

EFFECT OF TROGLITAZONE ON URINARY ALBUMIN EXCRETION AND GLOMERULARFILTRATION RATES IN INDIVIDUALS WITH PREDIABETES

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ABSTRACT

Diabetic nephropathy is a widely accepted consequence of diabetes mellitus and is considered a leading cause for chronic kidney diseases. Prediabetes is a risk for kidney diseases since kidney damage was shown to exist prior to the development of diabetes. Increase in urinary albumin excretion is considered the earliest sign of kidney damage. Besides urinary albumin excretion rate, improvement in kidney function can also be assessed by estimating glomerular filtration rate (eGFR) form serum creatinine (SCr) levels. Data was obtained from the diabetes prevention program, a large randomized trial which evaluated the effect of troglitazone, metformin, intensive lifestyle modifications, and placebo on the prevention of diabetes mellitus. Participants were evaluated at multiple different visits including annual and at confirmation visits. This study evaluated the effect of troglitazone on preserving kidney function which was measured by its effect on estimated glomerular filtration rate (eGFR) and on urine albumin excretion rate estimated from the ratio of urine albumin-to-urine creatinine ratio (ACR). Two subgroups were selected to analyze the changes produced by troglitazone treatment from baseline visit to 12 months in eGFR values and to confirmation visit in ACR values, troglitazone effect was compared to metformin, intensive lifestyle modifications (ILS), and placebo. A total of 2,335 and 423 individuals were included in the eGFR and ACR subgroups, respectively. Troglitazone and ILS produced a statistically significant increase in eGFR (14.71 ± 3.79 and 6.86 ± 1.85, respectively, P= 0.0001). Troglitazone produced higher percentage increase in eGFR compared to lifestyle arm, 17 percent versus 10 percent (troglitazone vs. metformin: $P < 0.001$; troglitazone vs. lifestyle: P= 0.18; troglitazone vs. placebo: $P < 0.001$). Only troglitazone showed a decrease in mean ACR values from baseline to confirmation visit (-1.6 mg/gm, ±1.45, P=0.27), the rest of the interventions showed an increase, all changes did not reach a statistical significance. In conclusion, findings demonstrated the renoprotective effect of the thiazolidinedione (TZDs) presented as an increase in eGFR values and a decrease in ACR values, although the latter did not reach a statistical significance.

Keywords: Troglitazone, Metformin, Lifestyle Modification, Urinary Albumin, Prediabetes, Glomerular filtration, eGFR

INTRODUCTION

Kidney disease is a widely accepted consequence of type 2 DM; prediabetes has also emerged as a risk factor for the development of CKD (Melsom et al., 2016; & De Nicola et al., 2016). In the National Health and Nutrition Examination Survey (NHANES), the prevalence of CKD in diagnosed diabetic individuals was found to be 40 percent, while it was 18 percent in prediabetic individuals. More than 40 percent of individuals with undiagnosed diabetes or prediabetes are already affected with CKD (Snyder et al., 2009). When evaluating the extent and progression of kidney damage.

Measurement or estimation GFR measurements were proven effective in both research and clinical settings. Using hard renal evidence such as the need for renal replacement therapy, death, or doubling of serum creatinine to examine the renal protective effects is of limited benefits in clinical research since extended periods of time are generally required before any of these elements occur. The inclusion of both GFR and ACR in renal risk evaluation and classification of CKD has been considered by many investigators (Matsushita et al., 2010). Remarkable number of diabetic subjects who appear to have CDK without signs of microalbuminuria were noticed in research (Caramori et al., 2003; MacIsaac et al., 2004; Yokoyama et al., 2009; Retnakaran, Cull, & Thorne et al., 2006 & Afghahi et al., 2011). This study evaluated the effect of troglitazone as a renal protective agent, this was measured by its effect on estimated glomerular filtration rate (eGFR) and on urine albumin excretion rate estimated from the ratio of urine albumin-to-urine creatinine ratio (ACR).

METHODS

Research Design: The data for this study were obtained from the Diabetes Prevention Program (DPP) Research Group. The original DPP was a 27-center randomized clinical trial to determine whether lifestyle modification or select pharmacological therapy would prevent or delay the onset of diabetes in individuals with impaired glucose tolerance (IGT). The original study included a total of 3819 prediabetic individuals, and at total of 585 were assigned to the troglitazone group (Diabetes Prevention Program Research Group (DPP), 1999; and DPP, 2000).

Our analysis selected two subgroups to analyze the changes produced by troglitazone treatment from baseline visit to 12 months in eGFR values and from baseline to confirmation visit in ACR values, troglitazone effect was compared to metformin, intensive lifestyle modifications (ILS), and placebo. A total of 2,335 and 423 individuals were included in the eGFR and ACR subgroups, respectively. The total number of participants in each subgroup was determined based on the number of participants with available values for these markers at the end determined end of study. The four arms included in the study are troglitazone (400mg every day), metformin (850mg twice daily), placebo, and lifestyle interventions. The troglitazone arm was discontinued in June 1998 (DPP Research Group, 1999). In this study we evaluated the effect of troglitazone on preserving kidney function which was measured by its effect on estimated glomerular filtration rate (eGFR) and on urine albumin excretion rate estimated from the ratio of urine albumin-to-urine creatinine ratio (ACR).

Statistical Analysis: Analysis was performed and presented using SPSS software. Baseline characteristics were reported as means and standard errors. Paired t-tests were conducted to analyze the main effects of troglitazone on renal markers. Partial Spearman correlation coefficients and accompanied P values were used to summarize the association between the main dependent variables at baseline with selected independent variables. The correlation analysis was shown as unadjusted, followed by adjusted analysis controlling for age, sex, and ethnicity, in attempt to adjust for these potential confounders. Correlation analysis was performed only on the troglitazone intervention arm. Multiple linear regression was performed to examine whether the changes in renal markers due to treatment with troglitazone are explained by a weight and waist circumference changes, and changes in measures of glycemia and insulin resistance. Our analysis used the following formula to obtain ACR values:

$$ACR\ (mg/Gm) = Urine\ albumin\ (mg/dL)/Urine\ Creatinine\ (Gm/dL)$$

GFR values were estimated from the MDRD equation using SCr, age, and ethnicity data provided from the NIDDK, the following version of MDRD was used to obtain eGFR values:

$$GFR\ (mL/min/1.73\ m^2) = 175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if African American}$$

Fasting insulin levels along with pretested models were both used as measures for insulin resistance. The homeostasis model assessment for insulin resistance (HOMA- IR). HOMA- IR was calculated using the following formula (Matthews et al., 1985):

$$HOMA\text{-}IR = \{fasting\ insulin\ \mu U/ml \times fasting\ glucose\ (mmol/l)\}\ /22.5$$

RESULTS

Table 1 describes the baseline characteristics of the individuals in the eGFR subgroup. Serum creatinine (SCr) levels were virtually equal in all interventions.

Table 1 Baseline renal characteristics for eGFR subgroup (Mean ± SE)

	Placebo	Troglitazone	Metformin	Lifestyle
HOMA- IR	7.0 ± 0.13	6.7 ± 0.22	7.2 ± 0.14	7.1 ± 0.42
Weight (kg)*	93.8 ± 0.72	95.1 ± 1.25	91.1 ± 0.67	90.7 ± 1.81
Waist-Circumference (cm)**	104.7 ± 0.47	105.3 ± 0.83	104.5 ± 0.48	106.7 ± 1.44

HbA1c (%)	5.9 ± 0.02	5.8 ± 0.03	5.9 ± 0.02	5.9 ± 0.04
Fasting Glucose	26.3 ± 0.48	24.7 ± 0.80	27.1 ± 0.49	25.9 ± 1.46
Fasting insulin	107.2 ± 0.25	109.3 ± 0.47	107.3 ± 0.25	109.5 ± 0.66
UAlb. overall n	1.51 ± 0.11 939	2.06 ± 0.51 278	1.75 ± 0.15 929	2.71 ± 0.84 159
Male n (%) UAlb.	1.44 ± 0.16 291	3.03 ± 1.23 105	2.01 ± 0.31 317	2.25 ± 0.82 60
Female n (%) U Alb.	1.55 ± 0.14 648	1.48 ± 0.32 173	1.63 ± 0.17 612	2.99 ± 1.25 99
UAlb. n (%) AA	2.08 ± 0.31 197	0.85 ± 0.10 47	2.47 ± 0.39 206	2.03 ± 0.71 32
UCr. (n)	140.6 ± 2.57 939	153.4 ± 5.49 278	142.3 ± 2.58 929	142.2 ± 6.18 159
Male n (%) UCr .	163.1 ± 4.57 291	185.6 ± 8.86 105	161.4 ± 4.31 317	160.5 ± 9.28 60
Female n (%) UCr	130.5 ± 3.03 648	133.8 ± 6.6 173	132.3 ± 3.15 612	131.1 ± 8.0 99
AA n (%) UCr	171.0 ± 6.57 197	172.7 ± 17.05 47	178.8 ± 6.07 206	174.9 ± 15.5 32
SCr overall (n)	0.78 ± 0.01 952	0.78 ± 0.01 280	0.79 ± 0.01 945	0.81 ± 0.01 161
Male n (%) SCr	0.93 ± 0.01 295	0.89 ± 0.01 105	0.93 ± 0.01 323	0.91 ± 0.02 60
Female n (%) SCr	0.71 ± 0.01 657	0.71 ± 6.6 175	0.71 ± 0.01 622	0.75 ± 0.01 101
AA n (%) SCr	0.81 ± 0.01 199	0.80 ± 0.02 48	0.82 ± .01 210	0.83 ± 0.03 34
Base ACR overall (N)	1.18 ± 0.09 939	1.57 ± 0.45 278	1.34 ± 0.11 929	2.12 ± 0.78 159
Males n (%) ACR	0.97 ± 0.11 291	1.63 ± 0.55 105	1.38 ± 0.22 317	1.33 ± 0.39 60
Females n (%) ACR	1.27 ± 0.13 648	1.54 ± .50 173	1.32 ± 0.13 612	2.66 ± 1.24 99
AA n (%) ACR	1.44 ± 0.24 197	0.55± 0.06 48	1.73 ± 0.29 206	1.03 ± 0.28 32
eGFR overall (n)	94.5 ± 1.09 950	94.8 ± 1.19 280	94.8 ± 0.83 944	90.6 ± 1.57 161
Males n (%) eGFR	92.3 ± 1.23 293	95.7 ± 1.68 105	91.7 ± 0.99 322	94.4 ± 2.63 60
Females n (%) eGFR	95.5 ± 1.47 657	94.3 ± 1.63 175	96.4 ± 1.14 622	88.4 ± 1.92 101
AA n (%) eGFR	97.8 ± 4.01 33	105.66 ± 4.62 15	104.4 ± 2.98 48	103.2± 1.83 198

* weight differences at 1 year from 6 months after randomization. ** waist circumference was taken at run-in visits (visits taking place after screening visit and prior to randomization

W Cir= Waist circumference, AA= African American, UAlb= Urine albumin (mg/dL), UCr= Urine Creatinine (mg/dL), SCr= Serum creatinine (mg/dL), ACR=Urine albumin-to-creatinine ratio (mg/Gm), eGFR= Estimated glomerular filtration rate.

Males showed higher mean SCr compared to females (0.92 vs 0.71), while African Americans averaged (0.82). Baseline eGFR values were virtually similar in the overall subgroup (93.7), African Americans averaged higher values (102.8). Spearman correlation analysis of eGFR subgroup gave multiple non-significant correlation results between the studied renal marker and selected metabolic and anthropometric variables, both with and without adjusting for age, sex, and ethnicity. Table 2 illustrates values of partial spearman correlation coefficients at baseline for eGFR and ACR with selected metabolic and anthropometric variables in the eGFR subgroup. The only significant correlations, although weak in magnitude, appeared in triglycerides, cholesterol, and CLDL levels with eGFR ($r = -0.12$ for triglycerides, $P= 0.05$, $r = -0.17$ for cholesterol, $P= 0.004$, and $r= -0.14$, $P=0.02$). The significant correlations shown between SCr and eGFR and between urine albumin and ACR were expected, since these values were used in the equation for eGFR estimation. Table 3 shows the same correlation analysis after adjusting for age, sex, and ethnicity, the correlation coefficient between CLDL and eGFR became insignificant. Tables 4 showed the results of baseline spearman correlation analysis in the troglitazone intervention arm for ACR and eGFR with selected variables in the ACR subgroup. Similar correlation results appeared after adjusting for age, sex, and ethnicity as shown in Table 5. The only statistically significant correlation appeared in the relationship of ACR with CRP and fibrinogen ($r= 0.57$, $P < 0.001$ and $r = 0.49$, $P < 0.001$, respectively). These correlation coefficients stayed the same after adjusting for demographic variables. Urine albumin demonstrated a very strong correlation with ACR, as expected since the values of urine albumin were included in the equation used to estimate ACR ratios. Figure 1 shows the mean Changes in eGFR at 1 year from baseline for the overall subgroup and for males, females, and African Americans in each of the 4 interventions.

As illustrated in Figure 1, only troglitazone and ILS showed significant improvement in mean eGFR values (14.71 ± 3.79 vs 6.87 ± 1.85, $P <0.001$, respectively). Both metformin and Placebo demonstrated a very small increase in eGFR, neither of the changes reached statistical significance. When we examined the effect by race, we found a decrease in eGFR at 1year due to all interventions, except for troglitazone, which resulted in an increase (3.11 ± 4.89, ns), although this change was not statistically significant. Females, on the other hand, presented with a significant increase in eGFR after 1 year of intervention in all treatment arms. Once more, the changes due to troglitazone exceeded the changes appeared with in ILS intervention group (21.67 ± 5.37 vs13.28 ± 2.34, respectively, $P < 0.001$ for both), while metformin produced a negligible increase (3.79 ± 1.16, $P <0.001$). In males, only troglitazone increased eGFR, the rest of the interventions showed reduction, all changes were not statistically significant.

Spearman correlational analysis between changes in ACR and changes in eGFR with changes in selected variables at 1 year from baseline was also performed. Changes in ACR presented significant correlation with changes in both CRP and fibrinogen, the magnitude of the correlation coefficients were virtually similar after adjusting for demographic variations. The rest of the correlations were not statistically significant.

Results from multiple linear correlation regression between the changes in renal markers produced statistically insignificant models. The results from the regression analysis were not suitable to explain the relationship between the changes in selected anthropometric and metabolic variables and the markers studied in this analysis.

Table 2. Partial spearman correlation coefficients of baseline (P-values) for eGFR and ACR with selected metabolic and anthropometric variables in the eGFR subgroup (n=270), troglitazone intervention

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CHOL	CLDL	UCRE	UALB	CREA	eGFR	ACR
eGFR	0.05 (NS)	0.004 (NS)	0.01 (NS)	0.06 (NS)	0.04 (NS)	-0.03 (NS)	0.03 (NS)	0.008 (NS)	0.06 (NS)	-0.12 (0.05)	-0.17 (0.004)	-0.14 (0.02)	0.07 (NS)	-0.07 (NS)	-0.72 (<0.001)	1.0	-0.06 (NS)
ACR mg/G	0.07 (NS)	0.10 (NS)	0.04 (NS)	-0.07 (NS)	-0.06 (NS)	-0.02 (NS)	-0.04 (NS)	0.10 (NS)	-0.07 (NS)	-0.06 (NS)	0.03 (NS)	0.02 (NS)	-0.002 (NS)	0.93 (<0.001)	0.07 (NS)	-0.08 (NS)	1.0

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen, tPA = Tissue Plasminogen Activator (ng/dL), W Cir = Waist Circumference (cm), FSG= Fasting Serum Glucose (mg/dL), FSI = Fasting Serum Insulin (micro units/mL), HOMA-IR = Homeostasis Model Assessment for Insulin Resistance, HBA1c = Glycosylated Hemoglobin Type A1C (%), TRIG = Triglycerides (mg/dL), CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate, ACR = Albumin to Creatinine Ratio

* waist Circumference was measured at run-in visits per DPP study. ** weight was measured at 6 months visits per DPP study

Table 3. Partial spearman correlation coefficients of baseline (p-values) for eGFR and ACR with selected metabolic and anthropometric variables in the eGFR subgroup adjusted for age, sex, and ethnicity (n=270), troglitazone intervention

	CRP	tPA	Fibr	W Cir	FSG	FSI	HOMA-IR	HBA1c	Weight*	TRIG	CHOL	CLDL	UCRE	UALB	CREA	eGFR	ACR
eGFR	0.02 (NS)	-.001 (NS)	0.2 (NS)	0.08 (NS)	0.01 (NS)	-0.03 (NS)	0.005 (NS)	0.02 (NS)	0.10 (NS)	-0.12 (0.05)	-0.14 (0.02)	-0.11 (NS)	0.03 (NS)	-0.07 (NS)	-0.89 (<0.001)	1.0	-0.07 (NS)
ACR mg/G	0.10 (NS)	0.09 (NS)	0.06 (NS)	-0.10 (NS)	-0.04 (NS)	-0.11 (NS)	-0.02 (NS)	0.10 (NS)	-0.06 (NS)	-0.07 (NS)	0.01 (NS)	0.01 (NS)	0.01 (NS)	0.93 (<0.001)	0.06 (NS)	-0.07 (NS)	1.0

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen, tPA = Tissue Plasminogen Activator (ng/dL), W Cir = Waist Circumference (cm), FSG= Fasting Serum Glucose (mg/dL), FSI = Fasting Serum Insulin (micro units/mL), HOMA-IR = Homeostasis Model Assessment for Insulin Resistance, HBA1c = Glycosylated Hemoglobin Type A1C (%), TRIG = Triglycerides (mg/dL), CHOL = Total Cholesterol, CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate, ACR = Albumin to Creatinine Ratio

* waist Circumference was measured at run-in visits per DPP study. ** weight was measured at 6 months visits per DPP study

Table 4. Partial correlation coefficients of baseline (P-values) for eGFR and ACR with selected metabolic and anthropometric variables in the ACR subgroup (n=60), troglitazone intervention

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CHOL	CLDL	UCRE	UALB	CREA	eGFR	ACR
eGFR	0.02 (NS)	-0.17 (NS)	-0.13 (NS)	0.13 (NS)	0.09 (NS)	0.05 (NS)	0.06 (NS)	-0.12 (NS)	0.14 (NS)	0.04 (NS)	0.04 (NS)	-0.08 (NS)	0.16 (NS)	-0.03 (NS)	-0.64 (<0.001)	1.00	-0.07 (NS)
ACR mg/G	0.55 (<0.001)	0.22 (NS)	0.48 (<0.001)	0.04 (NS)	0.02 (NS)	0.02 (NS)	-0.01 (NS)	-0.07 (NS)	0.08 (NS)	0.01 (NS)	0.11 (NS)	0.12 (NS)	0.15 (NS)	0.92 (<)	0.01 (NS)	-0.07 (NS)	1.00

CRP = C-Reactive Protein (mg/dL),Fibr= Fibrinogen, tPA = Tissue Plasminogen Activator (ng/dL), W Cir = Waist Circumference (cm), FSG= Fasting Serum Glucose (mg/dL), FSI = Fasting Serum Insulin (micro units/mL), HOMA-IR = Homeostasis Model Assessment for Insulin Resistance, HBA1c = Glycosylated Hemoglobin Type A1C (%), TRIG = Triglycerides (mg/dL), CHOL = Total Cholesterol, CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate, ACR = Albumin to Creatinine Ratio

* waist Circumference was measured at run-in visits per DPP study. ** weight was measured at 6 months visits per DPP study

Table 5. Partial correlation coefficients of baseline (P-values) for eGFR and ACR with selected metabolic and anthropometric variables in the ACR subgroup adjusted for age, sex, and ethnicity (n=60), troglitazone intervention

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CHOL	CLDL	UCRE	UALB	CREA	eGFR	ACR
eGFR	-0.05 (NS)	0.19 (NS)	-0.15 (NS)	0.14 (NS)	0.07 (NS)	0.02 (NS)	0.06 (NS)	-0.12 (NS)	0.16 (NS)	0.07 (NS)	0.001 (NS)	-0.06 (NS	0.13 (NS)	-0.07 (NS)	-0.83 (<0.001)		-0.08 (NS)
ACR mg/G	0.57 (<0.001)	0.22 (NS)	0.49 (<0.001)	0.04 (NS)	0.01 (NS)	-0.1 (NS)	-0.001 (NS)	-0.08 (NS)	0.07 (NS)	0.02 (NS)	0.02 (NS)	0.12 (NS)	0.13 (NS)	0.94 (<0.001)	-0.002 (NS)	-0.08 (NS)	

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen, tPA = Tissue Plasminogen Activator (ng/dL), W Cir = Waist Circumference (cm), FSG= Fasting Serum Glucose (mg/dL), FSI = Fasting Serum Insulin (micro units/mL), HOMA-IR = Homeostasis Model Assessment for Insulin Resistance, HBA1c = Glycosylated Hemoglobin Type A1C (%), TRIG = Triglycerides (mg/dL), CHOL = Total Cholesterol, CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate, ACR = Albumin to Creatinine Ratio

* waist Circumference was measured at run-in visits per DPP study. ** weight was measured at 6 months visits per DPP study

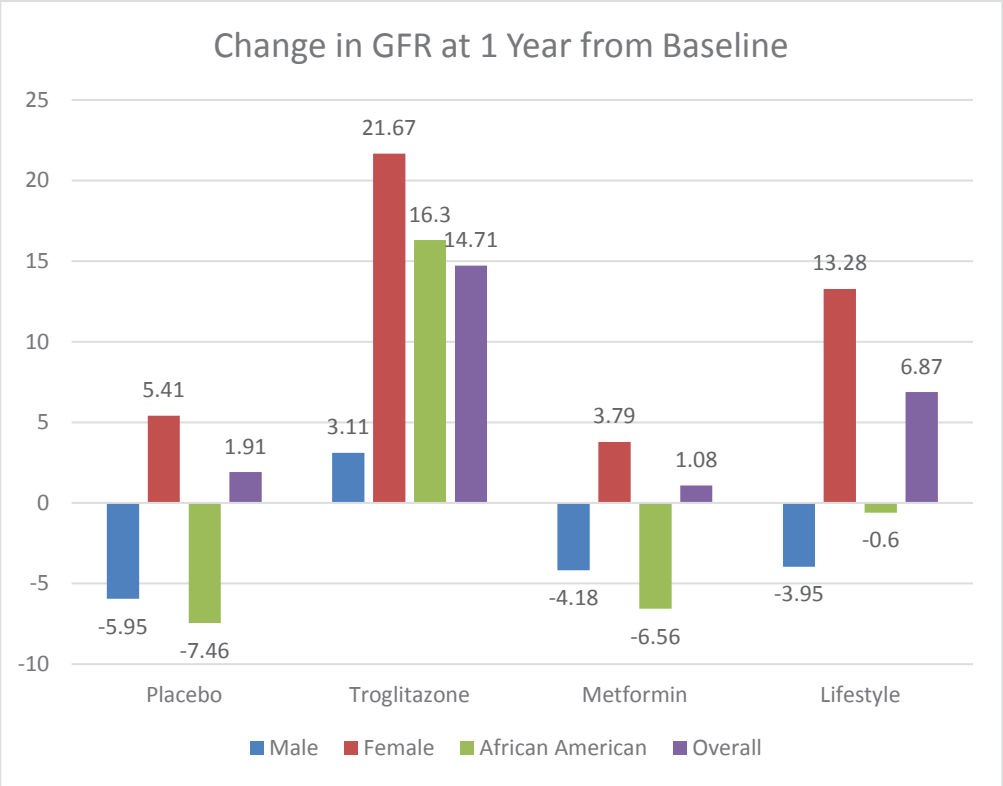

Figure 1. Mean Changes in eGFR at 1 year from baseline (Mean)

DISCUSSION

Troglitazone reported more than double the improvement in eGFR values at 1 year from baseline when compared to ILS, while metformin and placebo reported statistically non-significant changes as elucidated in the results section. Our findings regarding the role of TZDs in reducing GFR values are consistent with animal research (Yoshioka et al., 1993; & Baylis et al., 2003). Previous human research has also shown similar outcomes (Pistrosch et al., 2005; &Lachin et al., 2011). The DREAM trial, which included prediabetic patients, resembling the population included in our analysis, also demonstrated comparable findings to ours. Estimated GFR values decreased by more than 30 percent in the DREAM trial, although, these results were not statistically significant (Dagenais et al., 2008). Uniquely, our findings did reach a statistical significance.

The findings of this current study regarding the renal protective effects of TZDs were also measured by changes in ACR. Changes in ACR have been utilized extensively in clinical studies not only as end points, but also as intermediate outcome measures of renal disease progression. In fact, a decrease in urinary protein excretion is indicated as an independent measure of therapeutic efficacy in individuals with diabetic nephropathy (NKD, 2004; ADA, 2007; & Chobanian et al., 2003), especially in prediabetic subjects since renal pathological processes have recently been found to exist in the early stages of prediabetes (Tapp, Shaw, & Zimmet et al., 2004).

Most of the larger trials investigating the effect of TZDs on ACR have examined other TZD members, rosiglitazone and pioglitazone. The effect of troglitazone on ACR levels was examined in small studies and showed similar results as ours although the reduction was much higher in magnitude than the results shown in this analysis (Nakamura et al., 2001 & Imano et al., 1998). None of these studies exclusively analyzed prediabetic subjects. To date, there are no known studies which investigated the effect of troglitazone on albuminuria in prediabetic populations. Since diabetic nephropathy was proven to be in existence in prediabetic individuals before they were diagnosed with diabetes, our study was able to target this specific population.

This study also evaluated changes in mean ACR values stratified by sex and ethnicity. In women, only lifestyle and troglitazone decreased ACR from base line to CON visit. Whilst the mean changes produced by troglitazone were much higher than lifestyle (2.11± 2.02, P=0.3 and 0.1± 0.45, P=0.83, respectively), none of these changes reached a statistical significance. In men, only troglitazone produced a slight decrease in mean ACR values from baseline to confirmation visit, while the other three treatments increased these values. The increase in mean ACR values in lifestyle was much higher than the rest of the treatment groups

(11.03± 10.53, P=0.31). Among African Americans, all four treatment arms increased the value of ACR from baseline to confirmation visits.

Researchers have attributed the renal protective effects of TZDs to their role in the attenuation of the primary factors charged with the induction and progression of diabetic renal diseases, these include controlling of glycemia, lowering of blood pressure, and increasing insulin sensitivity (Sarafidis et al., 2006). The remarkable effects of TZDs on glycemic control was documented in multiple studies (Vilar et al., 2010). Previous research found evidence of correlation between changes in glycemia or changes in insulin sensitivity measures and changes in both eGFR and ACR (Sarafidis et al., 2010), our analysis was not able to draw such conclusions.

Other viable mechanistic processes explaining the renal protective effect of the TZDs has been suggested. Since functional PPARγ receptors, the main target for TZDs actions, have been recognized in the different components of the kidneys (Nicholas et al., 2001), research has suggested that TZDs may guard against kidney injury through their direct actions on PPARγ receptors (Guo et al., 2004). High glucose levels in addition to multiple different growth factors lead by growth factor β were shown to participate in the underlying process of kidney damage related to diabetic nephropathy (Sharma et al., 1995; & Blobe et al., 2000). PPARγ agonists, in addition to their proven effects in glycemic control (Desvergne et al., 1999), were shown to inhibit growth factor β expression thereby possibly contribute in the prevention or reversal of the cellular damage in diabetic kidneys (Guo et al., 2004). TZDs were also shown to improve renal endothelial function through restoration of nitric oxide production in the affected kidneys (Veelken et al., 2000; Pistrosch et al., 2005; & Chiarelli et al., 2000). In fact, several other studies have found the improvement in the renal endothelial function to occur independent of the TZDs glucose lowering effect (Schena et al., 2005). Such improvements were attributed to the role of the TZDs in the dilations of the blood vessels in the glomeruli, (Arima et al., 2002). The actions of TZDs in down regulating several proinflammatory genes and other genes contributing to renal fibrosis may also represent a conceivable mechanism behind their effect in protecting kidney damage (Ko et al., 2008).

Our correlation analysis failed to reach statistical significance when analyzing the relationship between the marker for albuminuria and for insulin resistance, opposite to what is shown by multiple previous studies. Previous research has suggested a strong association between albuminuria and insulin resistance (Palaniappan, et al., 2003; Groop et al., 1993; & Mykkanen et al., 1998). Mechanistically, the increase in insulin secretion was proposed to be a compensatory measure to counteract insulin resistance, this process was suggested to result in an increase in albuminuria due to the increase in blood flow to the kidneys driving up the filtration pressure, which ends up an increase in urinary albumin excretion rates (Miyazaki et al., 2007). This could present as a reasonable explanation for the underlying process though which TZDs decrease ACR levels. Although, a previous analysis suggested that improvement in glucose levels did not contribute in the TZDs renal effect (Sarafidis et al., 2010). Therefore, the possibility of the role of TZDs in reducing insulin levels and blood pressure may still be a major factor in their effect on urine albumin excretion (Sarafidis et al., 2010). This area remains a target for further structured research. In the present study, we demonstrated that elevated fibrinogen and CRP levels are in close association with levels of albuminuria, as expressed by ACR values. This association appeared to occur even after adjusting for various potential confounding factors previously shown to affect the levels of proteins in urine, such as age, ethnicity, and sex. These correlations displayed a strong magnitude for both fibrinogen and CRP ($r = 0.49$ and 0.57, both $P < 0.001$), respectively.

Our findings were supported by multiple previous studies delineating the close association between elevated fibrinogen and CRP levels with microalbuminuria (Agewall et al., 1995), including large trials such as the IRAS trial, (Festa & D'Agostino et al., 2000). In fact, our correlation coefficients are by far greater in magnitude compared to those from the IRAS ($r = 0.17$ for CRP and $r = 0.14$ for fibrinogen, both $P < 0.001$). The close association between elevated fibrinogen and CRP levels with microalbuminuria has been reported in previous research. This relationship associated microalbuminuria with inflammatory states in both diabetic and non-diabetic patients (Agewall et al., 1995; & Festa & D'Agostino et al., 2000). The small size of the ACR data analyzed in this study may pose as a limitation to interpret the outcome. Regardless of the high number of participants in the DPP, only limited data on urine albumin and urine creatinine were released. In addition, the limited data we used in our analysis extends from baseline to confirmation visits. Confirmation visits seldom extend up to or beyond the one-year time line used to examine other markers.

CONCLUSION

This study was able to demonstrate the renal protective effect of troglitazone, identified in the lowering of eGFR and ACR values, although the latter did not reach a statistical significance. Diabetic nephropathy is one of the major complications of prediabetes and diabetes and is considered a leading cause for chronic kidney diseases. Not to forget, the close association between renal and CV diseases. Our study also demonstrated the impact of age, ethnicity (especially African American race), and gender on the extent of the outcome of troglitazone on renal markers. Differences in eGFR values showed great variabilities based on sex and ethnicity.

It was clear from our findings that troglitazone lost its significance effects on eGFR levels shown in the overall subgroup when the effect was analyzed in males and African Americans populations. Out analysis was not able to associate the impact of changes in changes in weight and weight circumference, and of the changes in measures of glycemia and insulin resistance on the action of the troglitazone on renal markers. The design and scope of the analysis of our study did not allow us to establish mechanistic explanation behind the significant effects of troglitazone on renal markers, and whether the observed changes were related to the unique characteristics of this agent or simply a function of its ability to lower plasma glucose levels and improve insulin sensitivity

DISCLOSURES

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