Interconnection of Psoriasis with kidney disease: A Traditional Review

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Abstract. Psoriasis is characterized by abnormal hyperproliferation of keratinocytes with dysfunction in immune regulation. It has been postulated that psoriasis is a systemic entity rather than a solely dermatological disease. The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) are surging, and they have become a global health problem causing considerable morbidity and mortality worldwide. Kidney injury is defined as an anatomical alteration of the organ or the presence of proteinuria or hematuria. The exact mechanisms underlying the link between psoriasis and renal dysfunction remains not entirely understood. Many pathogenetic mechanisms are thought to be shared by psoriasis and end-stage renal disease like increased levels of cytokines, reactive oxygen species, impaired immune system leading to immune-mediated damage, and effect of drugs used to treat psoriasis leading to drug-induced damage to kidneys. The development of chronic renal failure in psoriasis seems to be connected to the chronic inflammatory state that causes a steady decline of all organs. A growing body of literature indicates the role of Th17 immune response in both renal inflammatory diseases and psoriasis. In this comprehensive review article, we will try to enlist and describe possible ways in which the linkage of psoriasis and kidney damage can be explained by exploring currently available literature from PubMed.

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1. Introduction & Background:
Psoriasis is one of the most common immune-mediated skin disorders characterized by abnormal hyperproliferation of keratinocytes. The reported prevalence of psoriasis ranges from 0.6 to 4.8% in the general population (Naldi, 2004). The pathogenesis of psoriasis is not entirely understood. Initially, it was thought to be related to the hyperproliferation of keratinocytes, but the good therapeutic responses to drugs targeting the immune system suggest the existence of dysfunction in immuno-regulation (Grandinetti et al., 2020).

The prevalence of chronic kidney disease and end-stage renal disease are surging, and they have become a global health problem causing considerable morbidity and mortality worldwide (Chen et al., 2009). Compared to other well-known cardiovascular and metabolic comorbidities, the relation between psoriasis and renal disease is largely unclear. A few small cross-sectional studies revealed an increased prevalence of microalbuminuria among patients with psoriasis (Cecchi et al., 1992; Szepietowski et al., 2000; Dervisoglu et al., 2012). A Taiwanese cross-sectional study showed that psoriatic people have a higher prevalence of kidney failure as compared to nonpsoriatic people (Yang et al., 2011). In a UK based cohort study, an increased risk of chronic kidney disease is seen in the population affected by moderate to severe psoriasis (Wan et al., 2013). A recent Taiwan based cohort study found an association of psoriasis with Chronic Kidney Disease (Chiu et al., 2015). The exact mechanisms linking psoriasis and renal dysfunction remain unclear.

Various proposed mechanisms like immune-mediated damage, chronic damage without an immunological mechanism, and drug-induced damage seem to be involved (Grandinetti et al., 2020).

Patients with diffuse psoriasis show an increased level of albumin in urine, which is an initial marker for glomerular dysfunction (Cecchi et al., 1992). Accelerated atherosclerosis can also predispose patients with psoriasis to an increased risk of developing chronic kidney damage and end-stage renal disease (ESRD), as suggested by epidemiologic studies. Although, the number of studies describing this association is still limited [ Wan et al., 2013; Chiu et al., 2015; Parisi et al., 2015; Yu et al., 2017]. Not only psoriasis by itself but systemic treatment for psoriasis causing renal damage is also a concern. Some
studies have investigated the effect of systemic treatment of psoriasis on kidneys leading to End-Stage Renal Disease (Lee et al., 2019).

An increasing body of data suggests that Th17 cells participate in the pathogenesis of psoriasis and glomerulonephritis (Hedrick et al., 2009; Turner et al., 2010). Biological agents used in the treatment of psoriasis may induce autoimmunity leading to renal damage; this evidence indicates the linkage of psoriasis with chronic kidney disease (Piga et al., 2014). The relation of psoriasis with kidney disease seems logical as the kidney is vulnerable to the toxic effects of various medications used in psoriatic patients. However, the underlying mechanisms that link the two diseases are not fully understood (Al-Harbi et al., 2017). This traditional review aims to explore the evidence regarding the association of renal involvement in patients affected by psoriasis (Menter et al., 2010).

2. Review:
2.1. Pathophysiology of Psoriasis:

Psoriasis is one of the most common immune-mediated inflammatory diseases, usually considered a pathological state characterized by exclusive skin involvement. Psoriasis is clinically defined by the formation of multiple inflammatory plaques on the skin. Initially, it was thought that there is only an abnormal multiplication of keratinocytes in psoriasis. However, clinical data collected from various experimental models have redefined the concept of psoriasis over time. Currently, the existence of the dysregulation of the immune system is hypothesized. This theory is supported by the presence of an increased number of T lymphocytes and dendritic cells in psoriatic lesions, and by the good therapeutic response to the medication directed against the immune system (Visconti et al., 2016).

An association between the adaptive and the innate immune system is formed by dendritic cells that activate these systems in psoriatic lesions (Ouyang et al., 2010). In some individuals, endogenous signals and cytokines can activate the innate immune system coexisting with an autoinflammatory response. While in others, there can be a T cell-mediated autoimmune response. Thus, psoriasis is a special kind of disease as it has features of not only inflammation but also certain attributes of autoimmune disease (Liang et al., 2017). As in Psoriasis, Inflammation is not limited to the psoriatic skin and has been shown to affect different organ systems. So, it has been postulated that psoriasis is a systemic entity rather than a solely dermatological disease. When compared to control subjects, psoriatic patients exhibit hyperlipidemia, hypertension, coronary artery disease, type 2 diabetes, and increased body mass (Rendon & Schäkel, 2019). This discussion so far elaborates on psoriasis' pathophysiology and the role of immune cells in producing psoriasis symptoms. Visconti et al. described the use of diagnostic tests for detection and, thus, early intervention to slow the progression of psoriasis (Visconti et al., 2016). Liang, Y et al. labeled psoriasis as a mixture of an autoimmune and inflammatory disorder (Liang et al., 2017).

In comparison, Rendon et al. pointed out the ongoing changing perception of psoriasis as a systemic disease and elaborated on genetics' role in the understanding disease process and thus identifying therapy response markers (Rendon & Schäkel, 2019).

Pathophysiology Of Kidney Injury In Psoriasis:

Kidney injury is defined as an anatomical alteration of the organ that might depict changes in the Renal function test and in urine routine examination. Kidney injury can, therefore, be diagnosed using direct methods like histologic abnormalities on renal biopsy or specific markers, such as albuminuria or proteinuria or abnormalities in urinary sediment or on imaging studies (González-Parra et al., 2016). Many pathogenetic mechanisms are thought to form a link between psoriasis and End-stage renal disease. First, the alteration in serum levels of different factors in a patient with psoriasis might damage kidneys, especially increased uric acid levels may cause tubular injury (Bruce et al., 2000). Second, comorbidities of psoriasis, like arterial hypertension, diabetes, and atherosclerosis, may take part in causing renal dysfunction.

Third, in psoriatic patients, there is an impairment of the immune system leading to T lymphocyte dysfunction and is linked to glomerular injury (Kim et al., 1998). Fourth, autoimmune disorders can cause glomerular impairment. Lastly, some of the drugs used to control psoriasis are nephrotoxic (González-Parra et al., 2016).

In Severe psoriatic disease, patients are at increased risk of chronic kidney disease and End-Stage Renal Disease. Also, patients taking non-steroidal anti-inflammatory medication have an increased tendency to develop renal complications (Wan et al., 2013; Chiu et al., 2015; Chi et al., 2015). The exact pathophysiological mechanism causing the additional risk for Chronic Kidney Disease and End-Stage Renal Disease in people with severe psoriasis remains unknown. Although psoriasis is a chronic inflammatory disease where major vessels' associated inflammation has been characterized (Rose et al., 2013).

The small vessel inflammation can also occur in the kidney in severe psoriasis (Chi et al., 2015). We found that treatment patterns that define psoriasis' severity are an independent risk factor for moderate to severe chronic kidney disease. These findings were confirmed when we evaluated the prevalence of chronic kidney disease based on psoriasis' severity as determined by the general practitioner’s categorization of affected body surface area. The combined data showed no association of Renal damage with the mild disease (Wan et al., 2013). Although it is known that psoriasis is an
inflammatory disease of the skin, the latest evidence has revealed its association with the kidney, too, as it causes increased albumin excretion in the urine leading to increased risk of Chronic Kidney disease (Szepietowski et al., 2000; Dervisoglu et al., 2012). In a population-based cohort study, Joy Wan et al. illustrated that moderate to severe psoriasis is associated with an increased risk of chronic kidney disease, not linked to any conventional risk factors (Wan et al., 2013). In another cross-sectional study, Yang et al. reported that renal failure is more prevalent in patients with severe psoriasis (Yang et al., 2011). Ching-Chi Chi et al. found that people with severe psoriasis were twice more likely to have incidental Chronic Kidney Disease and thrice more likely to have incidental End-Stage Renal Disease as compared to controls (Chi et al., 2015).

2.2. Immunological Link Between Psoriasis and Kidney Diseases:

The development of chronic renal failure in psoriasis is due to the increased production of cytokines that cause a steady decline of all organs, including the kidney (Davidovici et al., 2010). Also, cutaneous infiltration of activated T cells and the proliferation of keratinocytes, dendritic cells, and Langerhans cells, resulting in high concentrations of TNF-alpha in psoriatic lesions (Heuvels et al., 1999).

A growing body of literature indicates the role of Th17 immune response in both renal inflammatory diseases and psoriasis (Turner et al., 2010; Ooi et al., 2010; Mease, 2015). It has been suggested that out of all the cytokines associated with both ESRD and psoriasis, the most important is interleukin-17 because its levels are high in psoriatic skin lesions and the serum of psoriatic patients (Grandinetti et al., 2020). The disease severity of psoriasis, which is indicated by the Psoriasis Area and Severity Index score, is related to the serum level of IL-17 (Yilmaz et al., 2012). IL-17A plays an important role in the development of kidney diseases (for example, glomerulonephritis, nephrotic syndrome, diabetic nephropathy), acute renal allograft rejection. It also has a role in atherosclerosis and hypertension (Cortvrindt et al., 2017). A person with a diagnosed case of ESRD has increased levels of IL-17A producing effector memory T cells and decreased levels of naïve T cells, indicating an impairment of the body’s immune system (Chung et al., 2012). Indeed, the numbers of Th17 cells and Treg cells were reported to be increased and decreased, respectively, in patients on long-term hemodialysis (Lang et al., 2014).

Therefore, the continuous high serum levels of IL-17 in psoriatic patients are thought to induce inflammation of kidneys, thus causing end-stage renal disease (Lee et al., 2019). IL-17- producing Th17 cells induce renal inflammation by

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Table 1: The Most Important Studies Showing the Association Between Psoriasis and Kidney Disease.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Study Design</th>
<th>Result/conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wan et al.</td>
<td>2013</td>
<td>Cohort study</td>
<td>Moderate to severe psoriasis is associated with an increased risk of CKD independent of traditional risk factors. The clinical relevance of the absolute risk of chronic kidney disease attributable to psoriasis increases with age.</td>
</tr>
<tr>
<td>Chi et al.</td>
<td>2015</td>
<td>Cohort study</td>
<td>Severe psoriasis was twice more likely to have incident CKD and thrice more likely to have incident ESRD in comparison to those without psoriasis.</td>
</tr>
<tr>
<td>González-Parra et al.</td>
<td>2016</td>
<td>Systematic review</td>
<td>Creatinine, Glomerular filtration rate, and urine albumin should be checked annually in psoriatic patients, especially ones taking nephrotoxic drugs.</td>
</tr>
<tr>
<td>Visconti et al.</td>
<td>2016</td>
<td>Review article</td>
<td>Psoriasis is classified according to the extension of skin lesions. Also, drugs for the treatment of psoriasis can cause kidney damage.</td>
</tr>
<tr>
<td>Al-Harbi et al.</td>
<td>2017</td>
<td>Experimental study</td>
<td>Oxidative inflammation is an important contributor to psoriasis induced renal dysfunction. Involvement of Nitric Oxide synthase in psoriasis induced renal dysfunction.</td>
</tr>
<tr>
<td>Yu et al.</td>
<td>2017</td>
<td>Retrospective cohort study</td>
<td>Psoriasis is an independent risk factor of chronic renal failure and ESRD</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>2019</td>
<td>Cohort study</td>
<td>The risk of ESRD was increased in patients with psoriasis or psoriatic arthritis but not in those who received systemic treatment for psoriasis.</td>
</tr>
<tr>
<td>Ren et al.</td>
<td>2020</td>
<td>Review article</td>
<td>Psoriasis induced the expression of inflammatory cytokines, resulting in podocyte injury.</td>
</tr>
</tbody>
</table>
mediating preexisting cells, including tubular epithelial cells, mesangial cells, neutrophils, and macrophages (Turner et al., 2010; Kitching & Holdsworth, 2011). It has been known that certain inflammatory mediators correlate with the disease activity of psoriasis (Guzel et al., 2015; Hsieh et al., 2016). Chemerin is a chemokine that directs dendritic cells and macrophages to inflammatory sites; it not only correlates with Psoriasis Area and Severity Index but also with C-reactive protein levels in patients with psoriasis (Guzel et al., 2015). There are different pathophysiological events that can justify the connection between psoriatic inflammation and kidney dysfunction. One of the links might be oxidative stress (Al-Harbi et al., 2017). In advanced chronic kidney disease, the production of 8-oxo-deoxyguanosine, isoprostanes, and carbonyl proteins is increased, leading to oxidative stress (Galle, 2001; Miranda-Díaz et al., 2016; Scheuer et al., 2000; Pedraza-Chaverri et al., 2016). Oxidants released from active neutrophils and monocytes have a role in the pathogenesis of psoriasis-induced peripheral organ dysfunction. Further, it shows that oxidative inflammation is an important contributor to psoriasis induced renal dysfunction (Al-Harbi et al., 2017).

Table 1 summarizes and the main articles used in this study.

In an experimental study, Fang Ren et al. hypothesized a theory according to which a psoriasis-like skin disease activates Toll-like receptors (TLR), which activates MyD88 receptors and promotes the expression of MyD88 protein. MyD88 protein, in turn, increases the expression of NF-κB proteins, which then enhances the expression of NF-kBp65 protein, and augments levels of various inflammatory factors such as IL-1β, IL-6, TNF-α, IL-17, and IL-22. A significantly enhanced inflammatory response damages renal tubules and glomerular cells, main podocytes, and mesangial cells in the kidney and eventually produces renal injury (Ren et al., 2020). This suggested mechanism is shown in Figure 1.

Psoriasis, like dermatosis, induces an increase in TLR receptor expression and triggers a subsequent series of inflammatory reactions and kidney damage. Thus, psoriasis induces inflammatory cytokines' expression, resulting in podocyte injury and aggravating renal injury (Ren et al., 2020). It has been reported that moderate-to-severe psoriasis presents an increased risk for chronic kidney disease independent of traditional risk factors (Chiu et al., 2015; Rendon & Schäkel, 2019; Jabbar - Lopez et al., 2016). Naif O. Al-Harbi et al. showed that psoriasis-induced oxidative stress extends beyond the systemic compartment and also affects kidney function where Nitrogen Oxide synthase plays an important role. Naif O. Al-Harbi et al. also described an increase in kidney dysfunction during psoriatic inflammation, as depicted by increased serum creatinine, BUN levels, and renal Myeloperoxidase activity (Al-Harbi et al., 2017). Sakemi et al. described a case in which a patient with Membranous Glomerulonephritis and nephrotic syndrome later developed psoriasis. These findings demonstrate that certain immunological mechanisms that are responsible for secondary Membranous Glomerulonephritis could also be involved in causing full-blown disease and manifestations of psoriasis (Sakemi et al., 1996). In an experimental study, Fang Ren et al. demonstrated the expression of inflammatory factors (IL-1β, IL-6, TNF-α, IL-17, and IL-22) in serum and kidney tissue of psoriasis-like mice was significantly increased. All the data indicated that there is podocyte injury in psoriasis, which causes higher expressions of renal inflammatory cytokines that will eventually lead to (Ren et al., 2020). In a retrospective cohort study, Sebastian Yu et al. demonstrated that patients with psoriasis exhibited an increased risk of chronic renal failure and ESRD, but not an overall renal disease (Yu et al., 2017). In certain psoriatic patients, Myeloperoxidase activity, lipid hydroperoxides, protein carbonyls, and advanced oxidation protein products have also been found to be higher than healthy individuals (Chandrashekar et al., 2015; Naik et al., 2015; Kiyici et al., 2012). Further research needs to be done to determine the link between the increased level of the aforementioned enzymes and products with psoriasis and kidney injury.

3. Limitations:

Most of the studies included in the article had small sample sizes. Not enough studies have been carried out to determine the exact association between psoriasis and kidney disease, so the literature mainly consisted of the review articles.

4. Conclusions:

Psoriatic association with kidney disease was studied in this review article. It has been proposed that psoriasis is a systemic entity rather than a solely dermatological disease.
Compared to control subjects, psoriatic patients exhibit hyperlipidemia, hypertension, coronary artery disease, type 2 diabetes, and increased body mass. The pathogenesis of psoriasis is not fully known. In the past, it was attributed to the hyperproliferation of keratinocytes only, but now the good therapeutic responses to drugs targeting the immune system suggest the existence of dysfunction in immunoregulation. Moderate-to-severe psoriasis causes an increased risk for chronic kidney disease that is an independent risk factor.

The development of chronic renal failure in psoriasis seems to be connected to the chronic inflammatory state that causes a steady decline of all organs, including the kidneys. Many pathogenetic mechanisms are thought to be shared by psoriasis and End-stage renal disease. These include various cytokines (especially IL-17), reactive oxygen species, and medication used to treat psoriasis. All these mechanisms seem to cause podocyte injury that results in kidney injury. Hence, so far, the link between psoriasis and kidney disease is explained through cytokines and reactive oxygen species in this review article. Further research needs to be done to draw a definitive conclusion in the form of a meta-analysis to find a definitive link between psoriasis and kidney injury.

Conflict of Interest:
There was no conflict of interest by authors.

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