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Control of dglucose is Determinant of Renal Preservation in Diabetes

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ABSTRACT

We previously reported that dglucose is a strong predictor of renal function change in diabetes. This study is an expansion of a previous study with longer duration. Data was compared between first and last visits. Eighty five diabetic patients were treated with a combination of glargine or detemir and regular or fast acting insulin for 26.3 ± 24.6 (SD) months. Blood pressure was controlled by beta blockers, calcium channel blockers, sympathetic inhibitors, or a combination, and chlorthalidone in resistant cases. Angiotensin converting enzyme inhibitors and receptors blockers (ACEI/ARB) were excluded in order to reduce the risk of acute and chronic renal failure. Objectives were to determine if this paradigm of treatment prevents progression of diabetic nephropathy. Fasting (F) and 2-hour postprandial (2hPP), glucose, serum creatinine (Scr) and estimated glomerular filtration rate (eGFR); hemoglobin A1c(HbA1c); and sitting systolic and diastolic blood pressure (SBP, DBP) were recorded for first and last visits. Mean blood pressure (MBP) and differences (d, 2hPP-F) were calculated for glucose, Scr, and eGFR. Parameters between first and last visits were compared using a paired t-test adjusted for age, gender and duration of treatment with $P<0.05$ considered significant. No significant differences were found between first and last visits for F and 2hPP glucose, F and 2hPP Scr, and F and 2hPP eGFR, and HbA1c. dglucose, sitting SBP and MBP were significantly lower at last compared to first visit. Combining both visits, dglucose and HbA1c showed a direct and positive correlation with dScr.Change in post minus pretreatment values were significantly positively correlated between HbA1c and FBG, 2hPPG or dglucose. In conclusion the current study emphasizes the importance of control of dglucose (2hPP-F) with insulin in preserving renal function in diabetes.

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INTRODUCTION

We previously reported that dglucose better predicts renal function changes than fasting blood glucose (FBG) or 2-h postprandial blood glucose (2hPPG) in diabetes (1). Numerous studies have documented benefits of glucose control in order to prevent the progression of microvascular complications (2-4). However, it is not known which of the two uncontrolled glucose levels, FBG or 2hPPG, is more decisive in predicting diabetic nephropathy. According to practice guidelines, FBG is a more reliable indicator than 2hPPG, because 2hPPG is variable among patients thus reducing its predictive value (5). To obviate the dilemma concerning the validity of blood glucose levels between FBG and 2-hPPG, we have developed a novel approach with introduction of d (delta) glucose, which is the difference between 2hPPand F glucose levels (2hPP-F). In our previous studies, correlation coefficients were calculated for F, 2hPP or 2hPP-F (d) renal function variables such as dScr or deGFR versus those for glucose [1]. The present study is an expanded study and extended for a longer duration. The objective of present research was to determine if this paradigm of treatment prevents the progression of diabetic

nephropathy into end stage renal disease (ESRD). To that effect, dglucose is significantly reduced overtime and renal function remains unchanged between two periods in a cohort of diabetic patients treated with intensive insulin therapy.

METHODS

Data was obtained from a population of 85 diabetic patients from the clinic of one of the authors. Patients, 34 males and 51 females, mean age 60.8±13.8 (SD) years, were treated with a combination of glargine or detemir insulin after breakfast and after dinner and regular or fast acting insulin before each meal and at bedtime for a mean period of 26.3±24.6(SD) months. Blood pressure was controlled by beta blockers, calcium channel blockers, sympathetic inhibitors or a combination, and chlorthalidone in resistant cases. Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) were excluded in order to reduce the risk of acute and chronic renal failure (6,7). Fasting (F) and 2-hour postprandial (2hPP) glucose, F and 2hPP serum creatinine (Scr), F and 2hPP estimated glomerular filtration rate (eGFR), hemoglobin $A1_C$ ($HbA1_C$), sitting and standing systolic and diastolic blood pressure (SBP,DBP) were determined for the initial visit (pretreatment) and last visit (post treatment). Mean blood pressure (MBP, systolic + 2 diastolic/3) and differences (d, determined by 2hPP-F) were calculated for glucose, Scr and eGFR. Parameters between pre and post treatments were compared using a paired t-test adjusted for age, gender and days of treatment with $P<0.05$ considered significant. Combining values for pre and post treatment Spearman's rank correlation coefficients and P values were calculated for correlations between F, 2hPP and dglucose versus F, 2hPP and dScr, and versus F, 2hPP and deGFR and versus HbA1c; and HbA1c versus F, 2hPP and dScr; and versus F, 2hPP and deGFR. In addition, using combined data, Spearman's rank correlation coefficients and P values were calculated for correlations between SBP, DBP and MBP versus F, 2hPP and dglucose; F, 2hPP and dScr; and HbA1c.

Changes between post and pretreatment were calculated for F, 2hPP and d glucose, Scr, and eGFR; and HbA1c; and SBP, DBP and MBP. Changes between post and pretreatment in F, 2hPP, and d glucose were correlated to changes in F, 2hPP and dScr; F, 2hPP and deGFR; and HbA1c. Changes in HbA1c were correlated to changes in F, 2hPP and dScr and eGFR.

RESULTS

Pre and post treatment values were compared for F, 2hPP and dglucose, Scr and eGFR; HbA1c; and sitting and standing SBP, DBP and MBP (Table 1). There was no significant difference between last and first visit for F and 2hPP glucose. However dglucose was significantly lower at the last visit compared to the first visit. There was no significant difference between last and first visits for F, 2hPP and dSCR or eGFR, or in HbA1c. Sitting SBP and MBP were reduced in the last visit compared to the first and there was a trend towards a reduction in sitting DBP ($p=0.0546$). There was no change in standing SBP, DBP or MBP although numbers of patients studied were small.

When data from first and last visits were combined there was a significant positive correlation between HbA1c and F glucose, 2hPP glucose and dglucose (Figure 1). A significant positive correlation was not found between HbA1c and F Scr or 2hPP Scr when data from first & last visits were combined (Figure 2). In fact, when the correlation between HbA1c and F Scr were considered there was a significant negative correlation. There was however a significant positive correlation between HbA1c and dScr.

When data from first and last visits were combined, a positive correlation was found between dglucose and dScr (Figure 3). There was no correlation between F glucose and F, 2hPP or dScr or eGFR, between 2hPP glucose and F, 2hPP or dScr or eGFR; or between d glucose and F, 2hPP Scr or F, 2hPP or deGFR. Similarly there was no correlation between HbA1c or F, 2hPP Scr or eGFR. There was a positive correlation between F glucose and DBP ($P=0.0097$) and MBP ($P=0.0268$) but not SBP ($P = 0.5141$). There was no correlation between 2hPP glucose or HbA1c and sitting SBP, DBP, or MBP. There was no correlation between dScr, and sitting SBP, DBP or MBP (data not shown).

When changes between post and pretreatment were calculated and correlated there was a significant positive correlation between HbA1c and F, 2hPP and dglucose (Figure 4). There was no correlation between F, 2hPP and dglucose and F, 2hPP and dScr or eGFR; and HbA1c and F, 2hPP and dScr or eGFR.

Examples of the relationship between dglucose and dSCr are shown in Table 2. Shown are F, 2hPP and d glucose and Scr from five patients. The dScr is positive only in patients 2 and 5 with a dglucose greater than 50 mg/dL while the dScr is 0 when dScr is less than 50 mg/dL Noteworthy is the observation that

dScr is 0 in Patients 3 and 4 who have a high fasting glucose but a low dglucose (< 50mg/dL).

DISCUSSION

This investigation has examined the relationship between different glycemic parameters including F, 2hPP and dglucose, and HbA1c; and renal function parameters including F, 2hPP and dScr, F, 2hPP and deGFR to determine if a significant association occurs between them. Our aim was to define the most dependable glycemic parameter which can be used to predict renal function changes in the clinical care of diabetes. We found that dglucose (2hPP glucose - F glucose) is significantly reduced with intensive insulin therapy over a period of 25.4 ± 1.5 months in our diabetes cohort. We have also found that dglucose is significantly positively correlated to dScr thus reconfirming our previous observation (1), and further reinforcing that dglucose can be a reliable glycemic parameter to determine the progression of diabetic nephropathy. We have also found that higher the dglucose (≥ 50mg/dL), the more likely an increase in serum creatinine and decrease in eGFR will be noted. On the other hand, the lower the dglucose (< 50mg/dL), slight or no change in serum creatinine in the 2hPP period will be found (Table 2).

We also have noted a significant positive correlation between HbA1c and dScr (2hPP Scr - F Scr). Thus our study confirms a relationship between glycemic parameters and renal function when the difference is obtained between two time periods (2-h postprandial period - fasting).

There is no information in the literature similar to our study. Our study raises an important question which is how to reduce dglucose. Since dglucose is the difference between 2hPP glucose and F glucose, reduction of 2hPP glucose will decrease dglucose. Thus, elevated 2hPP glucose or postprandial hyperglycemia is a concern. Elevated postprandial hyperglycemia has consistently been reported to be a significant factor in cardiovascular disorders and mortality (8, 9, 10). However, the American Diabetes Association (ADA) stated that it is unclear as to whether excessive excursion of postprandial glucose has a significant impact on the development of diabetic microvascular or macrovascular complications independent of HbA1c levels (11). Our data has clarified that statement and confirmed that the impact of 2hPP glucose is not independent of HbA1c. Our data indicates that all four glycemic parameters including F glucose, 2hPP glucose, dglucose and HbA1c are interrelated (Figures 1 & 4). It should be reiterated that a better correlation was observed between 2hPPG and HbA1c than between FBG and HbA1c by previous authors. (12)

Notably, in our practice, patients receive intensified insulin therapy with regular or fast acting insulin before meals and glargine or detemir insulin after breakfast and dinner. There are limited studies, like ours, that have presented data on the relationship between glycemic parameters and renal function tests. However, a single study from Italy confirmed that 2hPP glucose greater than 200 mg/dL and HbA1c above 8% (established diabetes) are closely linked to a rapid decrease in GFR, whereas 2hPP glucose levels of less than 200 mg/dL and HbA1c below 8% are associated with trivial or no change in GFR (13). Our observations are in agreement with the above study.

In addition, when the relationships of glycemic parameters to renal function are considered, dglucose stands out in this study and in our previous study (1). In agreement with the importance of HbA1c in previous studies, we have found significant correlation between changes in post and pretreatment values of dglucose compared to HbA1c (Figure 4C). However lacking in the literature is the relationship between HbA1c and renal function tests. Our study confirms that if dglucose is 50 mg/dL or higher, the more likely will be a higher serum creatinine (Figure 3).

Our data on glycemic parameters is similar to that reported by Gerich (8). He showed from his database of volunteers, who had undergone glucose tolerance tests, that as HbA1c levels increase from less than 5% to over 7.5%, fasting plasma glucose increase from 90 mg/dL (5 mmol/L) to 125 mg/dL (6.9 mmol/L); whereas 2hPP values increase from 130 mg/dL (7.2 mmol/L) to 230 mg/dL (12.8 mmol/L). He advanced two reasons for these glycemic changes with a more dramatic change in 2hPP glucose. Firstly, more insulin is needed after meals to maintain normoglycemia than in the fasting state. Secondly, the deleterious effect of insulin resistance would be more manifest after meals since most postprandial glucose disposal occurs via insulin-sensitive pathways. However renal function data are missing in this study.

It has been stated that even patients with well controlled diabetes can go on to develop complications; this may be the results of cumulative effects of postprandial hyperglycemic episodes which are difficult to control by conventional therapy (14). It is needless to emphasize that intensive insulin therapy, as in previous studies (2-4), is fundamental to renal preservation in diabetes. Thus in our study, although postprandial hyperglycemia persisted, renal preservation is attained (Table 1). This is consistent with the finding of our cell culture studies in which we have found that the glucose levels in culture dishes may not change but insulin preserves cellular morphology from severe damage caused by high glucose (15). A previous study has reported that intensive glycemic control had no effect on the

progression of renal disease in the whole cohort. But this study did not define intensive glycemic control and provided no information on the type of therapy and glycemic parameters measured except a baseline mean HbA1c of 9.4% (16). This baseline high HbA1c, with no information on post treatment HbA1c, reflects severe postprandial hyperglycemia which according to our studies (6) and other studies (13), if not treated with intensive insulin therapy, will likely result in progression of diabetic nephropathy.

In our study, we achieved significant reduction in sitting SBP, near significant reduction in sitting DBP and significant reduction in sitting MBP in patients treated with antihypertensive drugs with exclusion of ACEI/ARB. A previous study has stated that ACEI/ARB drugs prevent diabetic nephropathy and delay progression (17). Our studies contradict that conclusion. Our previous studies (6) and other studies (7) have shown that ACEI/ARB drugs are associated with a high risk of end stage renal disease.

In conclusion, the new finding in our study is that dglucose convincingly relates to renal function changes. Since dglucose depends on 2hPP glucose, keeping 2hPP glucose under tight control with intensive insulin therapy is fundamentally important. Further, blood pressure control, avoiding the use of ACEI/ARB, is additive to renal protection in diabetes.

Table 1. Changes in blood glucose, hemoglobin A1c (HbA1c), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), and arterial blood pressure between post and pretreatment in a population of 85 diabetic patients

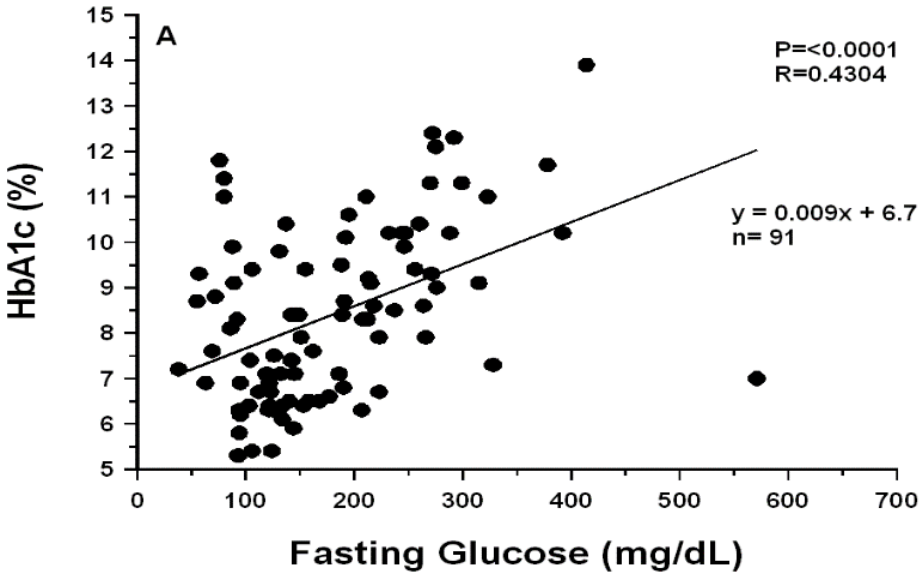
		First Visit		Last Visit*		First vs Last	Change	
Variable	**No**	**Mean**	**SD**	**Mean**	**SD**	**p †**	**Mean**	**SD**
Fasting Glucose (mg/dL)	59	175.2	83.6	166.2	87.9	0.5243	-9.7	107.6
2hPP Glucose (mg/dL)	57	244.0	98.2	217.2	94.8	0.1119	-26.8	124.2
dGlucose (mg/dL)	41	63.5	67.2	36.6	64.8	0.0449	-26.9	82.2
Fasting Serum Creatinine (mg/dL)	60	1.11	0.44	1.11	0.45	0.9364	0.21	1.19
2hPP Serum Creatinine (mg/dL)	50	1.22	0.53	1.27	0.60	0.5186	0.21	1.26
dSerum creatinine (mg/dL)	35	0.03	0.24	0.08	0.15	0.2410	0.06	0.26
Fasting eGFR (ml/min)	60	68.2	26.3	65.8	26.3	0.1419	-3.0	8.0
2hPP eGFR (ml/min)	50	61.0	24.3	58.5	23.0	0.2475	-2.5	15.2
deGFR (ml/min)	35	-3.4	9.9	-2.6	6.8	0.7287	0.5	12.3
HbA1C (%)	30	8.1	2.0	8.1	1.8	0.9786	-0.01	1.98
Sitting Systolic Pressure (mmHg)	74	133.1	17.1	128.4	13.9	0.0319	-4.8	18.5
Sitting Diastolic Pressure (mmHg)	74	81.8	11.9	78.9	12.4	0.0546	-2.9	12.7
Sitting Mean Pressure (mmHg)	74	98.9	11.3	95.4	10.9	0.0151	-3.5	12.0
Standing Systolic Pressure (mmHg)	13	133.8	19.4	126.9	9.9	0.2483	-6.9	19.7
Standing Diastolic Pressure (mmHg)	13	91.2	15.2	87.7	13.7	0.3716	-3.5	12.9
Standing Mean Pressure (mmHg)	13	105.4	15.9	100.8	9.5	0.2600	-4.6	13.5

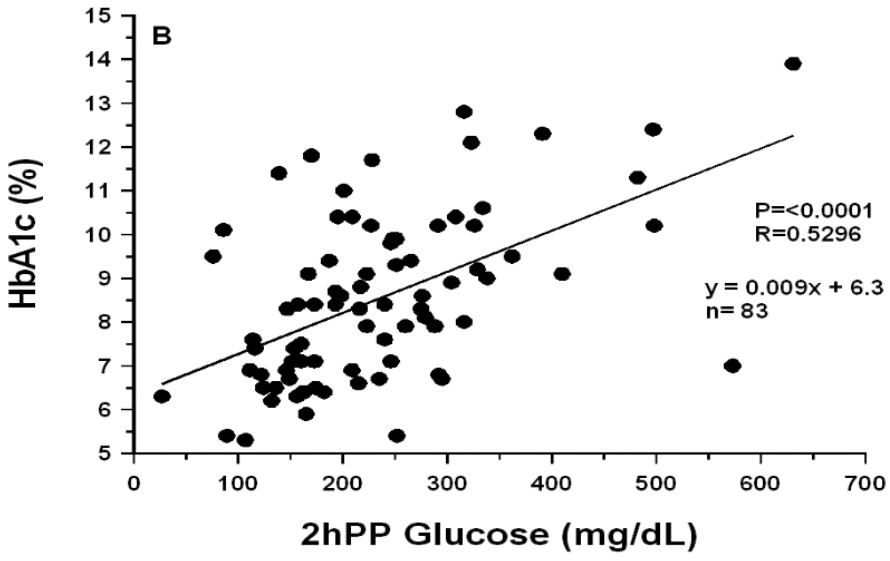
*** Mean time between visits 25.4 ± 1.5 (SD) months**
† paired t-test
2hPP = 2-h postprandial, d = 2hPP-Fasting, SD = standard deviation

Table 2. Examples of the relationship between dglucose and dScr

Patient	F glucose	2hPP glucose	dglucose mg/Dl	F Scr	2hPP Scr	dScr
1	151	178	27	1.6	1.6	0
2	141	270	129	1.6	1.7	0.1
3	193	214	21	1.7	1.7	0
4	207	207	0	1.0	1.0	0
5	109	232	123	1.3	1.5	0.2

F= fasting, 2hPP = 2-h postprandial, d = 2hPP-F, Scr = serum creatinine





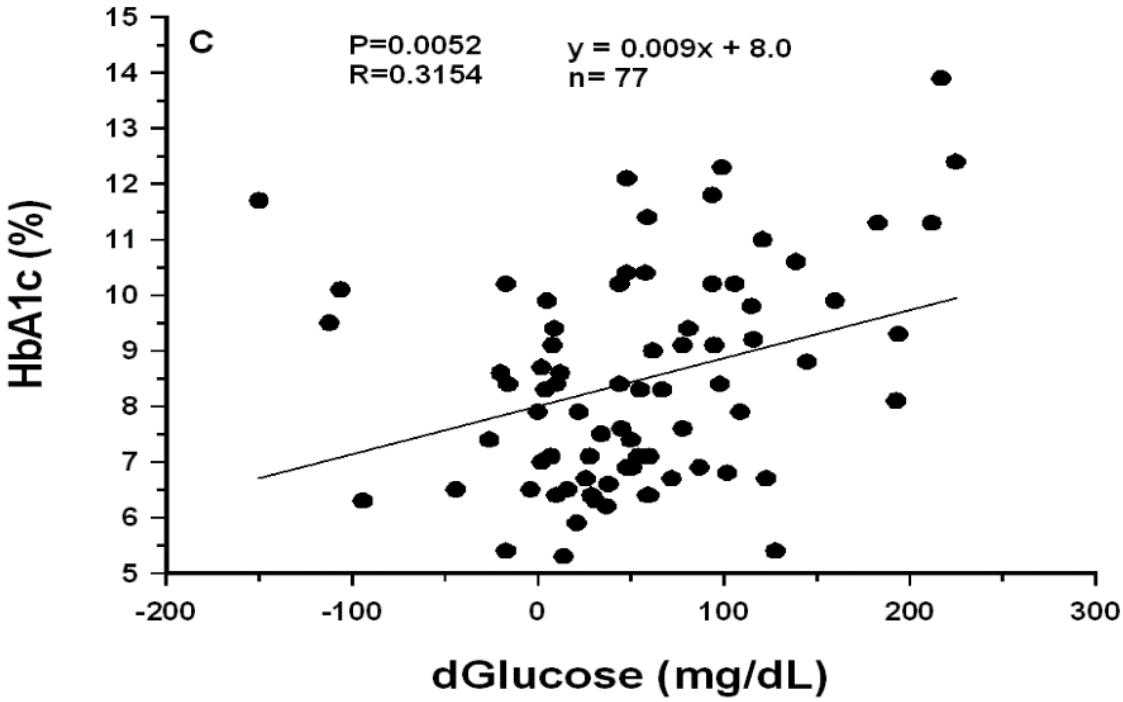
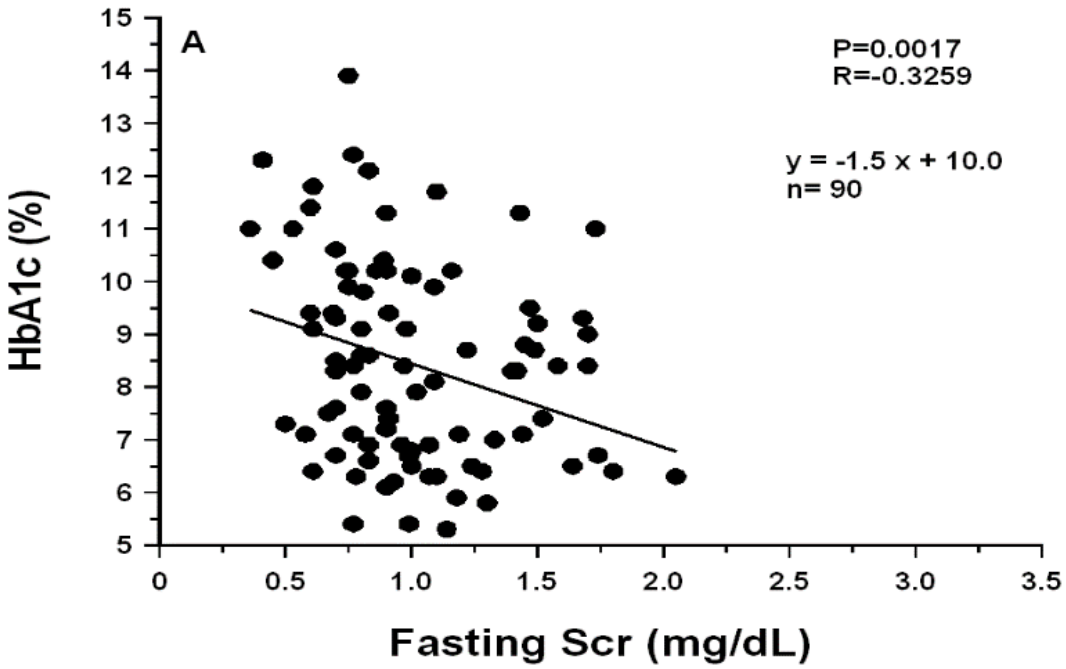


Figure 1. Correlation between hemoglobin A1c (HbA1c) and fasting glucose (A), 2hPP glucose (B) and dglucose (C). Pretreatment and post treatment values were combined. There was a significant correlation between HbA1c and fasting, 2hPP glucose and dglucose. Spearman's correlation coefficient. 2hPP = 2h postprandial. d = 2hPP- fasting.



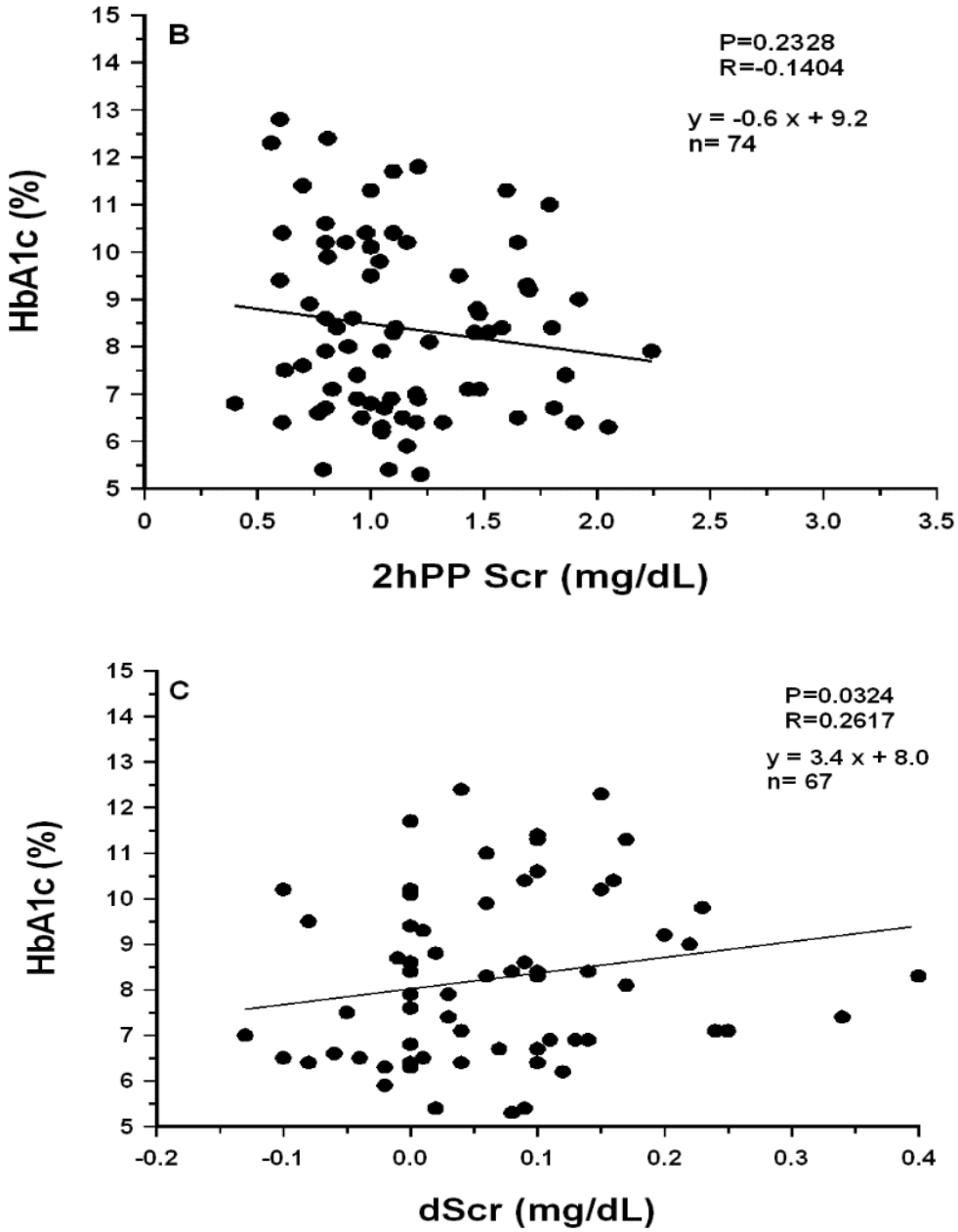


Figure 2. Correlation between hemoglobin A1c (HbA1c) and fasting serum creatinine (A), 2hPP serum creatinine (B) and dserum creatinine (C). Pretreatment and post treatment values were combined. There was a significant positive correlation between HbA1c and dserum creatinine but not between HbA1c and fasting serum cretonne or 2hPP serum creatinine. Spearman's correlation coefficient. 2hPP – 2h postprandial.

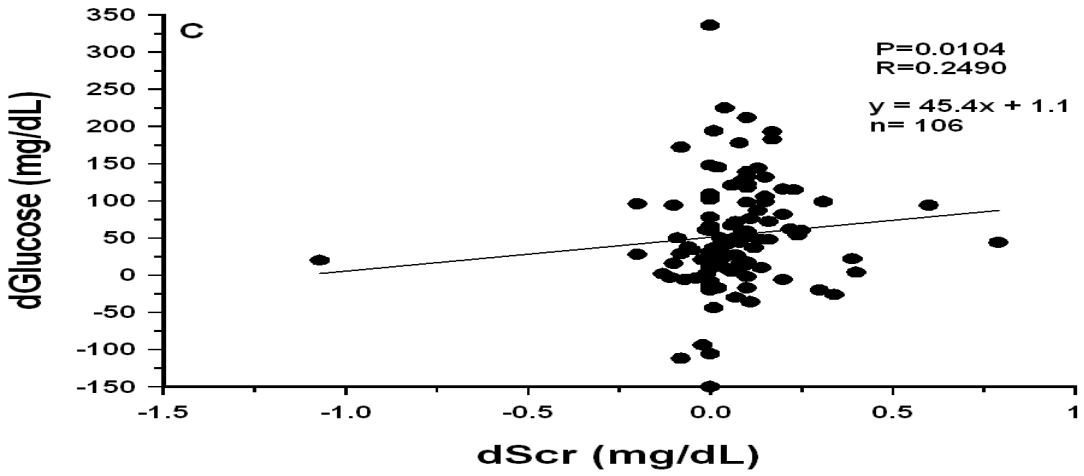
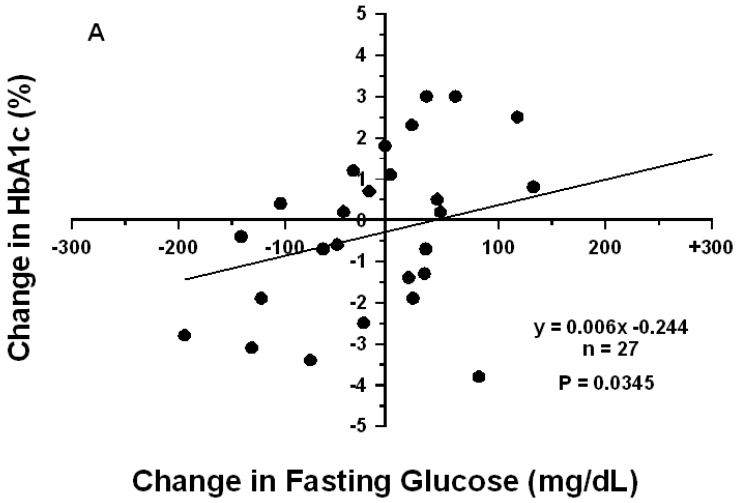
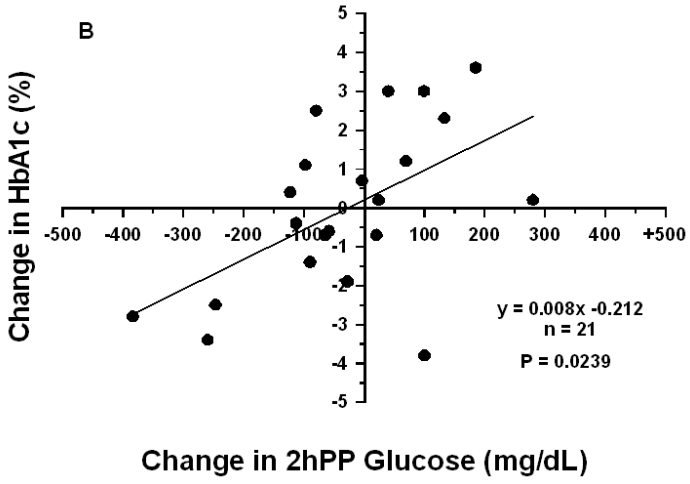


Figure 3. Correlation between dglucose and dserum creatinine. Pretreatment and post treatment values were combined. There was a significant correlation between dglucose and dserum creatinine. Spearman's correlation coefficient. d = 2-h postprandial – fasting.





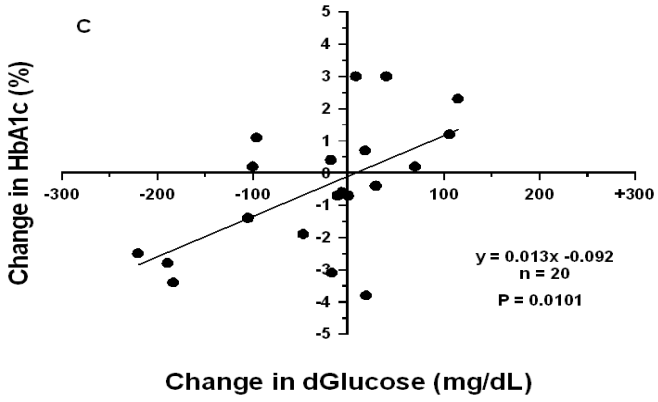


Figure 4. Correlation between changes in post and pretreatment values for HbA1c compared to changes in post and pretreatment values for fasting (A), 2hPP (B) and dglucose (C). 2hPP = 2-h postprandial, d = 2hPP-fasting

LEGENDS

Figure 1. Correlation between hemoglobin A1c (HbA1c) and fasting glucose (A), 2hPP glucose (B) and dglucose (C). Pretreatment and post treatment values were combined. There was a significant correlation between HbA1c and fasting, 2hPP glucose and dglucose. Spearman's correlation coefficient. 2hPP = 2h postprandial. d = 2hPP- fasting.

Figure 2. Correlation between hemoglobin A1c (HbA1c) and fasting serum creatinine (A), 2hPP serum creatinine (B) and dserum creatinine (C). Pretreatment and post treatment values were combined. There was a significant positive correlation between HbA1c and dserum creatinine but not between HbA1c and fasting serum cretonne or 2hPP serum creatinine. Spearman's correlation coefficient. 2hPP – 2h postprandial.

Figure 3. Correlation between dglucose and dserum creatinine. Pretreatment and post treatment values were combined. There was a significant correlation between dglucose and dserum creatinine. Spearman's correlation coefficient. d = 2-h postprandial – fasting.

Figure 4. Correlation between changes in post and pretreatment values for HbA1c compared to changes in post and pretreatment values for fasting (A), 2hPP (B) and dglucose (C). 2hPP = 2-h postprandial, d = 2hPP-fasting

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Conflict of Interest

None

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