; the umbilicus 10.21cm; and the lower abdomen 10.7cm. These abdominal measurements were consistent with the reduced visceral adiposity observed on Table 1.

All variables were analysed with t-tests for dependent means. The significance table of the variables are given on Table 8. Figure 2 displays the before and after photos of three of the subjects who gave consent for the pictures to be released. All subjects reported a subjective experience of what felt like strenuous exercise, which however, was comfortable and effortless.

Table 8 gives the results of t tests on all variables. The pre and post comparison of all variables demonstrated a highly significant statistical difference at the $p<0.00001$ (one in one hundred thousand shall not entertain such result) level, except for the fasting insulin of prediabetics that was significant at the $0<0.0001$ (one in ten thousand) lever, and the PP insulin of prediabetics that was significant at the $p<0.001$ (one in one thousand level).

Table 8. T-test Statistical Significance

	MEAN	*SS/df*	T VALUE	P VALUE	Significance level
Blood Glucose Fasting mg./dL Diabetics Decrease	-63.9	414.64	-14.38	P = 0.00001	P < 0.0001

Blood Glucose PP mg/dL Diabetics Decrease	-72.68	891.07	-11.16	P = 0.00001	P < 0.0001
Insulin Fasting mIU/ml Prediabetes Decrease	-22.8	390.6	-5.16	P = 0.0003	P < 0.001
Insulin PP mIU/ml Prediabetics Decrease	-55.64	3071.35	-4.49	P = 0.00013	P< 0.001
Triglycerides mg/dL Diabetics Decrease	-67.84	1056.27	-9.57	P = 0.00001	P < 0.0001
Triglycerides mg/dL Prediabetics Decrease	-40.29	630.05	-7.18	P = 0.00001	P < 0.0001
Upper Abdomen Reduction in cm	-9.65	244.55	T= -12.029159	P = 0.00001	P < 0.00001
Umbilicus Reduction in cm	-10.32	344.14	T= -10.849653	P = 0.00001	P < 0.00001
Lower Abdomen Reduction in cm	-11.5	553	T= -9.532945	P = 0.00001	P < 0.00001
CRP Decrease	-0.6	0.15	-6.64	P = 0.00001	P < 0.000
BMI Decrease	-7.56	14.72	-10.24	P = 0.00001	P < 0.0001
Overall Fat Decrease	-10.27	43.89	-8.06	P = 0.00001	P < 0.0001
Overall Visceral Fat Decrease	-8.51	30.14	-8.06	P = 0.00001	P < 0.0001
Skeletal Muscle Mass Increase	8.1	18.66	9.74	P = 0.00001	P< 0.00001
HDL mg/dL Prediabetics Increase	13.24	57.92	7.78	P = 0.00001	P < 0.00001
HDL mg/dL Diabetics Increase	16.33	120.72	6.81	P = 0.00001	P < 0.0001
Free T3 Increase	0.73	0.07	12.06	P = 0.00001	P < 0.00001

The Problem with Recommending Exercise: Few Follow

Several physicians treating diabetics recommend exercise and physical activity to either prevent the diabetic condition or avoid further complications via enhancing health and fitness. These recommendations are based on a large body of research. There are numerous problems with this notion, however:

a/ Obesity makes physical training cumbersome.

b/ Diabetic neuropathy increases fragility and resistance to movement.

c/ Clinical studies have demonstrated that certain modes of exercise may induce temporary hyperglycaemia and hyperinsulinemia in diabetics.

Gain Without Pain: T3 and CRP

There is a novel method from London University that offers a solution in between inertia and activity, an effortless exercise technique that can balance some of the diabetic metabolic issues, and jump start a more active lifestyle.

The results of our research achieved external validity of all variables by confirming previous findings. We demonstrated a statistically significant improvement in T3 levels for all subjects (100%). T3 was abnormally low in all subjects. However, after 20 treatments, T3 levels reached normalcy in 84% of the subjects. T3 improved significantly in the remaining 16% of the subjects but it did not reach the normal range. A statistically significant decrease of CRP was evidenced in 100% of the subjects, implying a notable reduction in low grade inflammation. 45% of diabetic and prediabetic subjects with previously abnormal levels of CRP, demonstrated normal CRP levels after the twenty treatments. The remaining 55% of subjects manifested a significant inflammation reduction as noted by decreased CRP levels which, however, did not reach the normal range.

Fasting and PP Glucose and Insulin

Both previously abnormally high fasting and postprandial (PP) glucose decreased considerably in all 21 diabetic subjects (100%). Nine of the diabetic subjects (43%) manifested normal fasting glucose levels after 20 treatments, while the fasting glucose of the remaining twelve diabetic subjects (57%) dropped down to the prediabetic level. Ten of the diabetic subjects (48%) manifested normal PP insulin levels, while the PP insulin of the remaining eleven diabetic subjects (52%) dropped to the prediabetic level after the 20 treatments. Prediabetics had more robust results as expected by their average younger age and baseline healthier status. Eighteen of prediabetics (90%)

manifested both normal fasting and PP insulin levels after the 20 treatments, while the fasting and PP insulin of the remaining two subjects (10%) remained within the prediabetic level.

Triglycerides and HDL

Triglycerides decreased in all 21 diabetic subjects (100%) juxtaposed by a consistent elevation in HDL. Despite the statistically significant improvement, the decrease and increase of Triglycerides and HDL respectively, did not reach normalcy for all subjects. Fifteen out of the 21 diabetics with abnormal triglycerides' levels displayed normal levels of triglycerides after twenty treatments (71%). 29% of diabetics manifested a notable decrease in triglycerides which, however, remained within the abnormal range. 45% of these diabetic subjects indicated HDL levels that were within the normal range. 55% manifested an increase in HDL which however, remained within the 'at risk' range.

All prediabetic subjects demonstrated a significant improvement in both triglycerides and HDL levels Eighteen prediabetic subjects 90% manifested normal triglycerides levels and 85% of prediabetics demonstrated HDL levels withing the normal range. 10% of prediabetics' triglycerides and 15% of prediabetic's HDL evidenced a significant improvement that was a little above the normal range.

BMI and cm Loss

BMI evidenced an average reduction of 23.8% in all subjects. Skeletal muscle mass increased by an average of 41.03% in all subjects, while all subjects indicated an overall fat and visceral adipose tissue reduction of an average 23.8% and 29.3% respectively. The visceral fat reduction was substantiated by the sonography reports of eleven diabetic subjects, 100% of which showed no fatty liver after the twenty treatments.

Subjects lost an average of 9.73 cm from the upper abdomen, 10.21 cm from the umbilicus and 10.7 cm from the lower abdomen, after 12 treatments. No consistent measurements were taken after the 12 treatments by the participating clinics. Therefore, this clinical study only included the data collected before and after 12 treatments. The range of cm loss was very wide, depending on the subjects age and severity of medical condition. Some subjects lost around 18cm on all body parts measured, while others lost only 6-7cm on all measurements. Additionally, the subjects' diet was not monitored, therefore eating habits and lifestyle choices may have affected cm loss.

Overall Improvement of the Diabetic Condition

Results indicated a remarkable improvement of the diabetic / prediabetic condition. This improvement was predicted by a large body of literature documenting that enhancing T3 and fitness result in a decrease of dyslipidaemia. A literature search reveals that the deleterious effects of inflammation, marked by abnormally high CRP levels is counteracted by an active lifestyle or effortless exercise that has repeatedly demonstrated a CRP reduction. Several studies using either regular or effortless exercise have displayed a significant decrease in both fasting and PP glucose and insulin. Research has repeatedly shown that a decrease in overall and visceral fat improves the diabetic and prediabetic conditions.

External Validity

Our findings support and validate the results of previous studies that some mode of exercise, effortful or effortless like the technology used, is necessary to enhance the health status of the diabetic and prediabetic conditions. The scope of our study was to offer an intermediate solution that can potentially commence a healthier lifestyle, but without implying or proposing that this novel method is a medical intervention or a conclusive treatment for Diabetes. All patients were instructed to continue taking their medications and remain under their physicians' care. Upon thorough examination of the results, it became apparent that the resistance to attaining normalcy appeared to be contingent to disease severity and age. A higher percentage of prediabetics when

compared to diabetics reached normalcy in all variables. Relatively speaking, diabetics denoted a substantial improvement without reaching the optimal level of health. This suggested the necessity of continuing with a lifestyle that includes fitness attained either by regular or effortless exercise, in conjunction with the medical treatments recommended. To speed up weight loss, a structured nutritional plan may be useful. The sonograph reports evidencing no fatty liver after 20 treatments validated the results of one of the previous studies that used the same London University technology. However, the sample size in previous studies was rather small and did not include magnetic resonance imaging diagnostic methods with a larger number of subjects.

Implications for Optimal Health

The results of this clinical study have significant implications for optimal health that can be enhanced and safeguarded by incorporating this effortless exercise technique as part of an exercise regimen to reduce lipids, blood glucose levels and insulin resistance. Physical training necessary to reduce visceral adiposity, along with its inherent inflammation and oxidative damage, is often experienced as exhausting, and demanding a lengthy commitment of several months to produce a visible body change. Obese diabetics and prediabetics usually resist exercise due to difficulty moving, embarrassment triggered by body image issues, neuropathic pain, fatiguing, discouragement due to prolonged effort with no fast results that is often demoralizing. Adopting the effortless alternative can bring the light at the end of the tunnel, and jumpstart an active lifestyle that will eventually improve their health.

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Conflict of Interest

The author declares that she has no conflict of interest since the study was conducted by independent. No funding was received by a third party or institution.

Ethical Standards

Statement of Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of

1. Ethical Principles for Medical Research involving Human Subjects
2. American Psychological Association (APA)
3. IELLIOS Research department for Development and invention of Innovative Technology

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SECTION 5

Hormonal Balance: The Shield of Health Against COVID-19

High CRP Levels Increase COVID-19 Vulnerability

The overproduction of inflammatory cytokines by the immune system to fight against the COVID-19 pathogen induces an excess synthesis of C-reactive protein (CRP). A simple prediction is that individuals with abnormally high CRP levels will be more susceptible to the virus' induced "cytokine storm," a defensive immune over activity going awry, as incessant white blood cells attack the host's vital organs [1-3]. COVID-19 highest mortality rate is associated with disorders clustered around low grade inflammation such as diabetes, cardiovascular disease (CVD), and respiratory defects that are often linked to obesity, measured by body mass index (BMI), and accumulation of adipose tissue enlarging abdomen circumference [4-8]. Fatalities have increased in up to over 88.1% infected individuals with a BMI>25 [9]. As expected, CRP is proportionally elevated depending on the degree of severity of COVID-19 infection [10, 11]. Liu et al. (2020) reported that CRP > 41.8 mg/L is usually associated with COVID-19 poor prognosis [12]. CRP elevations have been previously linked to post-stroke pneumonia [13].

Why Oestrogen Cannot Offer Full Protection Against COVID-19

Several investigators have hypothesized that oestrogen, which significantly increases during pregnancy, has a protective role in COVID-19 due to its alleged anti-inflammatory properties. This hypothesis involves a series of interactions with the immune system, including B cells that produce antibodies. This premise is supported by mortality rates which are 2.4 times higher in men than women in both COVID-19, and previous manifestations of the acute respiratory syndrome [14-17]. However, a study on 28 infected pregnant females produced no significant differences in COVID-19 severity, hospital stay or recovery time, when compared to 54 non-pregnant women [18]. A survey on 22,000 individuals found that CRP, one of the prominent markers of inflammation, is higher in females than males [19]. Independent research has

confirmed that oestrogen hormone replacement interventions increase CRP levels in healthy women [20-21]. These findings can either be interpreted as a contradiction to research that features CRP as a COVID-19 marker, or as attestation that oestrogen may not be a reliable variable in assessing COVID-19 risk level. Indeed there is evidence that while oestrogens may exert a systemic anti-inflammatory influence, cellular metabolic processes can actually reverse this advantage and enhance a pro-inflammatory action, depending on the complexity of the body's repair mechanisms [22].

Adiposity: Between a Rock and a Hard Place.

A more definitive identifier of COVID-19 susceptibility risk is adipose tissue due to the virus' affinity for the angiotensin-converting enzyme 2 (ACE2) receptors which are abundantly expressed in fat cells, offering open binding invitations to the virus, thus amplifying the probability of infection [23, 24]. Patients with diabetes, renal dysfunction, hypertension, CVD, coronary artery disease and the elderly are often treated with Angiotensin-converting enzyme inhibitors (ACEIs) which lower blood pressure because they suppress the angiotensin-converting enzyme (ACE) from elevating angiotensin II, a vasoconstrictor that increases blood pressure. According to animal studies increased ACE2 receptors, have reportedly manifested a greater vulnerability to COVID-19, followed by exacerbated symptomatology and eventual fatality [25, 26]. So here's the dilemma with ACEIs in the treatment of hypertension, CVD, diabetes and other disorders. ACEIs decrease blood pressure, but increase the chances of COVID-19 infection by increasing ACE2 receptors. So as soon as the high blood pressure problem is solved, the COVID-19 problem arises.

Toxicity Enhances COVID-19 Vulnerability

A recent report that highlights the adverse effects of smoking correlated the COVID-19 higher incidence of male deaths in China with an up to 50% increase in male smokers. These investigators made an early March prediction about a rising number of

Indonesian male smokers contracting the virus, which was validated a few months later, as cases started multiplying in Indonesia to over 1,950,276 by June 14, 2021 [27].

Perhaps the prevalence of the COVID-19 pandemic at a time of elevated environmental toxicity, and increasing rates of obesity up to 26.6% in Asian countries like China, and 50% plus in Western countries is not coincidental [28, 30]. Both subcutaneous and visceral adipose tissue (VAT) are associated with toxicity. Additionally, they both secrete the pro-inflammatory cytokine interleukin-6 (IL-6) in vivo that is closely associated to C reactive protein (CRP) and free fatty acids [31]. Both obesity and high CRP levels are associated with chronic bronchitis. CRP elevated concentrations are also encountered in increased concentrations of triglycerides, high low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL), but have a negative correlation with high density lipoprotein (HDL) [32].

The Proxies of Adiposity: Lipotoxicity, Hyperlipidemia & Elevated Triglycerides, LDL, VLDL

Excess adipose tissue appears to play a critical role in atherosclerosis, a vascular site-specific chronic inflammation, leading to disturbed blood flow as a result of abnormal levels of triglycerides that represent the core components of arterial plaques [33, 34]. Triglycerides are associated with low-grade inflammation. Hyperlipidemia is caused by elevations in the low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) which is the carrier of triglycerides, and is spotlighted as one of the key predictors of atherosclerosis [35, 36, 37, 38]. The blood transports lipids and lipoproteins to the liver, often causing lipotoxicity and insulin resistance [39]. Non-alcoholic (NA) steatosis or fatty liver, one of the consequences of visceral adiposity, is the result of an imbalance between intrahepatic triglycerides' production and export. It often progresses to steatohepatitis, fibrosis, and cirrhosis. Overall, lipotoxicity and inflammation are inherent in both subcutaneous and visceral fat, compromising health [40].

Creatinine and Bilirubin as Markers of COVID-19 Vulnerability

Creatinine is a waste product produced by normal muscular functioning. Cheng et al (2019) reported that 43.9% of admitted COVID-19 patients had proteinuria and creatinine kinase at the high risk level of 2.1 mg/dL (normal range is 0.5-1.1 mg/dL) [41]. Chan et al postulated that creatinine kinase appears to be one of the primary markers of COVID-19 [42]. A review analysis revealed abnormally elevated bilirubin in COVID-19 patients with mild symptomatology that proportionally increased as the COVID-19 pathology intensified [43]. Bilirubin is a waste product composite derived from haemoglobin catabolism. These findings delineate the importance of systemic detoxification in the service of health maintenance.

The Predictive Value of the Position of a Variable Within the Normal Range

Early diagnosis of variables that have risen to the upper end of the normal range, and which are potentially harmful when exacerbated, should be concerning before they climb into abnormality. In preventive interventions the position of a variable within the normal range has a predictive value, urging action before imbalances start engineering the foundation of a medical disorder. Several biological process may aimlessly continue rather than pause after fulfilling their objectives, as in the case of the "cytokine storm" that is initiated with all good intentions to protect the organism but ends up being lethal for COVID-19 patients. There are several examples that support this premise: High HDL, the health-enhancing form of cholesterol, reflects a systemic dysfunction in coronary artery disease (CAD) cases. Angeloni et al. (2013) postulated that cardiovascular disease may deteriorate during increased HDL levels, demonstrating that both endothelial repair and anti-inflammatory processes were significantly compromised at higher HDL levels. They recommended exploring HDL purposeful interactions, rather than merely the amount of HDL concentrations in evaluating the effects of HDL in both CAD and diabetes [44, 45]. More instances are found in cases of hyperinsulinemia that denotes a cellular insensitivity to insulin,

preluding the emergence of type 2 diabetes; and the enigma of hyperleptinemia and hyperphagia in obesity, where excessive levels of the appetite-controlling hormone, leptin, do not exert an orexigenic effect [46-49]. This paradox is based on leptin resistance, reflecting deficient intracellular signalling that fails to carry the leptin signals across the blood-brain barrier (BBB) [50,51]. Creatine promotes muscle strength, yet, in excess it provokes oxidative stress and increases uric acid [52]. A detailed evaluation of bilirubin, otherwise known as a toxic waste product, reviews evidence indicating that optimal bilirubin levels can effectively modulate oxidative stress and inflammation [53].

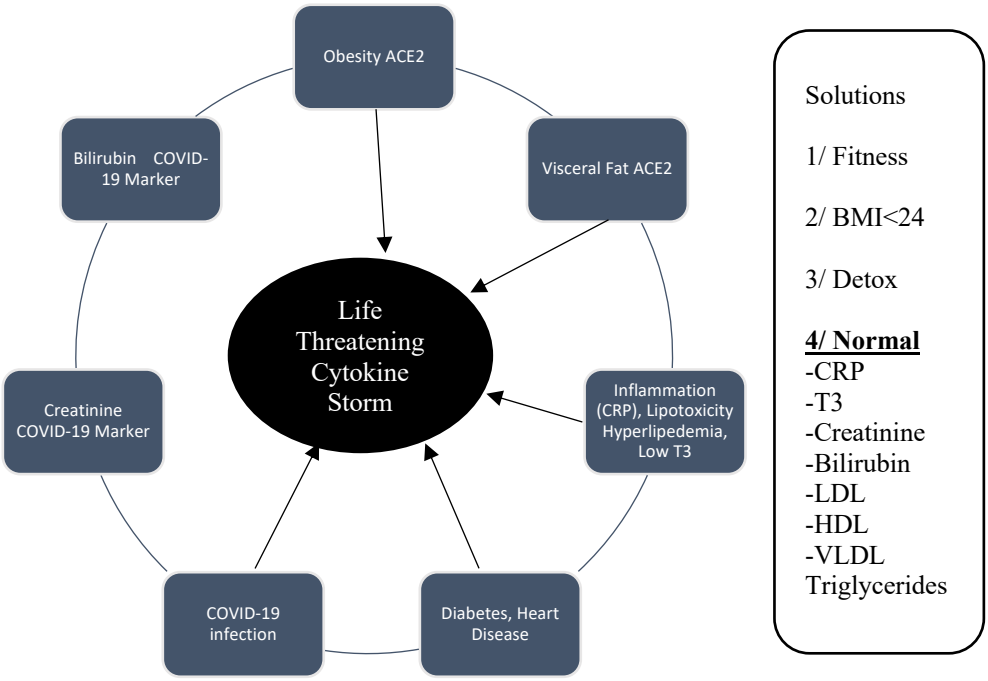

Figure 1. The Solutions to COVID-19 risk factors that increase mortality rates

The Deleterious Effects of Erratic Persistence

In conclusion, persistent processes like the "cytokine storm" that start from the necessary action of cytokines that are essential for the body, can eventually pulverise the organism by persevering erratically after their defensive advantage has been fulfilled. This phenomenon of inertia, where a biological process continues indiscriminately, beyond the completion of its purpose has devastating consequences

for immunity and wellbeing. A balanced profile may turn out to be the most efficient protector against COVID-19. Systemic balance demands a BMI well below 24, reduced visceral fat, and normal range concentrations of CRP, bilirubin, creatinine triglycerides, VLDL and HDL. A graphic representation of these concepts is displayed in Figure 1.

The Golden Mean of Moderation

In moderation, all body mechanisms are useful and purposeful. VLDL represents one of the primary transport mechanisms, carrying triglycerides that serve as an energy source. Adipose tissue stores and regulates metabolic energy playing a crucial role in body homeostasis. It consists of white, beige, and brown fat. White adipocytes serve as an energy bank and have a different ontogenetic origin than the brown and beige fat, which are thermogenic cells, involved in energy expenditure in the form of heat [54]. Oxidation of brown fatty acids is regulated by thyroid hormones, specifically T3, the active metabolite of the prohormone T4. T3 also regulates gene transcription throughout the body, accelerates resting energy expenditure, and is involved in lipolysis [55]. This interrelated process is given graphically in Figure 2.

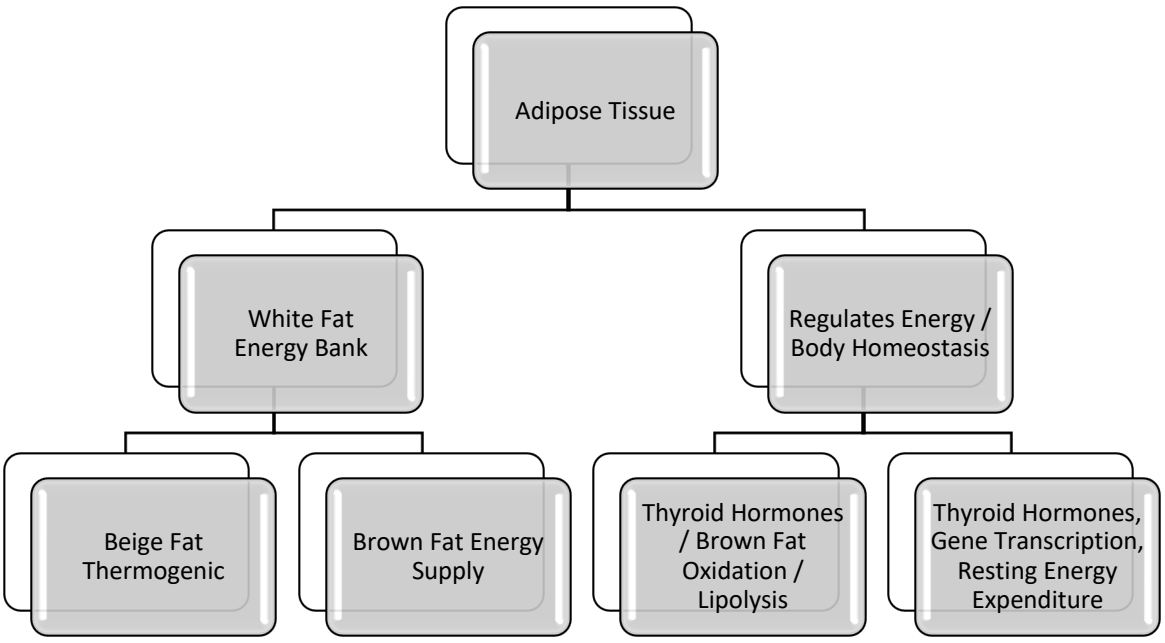

Figure 2. Adipose Tissue Function

Thyroid Dysfunction Empowers COVID-19

Thyroid dysfunction has been recently connected to both COVID-19 [56] and environmental toxicity [57]. Recent research compared 93 COVID-19 positive patients with 101 negative ones in the intensive care unit, and against 53 COVID-19 positive individuals in low intensive care. The intensive care COVID-19 positive patients were mostly men in their sixties, while the other two groups were mostly women in their seventies. The intensive care positive COVID-19 group evidenced significantly more thyrotoxicosis, a hypermetabolic condition reflecting excess thyroid hormones, which was attributed to the immune response against COVID-19. Their free triiodothyronine level (Free T3) was low suggesting a conversion impairment of free thyroxine (T4) to Free T3 [58]. This was interesting because thyrotoxicosis primarily affects 2-3 times more women than men and the majority of the COVID-19 intensive unit patients were males. Despite their gender, they demonstrated the highest incidence of thyroid dysfunction when compared to COVID-19 negative intensive unit patients, and COVID-19 patients with milder symptomatology who were mostly females [59]. It is probably that the body's defensive efforts to increase energy by an overactive thyroid, eventually disturbs hormonal balance provoking further health deterioration.

Thyroid and ACE2 Receptors

There is another, more interesting connection between thyroid and COVID-19, related to the virus' affinity for ACE2 receptors. Zhao et al. [60] reported increased ACE2 lung receptors in one male Asian subject – an unconvincingly small sample. However, more detailed extensive research on 31 human tissues did not identify the lungs as one of the primary organs associated with ACE2 receptors. In fact, they found upraised ACE2 expression in the thyroid, adipose tissue, heart, kidneys, small intestine and the male reproductive gland; and only moderate ACE2 expression in the lungs, colon, bladder, liver and adrenal gland; while muscle, brain, blood vessels and bone marrow had substantially less ACE2 expression than all other organs (Figure 3).

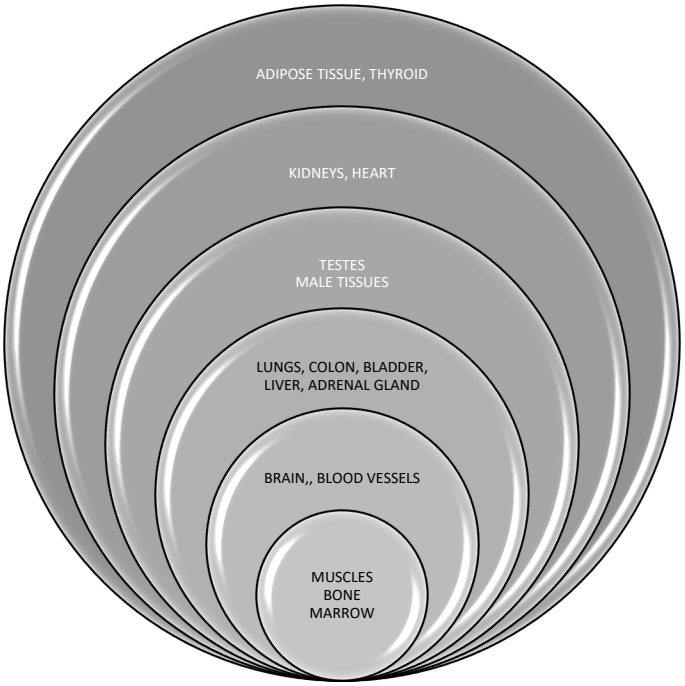

Figure 3. VITAL ORGANS UPRAISED ACE2 RECEPTORS. In order from the vital organs with the highest number of ACE2 receptors to the vital organs with the lowest number of ACE2 receptors. A higher the number of ACE2 receptors increases the COVID-19 entry points and the probability of the body being overwhelmed by the viral infection.

Males vs Females & Aged vs Young

These investigators found no significant differences between the different groups they examined that included males, females, a "younger" group under 45 years and an "older" one over 45 years, with the exception, of course, of the male tissues that may increase COVID-19 susceptibility in men. In other words, all four groups were equally vulnerable to COVID-19, primarily via the abundance of their ACE2 receptors in their adipose tissue, heart, thyroid, etc. However, when the immune responses of the four different groups were analysed, there was evidence of negative correlations between immune processes and ACE2 expression in the "younger" and females groups; while the "older" and male groups showed positive correlations between immune activity and ACE2 expression, manifesting a higher hyperinflammatory "cytokine storm" reaction, selectively increasing mortality rates in the "older" and male groups [61]. The male/female, young/old differential immune responses, along with the identified

multitude of ACE2 receptors in the heart, thyroid, adiposity and male tissues, explains the higher incidence of COVID-19 fatalities among men, older individuals, and obese patients with heart problems and diabetes, who are often diagnosed with a thyroid condition according to a large body of research [62-65].

Cortisol and COVID-19

Few papers associate cortisol directly with COVID-19, however, it appears that increased cortisol decreases survival rates [66]. High cortisol concentrations have been linked to disorders conspicuously featured among COVID-19 fatalities such as diabetes and heart disease [67-69].

Clinical Trial on the COVID-19 Susceptibility Variables

Recent studies that explored a new exercise alternative have reported a substantial decline in cortisol concentrations along with a significant decrease in VLDL, triglycerides, visceral adiposity and ghrelin accompanied by a normal range increase in Free T3, testosterone and leptin [70-72]. Another clinical trial on diabetic and pre-diabetic patients that utilized the same method revealed reductions in both fasting and PP insulin and glucose levels and a significant improvement in hepatic steatosis based on ultrasound imaging reports [73].

The purpose of the current clinical trial was to test whether this effortless exercise method would be effective in reducing Creatinine, Bilirubin, the C reactive Protein (CRP), the very low density lipoprotein (VLDL), Triglycerides and Visceral adipose tissue (VAT), while increasing the high density lipoprotein (HDL) and Free T3 (triiodothyronine). Overall, previous studies that used the same method demonstrated statistically significant reduction of VAT, Cortisol, CRP, VLDL and Triglycerides as well as glucose and insulin levels, while evidencing optimal levels of T3, HDL, Testosterone and a statistically significant increase in muscle mass [74, 75].

Methodology

We adopted the same technology used in the clinical studies cited in previous chapters. The technology was originally developed and built in London University by Gerald Pollock one of the co-inventors of the first pacemaker, and Donald Gilbert, a molecular biology London University professor, on the basis of extensive research on motor neurons. It has a maximum voltage of 15Vat 500Ω, 25V at 2000Ω, and 50V at 10KΩ. Any current generated by the voltage based on Ohm's law is minuscule and cannot be measured. It emits 24 unlimited resolution voltage-driven complex square waveforms, each synthesized by up to 4000 sine frequencies on the basis of a proprietary formula, with a resultant frequencies that ranges from 55Hz to 888Hz. The two waveform control knobs are manually combined to form 144 combinations, inducing 1000 full-body musculature contractions, each sustained for 8 seconds, with 2-secs rest time, mimicking slow-motion simulated exercises, or significantly faster ones that involuntarily twist and shake the body. The technology has 16 channels, isolated by separate transformers, reaching the skin via 8 three-pin din, and 8 four-pin din silver-plated tour-grade microphone cables, connected to gel pads. It complies with the EEC UK directive of electrical equipment safety applied standard EN 60601-1, and has a CE marketing directive of Class I with electromagnetic compatibility regulations applied standards EN50081-1 and EN50082-1. FDA clearance numbers are K132158 and K132179, applied to earlier versions of this technology with the same hardware design, intended for usage in physical medicine. The technology has had no known side effects in the past 20 years that it has been used in research and clinical practice for a variety of indications. The only contraindication, according to the FDA, is having an implanted device like a pacemaker. The main caution is pregnancy. Adverse reactions are limited to temporary skin redness from the pads that occurs sporadically, and usually dissipates within an hour. Measuring instruments included:

1) A blood test that examined levels of VLDL, HDL, triglycerides, Free T3, cortisol, CRP, creatinine and bilirubin.

2) A conductance instrument that calculated BMI and visceral fat.

3) A measuring tape.

Procedure

The results of forty adults 27-81 years of age with an average BMI of 32.42 participated and completed the clinical trial that took place in six different private clinics in separate countries. The measurements provided by the six clinics were different. The clinic that offered the results of thirty subjects, twenty females and ten males of Indian descent provided visceral fat and before and after abdomen measurements. The blood test results on CRP, Creatinine, Bilirubin, Cortisol, Free T3, HDL, VLDL and triglycerides of the ten Caucasian female patients were derived from the remaining five participating clinics. Initially, these five clinics only offered visceral fat scores but not tape measurements because the measurement variables were not part of the consent form. Eventually, the five clinics asked the ten females that were included in the study to consent on releasing their tape measurements so that the data of all 40 subjects was complete. All clinics reported that subjects were randomly selected out of a large number of individuals receiving treatments in this new exercise alternative. This research project was conducted after all the subjects had completed their treatments, therefore, neither the subjects, nor the technology operators were aware that the results would be eventually used in a clinical trial. All subjects became aware of this study when they were asked to sign a consent form to release their records for research purposes. The inclusion criteria were:

1. BMI >25.

2. Diabetics that were followed by physicians and their Diabetes was under control, were allowed to participate.

3. Hypertension patients that were followed by physicians and their Diabetes was under control, were allowed to participate.

4. Hypothyroid patients that were followed by physicians and their Diabetes was under control, were allowed to participate.

5. No prior experience or treatments with the same technology.

6. No additional or simultaneous treatment with any other technology.

The main exclusion criteria were:

1. Pregnancy or trying to become pregnant.

2. An implanted device like a cardiac pacemaker.

3. Severe medical and mental disorders.

4. Operation within the past six months.

5. Had received weight loss treatments in the past year.

6. On strict, well monitored diet.

All subjects had the right to discontinue treatment at any time. All subjects included in the study completed all twelve treatments. Every precaution was taken to protect the subjects' privacy and the confidentiality of their personal information. Subjects were not in a dependent relationship with the technology operators, the lab and measurement technicians, or the authors. The subjects did not receive specific instructions regarding changes in their lifestyles, and there was no methodical follow up of their food consumption. None of the technology operators, lab or measurement technicians had any known bias or personal interest in the direction of the results.

Five independent labs, (one from each private clinic that provided the blood tests), were assigned to take blood samples before and ten days after the completion of twelve one-hour treatments that took place three times a week, for four consequent weeks. Subjects were asked to fast for twelve hours prior to getting their blood tests. All six clinics had an attending physician in case any of the subjects had an adverse reaction. None of the subjects reported any adverse reactions.

Following blood tests and measurements, each subject went to a private treatment room and lay on a massage table while the gel pads and cables from the 16 channels of the device were attached on to his/her body by the technology operator. The cables from ten of the channels were attached on to the gel pads of the waist, upper and lower abdomen according to a standardized diagram, and the cables from the six remaining

channels were attached onto the gel pads placed along the lymphatic system pathways of the legs and arms, to enhance detoxification. The procedure was approved by the ethical boards of all clinics and was in accordance with the ethical standards and principles for medical research involving human subjects. Blood tests, Visceral Adipose Tissue (VAT) and tape measurements were also taken after the 12 treatments. Blood tests measured the following variables:

1. CRP
2. Cortisol
3. Creatinine
4. Bilirubin
5. VLDL
6. Triglycerides
7. HDL
8. Free T3

Results

The raw data from all six clinics results on VAT, and abdomen measurements are given on Table 1. Average VAT % decrease was -47%. The average Umbilicus measurement reduction was -10cm or around 9%. The average loss below the umbilicus measurements cm loss was -10cm or around 10% (Table 1). Results on the CRP and Cortisol blood test measurements are given on table 2. Table 3 gives the blood test results of the 10 Caucasian females on Creatinine and Bilirubin.

Table 1: *Results of 30 patients of Indian descent, 10 males and 20 females, and 10 Caucasian females on VAT, and measurements on Umbilicus and Below Umbilicus Tx=12.*

S	A	Medical Condition	VAT PreTx	VAT PostTx	Umbilicus Pre Tx	Umbilicus Post Tx	Below Umbilicus Pre Tx	Below Umbilicus Post Tx
F	54	Hypothyroid	34.6	23	138	130	137	131
F	43		33.4	18	110	104	120	105
F	49	Hypothyroid	24.4	7	102	95	105	98
M	47	Diabetes	33.4	21	136	126	139	128
F	39		36.7	20	124	111	127	112
F	28		29.4	8	102	95	104	97
M	45	Hypothyroid	24.9	11	103	96	99	95

M	27		31.2	14	115	100	118	107
F	34	Prediabetes	27.9	8.5	100	92	105	99
M	81	Diabetes	32.2	26.5	119	113	117	114
F	47	Hypertension	24.5	7	96	86	108	102
F	63		40.3	23	135	127	144	136
F	57		38.7	26	125	116	138	127
F	27		22.5	4	92	83	97	91
M	37		24.5	7	100	94	99	94
F	43		31.7	20.4	101	94	111	100
M	27	Prediabetes	28.2	9	110	104	112	105
F	35	Hypothyroid	34.0	15.5	118	113	129	122
M	61		28.8	17.6	106	99	108	100
M	55		26.7	8	105	99	101	97
F	38		34.5	14.5	121	116	126	118
M	36		34.0	13.5	124	118	123	118
F	34		27.8	9	96	90	106	100
F	46		30.0	11.5	110	100	115	109
F	43	Hypothyroid	45.5	25	141	135	143	136
F	32		26.8	12	100	88	105	95
F	39		25.2	10	95	85	104	95
M	68		27.3	17.2	113	108	104	99
F	36	Diabetes	32.1	16.5	115	106	114	105
F	42	Diabetes	20.3	8	97	86	101	91
F	56	Diabetes	29.7	21.6	142	115	145	122
F	52	Prediabetes	33.9	23.3	139	119	144	118
F	49	Hypertension	25.4	16.1	123	108	128	112
F	63	Hypertension	31.8	22.8	133	123	134	121
F	51	Hypothyroid	32.7	23.6	108	89	120	111
F	55	Hypothyroid	33.9	27.6	126	102	130	115
F	48	Hypothyroid	28.2	17.2	115	98	119	103
F	61	Hypertension	29.9	20.9	124	116	128	119
F	46	CVD	24.3	16.7	109	98	116	100
F	58	Hypothyroid	30.2	21.9	128	112	134	120
		Total	1181.3	642.4	4596	4189	4745	4367
		Average	30.29	16.08	115	105	119	109
		Average Loss	VAT	14.21	Umbilicus	10	Below Umbilicus	10
		% Lost	VAT	-47%	Umbilicus	-9%	Below Umbilicus	-9%

Table 2: *Blood Test Results on C-reactive protein (CRP) and Cortisol on 10 Caucasian Subjects Tx=12.*

CRP: <1.0 mg/dL. Low cardiovascular risk according to AHA/CDC

CRP: 1.0-3.0 mg/dL Average cardiovascular risk according to AHA/CDC

CRP: >3.0-10.0 mg/dL High cardiovascular risk according to AHA/CDC

G	A	Medical History	CRP Pre Tx mg/dL	CRP Post Tx mg/dL	Normal Range mg/dL	Cortisol Total, Serum ug/dL, Pre Tx	Cortisol Total, Serum ug/dL, Post Tx	Normal Range ug/dL
F	56	Diabetes	1.56	1.02	<1.00	18.44	15.66	3.09-25.0
F	52	Diabetes	1.09	1.06	<1.00	21.89	20.12	3.09-25.0
F	49	Diabetes	2.31	1.15	<1.00	24.98	18.47	3.09-25.0
F	63	Prediabetes	1.93	1.06	<1.00	23.43	21.98	3.09-25.0

F	51	Hypertension	1.43	1.22	<1.00	18.46	15.34	3.09-25.0
F	55	Hypertension	1.64	1.01	<1.00	19.33	14.75	3.09-25.0
F	48	Hypothyroid	1.04	0.86	<1.00	9.67	8.23	3.09-25.0
F	61	Hypothyroid	1.08	0.74	<1.00	14.76	10.65	3.09-25.0
F	46	Hypothyroid	1.84	0.98	<1.00	17.22	13.95	3.09-25.0
F	58	Hypertension	2.11	1.03	<1.00	21.28	17.24	3.09-25.0
MEAN TOTAL			**1.60mg/dL**	**1.01 mg/dL**		**18.95 ug/dL**	**15.64 ug/dL**	
Mean Average CRP % Decrease			**-36.87 mg/dL**		**Mean Average Cortisol % Decrease**		**-17.47% mg/dL**	

Table 3: Blood Test Results on Creatinine and Bilirubin on 10 Caucasian Females *Tx=12.*

G	A	Medical History	**Creatinine Serum Pre Tx mg/dL**	**Creatinine Serum Post Tx mg/dL**	**Creatinine Normal Range mg/dL**	**Bilirubin Pre Tx mg/dL**	**Bilirubin Pre Post Tx mg/dL**	**Bilirubin Normal Range mg/dL**
F	56	Diabetes	1.15	0.94	0.5-1.10	2.13	1.09	0.3-1.2
F	52	Diabetes	1.03	0.87	0.5-1.10	2.76	1.63	0.3-1.2
F	49	Diabetes	1.37	1.05	0.5-1.10	1.27	0.93	0.3-1.2
F	63	Prediabetes	1.23	0.96	0.5-1.10	2.35	1.78	0.3-1.2
F	51	Hypertension	1.14	1.02	0.5-1.10	2.18	1.03	0.3-1.2
F	55	Hypertension	1.04	1.01	0.5-1.10	2.23	1.16	0.3-1.2
F	48	Hypothyroid	0.97	0.82	0.5-1.10	1.53	0.83	0.3-1.2
F	61	Hypothyroid	1.18	0.98	0.5-1.10	1.93	0.95	0.3-1.2
F	46	Hypothyroid	1.11	0.87	0.5-1.10	1.22	1.07	0.3-1.2
F	58	Hypertension	1.96	1.23	0.5-1.10	2.17	1.26	0.3-1.2
Mean Average Creatinine % Decrease				**-19.67 mg/dL**		**Mean Average Bilirubin % Decrease**		**69.23 mg/dL**

Table 4: *Blood Test Results on VLDL and Triglycerides on 10 Caucasian Subjects Tx=12.*

Triglycerides Normal Range: <150 mg/dL. Borderline high: 150 to 199 mg/dL

Hypertriglyceridemia: 200 to 499 mg/dL High risk for pancreatitis : > or = 500 mg/dL

G	A	Medical History	VLDL Pre Tx mg/dL	VLDL Post Tx mg/dL	VLDL Normal Range mg/dL	Triglycerides Pre Tx mg/dL	Triglycerides Post Tx mg/dL	Triglycerides Normal Range mg/dL
F	56	Diabetes	39.64	27.33	5.0-40.0	144	137	<150
F	52	Diabetes	43.49	35.77	5.0-40.0	169	146	<150

F	49	Diabetes	27.44	18.28	5.0-40.0	129	114	<150
F	63	Prediabetes	45.22	32.86	5.0-40.0	163	152	<150
F	51	Hypertension	39.42	31.67	5.0-40.0	159	150	<150
F	55	Hypertension	42.55	36.20	5.0-40.0	173	159	<150
F	48	Hypothyroid	37.52	29.38	5.0-40.0	153	139	<150
F	61	Hypothyroid	41.87	36.24	5.0-40.0	175	148	<150
F	46	Hypothyroid	14.76	9.23	5.0-40.0	136	129	<150
F	58	Hypertension	43.92	37.56	5.0-40.0	182	157	<150
Mean Total VLDL			**37.58**	**29.45**		**158**	**143.1**	Mean Total Triglycerides
Mean Average VLDL % Decrease			**-8.13% mg/dL**		**Mean Average Triglycerides % Decrease**			**-14.9% mg/dL**

Table 5: Blood Test Results on HDL and Free T3 on 10 Caucasian Subjects. Tx=12 .

High-Density Lipoprotein (HDL) Normal Range: Men > 60 mg/dL; Women > 60 mg/dL

High-Density Lipoprotein (HDL) At Risk: Men: <40 mg/dL; Women < 50 mg/dL

G	A	Medical History	HDL PRE mg/dL	HDL POST mg/dL	HDL Normal Range pg/mL	Free T3 PRE pg/mL	Free T3 POST pg/mL	Free T3 Normal Range pg/mL
F	56	Diabetes	53	61	>60	2.29	2.89	2.30-4.20
F	52	Diabetes	39	57	>60	2.12	2.68	2.30-4.20
F	49	Diabetes	61	79	>60	1.32	2.49	2.30-4.20
F	63	Prediabetes	46	64	>60	1.97	2.69	2.30-4.20
F	51	Hypertension	41	55	>60	1.18	2.25	2.30-4.20
F	55	Hypertension	43	51	>60	1.43	2.36	2.30-4.20
F	48	Hypothyroid	63	76	>60	1.63	2.11	2.30-4.20
F	61	Hypothyroid	52	71	>60	1.96	2.95	2.30-4.20
F	46	Hypothyroid	59	68	>60	2.25	2.33	2.30-4.20
F	58	Hypertension	38	52	>60	1.37	2.16	2.30-4.20
Mean Total HDL			49.5 mg/dL	63.4 mg/dL		1.75 pg/mL	2.49 pg/mL	Mean Total Free T3
Mean Average % Increase				+28.08% mg/dL		Mean Average % Increase		+42.28 pg/mL

Table 6: T-Tests Statistical Significance Results on Blood Tests and Measurement Variables.

	Mean	S^2 =SS/df	S2*M* =S2/N	SM= $\sqrt{S^2M}$	T Value	p Value	P
VLDL	-8.13	6.23	0.62	0.79	-10.3	0.00001	P<0.00001
Triglycerides	-15.2	54.4	5.44	2.33	-.652	0.00005	P<0.0001
Free T-3	0.74	0.11	0.01	0.1	7.19	0.00003	P<0.0001
Bilirubin	-0.08	0.12	0.01	0.11	-7.26	0.00002	P<0.0001
Creatinine	-0.24	0.04	0	0.06	-4.06	0.00143	P<0.01
CRP	-0.59	0.16	0.02	0.13	-4.72	0.00055	P<0.001
Cortisol	-3.31	2.52	0.25	0.5	-6.59	0.0005	P<0.001
HDL	13.9	18.99	1.9	1.38	10.09	0.00001	P<0.00001
Visceral Adipose Tissue	-4.59	8.34	0.21	0.46	-10.05	0.00001	P<0.00001
BMI	-2.15	1.06	0.03	0.16	-13/21	0.00001	P<0.00001
Umbilicus, cm	-8	6.28	0.21	0.46	-17.49	0.00001	P<0.00001
Below Umbilicus, cm	-7.77	8.81	0.29	0.54	-14.34	0.00001	P<0.00001

CRP and cortisol decreases were -36.87% mg/dL and -17.47% ug/dL respectively (Table 2). Prior to treatment, CRP was above the normal range for all subjects. It descended into the borderline normal range after the 12 treatments. Cortisol decreased within the normal range (Table 2).

Seven out of ten subjects had abnormal levels of creatinine prior to treatments. All subjects manifested creatinine concentrations within the normal range after treatment. The average percentage decrease of creatinine was -19.67% (Table 3). Bilirubin was at the upper end of the normal range prior to treatments and decreased towards the middle part of the normal range after the twelve procedures. The significance of being at the upper part of the normal range is the high probability of rising into abnormality,

increasing health risk. The mean average percentage decrease of bilirubin was -69.23% (Table 3).

VLDL and Triglycerides percentage decreases were -8.13% mg/dL and -14.9% mg/dL respectively (Table 4). Triglycerides that was within the borderline risk range before treatment, descended into the normal range after treatment. HDL and Free T3 increases were +28.08% mg/dL and +42.28% pg/mL, respectively (Table 5). The mean average level of HDL and Free T3 that were previously below normalcy, were elevated into the normal range. The data was statistically analysed by the T-test for dependent means. Results for all variables along with the statistical significance are given on Table 6.

The Purpose of the Clinical Trial

The scope of this project was to identify health risks that could potentially exacerbate vulnerability and symptomatology in this pandemic. The focus was on prevention and protection rather than treatment, since the clinical trials were conducted on patients with disorders often associated with COVID-19, like diabetes, hypertension and hypothyroid who had tested negative for the virus. We explored the interactions between VLDL, triglycerides and HDL, before and after an exercise alternative that has been previously shown to enhance health. Results revealed a robust decrease in VLDL and triglycerides juxtaposed by upraised HDL, but without HDL being overly elevated that could also pose a health risk as previously discussed [44, 45]. Tape measurements delineating a significant cm reduction, appeared to corroborate with the evidence of visceral fat reduction. Consistent with this configuration, Free T3 values were significantly elevated, but without rising above the normal range. Visceral fat reduction and optimal Free T3 concentrations are important in light of the documented affinity of COVID-19 for ACE2 receptors that are reportedly abundant in adiposity and the thyroid. Additionally because dysfunctional metabolism may be one of the primary causes of obesity. The abundance of ACE2 receptors in adiposity, along with a

malfunctioning thyroid may be some of the reason why a BMI>25 escalates COVID-19 susceptibility and fatality [9]. Weight management appears to be one of the necessities in containing the virus. Lockdowns and social distancing encourage inactivity and food consumption, which consequently accumulate adiposity along with inflammation and toxicity due to limited opportunities for movement and lymphatic drainage.

External Validity

The current results replicate and provide reliability for previous studies [70-73] and provide evidence for reduced inflammation and toxicity by the statistically significant reductions of the CRP, creatinine and bilirubin. However, not all subjects' CRP descended within the normal range, suggesting the requirement for more treatments or adding exercise and nutrition to secure a more optimal health status. Bilirubin and creatinine that were initially abnormal, demonstrated a mean average that appeared to settle within the normal range after twelve treatments, suggesting that this method can be utilized to enhance detoxification as a health enhancement technique that can either temporarily replace or contribute to an active lifestyle along with proper nutrition.

Methodological Limitations

The sample of 10 females that provided the results on CRP, creatinine and bilirubin was small and did not include males. A larger more diverse sample is imperative to substantiate and generalize these findings in order to confirm external validity. Ultrasound or magnetic resonance imaging techniques would also be useful in assessing the progress of patients with hepatic steatosis and more accurately validate the visceral adipose tissue reduction that was consistently observed in all forty patients.

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Conflict of Interest

The author declares no conflict of interest. This study was conducted by independent operators that were not employed or contracted by the author.

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Ethical Standards

Statement of Ethical Approval

This study was performed in accordance with the ethical standards of medical research involving human participants as cited by:

1. Ethical Principles for Medical Research involving Human Subjects
2. American Psychological Association (APA)
3. IELLIOS Research department for Development and invention of Innovative Technology.

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SECTION 6

COVID-19 Susceptibility Factors and the Shield of Health

David and Goliath

The global health crisis of the severe acute respiratory syndrome coronavirus 2 (COVID-19) resembles the initially unforeseen results of the David and Goliath battle: the microscopic virus winning over our giant recourses and medical advances, ultimately leading to devastating consequences that range from lockdowns and economic disruption to family and personal tragedies with over a million deaths worldwide.

This chapter examines COVID-19 (COVID-19) available treatments and prophylactic methods that included interventions associated with the 'type II transmembrane serine protease' (TMPRSS2). Some of these therapeutics obstruct the fusion between the COVID-19 Spike proteins and ACE2 receptors, while others limit the viral RNA replication via newly developed medications like Remdesivir.

ACE2 receptors have a protective function against high blood pressure associated disorders. Abundance of ACE2 receptors is important in lowering blood pressure, yet, deleterious when it comes to COVID-19 since they serve as main viral portals, elevating the probability of infection. Human tissues' analysis reveals a higher ACE2 expression in adipose tissue, placing obesity-related conditions in the eye of the pandemic storm. It primarily exposes males due the surge of ACE2 receptors in the testes, and relatively higher positive ACE2 correlations with certain immune cells in the lungs, thyroid, adrenals, liver and colon. Older individuals are also within this high vulnerability category due the positive ACE2/immune cells correlation in the lungs. Females manifest higher ACE2 correlations with immune cells in the heart. The remaining tissues manifest ACE2/immunity expressions which appear to be are equivalent in both sexes, indicating that despite its preference for males, the threat of COVID-19 can easily target females.

The gathering of the "cytokine storm," reflects the aggravated immune response defensively propelled to annihilate the virus that indiscriminately perseveres, rampaging the host's vital organs. Chronic inflammation accumulated by sedentary lifestyles, age-induced hormonal imbalance, and visceral adiposity predispose the body to the cytokine storm, spotlighting the detrimental aftermath of metabolic dysfunction, increased cortisol and dysregulated appetite hormones, promoting excessive food consumption and escalating adiposity. ACE 2 expression is suppressed in the skeletal muscle, rendering fitness and weight management an effective COVID-19 preventive intervention, along with social distancing, hygiene, and facial coverings. Physical activity, or exercise alternative methods have recently presented statistically significant evidence of reduced inflammation as measured by CRP, diminished triglycerides, visceral fat, cortisol and the orexigenic hormone ghrelin, juxtaposed by optimal increases of IGF-1, skeletal muscle mass, Free T3, HDL, and the anorexic hormone leptin.

COVID-19 Treatment & Prevention Methods

The purpose of this review is to analyse the six primary strategies currently available in the prevention and treatment of COVID-19. Generally speaking these are:
1/ Inhibit the 'type II transmembrane serine protease' (TMPRSS2) that primes both ACE2 receptors and the Covid's Spike (S1, S2) glycoproteins to facilitate their fusion.
2/ Regulate the 'A Disintegrin And Metalloprotease 17'(ADAM17)
3/ Obstruct the action of the Nucleocapsid (N) proteins involved in the replication of the viral DNA.
4/ Practice prophylactic measures or techniques to reduce inflammation and modulate the rampaging immune response leading to the "cytokine storm" that culminates in high mortality rates.
5/ Protect against infection with hygiene, face coverings and social distancing.
6/ Capitalize on wellbeing via a lifestyle that promotes optimal weight, fitness and hormonal balance to defend against severe symptomatology.

Ang II and ACE2 Receptors

The imminent fusion between COVID-19 Spike (S) proteins and angiotensin enzyme-2 (ACE2) receptors preludes the viral entry into human cells, placing the focus on the hierarchic multi-dimensional activity of the renin angiotensin system (RAS) [1]. Angiotensin enzyme (ACE) cleaves Ang II from Ang I, hence increasing Ang II , which can be then transformed into Ang III and IV. Angiotensin II is a vasoconstrictor hormone that increases blood pressure. ACE2 catalyses Ang II, generating Ang (1-7), a vasodilator agent that features antioxidant and anti-inflammatory effects. Hence, ACE2 performs a protective function on the heart, the vessels and possibly the kidneys. On the other hand, ACE, which actually determines the Ang II production, results in the degradation of Ang (1-7) [2, 3, 5, 6]. Based on this simultaneous mosaic of processes, ACE inhibitors (ACEIs) decrease the production of Ang II, and increase the Ang (1-7) in the system, decreasing inflammation and blood pressure. With regards to COVID-19, as ACEIs compromise the levels of Ang II, they reduce the concentrations of 'A Disintegrin And Metalloprotease 17' (ADAM17) which is normally promoted by Ang II. ADAM17 can cleave ACE2 from the cellular membrane, shedding it into body fluids. As ACE2 receptors fuse with the S protein, shedding into body fluids may carry viral particles throughout the body infecting vital organs. Increased soluble ACE2 in the blood, increases with age. And here comes an event that appears different depending on the observation angle. Increased ADAM17 increases shedding. This deprives the organism from the anti-inflammatory effects of ACE2 receptors as they catalyse Angiotensin II into Angiotensin (1-7). By the same token, increased ADMAM 17 shedding reduces the number of ACE2 receptors restricting COVID-19 entry. On the other hand, ADAM 17 sheddase increases the soluble form of ACE2 receptors, turning body fluids into COVID-19 carriers, spreading the virus throughout the system [7, 8].

The type II transmembrane serine protease' (TMPRSS2) cleaves both the ACE2 receptor and the viral S proteins, preparing them to fit into each other, hence facilitating

the ominous proliferation of COVID-19 [9]. This priming action of TMPRSS2 is necessary for the S/ACE2 fusion that commences the viral advancement into the body. These relationships are graphically described in Figure 1.

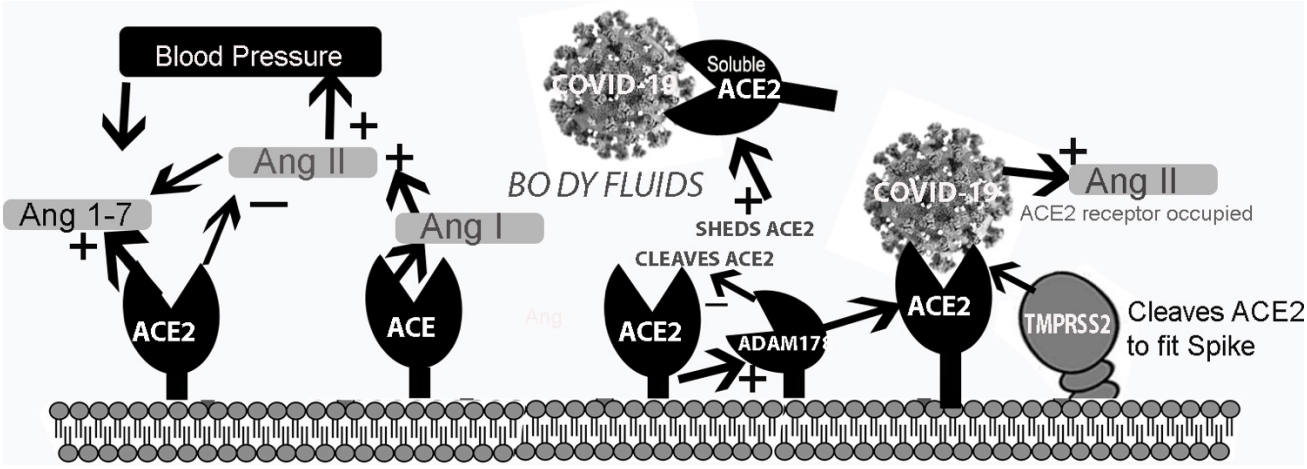

Figure 1. ACE increases Angiotensin II (Ang II), a vasoconstrictor that increases blood pressure. ACE2 decreases Ang II. It catalyses Ang II into Ang 1=7, a vasodilator with anti-inflammatory actions that protects the heart and kidneys. However, COVID-19 has an affinity for ACE2 receptors. COVID-19 occupies ACE2, hindering their normal process of catalysing Ang II into Ang 1-7. As a result of COVID-19 invading ACE2 receptors, Ang II increases. TMPRSS2 cleaves the ACE2 receptor facilitating its fusion of the COVID-19 Spike Protein with the ACE 2 receptor. ACE2 increases ADAM17 which cleaves and sheds ACE2 receptors into the body fluids (blood, saliva, semen, vaginal fluids, mucus, urine, etc). At first sight this appears to be a process that will reduce the ACE2 receptors on the cellular membrane therefore limiting the COVID-19 invasion. However, COVID-19 can fuse in the ACE2 receptors in the body fluids, hence increasing the COVID-19 transmissibility inside the body.

Ang II is functional in upregulating ADAM17 that is involved in the ACE2 shedding. Ang II increases inflammation, oxidative stress and has been associated with atherosclerosis [10]; ACE2 catalyses Ang II, acting as a protective mechanism against the blood pressure increase induced by Ang II that would otherwise be deleterious to diseases such as hypertension, diabetes, and cardiovascular illness. COVID-19 occupies ACE2 receptors, compromising their anti-inflammatory function, resulting in an increase in Ang II. ACE2 receptors diminish with age. From the one hand a reduced number of ACE2 receptors limits the entry points of COVID-19. On the other hand, a decreased number of ACE2 receptors will increase inflammation and increase risk of

injury in the lungs [11]. ACE2 receptors protect the lungs from pulmonary vasoconstriction and remodelling, they prevent myocardial hypertrophy and high blood pressure; yet, by the same token, they serve as a COVID-19 gateway, exposing the body to the deleterious effects of the virus. Ang II increases pulmonary edema and vascular permeability that can result in ARDS; it induces atherosclerosis, hypertension and possible heart failure. The lethal effects of COVID-19 are more pronounced in pre-existing cardiac and pulmonary disorders, spotlighting the dualistic function of ACE2 receptors that can be an advantage in the absence of COVID-19 and a disadvantage in the presence of COVID19. The COVID-19 invasion not only infects the body, but seizes ACE2 receptors disabling them from protecting the vital organs, because they no longer reduce inflammation and control blood pressure. With the ACE2 receptors infested by the Spike proteins, the anti-inflammatory Angiotensin 1-7 decreases, Angiotensin II increases, elevating blood pressure, and treatment against COVID-19 becomes insurmountable with individuals exposed to metabolic disadvantage, inflammation and internal impairment.

ACE2 in Males & Females.

Aged women and men, over the age of 50 years, manifest a slightly higher number of ACE2 receptors with a median number of 61.71 for women and 59.75 for men. Younger females also demonstrate a slightly higher expression or ACE2 receptors than younger males (women median 71.11 / men median 70.5). Regression analysis revealed a B value of 0.959 for women versus 0.664 for men for ACE2 receptors. With regards to the ACE receptors, the median of ACE in older women was 820.3 in contrast to older males whose median was 841.4. The ACE median of younger females was 815.9, while the median of ACE in younger males was significantly less, with a median of 744.4. Overall, both younger and older females had a slightly higher number of ACE2 receptors than both younger and older males. However when it came to ACE receptors, older males had higher ACE receptors expression than older women. While younger women had significantly more ACE receptors than men, while [12].

Analysis of ACE2 receptors in donors' lung cells indicated that individual differences may contribute to a divergence in human COVID-19 susceptibility. Although the sample size was small, one of the donors evidenced five-fold higher ACE2 expression that could potentially increase his viral vulnerability. Lung ACE2 receptors are expressed by both Alveolar Type I (AT1), and Type 2 and Alveolar Type II (AT2) cells. AT1 cover 95% of the internal alveolar compartment, the lungs air bags, forming the air-blood barrier where gas exchange occurs. AT2 cells are involved in maintaining homeostasis in the alveolar region. They are the caretakers of the AT1 compartment and they can differentiate into AT1 cells to assist in the repair of traumatized lungs. This experimental project revealed that the virus targets AT2 cells that express the ACE2 receptors in the lungs, debilitating the AT2 protective functions over AT1 cells and exposing the lungs to inexorable alveolar corrosion. Again, a rather interesting choice by a virus that cannot possibly be endowed by intelligence, and yet it behaves as if it is following a strategic plan [13].

ACE2 Expression: Lower in Children & Higher in Smokers and Asthmatics

TMPRSS2 cleaves the ACE2 receptors to facilitate their fusion with the Spike protein (Figure 1). The following findings are reported by research:

1. TMPRSS2 and ACE2 receptors are upregulated in the lungs' airways of smoker.
2. ACE2 expression is elevated in the blood of Asthmatics. Plasma soluble ACE2 receptors seized by the virus may be able to transfer COVID-19 and spread the infection faster within the system.
3. TMPRSS2 and ACE2 are elevated in the blood of patients with hypertension
4. Both the nasal and bronchial TMPRSS2 and ACE2 expression are lower in children when juxtaposed to adults. This finding regards both the upper and lower airway of the respiratory track.
5. However, there were no differences between children and adults in the TMPRSS2 and ACE2 blood expression levels.

6. Additionally, there are no differences between children and adults in the TMPRSS2 and ACE2 blood expression levels when compared to diabetics or patients with chronic obstructive pulmonary disease.
7. The upper airway of the respiratory track has a higher number of both TMPRSS2 and ACE2 receptors than the lower airway.
8. TMPRSS2 and ACE2 receptors are more abundantly found in the lungs of patients with chronic obstructive pulmonary disease [14].

If there is no variance in the ACE2 receptors and the TMPRSS2 protease that cleaves them for better fitting in the blood of children vs adults and children / adults vs patients with lung disease and diabetes could the following assumptions be simultaneously true?

A. ADAM17 sheddase activity increases COVID-19 susceptibility in patients with asthma and hypertension by increasing the number of COVID-19 transmission via the blood as a result of ADAM17 cleaving and shedding ACE2 receptors that are potentially infected or can be infected by COVID-19 into body fluids.
B. If ACE2 receptors are not found in abundance in the blood of children or healthy what does that mean in terms of the ADAM17 sheddase activity?
C. COVID-19 highjacks ACE2 receptors compromising their regular functions (Figure 1). ACE2 receptors are instrumental in decreasing the inflammatory vasoconstrictor Ang II. ACE2 receptors may be unable to inhibit Ang II following COVID-19 invasion, leading to increased levels of Ang II and decreased levels of the anti-inflammatory agent Ang 1-7. The potential increase of Ang II will increase blood pressure, will exacerbate pulmonary inflammation, and will adversely affect hypertension and heart disease.
D. ADAM17 sheddase activity does not exclusively affect the ACE2 receptors. ADAM17 cleaves and sheds pro-inflammatory proteins like interleukin-6 (IL6) and the tumour necrotic factor alpha (TNF-a) which is the protagonist of the "cytokine storm," (discussed in greater detail below), in pathological systemic configurations with inherent oxidative stress and inflammation, reflected in

obesity and type 2 Diabetes. ADAM17 is also known as TACE (tumour necrosis factor alpha converting enzyme).

E. ADAM17 appears to have a "Dr Jekyl – Mr. Hide" duality in hepatic processes, on one hand preventing hepatocytes' apoptosis and on the other exacerbating liver inflammation and hepatosteatosis preluding the generation of the metabolic syndrome.
F. ADAM17 expression is upregulated by glucose in the kidneys of diabetics, indicating that hindering ADAM17 expression may benefit diabetic nephropathy.

ADAM 17 Sheddase Examined

Overall, there seems to be evidence that ADAM17 cleaving and shedding increases soluble ACE2 receptors floating in body fluids that could potentially compete with the ACE2 receptors in cellular membranes both enhancing the transmission of COVID-19. Silencing both ACE2 receptors and ADAM17 appear to inhibit the virus [15]. However, that does not appear to be the whole story, since silencing ACE2 receptors will inadvertently neutralize the protective function of this enzyme in reducing inflammation. Again, the distinct diversity between a balanced and an imbalanced body comes centre-stage, an observation validated by the significant discrepancy between COVID-19 mortality rate for relatively healthy adults, which is approximately 0.9% as contrasted to patients with pre-existing medical disorders such as Hypertension (6.3% Diabetes (7.3%) and Cardiovascular disease (10.5.%) [16].

The Complex Testimony of Human Tissues

COVID-19 affects the upper respiratory track with flu-like symptoms, and the lower respiratory system by symptoms including difficulty breathing that may evolve into pneumonia or the Acute Respiratory Distress Syndrome (ARDS). Counterintuitively, the lungs do not encapsulate the greatest multitude of ACE2 receptors. The analysis of 31 normal human tissues revealed that adipose tissue, heart, testes, kidneys and small intestines had the highest ACE2 expression, rendering these organs the primary COVID-19 targets, representing the most vulnerable points of viral entry. The lungs,

adrenal gland, bladder, liver and colon manifest a moderate ACE2 expression, while the muscle, the brain, blood vessels, spleen and bone marrow evince the lowest ACE2 expression [17, 18].

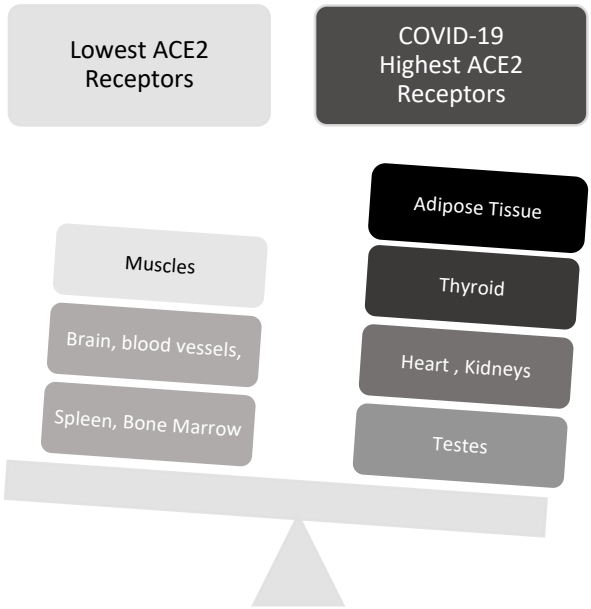

Figure 2 below, offers the graphic representations of the highest and lowest ACE2 receptors in human tissues.

These investigators also explored male, female, young and old immune cells including:

a) B cells, lymphocytes that develop into plasma cells producing antibodies that can protect the organism in the initial viral attack.

b) Natural killer cells (NK).

c) CD8+ cells which include cytotoxic T cells that specifically target viral infections;

d) Interferons, that represent proteins designed to inhibit viral replication, as well as T cells' suppressors, designed to restrain an overreactive immune system.

Males' ACE2 expressions in the lungs, thyroid, liver, colon, kidney, stomach and pancreas were linked with increased levels of B, NK, CD8+ T cells and interferons. On the other hand, females' ACE2 expressions in the lungs and thyroid were associated with decreased levels of B, NK, CD8+ T cells.

Increased ACE2 expression in the female heart tissues was accompanied by increased B, NK, CE8+ T cells and interferons, unlike male heart tissues, where ACE2 receptors and immune cells featured a negative correlation. ACE2 receptors in the kidneys, skin, stomach, and adipose tissue were associated with an increased levels of immune cells in both sexes.

ACE2 Receptors in the Young versus the Aged

Immune cells were positively correlated with the ACE2 receptors in lung tissues of older individuals over 45 years and negatively correlated with the ACE2 receptors of lung tissues of younger individuals under 45 years of age. These results reflect a male vulnerability in terms of the positive ACE2/immune cells' correlation with the lungs and thyroid tissues, especially in elderly males. On the other hand, the heart tissues of females demonstrated positive ACE2/immune cells' correlations making women more vulnerable with regards to that vital organ.

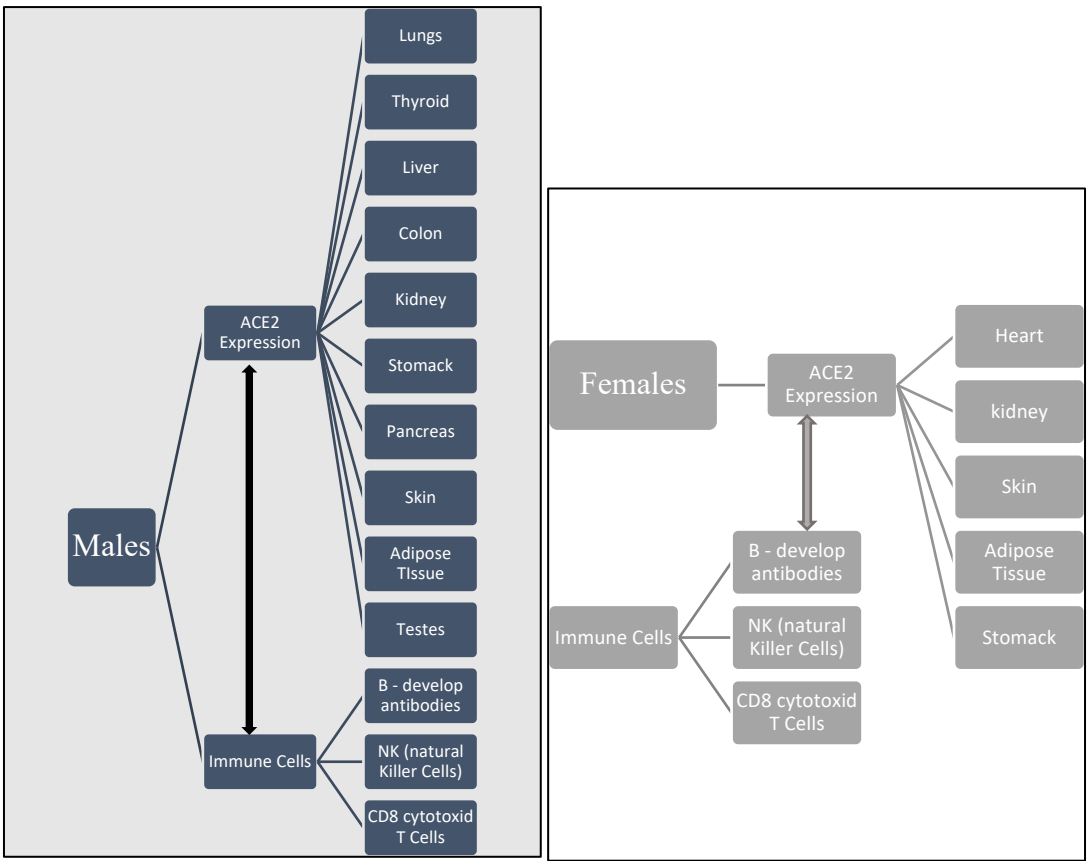

Figure 3. ACE2 receptors expression of males and females' vital organs tissues.

The ACE2/immunity cells' positive correlations of the remaining tissues appeared to be similar in both sexes. The positive ACE2/immunity correlations in certain vital organs may prelude the eventual mushrooming of the overstated immune response, accelerating the lethal consequences of the cytokine storm, a process during which lymphocytes, leukocytes, interferons and NK cells spin out of control in an overly

aggressive attack against the virus increasing mortality rates. The positive ACE2/immunity correlations in male lungs, testes and thyroid tissues, and older individuals' lung tissues when compared to females and younger people respectively, may explain the higher COVID-19 lethality among males and the eldest [19]. The higher correlation between ACE2 receptors and immune cells in female heart tissues, as well as the fact that such positive correlations are equivalent in both males' and females' kidneys, skin, stomach, and adipose tissue, warns against reaching the conclusion that women are indiscriminately less susceptible to the disease. Therefore, a thorough medical evaluation of the entire health status is necessary in evaluating COVID-19 prognosis in females. More research focused on human tissues' analysis from COVID-19 patients may be necessary to further elucidate the molecular interactions between ACE2 receptors and the complex network of immune activity. These above mentioned correlations are graphically displayed in Figure 3.

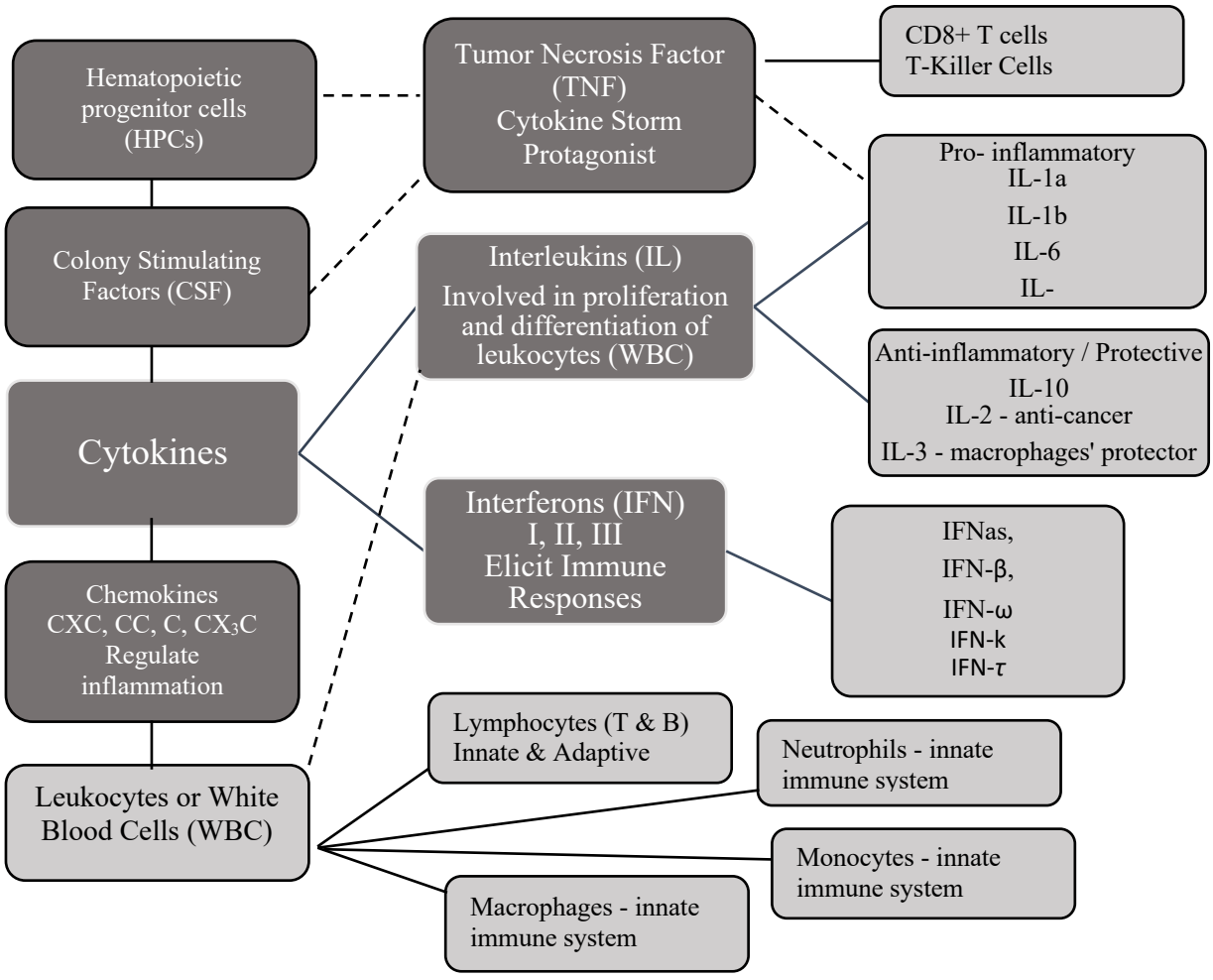

Figure 4. Immune system cells involved in the Cytokine Storm

The COVID-19 "Plan B." Possible viral Entry via Alternate Pathways

The observation that the lungs do not comprise the highest number of ACE2 receptors is interesting in light that COVID-19 causes a severe acute respiratory syndrome (SARS) reflected in one of its synonyms, SARS- CoV2. Early research [20] postulated that SARS-CoV is absorbed via an endosomal pathway. Trypsin and thermolysin appear to allow for viral penetration directly from the cellular surface into the protein replication machinery in the cytoplasm. Then, proteases like elastase, another digestive enzyme, facilitate viral contamination of the lungs. Endosomes are specialized subunits inside the cell, where transported molecules can be organized prior to being delivered to lysosomes for processing. Trypsin is synthesized by the pancreas and is involved in the digestion process that begins in the stomach. Therefore, COVID-19 "Plan A" is to fuse with the ACE2 receptor, escalate Ang II, and increase inflammation. "Plan B" is to exploit the digestive enzyme trypsin that allows COVID-19 to be absorbed into the cell directly, bypassing ACE2 receptors. Thermolysin is also part of this "Plan B" due to its propensity to catalyse the hydrolysis of hydrophobic amino acids. Recent studies have suggested that an anti-trypsin protein, the anti-inflammatory Alpha-1 Anti-Trypsin (ATT), may offer protection against COVID-19 infection. ATT is also known as a serine protease inhibitor (SERPIN), and it is designed to provide the primary defence against digestive enzymes such as trypsin or elastase which, as noted above, are promoting viral transmission in the liver [21]. ATT also supresses inflammatory cytokines like IL-6 both in vitro and in vivo [22]. Aged ATT deficient individuals who are smokers or are exposed to environmental pollution manifest an increased vulnerability in developing pulmonary diseases [23].

The Mechanics of the Cytokine Storm

Cytokine storm reflects a persistent immune response, defensively propelled to fight the virus, that blindly perseveres, rampaging the infected vital organs with lethal consequences [24, 25]. Cytokines are pleiotropic, multifunctional bio-communication

agents composed by diverse, yet interconnected entities, including the following categories that are graphically displayed in figure 4:

1. Interferons (INFs) which regulate immune activity and are classified into I, II, and III subtypes; INFs type I (IFN-αs, IFN-β, IFN-ω, IFN-κ, and IFN-τ) are crucial in eliciting immune responses against viral infections [26, 27].
2. Interleukins (IL) which are vital in stimulating the immune system; they are involved in the proliferation, differentiation and survival of leukocytes, otherwise known as white blood cells (WBCs). Interleukin-2 (IL-2) is a signalling molecule that has been used to treat cancer, while Interleukin-3 (IL-3) has a protective function regarding the survival of macrophages and mast cells, and a preventive one against cellular apoptosis [28]. Interleukins have both pro-and anti-inflammatory properties. Interleukins-1a and 1b (IL-1a and IL-1b) are proinflammatory. IL-6 is both a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-8 in involved in elevating inflammation [29]. IL-10 is largely accepted as an anti-inflammatory cytokine [30].
3. Chemokines which are mostly pro-inflammatory, recruit leukocytes and other immune cells, like neutrophils and monocytes, macrophages and lymphocytes that are activated by injury to attack viral entities. Leukocytes demonstrate a positive chemotaxis - a Greek work that reflects a chemically driven movement towards a stimulus. Leukocytes shift from blood vessels towards, and into bodily tissues initiating inflammation. Chemokines are primarily classified into CXC, CC, C, and CX_3C 3 subtypes [31].
4. Colony-stimulating factors (CSFs) activate the genesis of hematopoietic progenitor cells (HPCs), and are closely associated to inflammation via an intertwined network that features IL-1 and the tumour necrosis factors (TNF) [32].
5. Tumour Necrosis Factor (TNF) stimulates cytotoxic T lymphocytes (CTL), or otherwise known as T-killer cells, or CD8+ T-cells. TNF is a protagonist in the emergence of the cytokine storm and has been associated with chronic inflammation [33, 34].

IL-1b is one of the central cytokines driving the lungs' proinflammatory processes [35]. The lungs' inflammatory condition provokes renal epithelial cell apoptosis and eventual renal dysfunction [36]. This happens as inflammation overflows from the lungs into the circulation, igniting systemic sepsis where TNF, IL-1b and IL-8 are eventually accompanied by a more substantial increase of IL-6, followed by the anti-inflammatory cytokine IL-10. This sequence suggests that IL-6 is stimulated by TNF and IL-1b which are manifested during the earlier stage of the infection [37, 38]. The clinical manifestations of the cytokine storm appear to resemble a sepsis syndrome, or a Systemic Inflammatory Response Syndrome (SIRS), induced by the host's dysregulated response to infection. This may be partly genetically determined [39], while a sedentary lifestyle that accumulates adiposity and instigates inflammation, may be a major contributor to immune aberration evoking the cytokine storm. Interleukins (IL-1, IL-2, IL-6, IL-8) and TNF, along with the inflammatory marker C-Reactive Protein (CRP) are prominent in both subcutaneous and visceral adipose tissue, increasing the probability of COVID-19 infection, due to the abundance of ACE2 receptors in adipose tissue, while exposing the organism to the cytokine storm, due to the pre-existing elevated inflammatory condition [40, 41, 42, 43, 44, 45, 46 47].

Immune Homeostasis, the Chaperon of Health

Health is based on immune homeostasis which depends on a balance between proinflammatory cytokines and their inhibitors. For example, TNFR1 is the inhibitor of TNF, and IL-1RA is the inhibitor of IL-1b [48]. The disturbance of this balance is followed by the flaring of the cytokine storm. It is unclear if the immune cells' ability to distinguish the virus from the infected tissues is compromised, or whether immune efficiency has deteriorated altogether. Autopsies, which obviously take place after the death of COVID-19 patients, have revealed minimal lymphocytes and neutrophils, yet a relatively larger number of macrophages, whose primary function is to engulf foreign substances and cellular debris [49]. Admittedly, an autopsy depicts a biological landscape after the war against the virus is over, and may not represent the processes occurring during the battle. Possibly, the excessive effort to overcome the virus

depletes energy in the form of Adenosine Triphosphate (ATP), promoting lymphocytes' and neutrophils' apoptosis [50]. Energy depletion, however, does not accurately describe the entire process of why and how the immune activity turns against itself during the cytokine storm.

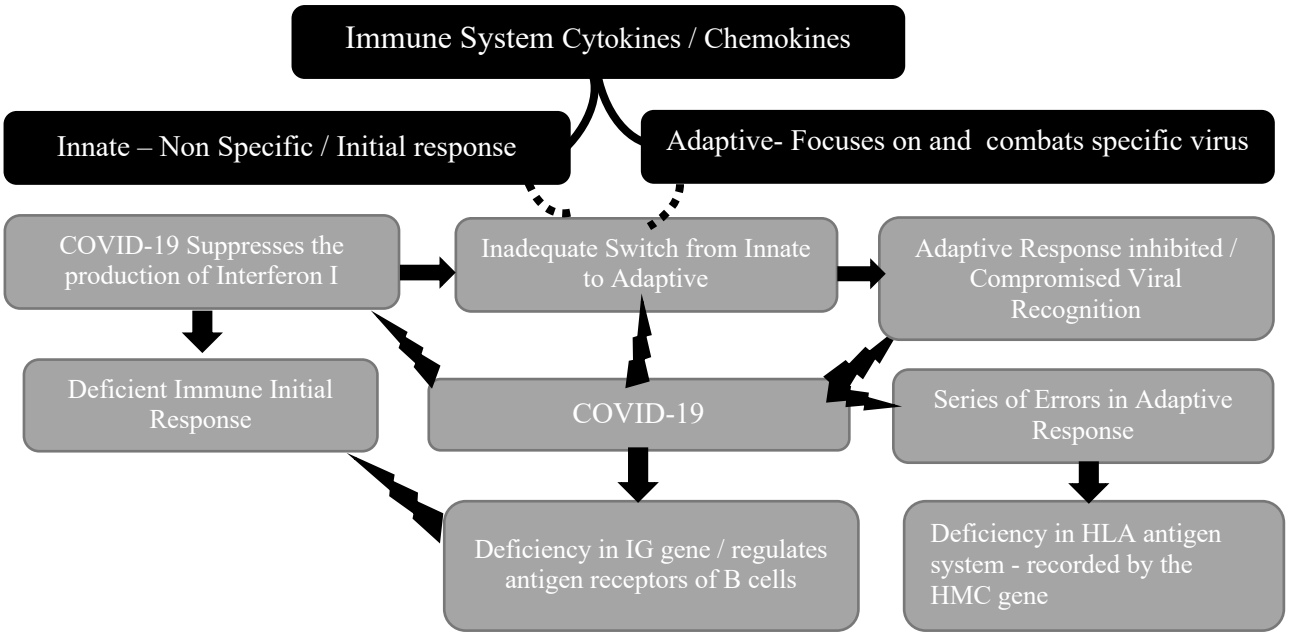

Figure 5. Innate and Adaptive Immune System

Innate versus Adaptive Immune Response

Initially, cytokines regulate an innate or non-specific line of immune defence. This evolves into the adaptive immune response that focuses on the specific virus, a critical switch largely controlled by cytokines and chemokines. The cytokine storm is either the result of:

a) a deficient initial response;

b) an inadequate switch between the innate and adaptive defences, hence compromising viral identification;

c) a series of errors during the adaptive stage, obscuring immune ability to distinguish between self and non-self, attacking and rampaging the vital organs of the host.

COVID-19 interferes with Interferon type I

A number of investigators have postulated that insufficient production of Interferon

(INF) type I can impair immune innate action [51, 45, 53]. A recent review suggests that coronavirus is designed to hinder the critical process of viral recognition, and suppresses the production of IFN type I, ultimately inhibiting the emergence of the adaptive immune response [54]. IFN type I was reportedly lower in a patient with poor prognosis and outcome [55].

Chemokines CXCL2 and CCL10

The Interferon-induced chemokines CXCL2 and CCL10 appear to be associated with disease severity, and there is evidence that patients with elevated CXCL10 have a larger number of fatalities [56, 57].

The IG Gene Crucial for the Innate Response

There is evidence of defects related to the Immunoglobulin (IG) gene that regulates antigen receptors of the B cells. B cells secrete antibodies which target both bacteria and viruses, unlike T cells that can only recognize viral antigens [58].

The HMC Gene Crucial for the Adaptive Response

There is evidence that severely ill patients are deficient in the human leukocyte antigen (HLA) system of proteins which are recorded by the major histocompatibility complex (HMC) gene. HMC genes that encode many proteins involved in T cells antigens that are active during the adaptive response, are upregulated in recovered patients but not in deteriorated ones. HMC genes are essential for the adaptive immune response, therefore, possibly the transition from the innate to the adaptive immune response may be flawed. As a result the immune target remains non-specific, with compromised recognition of the actual virus, resulting in an indiscriminate general attack that involves the tissues of vital organs with inevitable deleterious circumstances [59, 60].

COVID-19 Therapeutics

The World Health Organization (WHO) has indicated oral or intravenous corticosteroids may be beneficial for COVID-19 patients in critical care.

1. Dexamethasone has significant anti-inflammatory and immunosuppressant effects to suppress and protect against the deleterious consequences of the cytokine storm.
2. It should be noted that self-medication with any drug or antibiotics is not recommended.
3. The World Health Organization WHO advices against the use of corticosteroids for patients who do not exhibit severe COVID-19 symptomatology, because corticosteroids will suppress their immune system when its most needed to fight the virus as well as certain adaptive inflammatory processes designed to protect the body. Corticosteroids are only recommended for patients taken by the cytokine storm when the immune system has gone awry, sinking into a blind hyperinflammatory state, where white blood cells indiscriminately attack both the virus and the vital organs that contain it, eventually killing the patient [61].
4. The FDA has created the Coronavirus Treatment Acceleration Program (CTAP) which examines a number of different therapeutics that include:

    a. 50 plus antivirals, designed to stop the virus from multiplying;

    b. 50 plus cell and gene therapies that include cellular immunotherapies and stem cells, or manipulate gene expression, respectively;

    c. 130 plus immunomodulators like the therapeutic dexamethasone described above;

    d. Sixty plus neutralizing antibodies that include convalescent plasma and hyperimmune globulin that contain antibodies from COVID-19 patients, manufactured antibodies or animal-sourced antibodies [62]

COVID-19 Therapeutics Given Emergency Authorization by the FDA

A. Recombinant humanized monoclonal antibody Therapies and others: To be administered only by healthcare providers.

1**. Actemra:** It has a binding affinity for interleukin-6 (IL-6) receptors, a proinflammatory cytokine involved in the cytokine storm. It is only recommended for severely ill hospitalised adult and pediatric patients, two years and above, who need

supplemental oxygen or are sustained by a ventilator as a result of their immune system being overwhelmed by hyperinflammation [63].

2**. Sotrovimab**: recombinant human IgG1k (immunoglobulin G1k) monoclonal antibody, designed to protect the body from infection with a binding affinity to the COVID-19 Spike protein epitopes, the viral cite that is recognized by the immune system. It is effective in treating mild to moderate COVID-19 infections in adults and children over 12 years of age that weigh at least 40kgs [64].

3. **Bamlanivimab and Etesevimab** that are administered together to adult or pediatric patients over 12 years that weight at least 40 kgs with mild or moderate symptomatology of the COVID-19 infection. Bamlanivimab and Etesevimab neutralize IgG1 monoclonal antibodies that bind to overlapping Spike protein epitopes [65].

4. **Casirivimab and Imdevimab (REGEN-COV).** These are recombinant human IgG1 monoclonal antibodies that target the binding domain of the Spike protein, preventing it from fusing with ACE2 receptors. They are to be administered together to COVID-19 outpatients that include both adults and children above 12 years or age that weigh at least 40 Kgs, to avoid further deterioration and hospitalization [66].

5. **Baricitinib (Olumiant) in combination with Remdesivir (Veklury**). This compound is appropriate for hospitalized adults and pediatric patients over 2 years of age that are suspected of or confirmed with a COVID-19 infection. These patients should be ill enough to require supplemental oxygen or invasive / non-invasive mechanical ventilation. Baricitinib is a Janus kinase (JAK) inhibitor. They prevent the signalling of the JAKs' intracellular enzymes stimulated by the intertwined actions of cytokine and growth factor-receptors that control the formation, development and differentiation of blood cells, and the functions of immune cells. Adding Baricitinib to Remdesivir therapy appeared to be more effective than merely administering Remdesivir [67].

6. **Remdesivir (Veklury)** was approved by the FDA on October 2020 for COVIE-19 infected adults and pediatric patients over 12 years of age and weighing at least 40 Kgs, that may require hospitalization [68]. Remdesivir is designed to inhibit viral DNA

Replication. As previously stated Nucleocapsid (N) proteins are instrumental in the viral RNA replication and transcription that is facilitated by the RNA-dependent RNA polymerase 12 (RdRp), or otherwise known as non-structural protein 12 (nsp12) in collaboration with the non-structural proteins nsp7 and nsp8. Nsp12 is the primary target of Remdesivir, a nucleotide analogue (NA) antiviral inhibitor that has recently gained popularity in the treatment of COVID-19 by inhibiting viral RNA replication [69, 70, 71, 72, 73, 74, 75]. Clinical research found a statistically significant advantage of COVID-19 patients receiving a 5-day Remdesivir course vs standard care, but no difference between the 5- and 10-day Remdesivir courses [76]. However, a data analysis shows only a small clinical improvement between the 5-day / 10-day Remdesivir groups when juxtaposed against the standard care group. From the 193 patients who received a 10-day Remdesivir course, 2 died and one required invasive mechanical ventilation, while 0 needed non-invasive ventilations. From the 191 patients who received a 5-day Remdesivir course, 0 died or required invasive mechanical ventilation, while 5 needed non-invasive ventilation. From the 200 standard care patients, 4 died, 4 required invasive mechanical ventilation, and 7 required non-invasive ventilation. Subsequent evidence with 1,300 participants revealed that Remdesivir may speed up clinical improvement and reduce fatalities in severely ill patients. Overall, most current research provides low certainty, and a weak recommendation for Remdesivir in the treatment of COVID-19 [77, 78, 79, 80].

7. **COVID-19 Convalescent Plasma.** This is meant for the treatment of hospitalized patients infected by COVID-19 with severe symptomatology and with impaired humoral immunity,. It is human plasma that contains COVID-19 antibodies, collected by COVID-19 infected individuals [81].

Protective Methods.

The extensive person-to-person transmission of COVID-19 by asymptomatic individuals or those at the initial stages of the disease has driven the World Health Organization (WHO) to reverse their original recommendation in which they did not require face coverings [82, 83, 84, 85, 86, 87]. Wearing masks can protect the public

from those who have already contracted the virus, while being a successful prophylactic measure in reducing the viral load when one is near infected individuals [88, 89, 90]. Social models emerging from Taiwan, China and Hong Kong where a large part of the population wears masks have demonstrated both a lower infection and mortality rate, unlike countries like the USA where not wearing a mask is considered as a right to personal freedom [91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103]. Hygiene and social distancing are globally accepted as additional protection methods against COVID-19.

Capitalize on Wellbeing

Visceral Adiposity: the Number One Public Enemy

A retrospective clinical trial on 150 COVID-19 patients demonstrated that Visceral adiposity ($p=0.032$ $p<0.05$), age ($p=0.009$ $p<0.01$) and inflammation measured by C-reactive protein (CRP - $p<0.0001$), were positively correlated with poor prognosis and elevated mortality rates [104]. Another clinical study used computer tomography (CT) to determine the presence of Visceral Adipose Tissue (VAT) in COVID-19 infected patients. BMI did not distinguish between patients in the normal ward and Intensive Care Unit (ICU) with or without mechanical ventilation. In fact the ICU patients without mechanical ventilation had a slightly higher BMI. ICU patients that did not required mechanical ventilation manifested larger amounts of subcutaneous fat; however, the most severely ill ICU patients that required mechanical ventilation were distinguished by their accumulated VAT. These investigators concluded that VAT may be a possible predictor of exacerbated symptomatology and poor prognosis after contracting COVID-19 [105]. These results were confirmed by another CT study examining hepatic steatosis associated with visceral fat as sell as epicardial adipose tissue (EAT) in younger COVID-19 patients under 40 years of age that classified VAT as one of the primary risk factors of viral vulnerability and disease severity [106].

Fitness Comes to the Rescue of Health

VAT has a higher expression of ACE2 receptors, which, as previously noted, represent

the entry points of COVID-19, in contrast to muscle tissue that has the lowest expression of ACE2 receptors. Therefore, any method that reduces VAT, utilizing it as an energy source to increase muscle can serve as a protective and preventive measure to safeguard health during this pandemic. VAT generates more fatty acids, angiotensinogen, and the proinflammatory cytokine interleukin-6 than subcutaneous adipose tissue (SAT) [107]. Glucose and fatty acids metabolism provide the energy both for the basal metabolic processes that sustain life during rest, and the increased demand for energy during exercise where myokines like Insulin Growth Factor-1 (IGF-1), Fibroblast Growth Factor2 (FGF2), interleukins-6 (IL-6) and IL-7 are involved in muscle hypertrophy [108, 109]. Experiments where artificially elevated free fatty acids were added during sustained physical activity found that the metabolic process initially used carbohydrates in the first 15 minutes, decreasing glycogen by 50%, and increasing fat oxidation by 15% after 30 minutes [110, 111]. Fat metabolism reflects a complex process that commences with the release of free fatty acids (FFA) from the adipose tissue, which are transferred across the membranes of muscle cells, where they bind with protein receptors in the cytoplasm, with the mitochondria being the final destination, where the oxidation process, i.e. burning fat via oxygen takes place. This sequence of events results in the release of electrons, which in turn push protons to mobilize the energy production process by spinning the ATPace synthase anabolic enzyme clockwise, to add a phosphate to Adenosine Diphosphate (ADP), via the transmembrane proton gradient to compose Adenosine Triphosphate molecular energy [112, 113, 114, 115, 116, 117].

The Importance of Hormones in Lipolysis

Growth Hormone (GH) appears to be instrumental in reducing visceral fat on the basis of a 12 month computed tomography (CT) clinical trials that administered recombinant human GH to 40 postmenopausal women, demonstrating reduced visceral fat tissue upon completion [118]. A clinical trial in Europe demonstrated a high correlation between leptin and VAT [119], however, other studies with Asian men and African American women indicated that leptin is associated with overall fat rather than VAT

specifically. Overall, relatively to SAT, VAT is presumed to secrete less anorexic hormone leptin.

VAT appears to be a reliable predictor of insulin sensitivity, elevated levels of triglycerides and inhibited high density lipoproteins (HDL) [120, 121]. VAT is also associated with triiodothyronine (T3) and the identifier of atherosclerosis pulse wave velocity (PWV) [122].

Weight Loss Laser and RF Technology

Weight management solutions including lasers and RF primarily address subcutaneous fat reduction with no evidence of increased fitness; additionally, there are several reports of eventual escalated inflammation following some of these procedures [123, 124, 125, 126, 127, 128]. Pre-existing inflammation can potentially exacerbate the deleterious immune response termed “cytokine storm” that is detected in COVID-19 severe cases; therefore, inflammation inducing procedures may be counterproductive and conceivably dangerous.

The Double Edged Sword of Exercise

Physical fitness has been deemed a health enhancing solution by a number of research projects. On the other hand, there is evidence that exercise may induce asthma that usually exacerbates COVID-19 symptomatology, or provoke an inverse cortisol/testosterone relationship, while supressing the anorexic hormone leptin, thus increasing food consumption [129, 130, 131, 132, 133].

Effortless Exercise: The Alternative

Recent studies report an advantage with an exercise alternative method invented in London University that results in hormonal balance, and enhanced wellbeing as measured by statistically significant decreases of visceral fat, inflammation, CRP, BMI and Triglycerides, juxtaposed by optimal increases of skeletal muscle mass, Free T3, IGF-1 and HDL [134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144]. The variables involved were the following:

1. Visceral Adipose Tissue (VAT)
2. Skeletal Muscle Mass (SMM)
3. Cortisol
4. C Reactive Protein (CRP)
5. High Density Lipoprotein (HDL)
6. Triglycerides
7. Insulin Growth Factor-1
8. Free Triidothyronine (T3)
9. Leptin
10. Ghrelin

Methodology

We adopted the same London University technology used in the clinical studies cited in previous chapters. The technology was invented by Gerald Pollock, one of the co-inventors of the first pacemaker, and Donald Gilbert, a molecular biology London University professor, on the basis of his extensive research on cellular behaviours. It was built in London University over a period of 17 years with its first version completed in 1994. It was further researched and updated in the Business Innovation Centre by Gerry Pollock for another 18 years until 2012 when he died. Then, further research was conducted by a group of scientists that is ongoing currently. The technology is designed to give 8 seconds full contractions involving the coordinated muscles of the entire body working together as it happens in strenuous exercise. Unlike muscle stimulators that are either current, or combined current and voltage driven, this novel technology is exclusively voltage driven and does not depend on current. It emits 24 unlimited resolution voltage-driven complex square waveforms, each synthesized by up to 4000 sine frequencies on the basis of a proprietary formula. Any current generated by the voltage based on Ohm's law is in the low microcurrent range and cannot be directly measured, since the device's output is solely based on voltage and not on current. The technology is manually operated to combine the 12 lower frequency

complex resultant waveforms on the one side of the apparatus with the 12 higher frequency complex resultant waveforms on the opposite side to offer long contractions that hold the muscles for eight seconds and which are usually experienced as simulated resistance, endurance and strength exercises. The sensation is vigorous but painless and reportedly pleasant. The technology complies with the EEC UK directive of electrical equipment safety applied standard EN 60601-1, and has a CE marketing directive of Class I with electromagnetic compatibility regulations applied standards EN50081-1 and EN50082-1. FDA clearance numbers are K132158 and K132179, applied to earlier versions of this technology with the same hardware design, intended for usage in physical medicine. The only contraindication, according to the FDA, is having an implanted device like a pacemaker. The main caution is pregnancy. Adverse reactions are limited to temporary skin redness from the pads that occurs sporadically, and usually dissipates within an hour. Measuring instruments included:

1) A blood test that examined levels of HDL, triglycerides, Free T3, IGF-1, cortisol, CRP, Leptin and Ghrelin.

2) A conductance instrument that calculated BMI, VAT and SMM

3) A measuring tape.

Procedure

The data of 89 subjects was collected from four private clinics located in different parts of the world. The participants were 27-81 years of age with an average BMI of 32.96. They completed 12 -15 treatments with the technology described in the methodology section, before they were approached to give their consent to be included in the study. The subjects results on the blood tests, conductance scale and measuring tape after 12 treatments were compared against their baseline before any treatment was initiated. Different clinics tested different variables, therefore certain variables like the CRP and Cortisol were only based on 10 subjects. The number of subjects and number of treatments they received before and after they were tested on a particular variable are given below:

1. Clinic A. 29 subjects had scores on VAT and SMM after 12 treatments, 20 females and 9 males. 21 out of these 28 subjects had been diagnosed with hyperphagia. Two of the subjects diagnosed with hyperphagia were diabetics and four were prediabetics. These same 29 subjects also had provided their blood test results of Leptin and Ghrelin after 12 treatments.
2. Clinic B. 10 Females gave their blood test results on CRP and Cortisol after 15 treatments. All subjects had been diagnosed with at least one medical disorder. One of these subjects was diabetic and 5 were pre-diabetics. Seven out of the 10 subjects had non-alcoholic steatosis, or what is commonly known as fatty liver.
3. Clinic C. 30 subjects, 22 females and 8 males had results on HDL and Triglycerides after 15 treatments. Thirteen out of these subjects were diabetics and thirteen were prediabetics. Five of these subjects also suffered by hypothyroidism. Four of them had hypertension and one of them had heart disease.
4. Clinic D. 20 subjects, 15 females and 5 males released their blood test results on Free T3 and IGF-1 after 12 treatments. Ten out of 15 of these females had hyperphagia. Two out of these ten females also had diabetes. Four of them had prediabetes in addition to hyperphagia and two had hypertension. Ten out of the 20 subjects, five males and five females did not have a reported medical disorder.

The procedure was standardized because all four clinics had been trained by the same trainer and were following the same principle on the basis of the same manual. Getting results after the treatments had been completed secured a double blind design for this clinical trial, since neither the patients included in these studies, nor the operators or even the clinic managers were aware that the data produced would be eventually used for research purposes. All data was collected from the clinics' records. It was hypothesized that evaluating the statistical significance of results received from different world locations would reinforce external validity, provided that the results were consistently in the same direction and did not present fluctuation in the variables tested by the four clinics.

All clinics reported that subjects were randomly selected out of a large number of individuals receiving treatments with what they termed as a new, effortless exercise alternative. They also reported that all subjects completed the treatments willingly and that there was an attending physician in all clinics in case any subject experienced any adverse reactions or side effects. None of the subjects reported any adverse reactions or side effects The inclusion criteria were:

1. BMI >25.

2. Diabetics and prediabetics that were followed by physicians and their diabetic or prediabetic status was under control.

3. Hypertension and Heart Disease patients that were followed by physicians and their medical conditions were under control.

4. Hypothyroid patients and those with hyperphagia were followed by physicians and their conditions were under control.

5. No prior experience or treatments with the same technology. This was important to control the baseline level.

6. A sedentary lifestyle that did not include diet or regular exercise.

7. No additional or simultaneous treatment with any other technology.

The main exclusion criteria were:

1. Pregnancy or trying to become pregnant.

2. An implanted device like a cardiac pacemaker.

3. Severe medical and mental disorders.

4. Operation within the past six months.

5. Had recently received weight loss treatments in the past year.

6. On a strict or well monitored diet.

Every precaution was taken to protect the subjects' privacy and the confidentiality of their personal information. Subjects were not in a dependent relationship with the technology operators, the lab and measurement technicians, or the authors. The subjects did not receive specific instructions regarding changes in their lifestyles, and there was no methodical follow up of their food consumption. None of the technology operators, lab or measurement technicians had any known bias or personal interest in the direction of the results.

Five independent labs, (one from each private clinic that provided the blood tests), were assigned to take blood samples before and ten days after the completion of twelve one-hour treatments that took place three times a week, for four consecutive weeks. Subjects were asked to fast for twelve hours prior to getting their blood tests.

Following blood tests, tape and conductance scale measurements, each subject went to a private treatment room and lay on a massage table while the gel pads and cables from the 16 channels of the device were attached on to his/her body by the technology operator. The cables from ten of the channels were attached on to the gel pads of the waist, upper and lower abdomen according to a standardized diagram, and the cables from the six remaining channels were attached onto the gel pads placed along the lymphatic system pathways of the legs and arms, to enhance detoxification. The procedure was approved by the ethical boards of all clinics and was in accordance with the ethical standards and principles for medical research involving human subjects. Blood tests, Visceral Adipose Tissue (VAT) and tape measurements were also taken after all treatments had been completed.

Data Results Analysis:

Statistical significance was established by the Analysis of Variance. Visceral adipose tissue (VAT) decrease and skeletal mass (SMM) increase of 29 patients, 20 females and 9 males with an average BMI of 29.9 are shown on Table 1. Table 2 reflects the results of the same patients indicating a statistically significant increase in the anorexic hormone leptin contrasted by an optimal decrease in the orexigenic hormone

ghrelin. Table 3 depicts leptin ranges in relation to body mass index. Table 4 shows the inflammation reduction as measured by CRP and the cortisol decrease of 10 females with an average BMI of 32.91 and at least one medical condition.

Table 1. Results of 29 Subjects on BMI, Visceral Adipose Tissue (VAT) and Skeletal Muscle Mass (SMM) Tx=15. Abbreviations: G=gender; A=age

G /A	Medical History	BMI Pre	BMI Post	BMI % Decrease	VAT Pre	VAT Post	VAT % Decrease	SMM Pre	SMM Post	SMM % Increase
F/ 48	Diabetes Hyperphagia	31.2	29.3	6.1%	142.6	119.4	-16.28%	12.74	14.66	+15.07%
F/ 54	Diabetes Hyperphagia	30.4	28.6	5.9%	138.5	112.3	-18.94%	11.45	12.95	+13.10%
F/ 56	Prediabetes Hyperphagia	31.6	29.9	5.37%	144.2	121.1	-23.11%	12.66	14.76	+6.58%
F/ 47	Hyperphagia	28.7	26.7	6.9%	123.5	96.48	-21.91%	16.86	19.45	+15.36%
F/ 52	Prediabetes Hyperphagia	26.8	24.9	7.1%	104.3	89.23	-14.51%	11.99	14.27	+19.01%
F/ 49	Hyperphagia	27.1	24.6	9.2%	108.9	87.44	-19.73%	12.67	16.59	+30.93%
F/ 58	Prediabetes Hyperphagia	29.5	25.9	12.2%	119.6	98.66	-17.55%	11.32	12.60	+11.30%
F/ 50	Hyperphagia	27.3	25.3	7.3%	117.8	95.64	-18.81%	11.04	13.96	+26.45%
F/ 55	Prediabetes Hyperphagia	27.1	24.8	8.5%	98.77	81.32	-17.66%	12.30	13.94	+13.33%
F/ 49	Hyperphagia	29.5	26.3	11.5%	121.6	105.2	-13.47%	12.15	13.93	+14.65%
M/ 39	Hyperphagia	33.8	29.4	14.9%	139.3	93.80	-32.66%	36.40	43.80	+20.3%
M / 40	Hyperphagia	29.6	25.7	13.2%	102.2	69.30	-32.19%	30.30	38.60	+27.39%
F / 39		26.1	23.2	11.1%	93.50	58.30	-37.64%	18.40	27.00	+46.79%
F / 41		25.9	22.7	12.4%	85.50	61.40	-28.30%	17.00	26.80	+57.64%
M / 40		24.8	22.4	9.7%	76.40	48.80	-36.12%	37.80	44.80	+18.5%
M / 42	Hyperphagia	28.6	24.7	13.6%	118.6	89.30	-24.70%	29.40	38.30	+30.27%
F / 48		27.3	23.8	12.9%	98.80	70.60	-28.54%	17.20	26.80	+55.81%
F / 43	Hyperphagia	29.4	26.2	10.9%	102.7	77.30	-24.73%	19.80	28.80	+45.45%
M / 39	Hyperphagia	33.2	30.5	8.1%	145.3	104.3	-28.18%	29.80	37.22	+25.89%
F / 42		28.9	24.7	14.5%	109.8	74.67	-31.99%	17.95	26.63	+48.35%
F / 42		29.7	25.7	13.5%	128.9	113.1	-12.27%	27.65	30.87	+11.64%
M / 36	Hyperphagia	33.3	26.9	20.1%	131.2	98.53	-24.9%	33.30	39.60	+18.91%
M / 39	Hyperphagia	34.2	27.3	20.2%	119.6	96.62	-19.26%	36.40	39.80	+9.34%
M / 43	Hyperphagia	32.8	26.4	19.5%	99.56	79.34	-20.22%	27.13	31.95	+17.75%

M / 35		29.6	25.9	14.2%	121.6	104.2	-14.29%	17.57	23.32	+32.72%
F / 42	Hyperphagia	35.2	27.4	22.2%	129.7	109.2	-15.76%	20.16	24.53	+21.67%
F / 45	Hyperphagia	33.8	26.1	22.8%	109.6	95.85	-12.56%	16.89	22.85	+35.28%
F / 49	Hyperphagia	32.6	27.8	14.7%	122.6	87.85	-28.38%	20.73	25.52	+23.11%
F / 38		28.9	24.5	15.2%	134.6	112.8	-16.22%	16.83	23.18	+37.73%
	BMI DECREASE	**29.9**	**26.1**	**12.7%**	**Mean Average Visceral Fat % Decrease**		**-22.4%**	**Mean Average SMM % Increase**		**+25.87%**

Table 2. *Blood Plasma Results of 29 Subjects with an average BMI of 29.9 on Leptin (Reference Ranges of Leptin Levels According to Body Mass Index, Gender and Development Stage [Table 3]. Blood Plasma Results on Ghrelin for overweight individuals: 340-450 pg/mL. Ghrelin normal range for normal weight individuals: 520-700 pg/mL. Abbreviations: G=gender; A=age*

G /A	Medical History	BMI	Leptin Pre (ng/ml)	Leptin Post (ng/ml)	Leptin Normal Range (ng/ml)	Leptin % Increase ng/ml	Ghrelin Pre pg/ml	Ghrelin Post pg/ml	Ghrelin Normal Range pg/ml	Ghrelin % Decrease pg/ml
F/ 48	Diabetes Hyperphagia	31.2	21.45	27.44	12-67.5	+27.9%	483	414	340-450	-14.28%
F/ 54	Diabetes Hyperphagia	30.4	14.63	18.08	10.6-58	+23.5%	488	463	340-450	-5.13%
F/ 56	Prediabetes Hyperphagia	31.6	10.67	13.66	12-67.5	+28.%	462	398	340-450	-13.85%
F/ 47	Hyperphagia	28.7	7.09	11.33	7.9-43.5	+59.8%	345	376	340-450	-8.98%
F/ 52	Prediabetes Hyperphagia	26.8	12.34	15.12	5.9-32.4	+22.5%	498	453	340-450	-9.03%
F/ 49	Hyperphagia	27.1	10.65	12.39	6.8-37.5	+16.3%	357	313	340-450	-12.32%
F/ 58	Prediabetes Hyperphagia	29.5	20.66	21.45	9.1-50.4	+3.8%	387	364	340-450	-5.94%
F/ 50	Hyperphagia	27.3	11.65	15.43	6.8-37.5	+3.8%	401	389	340-450	-2.99%
F/ 55	Prediabetes Hyperphagia	27.1	15.24	18.56	6.8-37.5	+21.8%	465	432	340-450	-7.09%
F/ 49	Hyperphagia	29.5	18.54	19.82	9.1-50.4	+6.9%	474	439	340-450	-7.38%
M/39	Hyperphagia	33.8	7.38	7.84	**14-78.2**	+6.2%	683	614	340-450	-10.1%
M/40	Hyperphagia	29.6	6.25	7.03	9.1-50.4	+12.4%	588	576	340-450	-2%
F/39		26.1	12.43	13.22	**5.9-32.4**	+6.3%	612	584	340-450	-4.5%
F/41		25.9	11.98	12.09	**5.1-28.0**	+0.9%	599	543	520-700	-9.34%
M/40		24.8	5.53	5.94	**4.4-24.2**	+7.4%	602	553	520-700	-8.13%
M/42	Hyperphagia	28.6	6.42	6.97	**7.9-43.5**	+8.5%	603	576	340-450	-4.47%

F/48		27.3	10.87	11.84	**6.8-37.5**	+8.9%	687	612	340-450	-10.9%
F/ 43	Hyperphagia	29.4	9.89	10.54	9-50.4	+3.5%	623	565	520-700	-9.30%
M/39	Hyperphagia	33.2	5.47	6.01	**16-90.5**	+4.1%	589	532	340-450	-9.71%
F/42		28.9	9.99	10.83	**7.9-43.5**	+6.4%	634	513	340-450	-19.08%
F/42		29.7	3.69	3.98	**9.1-50.4**	+7.8%	687	602	340-450	-12.37%
M/36	Hyperphagia	33.3	4.43	4.98	**16-90.5**	+9.7%	695	634	340-450	-8.77%
M/39	Hyperphagia	34.2	5.62	6.22	**19-105**	+10.6%	598	552	340-450	-7.69%
M/43	Hyperphagia	32.8	6.15	6.83	**14-78.2**	+11.0%	629	587	340-450	-6.68%
M/35		29.6	9.16	9.74	**9.1-50.4**	+6.3%	577	542	340-450	-6.06%
F/42	Hyperphagia	35.2	5.23	6.09	**22.-121**	+16.4%	659	613	340-450	-6.99%
F/45	Hyperphagia	33.8	7.22	8.17	**16-90.5**	**+13.1%**	644	617	340-450	-4.19%
F/49	Hyperphagia	32.6	12.34	13.22	**14-78.2**	+7.1%	569	536	340-450	-5.79%
F/38		28.9	11.38	13.08	**7.9-43.5**	+14.9%	499	461	340-450	-7.62%
Average BMI		**29.9**	**Mean Average Leptin % Increase**			**12.99%**	**Mean Average Ghrelin % Decrease**			**-8.30%**

Table 3. Leptin Ranges by Body Mass Index ng/mL

BMI	Range	BMI	Range
11	0.7 - 3.6	24	4.4 -24.2
12	0.8 - 4.2	25	5.1 -28.0
13	0.9 - 4.8	26	5.9 -32.4
14	1.0 - 5.6	27	6.8 -37.5
15	1.2 - 6.5	28	7.9 -43.5
16	1.4 - 7.5	29	9.1 -50.4
17	1.6 - 8.7	30	10.6 -58.3
18	1.8 - 10.0	31	12.2 -67.5
19	2.1 - 11.6	32	14.1 -78.2
20	2.4 - 13.4	33	16.4 -90.5
21	2.8 - 15.6	34	19.0 -105.0
22	3.3 - 18.0	35	22.0 - 121.0
23	3.8 - 20.9	36	25.4 - 141.0

Table 4. *Blood Test Results on 10 Female Subjects with an average BMI of 32.9 for C-reactive protein (CRP) and Cortisol. Abbreviations: G=gender; A=age*

CRP: <1.0 mg/dL. Low cardiovascular risk according to AHA/CDC

CRP: 1.0-3.0 mg/dL Average cardiovascular risk according to AHA/CDC

CRP: >3.0-10.0 mg/dL High cardiovascular risk according to AHA/CDC

G	A	Medical History	BMI Pre	CRP Pre mg/dL	CRP Post	CRP Normal	Cortisol Total, Serum	Cortisol	Cortisol Normal

					mg/dL	Range mg/dL	ug/dL, Pre	Total, Serum ug/dL, Post	Range ug/dL
F	56	Diabetes Fatty Liver	32.6	1.56	1.02	<1.00	18.44	15.66	3.09-25.0
F	52	Prediabetes Fatty Liver	36.5	1.09	1.06	<1.00	21.89	20.12	3.09-25.0
F	49	Hypertension Hypothyroidism	28.6	2.31	1.15	<1.00	24.98	18.47	3.09-25.0
F	63	Hypertension Fatty Liver	34.9	1.93	1.06	<1.00	23.43	21.98	3.09-25.0
F	51	Prediabetes Hypertension Hypothyroidism	34.2	1.43	1.22	<1.00	18.46	15.34	3.09-25.0
F	55	Prediabetes Fatty Liver Hypothyroidism	35.4	1.64	1.01	<1.00	19.33	14.75	3.09-25.0
F	48	Prediabetes Fatty Liver Hypothyroidism	30.9	1.04	0.86	<1.00	9.67	8.23	3.09-25.0
F	61	Hypertension Fatty Liver	32.7	1.08	0.74	<1.00	14.76	10.65	3.09-25.0
F	46	Heart Disease	29.5	1.84	0.98	<1.00	17.22	13.95	3.09-25.0
F	58	Prediabetes Fatty Liver Hypothyroidism	33.8	2.11	1.03	<1.00	21.28	17.24	3.09-25.0
Mean Average CRP % Decrease					**-36.87 mg/dL**		**Mean Average Cortisol % Decrease**	**-17.47% ug/dL**	

Table 5 reflects the results of 30 subjects, 22 females and 8 males with an average BMI of 32.96 on HDL and Triglycerides. Thirteen out of these subjects were diabetics and thirteen were prediabetics.

Table 5. *Blood Test Results on 30 subjects. Abbreviations: G=gender; A=age. PreD=Prediabetes; HypoT=Hypothyroidism; HyperT= Hypertension; Heart D= Heart Disease; Medical Hi= Medical History NR=Normal Range; TriglyceR= Triglycerides*
High-Density Lipoprotein (HDL) Normal Range: Men > 60 mg/dL; Women > 60 mg/dL
High-Density Lipoprotein (HDL) At Risk: Men: <40 mg/dL; Women < 50 mg/dL

G/A	BMI	Medical Hi	HDL Pre mg/dL	HDL Post mg/dL	HDL NR mg/mL	TriglyceR Pre mg/dL	TriglyceR mg/dL Post Tx	TriglyceR NR mg/dL
F/56	32.6	Diabetes Fatty Liver	53	61	>60	144	137	<150

F/52	36.5	PreD Fatty Liver	39	57	>60	169	146	<150
F/49	28.6	HyperT HypoT	61	79	>60	129	114	<150
F/63	34.9	HyperT Fatty Liver	46	64	>60	163	152	<150
F/51	34.2	PreD HyperT HypoT	41	55	>60	159	150	<150
F/55	35.4	PreD Fatty Liver HypoT	43	51	>60	173	159	<150
F/48	30.9	PreD Fatty Liver HypoT	63	76	>60	153	139	<150
F/61	32.7	HyperT Fatty Liver	52	71	>60	175	148	<150
F/46	29.5	Heart D	59	68	>60	136	129	<150
F/58	33.8	PreD Fatty Liver HypoT	38	52	>60	182	157	<150
F/45	34.4	Diabetes	32	39	>60	203	158	<150
M/69	28.5	Diabetes	35	47	>60	215	128	<150
M/46	35.3	Diabetes	28	37	>60	230	153	<150
F/50	38	Diabetes	49.6	53	>60	86.7	84.3	<150
F/49	40.5	Diabetes	34.5	38	>60	103	88	<150
F/46	36.2	Diabetes	32	39	>60	287	176	<150
M/48	38.5	Diabetes	29	41	>60	266	147	<150
F/44	38.2	Diabetes	30	35	>60	283	189	<150
F/43	27.7	PreD	36	42	>60	294	197	<150
F/27	35.4	PreD	36	48	>60	192	126	<150
F/63	30.7	PreD	45	47	>60	155	117	<150
F/24	33.9	PreD	45	52	>60	88	86	<150
F/30	32.0	PreD	37	46	>60	156	124	<150
F/45	30.1	Diabetes	33	40	>60	225	179	<150
F/47	25.1	Diabetes	31	41	>60	237	188	<150
M/45	29.4	Diabetes	41	45	>60	112	105	<150
M/82	34.5	Diabetes	26	38	>60	97	94	<150
M/15	31.8	PreD	36	42	>60	187	132	<150
M/58	28.9	PreD	43.1	46.8	>60	141	136	<150
M/46	30.6	PreD	52.3	56	>60	262	158	<150

BMI	32.96	Total HDL %	+22.84%	Total Triglycerides %	-40.84%

Table 6 reflects the results of 20 subjects, 15 females and 5 males on Free T3 and IGF-1.

Table 6. Blood Test Results on 20 Subject

IGF-1 and Free T3 for each subject. Abbreviations: G=gender; A=Age

G/A	Medical History	IGF-1 PRE nmol/L	IGF-1 POST nmol/L	Normal Range nmol/L	IFG-1% Increase nmol/L	Free T3 PRE nmol/L	Free T3 POST nmol/L	Normal Range nmol/L	% Increase nmol/L
M/32	None known	25.97	30.35	15.08-32.5	+16.86%	2.98	4.22	2.63-5.7	+41%
M/35	None known	23.98	31.12	15.08-32.5	+29.77%	3.69	4.98	2.63-5.7	+34.95%
F/36	None known	16.33	20.75	11.25-28.8	+27.06%	4.77	5.37	2.63-5.7	+12.5%
F/35	None known	15.14	19.21	11.25-28.8	+26.88%	4.56	5.31	2.63-5.7	+16.44%
M/37	None known	22.27	28.11	15.08-32.5	+26.22%	4.15	5.47	2.63-5.7	+31.80%
M/39	None known	26.98	30.52	15.08-32.5	+11.80%	3.29	4.86	2.63-5.7	+47.7%
F/39	None known	15.86	21.08	11.25-28.8	+32.91%	4.36	5.64	2.63-5.7	+29.35%
F/32	None known	18.55	23.50	11.25-28.8	+26.68%	3.66	4.79	2.63-5.7	+30.87%
M/36	None known	24.56	31.34	15.08-32.5	+27.60%	3.19	4.12	2.63-5.7	+29.15%
F/33	None known	19.34	25.66	11.25-28.8	+32.67%	4.09	5.12	2.63-5.7	+25.18%
F/ 48	Diabetes Hyperphagia	12.23	14.17	11.25-28.8	+14.86%	2.19	2.88	2.63-5.7	+31.50%
F/ 54	Diabetes Hyperphagia	11.65	12.33	11.25-28.8	+5.83%	2.34	2.76	2.63-5.7	+34.95%
F/ 56	Prediabetes Hyperphagia	11.17	12.79	11.25-28.8	+14.50%	1.98	2.64	2.63-5.7	+33.33%
F/ 47	Hyperphagia	13.94	17.21	11.25-28.8	+23.45%	2.67	2.93	2.63-5.7	+9.73%
F/ 52	Prediabetes Hypertension Hyperphagia	12.27	14.32	11.25-28.8	+7.65%	2.32	2.89	2.63-5.7	+21.98%
F/ 49	Hyperphagia	12.18	14.72	11.25-28.8	+20.85%	2.89	3.05	2.63-5.7	+5.53%
F/ 58	Prediabetes Hypertension Hyperphagia	10.21	11.99	11.25-28.8	+17.43%	2.29	2.78	2.63-5.7	+21.39%
F/ 50	Hyperphagia	12.87	14.36	11.25-28.8	+11.57%	2.68	3.29	2.63-5.7	+22.76%
F/ 55	Prediabetes Hyperphagia	11.43	12.85	11.25-28.8	+12.42%	2.16	2.59	2.63-5.7	+19.91%
F/ 49	Hyperphagia	13.82	15.26	11.25-28.8	+10.41%	2.86	3.11	2.63-5.7	+8.74%
		Total IGF-1 % Increase			+20.81%	Total Free T3 % Increase			+27%

Table 7 shows the significance values for all variables after the data was analysed with ANOVA for repeated measures. Results yielded highly statistically significant results. Visceral fat decrease was accompanied with increased skeletal muscle mass. IGF-1, Free T3 and Leptin increased within the

normal range, while cortisol and ghrelin decreased but without descending into abnormality. These results demonstrated a centralized tendency towards hormonal balance and optimal appetite regulation resulting by a healthy proportional interaction between the anorexic hormone leptin, juxtaposed by the relatively suppressed concentrations of the orexigenic hormone ghrelin, combined with reduced cortisol that is known to provoke stress-eating behaviours. Elevated HDL was accompanied by diminished triglycerides.

Table 7. Analysis of Variance Statistical Significance Results on all variable
Abbreviations: BT: Between Treatments / WT: Within Treatments / E: Error

	SS	df	MS	F-Ratio Value	p-Value	Significance Level
Visceral Fat and Skeletal Muscle Mass with respect to BMI	BT: 200125.5873 WT:23548.7737 E:14365.2314	BT:3 WT:112 Error:84	BT: 66708.5291 WT: 210.2569 E: 171.0147	***F* = 390.074**	<0.00001	P<0.0001
Leptin & Ghrelin with respect to BMI	BT: 7973224.9161 WT526895.232 E: 286246.947	BT:3 WT:112 E:84	BT: 2657741.6387 WT: 4704.4217 E: 3407.7017	***F* = 779.92202**	<0.00001	P<0.0001
CRP & Cortisol with respect to BMI	BT: 2611.4641 WT: 334.1695 E: 158.7755	BT:3 WT:36 E:27	BT: 870.488 WT: 9.2825 E: 5.8806	***F* = 148.02771**	<0.00001	P<0.0001
HDL & Triglycerides with respect to BMI	BT: 418381.4549 WT: 137444.281 E: 88582.5476	BT:3 WT:116 E:87	BT: 139460.485 WT:1184.8645 E: 1184.8645	***F* = 136.96899**	<0.00001	P<0.0001
IGF-1 & Free T3	BT: 4489.9666 WT: 1570.9796 E: 652.5712	BT:3 WT:76 E:57	BT: 1496.6555 WT: 20.6708 E: 11.4486	***F* = 130.72807**	<0.00001	P<0.0001

Methods to Combat the Invisible Enemy

Human immunity seems to be vulnerable and unprepared to combat this new invisible enemy, COVID-19 that has succeeded in infecting over 196,006,221 individuals worldwide, resulting in 4,193,332 deaths by July 2021. Worst of all, the danger is exacerbated from within during the cytokine storm, where immune defenses fail to distinguish self from non-self, vandalizing the vital organs of the host.

ACE2 Receptors: The Official Portals of COVID-19

The virus enters the system via ACE2 receptors. COVID-19 occupies ACE2. Immobilized ACE2 receptors cannot fulfil their function of transforming Angiotensin II (Ang II) into Angiotensin (1-7) an anti-inflammatory agent that reduces blood pressure. Angiotensin II increases inflammation and blood pressure. High blood pressure is deleterious to diseases such as hypertension, diabetes, and cardiovascular illness, Therefore, COVID-19 predictably threatens these conditions by seizing ACE2 receptors that normally catalyse AngII controlling blood pressure. Hypertension, diabetes and heart disease represent some of the most common pre-existing conditions with elevated mortality rates following COVID-19 infection. Additionally, elevated Ang II increases concentrations of 'A Disintegrin And Metalloprotease 17' (ADAM17) that is involved in the shedding of ACE2 receptors, and the processing of the tumour necrotic factor alpha (TNF-a) that plays a key role in the cytokine storm.

The Variability of ACE2 Receptors in Human Tissues

Human tissues' research has revealed a multitude of ACE2 receptors in adipose tissue, heart, kidneys, thyroid, testes and small intestines with relatively less ACE2 expression in the muscle, brain, spleen and blood vessels. Lungs, liver, adrenal gland, bladder and colon seem to be somewhere in between. Investigation of immune cells in four groups that consisted of males, females, younger and older individuals, has revealed a greater susceptibility among the elderly in terms of increased immune cells in the lungs. Males were characterized by a higher ACE2 expression in the testes, and an increased number of immune cells / ACE2 positive correlations in the lungs, thyroid, adrenals, liver and colon. In contrast, females presented a higher positive correlation between immune cells and heart tissues' ACE2 receptors. All other vital organ tissues manifested equivalent levels of positive correlations between immune cells and ACE2 receptors in both sexes. In other words, there may be a COVID-19 preference for males and older individuals, but without a safety guarantee for females that may be equally susceptible in certain cases.

Cytokine Stork: The State of Panic

A literature review of the immune overreaction during the cytokine storm suggests a possible imbalance between pro-inflammatory cytokines and their inhibitors, a deficient innate response due to insufficient production of INF type I, or a dysregulated transition from the non-specific / innate to the adaptive immune response that is designed to recognize and tailored an appropriate attack against a particular threat, represented in this case by COVID-19. Unfortunately a series of errors or malfunctions amplifies the immune response into a frenzied overreaction, that fails to exterminate the virus, yet perseveres aimlessly, injuring the body. Recent reports indicate that COVID-19 is empowered by hindering the critical process of viral recognition during the adaptive immune response.

Defensive Strategies Against COVID-19

Protective techniques including face coverings, social distancing, thorough hygiene, as well as prevention via fitness, health enhancement, and weight management, appear to be the most reliable methods of limiting the spread of the pandemic. Visceral adipose tissue (VAT) is strongly linked to COVID-19 severely ill patients in ICU needing mechanical ventilation, irrespective of BMI which does not distinguish between patients in normal wards and ICU. VAT has a higher expression of ACE2 receptors which represent the COVID-19 cellular portals. VAT generates more fatty acids, angiotensinogen, and the pro-inflammatory interleukin-6 (IL-6). During exercise that is either physical or effortless VAT can be utilized as an energy source to increase muscle mass. Muscle features the least ACE2 receptors, therefore limiting COVID-19 intra transmission within the cells. Therefore, increasing muscle mass can probably serve as a protective and preventive measure in safeguarding health from an excess of COVID-19 viral load. Lasers and RF primarily address subcutaneous fat reduction with no evidence of increased fitness, and often report escalated inflammation following some of these procedures. Physical activity has universally accepted benefits, but also a downside by provoking an inverse cortisol/testosterone relationship, while supressing

the anorexic hormone leptin, thus increasing food consumption. Recent research on an effortless exercise intervention presents statistically significant VAT and inflammation reduction, juxtaposed by skeletal muscle mass increase, along with reduced lipids, cortisol and the orexigenic hormone ghrelin; importantly, it also elevates Free T3, IGF-1 and the anorexic hormone leptin within the normal range, offering an optimal alternative to fast efficient fitness. These clinical trials, however, are mostly based on small samples, in the absence of imaging techniques that can substantiate their results, warranting the need for additional research.

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Conflict of Interest

The author declares no conflict of interests. This study was conducted by independent operators that were not employed or contracted by the author.

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EPILOGUE:

Questions and Answers

1. **Q: Should I be vaccinated?**

   A: Clinical trials gathered by the U.S. National Institute of Allergy and Infectious Diseases [1] report that 95.5% of individuals with severe COVID-19 symptomatology resulting in death are unvaccinated. Only 0.05% of vaccinated individual suffer life threatening or fatal COVID-19 infections. According to the World Health Organization a total of 3,696,135,440 people have been vaccinates as of July 25, 2021 [2]. The vaccines have high efficacy. Reported serious adverse effects are rare. Temporary pain and swelling limited to the vaccination side, transient headaches and fatigue attest to the exhaustive insurmountable labour of the immune system as it reassembles for a winning battle. Overall, the benefits of the vaccines available appear to be greater than the risks involved in contracting any of the highly contagious COVID-19 variants [3].

2. **Q: Why be vaccinated?**

   A: All evidence indicates that the benefits of vaccination surpass its risks. COVID-19 transmissibility rate is generally lower among vaccinated individuals. Importantly, this disease is not like cancer or diabetes that advance or improve affecting primarily the individual without endangering the community. Anyone infected by COVID-19 puts everyone around them at risk: both friends and enemies, family members and strangers. The diagnosis of cancer is frightening because as the malignancy spreads, it tarnishes the vital organs destroying life. COVID-19 does not only target one person but everything and everyone around us, including the surfaces we touch and the air we breathe. COVID-19 is a public cancer that can ravage families, societies, economies, expanding to devastate the planet Earth. Vaccines can reinforce the immune system with antibodies which ultimately restrict or prevent viral entry. Vaccines provide the keys to seal our doors and keep the invisible enemy outside. A detailed explanation on vaccines'

safety and effectiveness is given in section 1, along with their importance, in light of an uprise of progressively more infectious variants.

3. **Q: What can Stop COVID-19 from Entering our Bodies?**

   A: One of the most significant goals of the vaccine is to promote immune production of antibodies that will restrict or prevent COVID-19 entry. 80% of vaccines trigger antibodies that can bind with the Spike protein after only 10 days of the first dose. 100% of vaccines induce T-cells, specifically designed to target the Spike protein and defend us against the multifaceted manifestations of COVID-19 [4].

   Antibodies are Y shaped proteins. Certain antibodies recognize the S1 glycoprotein and fit onto the viral antigens like a key to a lock. This prohibits the virus from binding with the ACE2 cellular receptor, thus preventing viral entry. Other ones can neutralize the heptad repeat 2 (HR2) domain to impede the fusion between the Spike subunit S2 with the ACE2 receptor, thus avoiding the release of the viral contents into the cells. So even if the S1 subunit of Spike protein binds with the ACE2 receptor, the second step of antigen/receptor fusion is compromised, disallowing COVID-19 entry into the cells. Prohibiting COVID-19 invasion into the cells impedes the virus from highjacking our cellular machinery and exploiting for the purpose of its replication. In short, the antibodies obstruct COVID-19 from entering and spreading within the body [5].

4. **Q: Do I still need to wear a face covering after I have been vaccinated?**

   A: The data so far suggests that developing antibodies or T-cells that specialize in the Spike protein can protect us against developing severe COVID-19 symptomatology or dying. However, whether or not a vaccine completely protect us from being infected by COVID-19 is altogether a different story. Besides, statistics pertain to large numbers of people but not to individuals. 95% efficacy means that there is a small 5% of individuals that remain unprotected.

The consensus from several clinical studies seems to be that vaccinated people do not infect others with regards to the Alpha variant that manifested the highest transmissibility rate until the Delta variant came along. However, there is always a small percentage that reacts unlike what is considered statistically significant. Moreover, it is possible that vaccinated but unmasked individuals can contract COVID-19, have no symptoms because of the protective antibodies and T-cells developed as a result of the vaccination, and therefore, be incognizant that they endanger others. Because they have refused to wear a mask, they can contaminate people in their proximity who are not yet fully vaccinated, because it takes at least two doses of most vaccines to shield the body from the virus. Or there may be cases where unmasked vaccinated people are infected with COVID-19 and transmit the virus to those who cannot be vaccinated due to health reasons, or children, turning them into COVID-19 carriers propagating the COVID-19 epidemic. By being unmasked, such vaccinated individuals will start a chain reaction, merely by carrying the virus and transmitting it to others, perpetuating the destructive vicious circle of the pandemic, and giving COVID-19 one yet opportunity to invent new ways to adapt in a human body, forming novel, incrementally more contagious mutations that come back to attack us with a vengeance. In other words there may be a future unprecedented COVID-19 mutant that suddenly appears, evading antibody detection and escalating COVID-19 transmissibility among vaccinated people. All this nightmarish downfall can stop by wearing a face covering to protect both ourselves from the onset of next generation, yet unknown mutations, and protect others from being infected from asymptomatic individuals. A face mask is a small price to pay to keep ourselves and our communities safe.

Recent unpublished data regarding the increased transmissibility of the Delta variant was cited on July 28, 2021 by Dr Antony Fauci, the director of the US National Institute of Allergy and Infectious Diseases, and chief medical advisor to the US president. So far, the data indicated that vaccinated individuals infected

by the Alpha variant have very low viral loads in their nasal fairings, and therefore, are not contagious. On the other hand, vaccinated people infected by the Delta variant have a viral load in their nasal fairing that is 1000 greater than what was formerly observed with the Alpha variant. When vaccinated individuals are infected by the Delta variant, they will contaminate everyone around them, unless they are wearing a face mask. Additionally, earlier data supported the assumption that the Alpha variant did not afflict children. The current statistics suggest that children are quite susceptible to the Delta variant. Now, that the Delta variant is spreading around the world, both vaccinated and unvaccinated adults should take precautions, that can be very easily accomplished by a face covering, to avoid infecting their children or other people's children.

5. **Q: If I can still contract COVID-19 then why get vaccinated?**

   A: According to research, 95.5% of vaccinated people avoid noxious symptomatology and survive. Simply contracting the virus and shaking it off in a few days, cannot be compared with being debilitated for weeks or months or leaving your last breath in some hospital. It is the degree of infection and the severity of symptomatology that make the crucial distinction between vaccination and the lack of it. The goal is for the world to fight this COVID-19 pandemic together. Non-compliance with vaccines or face coverings does nothing more than help COVID-19 evolve into more contagious and dangerous versions of itself.

6. **Q: How Do Humans Empower COVID-19?**

   A: COVID-19 is more cunning, multifaceted and resourceful than other coronaviruses. In the pursuit of its endurance and subsistence, COVID-19 evolves within our bodies. It mutates strategically, revising errors that extinguished previous coronaviruses. Several people within certain countries are oblivious, ignoring the facts unfolded in front of them that delineate the speedy

extraordinary adaptation of COVID-19 that continuously increases its transmissibility. They refuse to adjust to the grave risk that COVID-19 poses. In other words, they do not take COVID-19 seriously. They are under the impression that they can still go about their lives as if nothing has changed. They see COVID-19 as a passing nuisance, despite flagrant evidence that this pandemic is becoming progressively more transmissible with every new emerging variant. They refuse to be vaccinated or use face coverings to protect themselves and others. They do not believe that the danger is real until the virus has infiltrated their lives bringing desolation and despair in its passage. Therefore, the answer to this question is yes. COVID-19 is only part of the problem. Misinformation, ignorance and individuals who defy the need to sacrifice convenience for the safety of their communities is the other side of the problem.

7. **Q: What makes COVID-19 so Dangerous?**

   A: COVID-19 places the immune system on check. It has a ten-fold stronger hold on ACE2 receptors that its predecessor, SARS-CoV. ACE2 receptors catalyse Angiotensin II into Angiotensin 1-7 which is anti-inflammatory and lowers blood pressure. This process is compromised when COVID-19 seizes and occupies ACE2 receptors leaving the system with excess Angiotensin II. Angiotensin II constricts the blood vessels, obstructing blood flow, thus increasing blood pressure, while inducing an inflammatory response in the vascular wall. Increased blood pressure is deleterious to a number of medical conditions including hypertension, cardiovascular disease and diabetes, which manifest the highest mortality rates after COVID-19 infection. So just by binding to the ACE2 receptors COVID-19, debilitates the anti-inflammatory and anti-fibrotic functions of ACE2 receptors that can no longer catalyse Angiotensin II. The inevitable result of this process is escalated inflammation, vasoconstriction and high blood pressure, preluding the eventual catastrophic immune reaction termed “cytokine storm.”

8. **Q: COVID-19 disables the Immune System. How?**

A: COVID-19 blinds the immune system by impairing its capacity to recognize the virus and target it directly. Shooting in the dark, the white blood cells indiscriminately attack the vital organs that contain the virus, failing to distinguish self from non-self. This consists of two processes: Under normal circumstances, the innate response emerges immediately in the presence of a foreign agent's invasion. Innate immune system is largely non-specific and serves as a general defensive strategy. Subsequently, the adaptive immune response is activated that is specifically designed to recognize and attack the virus. A recent review suggests that coronavirus is designed to hinder the critical process of viral recognition, and suppress the production of Interferon (IFN) type I, ultimately impairing the competence of the adaptive immune system to identify the position of the virus within the organism and distinguish it from the host's healthy cells [6, 7]. If the adaptive system cannot discover the virus' hiding place, then exterminating the virus will most likely fail. The immune system will attack, destroy healthy cells, yet the virus, safely concealed from the blind giant, shall survive. The immune system, will mobilize all its defensive mechanisms cytokines, interferons, interleukins, cytokines, leukocytes or white blood cells, colony stimulating factors, tumour necrosis factors, the protagonist of the cytokine storm, along with CD8-T cells or killer cells. But the virus will remain out of sight and the onslaught will end up annihilating the host.

Another possibility is that COVID-19 affects the Immunoglobulin (IG) gene that regulates the antigen receptors of B cells which secrete antibodies and are a crucial aspect of the immune system [8]. Without antibodies, the body cannot defend against COVID-19 invasion.

A third possibility is that COVID-19 interferes with the major histocompatibility complex (HMC) genes that encode many proteins involved in T-cells antigens, which are part of the adaptive immune response. This is directly related to

undermining the adaptive immune system. T-cells are like immune soldiers unleashed against the viral assault. Proteins within the cell are like the brains of a cell. Immune soldiers shall suffer "brain damage" as COVID-19 disqualifies the HMC gene that encodes the proteins (the brains) necessary for the T-cells to function. Inevitably, the immune system will lose both the battle and the war because its soldiers are deficient. Unable to defend against the virus the host will collapse.

Defects related to the INF type 1 and the IG gene, which subsequently affects the antibody production by B cells, interferes with the switch from the innate to the adaptive sector of immunity, leaving the adaptive immune response in a state of disarray especially if the HMC gene is damaged. The adaptive immune system shall predictably fail to recognize the virus, firing against anything in sight, ravaging the vital organs and killing the host [9, 10]. The phenomenon or the cytokine storm is discussed in greater detail in Section 6 and throughout this book.

9. **Q: What is a cytokine storm?**
   A: It is what kills us. The virus does not want the host to die. Mortality is collateral damage during the immune system's war against the invisible enemy.

10. **Q: How is COVID-19 more sophisticated than other coronaviruses?**
    A: Viruses randomly mutate in order to adapt within the diverse biological environments of different hosts, so that they avoid detection. Mutations are like a disguise that helps a virus hide unobserved, to get out of its radar of the immune system, and cunningly mislead it. The word "random" entails that several of these transformation will lead to mistakes on the part of the virus, and as the errors pile up, the virus will be eventually extinguished.

    In real situations we are observing that after over 300,000 transformation, COVID-19 has achieved the unthinkable which is the exact opposite. Rather than eradicating itself, COVID-19 empowers itself with every new variant. Novel

mutants have expanded the COVID-19 infectiousness, increasing its transmissibility from 70% to 100% globally with this next generation Delta variant. Uprising COVID-19 mutants are now challenging the effectiveness of several emerging medications and vaccines.

The question is how could that happen during a random process, where what can go wrong will go wrong? A mutation is basically the result of at least one amino acid substitution from one position to another. How can COVID-19 manoeuvre away from all amino acid rearrangements that could potentially obliterate it and only adopt amino acid swapping that enhance its efficacy and potency? The answer is that we "don't know." All we can suggest is that this is exactly what COVID-19 seems to be doing.

An example is Van Dorp et al (2020) study that reported changes in the COVID-19 non-structural proteins Nsp6, Nsp11, Nsp13 as well as the trimeric spike [11]. However, if instead of the Nsp6, Nsp11 and Nsp13, the non-structural proteins Nsp7, Nsp8, and Nsp12 in association with Nsp14 were involved, the COVID-19 capacity to replicate long viral RNA would have been compromised, eventually leading to the degradation of the virus [12]. COVID-19 Non-structural protein (Nsp) transformations are adaptive allowing the virus to survive, in contrast to other coronavirus Nsp transformations that lead to the eventual extinction of the disease. This is discussed in greater detail in Section 1.

11. **Q: Why there are more deaths among men than women?**

A: Initially scientists thought that oestradiol protects women. However, according to the contradictory results of recent published data oestradiol does not appear to be a reliable protective shield against COVID-19. On the other hand, male testes have an abundance of ACE2 receptors which serve as the COVID-19 entry points into the cells. Additionally, research on human tissues has revealed

that the immune responses between males and females are different. For example ACE2 expression in male vital organs was associated with an elevation of immune cells, such as B cells that develop antibodies, NK or natural killer cells and CD8+ or cytotoxic T cells. Specifically, this exacerbated immune response in males involved positive correlations between immune cells and ACE2 receptors in the following vital organs: lungs, thyroid, live, colon, kidney, stomach, pancreas, skin, adipose tissue and testes. While females' ACE2 receptors in the lungs and thyroid was associated with decreased levels of B, NK, CD8+ T cells. On the other hand, upregulated ACE2 expression in the female heart tissues was accompanied by increased B, NK, CE8+ T cells and Interferons, unlike male heart tissues, where ACE2 receptors and immune cells featured a negative correlation. ACE2 receptors in the kidneys, skin, stomach, and adipose tissue were associated with increased levels of immune cells in both sexes. [13]. Basically, males appear to be biologically more vulnerable to COVID-19 than females as a result of the relatively higher positive correlations between ACE2 receptors and immune cells in a greater number of male rather than female vital organs.

There may be additional reasons associated to toxicity such as smoking that some countries report to be more frequent among males than females, environmental pollution or higher exposure for working men who support women that are sheltered at home due to pregnancy or other social arrangement.

12. Q: Is there an affinity between adipose tissue and COVID-19?

A: Fat cells are abundant in ACE2 receptors, which are the chosen COVID-19 portal into the cells. The greater the number of ACE2 receptors, the higher the chance of being targeted by COVID-19.

Additionally, both subcutaneous and visceral adiposity withhold toxicity. In general, toxic stressors, including neurotoxic, biological, physical, chemical,

psychological and psychosocial irritants, may lead to immune degradation, rendering the body an easy prey to COVID-19.

Reducing BMI and increasing fitness appear to be some of the most fundamental protective methods against COVID-19. We emphasize optimal BMI rather than merely recommending weight loss, because there are several ways to reduce fat that may be deleterious to health, because they increase inflammation or result in systemic hyperstimulation as it happens with some slimming products. Some diet pills that speed up metabolism and suppress appetite can lead to increased blood pressure, lung and heart problems that will provoke rather than prevent COVID-19 severe symptomatology.

Health and hormonal balance are the cornerstones of a preventive strategy against COVID-19 and anything that can undermine health or disorganize hormones into a disequilibrium is detrimental exposing the body to all kinds of medical issues, in addition to increasing vulnerability to becoming severely ill with COVID-19. Research has reported that prescribed slimming preparations may cause pulmonary hypertension and serotonin neurotoxicity that can be expressed in anxiety and depression, sleep disturbances and cognitive defects [14].

13. Q: How about RF and Laser lipolysis?

A: Weight loss is only one aspect of health that largely depends on fitness, optimal lifestyle choices, hormonal balance, the absence of stress and so much more. Both laser and RF can offer fast lipolysis, but results will rebound with lipolysis alone. Without detoxification or the fitness factor, toxicity will disorganize the hormonal reciprocity of leptin and ghrelin resulting in constant hunger. Hormonal equilibrium is crucial in balancing disproportional levels of complementary hormones like the appetite regulating leptin and ghrelin or optimize cortisol to control food consumption. Neither lasers nor RF is in anyway designed to balance hormones, increase fitness or detox.

The sparce studies that report visceral fat reduction following laser or radiofrequency procedures, combine lasers with exercise, making it impossible to distinguish which contributed to the result. Moreover, they manifest methodological difficulties, such as internal validity flaws related to instrumentation or failure to duplicate the study which is a threat to external validity.

Importantly, there are several reports of eventual escalated inflammation following radiofrequency procedures [15, 16, 17, 18, 19]. Radiofrequency replaces pre-existing inflammation inherent in adipose tissue with radiofrequency induced inflammation. Whether inflammation is the result of excess adipose tissue or the after effect of the radiofrequency procedure, the outcome will be the same. Inflammation, irrespective of its source, will most likely exacerbate the deleterious immune response termed “cytokine storm” that is detected in COVID-19 severe cases with often lethal consequences. This line of reasoning renders any procedure that increases inflammation counterproductive. and conceivably dangerous during this pandemic.

14. Q: What is the Importance of Fitness?

A: During exercise, or its alternative that was introduced by a series of clinical trials, the body uses fat as an energy source to build muscle. As previously reported, adipose tissue displays an abundance of ACE2 receptors. COVID-19 Spike protein binds and fuses with the ACE2, releasing its viral contents into the cells. Fat is to COVID-19 what a flower field is to the bees. However, the more sparce the ACE2 receptors are, the less the opportunities COVID-19 will have to enter into the cells and commandeer our molecular machineries to duplicate itself. ACE2 receptors expression is very limited in the muscle, according to research in human tissues [20]. The premise should be now clarified: The greater the number of ACE2 receptors as it is in the adipose tissue, the more the chances of

COVID-19 spreading and overwhelming the body. The diminished ACE2 expression in muscle tissues, reduces the COVID-19 chances to proliferate, and gives the immune system more time to assemble its defences. In a war, the size of the armed forces attacking, and the time of gathering recourses to defend and counterattack is crucial. Similarly, the COVID-19 rate of transmissibility within the human body will depend on the number of COVID-19 receptors the virus can seize. There are many in the fat, and a relatively low number in the muscles. This does not mean that muscular individuals cannot contract COVID-19. Anyone can be prey to this savvy new virus. It is not whether or not we can be infected, but the speed of duplication and the magnitude of the viral contagion in our cellular networks that determine the difference between mild and severe symptomatology, or between life and death.

15. Q: What are the COVID-19 key vulnerability factors?

A: Several factors that undermine health contribute to increased COVID-19 vulnerability, some of which are listed below.

1. Elevated low density lipoprotein (LDL)
2. Upraised very low density lipoprotein (VLDL)
3. Inadequate levels of high density lipoprotein (HDL)
4. Testosterone below the normal range
5. Escalated Cortisol
6. Reduced thyroid function and compromised metabolism. Low T3.
7. Excess Visceral Adipose Tissue
8. Excess overall fat and obesity
9. Sedentary lifestyles
10. Absence of Fitness via either regular physical exercise or its effortless alternative
11. Growth Factor below the normal range
12. Elevated Bilirubin
13. Abnormal levels of Creatinine

14. Upraised C reactive protein (CRP)

16. Elevated proinflammatory Interleukins

17. Upheaved tumour necrosis factor

18. Heightened numbers of leucocytes, or white blood cells that are involved in both the adaptive and the immune system response to invading microorganisms.

19. Hyperleptinemia

20. A disturbance in the balance of appetite hormone leptin and ghrelin resulting in hunger that inevitably leads to weight gain

21. Hyperglycaemia.

22. Insulin Resistance

23. Low BMR

25. High BMI

26. Old Age

27. Hormonal Imbalance

28. Being a Male

29. Fatty Liver

30. Increased lymphocytes, a type of white blood cells designed to recognize antigens that is primarily involved in the adaptive immune response. Lymphocytes indicate the presence of an infection or inflammation.

31. Pre-existing medical disorders, some of which are: Asthma, Diabetes, Cardiovascular illness, Hypertension, chronic respiratory disease, chronic liver disease, immunosuppressed conditions, lupus, rheumatoid arthritis, psoriasis, cancer, organ transplant, asplenia, stroke or other neurological conditions [21]

32. Increased oxidative stress. Toxicity. Environmental pollution, smoking.

33. Psychological Stress

34. Crowded places

35. Coughing, sneezing, talking, socially interacting without a facial covering.

16. Q: What are the advantages of exercising?

A: Individuals with medical disorders have demonstrated the highest COVID-19

susceptibility rate. Exercise is the golden rule most frequently recommended by most medical professionals as part of empowering immunity [22, 23, 24, 25]. There is a large body of research specifically postulating that exercise:

1. Uses fat as an energy source to build muscle
2. It decreases low density lipoprotein [26, 27]
3. It reduces inflammation [28]
4. It is necessary to treat hyperlipidemia and obesity [29, 30]
5. It decreases hyperglycaemia [31, 32, 33]
6. It enhances the growth hormone response (HGH). HGH is not only involved in muscle building but bone integrity, collagen regulation and increased fat metabolism [34]
7. Animal studies have postulated that exercise influences lymphocyte function.
7. It decreases visceral fat that can be deleterious to vital organs
8. It reduces the incidence of fatty liver
9. It reduces overall fat
10. After 9 days of repeated physical activity fat oxidation was increased to an additional 24% within one hour, the equivalent to 4.5 kilograms of burned fat. [35].

17.Q: Are there any adverse effects related to exercise?

A: Exercise has many advantages. There are, however, some disadvantages.

1. In the above study [36], training was reported to upregulate the gene expression of the fatty acid translocase (FAT/CD36) that mediates fatty acid effects on insulin secretion, but it also enhanced the constitutive expression of PR gene 1, (CPR1) that is a suppressor of pathogen signalling.
2. Prolonged exercise decreases leptin concentrations by 32% and increases free fatty acids as expected by the understanding that free fatty acids act as an energy replenishment mechanism after energy expenditure [37]. However, leptin reduction will reinforce increased food consumption after exercise, undermining the weight loss benefits.

3. Excessive exercise is perceived by the body as a form of stress and stimulates the release of cortisol that may cause tissue breakdown with over training leading to stress eating behaviours that are bound to compromise the benefits of exercise [38].

4. Cortisol is involved in the conversion of protein to glucose potentially predisposing older individuals to type II diabetes [39].

5. Strenuous exercise, necessary to reduce visceral adipose tissue, is associated with a negative relationship between cortisol and testosterone. In other words, cortisol increases with a reciprocal decrease of testosterone. High cortisol may precipitate weight gain, a higher susceptibility to infections, puffy or flushed face, mood swings, anxiety, acne and other skin disorders and a higher risk for bone fractures and osteoporosis. Low testosterone will induce weight gain, fatigue, depression, joint pain, muscle weakness, respiratory problems and compromised sexual drive. Therefore, both of these complementary hormonal fluctuations are in the wrong direction leading to hormonal imbalance that may ultimately offset the benefits obtained during exercise [40,].

6. Importantly, during overtraining, which is often necessary for visceral fat reduction muscle-derived IL-6 is released into the circulation in high amounts resulting in increased inflammation [41].

18. Q: Is there an alternative to exercise?

A: A number of clinical studies have indicated that there is an alternative to exercise, a technology discovered in London University by the co-inventor of the first pacemaker, Gerald Pollock. This effortless exercise technique appears to solve the inverse negative cortisol / testosterone problem by demonstrating an increase in testosterone and a decrease of cortisol, but without any of these two variables falling outside the normal range. In short, cortisol appears to descend towards the bottom of the normal range in subjects with high cortisol, yet remain stable in individuals whose cortisol was already closer to the lower end of this dimension. In contrast, testosterone appeared to climb towards the peak of the

normal range in subjects with low testosterone or remain unchanged in those who already manifested high testosterone levels. Other observed benefits following a course of treatments that varied from 12 to 20 treatments depending on the research project were as follows:

1. Growth Hormone ascended towards the peak of the normal range.
2. T3 was also elevated toward the top of the normal range.
3. There was a significant decrease in inflammation as indicated by the C reactive protein (CRP).
4. The very low density lipoprotein (VLDL) was significantly reduced.
5. The very high density lipoprotein (HDL) was significantly increased.
6. Triglycerides indicated a decline, returning into normalcy.
7. Creatine dropped down to be within the normal range.
8. Bilirubin was significantly reduced to be within normalcy.
9. Both fasting and postprandial glucose in diabetic patients descended to either prediabetic levels or within normalcy.
10. Both fasting and postprandial insulin in prediabetic patients descended to either prediabetic levels or within normalcy.
11. There was a significant decrease in visceral fat.
12. Subcutaneous fat was also significantly reduced.
13. A significant decrease in BMI was demonstrated.
14. The basal metabolic rate (BMR) was optimally elevated.
15. There was a significant increase in skeletal muscle mass.
16. Leptin and Ghrelin returned to optimal levels.
17. Subjects reported normal appetite without cravings.
18. There was a substantial weight loss in kgs and upper abdomen, waist and lower abdomen reduction in cm.
19. No adverse reactions or side effects were observed or reported by any of the subjects.

19.Q: Can a healthy lifestyle, exercise or its alternative prevent COVID-19 infection?

A: Fitness and optimal lifestyle choices are the shield of health. But we are still at war with COVID-19. In a war casualties can happen at any time. The survival of the fittest is the golden rule that applies here. But that alone is not enough. We need sophisticated defences like the vaccines, and effective pharmaceuticals to combat this cunning multifaceted virus. Everyone exposed to the virus will contract it. But what determines the severity of symptomatology or the chance of fatality is what comes next. Fitness and hormonal balance enhance our health status along with our immunity. Vaccines trigger the production of immune defences, the weapons we can use to prohibit or restrict viral entry or survive its deleterious consequences. Hence the importance of taking all precautions possible against this inconspicuous invisible enemy that is always a step ahead.

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Dedicated to:

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