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International Journal of Current Research
Vol. 9, Issue, 11, pp.60594-60606, November, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

THE EFFECT OF TROGLITAZONE ON COAGULATION MARKERS AMONG INDIVIDUALS WITH PREDIABETES

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ARTICLE INFO

Article History:
Received 12th August, 2017
Received in revised form
26th September, 2017
Accepted 21st October, 2017
Published online 30th November, 2017

Key words:
Chlorophyll, Phytoplankton,
Ultra-oligotrophic,
Mesotrophic,
Eutrophic and Lagoon.

ABSTRACT

The present work is focused on coagulation defects associated with prediabetes, which are reflected in laboratory abnormalities of coagulation markers, such as fibrinogen and tPA. These markers are associated with increased risks of thrombosis which are associated with increased risks of cardiovascular (CV) events, including myocardial infarction (MI), coronary heart disease (CHD), and other forms of atherosclerosis. The Diabetes Prevention Program (DPP) trial was designed to study the effect of four different interventions (Intensive Lifestyle (ILS) modifications, metformin, troglitazone, and placebo) on the development and progression of diabetes in subjects with Impaired glucose tolerance (IGT). In this study we analyzed the effect of troglitazone on coagulation markers including fibrinogen and tPA in the DPP population.

Materials and Methods: Our analysis selected a subgroup (n= 3,171) from the original DPP population. The effect of troglitazone on coagulation markers was measured by analyzing its effects on the levels of fibrinogen and tPA at baseline and at 12 months and compared to the other three interventions (ILS, metformin, and placebo).

Results: Troglitazone reduced fibrinogen levels, median percent change of - 6.65% ($p < 0.001$) for all between group analysis: troglitazone vs. lifestyle, troglitazone vs. metformin, and troglitazone vs. placebo). This change revealed the highest change among all other interventions as reported in the previous DPP studies. Troglitazone also produced the highest median percent reduction in tPA levels (-21.39%) comparted to -20.41% in the lifestyle, -18.00% in the metformin, and -6.25% in the placebo intervention.

Discussion and Conclusions: Our study demonstrated the benefits of the TZDs in reducing certain CV surrogate risk markers due to the treatment with troglitazone for 12 months. These benefits appeared as a decrease in the levels of coagulation markers including fibrinogen and tPA. These benefits are of special value especially in such a population already at increased risk for CV morbidity and mortality. The effects of troglitazone on these markers exceed that of metformin. Our analysis was unable to associate the effect of changes in weigh and waist circumference, and changes in measures of glycemia and insulin resistance with the main effect of troglitazone on coagulation markers.

Citation: Khalid Mokhtar, Pharm, D., Elgenaid Hamadain Hamed Benghuzzi, FBSE, FAIMBE; Michelle Tucci, FBSE; Kenneth Butler, Donna Sullivan, Felicia Tardy, and Ibrahim Jamil, 2017. "Diabetes Prevention Modalities: The Effect of Troglitazone on coagulation Markers among Prediabetes Individuals", *International Journal of Current Research*, 9, (11), 60594-60606.

INTRODUCTION

Cardiovascular diseases (CVD) remain the global leading cause of death resulting in 17.3 million deaths according to the 2012 and 2013 worldwide estimate (Laslett *et al*., 2012). Diabetic individuals are at increased risk of thrombosis and other cerebral and cardiovascular risks.

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High percentage of the diabetic population is at an increased risk of morbidity and mortality due to thrombotic events (Calles-Escandon *et al*., 1999; Sacco, 1995). Type 2 DM has been reported to be associated with two to four folds increase in atherosclerotic vascular diseases and its complications (Uwaifo and Ratner, 2007; Vaccaro *et al*., 2004). In 2002, the National Cholesterol Education Program report elevated diabetes to the highest risk category by assigning diabetes a coronary heart disease risk equivalent (National Cholesterol Education Program (NCEP), 2002).

The rate of death from CHD is much higher in patients with diabetes than in those without (Huxley *et al*, 2006); about 65 percent of estimated diabetes related death in patients over 65 years of age was attributed to MI and 16 percent to stroke (CDC, 2011). The risk for CVD exists in prediabetic stages before the onset of diabetes. In fact, an increase in the risks for CVD has been reported to occur in blood glucose levels below the threshold for prediabetes (Shaye *et al*., 2012), and mortality due CVDs was proven to be similar in both prediabetic and diabetic individuals (Levitzky, *et al*., 2008). Prediabetes has also been on the rise, about 34 percent of the adult population in the U.S., accounting for more than 84 million people, had prediabetes in 2015, almost half, 48.3 percent, of adults 65 years or older had prediabetes. Based on the 2011- 2014 National Health and Nutrition Examination Survey (NHANES), more men than women, after adjusting for age, had prediabetes, no difference in the prevalence of prediabetes was reported among racial and ethnic groups (CDC, 2017; and ADA, 2017). Prediabetes, a condition typically defined as glycemic parameters above normal but below diagnostic criteria for diabetes, is also on the rise (CDC, 2014). Prediabetes constitutes a major health problem due to its common presence in high proportion of apparently healthy populations, therefore leading to considerable health problems associated with overt diabetes (Ligthart *et al*., 2016). According to the CDC 2014 reports, prediabetes affects 37 percent of U.S. adults aged 20 years or older, the estimates rises to 51 percent in individuals 65 years or older (CDC, 2014). After adjusting for age differences, CDC reported that the percentage of adults aged 20 years or above affected by prediabetes was similar across ethnic lines, about 35 percent for Hispanic whites, 39 percent for non-Hispanic blacks, and 38 percent for Hispanics (CDC, 2014). Estimates for the progression from prediabetes to diabetes have differed based on population characteristics and the diagnosing criteria (Forouhi *et al*., 2007; Nathan *et al*., 2007), an expert panel from the ADA estimates that 70 percent of individuals with prediabetes will eventually develop diabetes (Tabak *et al*., 2012), while the DPP outcomes study estimated an annual rate of only 11% (Knowler *et al*., 2009).

Hypercoagulable defects, which are reflected in laboratory abnormalities of coagulation markers, such as fibrinogen and tPA, are associated with increased risks of thrombosis (Schafer, 1985). Hemostasis and coagulation system are maintained mainly by equilibrium between tPA levels and its inhibitors, mainly (Plasminogen activator inhibitor-1) PAI-1 (Collen and Lijnen. 1991). Several studies have reported on the association between the levels of tPA and PAI with acute thrombotic disorders (Hamsten *et al*., 1985; and Ridker and Vaughan *et al*., 1992). Decreased fibrinolysis, reflected in Increased plasma concentration of PAI or impaired release of tPA and elevated plasma levels of tPA antigen, is reported to be associated with increased risks of CV events, including MI, CHD and other forms of atherosclerosis (Cortellaro *et al*., 1993; Held *et al*., 1997; Thompson *et al*., 1995; Kannel *et al*., 2005; Juhan-Vague *et al*., 1996, and Folsom *et al*., 1998). The close association between elevated tPA concentration and increased risks of MI and atherosclerosis has been suggested in the literature (Pedersen *et al*., 2016; Lowe *et al*., 2004; Wannamethee *et al*., 2009; and Borissoff *et al*., 2011).

The medical literature has documented the strong association between inflammatory and coagulation markers, including (C-reactive protein) CRP and fibrinogen, and the component of insulin resistance (Festa and D'Agostino *et al*., 2000; Han *et al*., 2002; Juhan-Vague *et al*., 1993; and Ndumele *et al*., 2006). Elevated fibrinogen levels have been found to be associated with traditional CV risk factors and have been considered as an independent risk factor for CVDs (Stec *et al*., 2000; Barasch *et al*., 1995; and Krobot *et al*., 1992). Additionally, the close association between insulin resistance and levels of inflammatory and coagulation markers with CV events such as ischemic heart disease and MI has been documented in multiple research including large clinical trials (Gruzdeva *et al*., 2013; Fernández *et al*., 2003; and Smit *et al*., 2006). The correlation between insulin resistance and impaired fibrinolysis due to elevated level of PAI-1, and consequently tPA activity, and fibrinogen levels in subjects with and without diabetes has been highlighted in multiple studies including the Framingham Offspring Study and the Insulin Resistance Atherosclerosis Study (IRAS) (Bastard *et al*., 2000; and Meigs *et al*., 2000; and Festa and D'Agostino *et al*., 1999).

RESEARCH DESIGN AND METHODS

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 IGT. The protocol for DPP has been previously documented in previous publications which included the study design, recruitment and measurement methods, and main characteristics of the overall population (Diabetes Prevention Program Research Group (DPP), 1999; and DPP, 2000). Inclusion criteria were age ≥25 years, fasting serum glucose (FSG) levels between 5.6–7.7 mmol/l before June 1997 and between 5.3–6.9 mmol/l after that date, and BMI of ≥24 kg/m^2 (DPP Research Group, 1999). Our study utilized the data from the DPP. The original study by the DPP group included a total of 3819 prediabetic individuals. Out of the total participants, 585 were assigned to troglitazone.

Our analysis selected a subgroup (n= 3,171) from the original DPP population to analyze tPA and fibrinogen. The total number of participants in this subgroup was determined based on the number of participants with available values for these markers at the end of 1 year from randomization. A total of 291 were in the troglitazone intervention arm (400mg every day), the rest were in the other three interventions including placebo, lifestyle, and metformin (850mg twice a day). The troglitazone arm was discontinued in June 1998 (DPP Research Group, 1999). In this report, we examine the effects of troglitazone on levels of fibrinogen and tPA. We also evaluate the effect of changes in selected measures, particularly changes in measures of insulin resistance and glycemia, obesity, and lipid profile; on the changes in these coagulation markers.

Statistical Analysis

Descriptive analysis at baseline of all variables were generated for each of the four treatment arms. 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 coagulation 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. Partial Spearman correlation was also performed to summarize the association between the changes in the main coagulation markers at 1 year

from baseline to understand whether the greater changes in the variables were affected by changes in weight, waist circumference, insulin resistance measures, or hemoglobin A1c (HbA1c). 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 fibrinogen and tPA due to treatment with troglitazone are explained by a weight and waist circumference changes, and changes in measures of glycemia and insulin resistance. The changes from baseline for fibrinogen, and tPA are shown as mean changes and SE, they were also summarized as the percent change from baseline. The percentage is calculated as [(value at 1 year – baseline value) x 100/baseline value] (Haffner *et al*, 2005). Median percent changes for tPA and fibrinogen were tested using nonparametric Wilcoxon's test. fasting insulin levels along with a pretested model 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- IR= {fasting insulin μU/ml × fasting glucose (mmol/l)} /22.5

RESULTS

As indicated in Table 1, baseline characteristics for the studied population is presented by intervention groups including placebo (n = 956), troglitazone (n = 291), metformin (n = 962), and ILS (n = 962). As might be expected from the primary selection by the DPP investigators, participants in all four interventions have similar baseline characteristics, females constituted an average of 66 percent while males are 34 percent. Same proportions of females to males were retained across the different interventions. African Americans constituted about 19 percent of the overall population. Baseline lab values including HbA1c, fasting insulin, fasting glucose, triglycerides, were virtually equal. Coagulation markers and HOMA-IR values were also virtually similar in all interventions. Values for fibrinogen were similar in each intervention, women exhibited higher mean values for fibrinogen values than men (395 vs 355, respectively), while tPA values showed the opposite pattern, with higher values shown in males compared to females (12.5 vs 10.7, respectively). African Americans also showed higher baseline values for fibrinogen compared to males and to the overall average, while they also showed lower values for tPA. Waist circumferences at run-in visit were the same across interventions, while weight at 6 months after randomization was lower in the lifestyle compared to the mean weight in the three other arms (87 ± 0.66 vs. 93 ±0.87). Baseline correlations for selected variables with fibrinogen and tPA was tabulated in Table 2. Both weight and waist circumference along with fasting glucose and HOMA-IR were all significantly and positivity correlated with tPA and fibrinogen. The magnitude of the correlations was similar with moderate strength, except for the correlation between fibrinogen in relation to fasting glucose and HOMA-IR which showed a relatively weaker correlation. HbA1c was also significantly correlated with fibrinogen and tPA. Fibrinogen and CRP showed a strong and significant correlation (r = 0.53, P <0.001). The outcomes for the partial correlation analysis after adjusting for age, sex, and ethnicity was summarized in Table 3. This analysis showed similar baseline correlation results for coagulation makers and the selected variables, except for the correlation of fasting glucose and fibrinogen which resulted in significant values, as opposed to the unadjusted analysis, with weak correlation coefficient.

As illustrated in table 6, which represents the changes in selected anthropometric and metabolic variables resulted from the effect of the different four interventions in the overall DPP population. It appears that troglitazone significantly reduced the levels of fasting insulin and HOMA-IR values at 1 year from baseline, both values resembled the magnitude of the effect of this agent on insulin resistance. Troglitazone showed greater reductions compared to metformin in the mean values of both fasting glucose levels (-4.06 vs -3.60, respectively, both P <0.001) and HOMA-IR (-1.22 vs –1.19, respectively, both P <0.001), while lifestyle exceeded these values. On lipid profile elements, all four interventions significantly reduced triglycerides levels, although troglitazone resulted in the highest mean reductions followed by lifestyle (-27.28 ± 3.88 vs. -25.78 ± 2.29, respectively, both P <0.01), while metformin exhibited the lowest mean reductions (-5.34 ± 2.16, P = 0.01). Troglitazone did increase the C-LDL levels (different from all other interventions which showed a decrease), however the change was statistically insignificant. Change in coagulation markers at 1 year from baseline was reported as median percentage values. As presented in Figure 1a, troglitazone demonstrated a decrease of 6.65% in fibrinogen levels (p <0.001) for all between group analysis: troglitazone vs. lifestyle, troglitazone vs. metformin, and troglitazone vs. placebo), this change represented the highest change among all other intervention as reported in the previous DPP study (Haffner *et al*., 2005). Figure 1a also presents the changes in fibrinogen due to the other three interventions, these results were already published by Haffner *et al*. Our analysis also showed the effect of the intervention on tPA values after 1 year from randomization. All four interventions manifested significant changes in tPA values (P <0.001), the highest mean values were shown among the participants treated with troglitazone (figure 1b). The median percentage change in tPA was -21.39% in the troglitazone, -20.41% in the lifestyle, -18.00% in the metformin, and -6.25% in the placebo intervention (lifestyle vs. metformin: P = 0.003; lifestyle vs. placebo: P < 0.001; metformin vs. placebo: P = 0.309; lifestyle vs. troglitazone: P < 0.001; metformin vs. troglitazone: P < 0.001; Placebo vs. troglitazone: P < 0.001).

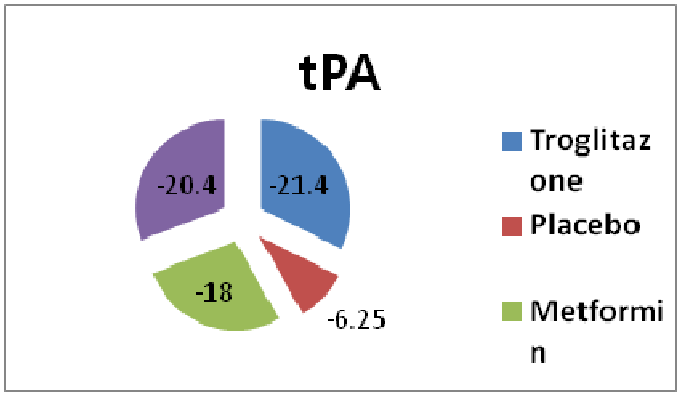

Figure 1b. Median percent change in overall tPA levels after 1 year of treatment with troglitazone

Table 1. Descriptive baseline characteristics in the inflammatory subgroup, displayed by intervention arms

	Placebo	Troglitazone	Metformin	Lifestyle
Overall n	956	291	962	962
Fibr	385.2±2.71	383.4± 5.42	378.9 ± 2.76	384.1 ± 2.75
tPA	11.4 ± 0.13	12.1 ± 0.32	11.2 ± 0.14	11.3 ± 0.14
Weight*	94 ± 0.72	95 ± 1.23	91 ± 0.67	87 ± 0.66
W Cir**	105 ± 0.47	105± 0.83	105 ± 0.48	105 ± 0.49
HbA1c	5.9 ± 0.02	5.8± 0.03	5.9±0.02	5.9±0.02
HOMA-IR	7.0 ± 0.13	6.8± 0.23	7.2±0.13	7.0±0.14
FSI	26.4 ± 0.47	25.0 ± 0.82	27.0±0.48	26.5±0.5
FSG	107.4 ± 0.25	109.0 ± 0.46	107.3 ± 0.25	107.0 ± 0.24
TRIG	167.3 ± 2.97	161.9±6.2	159.1±2.91	163.0±3.1
CLDL	125.1±1.07	122.4±1.83	125.1±1.04	126.2±1.05
Males (%)	310 (32%)	110 (38%)	345 (36%)	317 (33%)
Fibr	358.3 ± 4.66	353.3 ± 9.08	352.4 ± 4.29	359.3 ± 4.09
tPA	12.6 ± 0.24	12.9 ± 0.42	12.5 ± 0.26	12.6 ± .24
Females (%)	656 (68%)	183 (63%)	620 (64%)	649 (67%)
Fibr	397.9 ± 3.22	401.4 ± 6.41	393.8 ± 3.43	396.1 ± 3.48
tPA	10.8 ± 0.15	11.6 ± 0.45	10.4 ± 0.15	10.7 ± 0.17
AA (%)	203 (21%)	51 (18%)	209 (22%)	185 (19%)
Fibr	411.1 ± 6.7	390.1± 12.2	402.8 ± 6.7	394.9 ± 6.1
tPA	10.84 ± 0.27	10.28 ± 0.59	10.51 ± 0.23	10.49 ± 0.27

tPA = Tissue Plasminogen Activator (ng/dL), Fibr= Fibrinogen, W Cir = Waist Circumference (cm), FSG= Fasting Serum Glucose (mg/dL), FSI = Fasting Serum Insulin (µu/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 2. Partial spearman correlation coefficients of baseline values (p-values) of CRP, tPA, and fibrinogen with selected metabolic and anthropometric variables (troglitazone arm)

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CHOL	CLDL	UCRE	UALB	SCr	eGFR
tPA	0.04 NS)		0.13 (0.04)	0.20 (0.001)	0.22 (<0.001)	0.16 (0.006)	0.23 (<0.001)	0.12 (0.040)	0.22 (<0.001)	0.13 (0.030)	0.4 (NS)	0.04 (NS)	0.09 (NS)	0.14 (0.20)	0.01 (NS)	0.01 (NS)
Fibr	0.53 (<0.001)	0.13 (0.04)		0.31 (<0.001)	0.16 (0.006)	0.11 (NS)	0.18 (0.003)	0.22 (<0.001)	0.26 (<0.001)	-0.03 (NS)	0.08 (NS)	0.10 (NS)	0.02 (NS)	0.09 (NS)	0.16 (0.007)	0.01 (NS)

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen (mg/dL), 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 (mg/dL), CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate

* Waist Circumference was measured at run-in visits per DPP study

** weight was measured at 6 months visits

Table 6. Mean changes ± SE (P-values) from baseline by treatment group for overall population

	Placebo	Troglitazone	Metformin	Lifestyle
n	962	527	958	961
Weight[a]	0.34 ± 1.01 (ns)	***3.22 ± 2.33 (ns)	0.22 ± 0.96 (ns)	-0.28 ± 0.9 (ns)
W Cir[b]	-0.97 ± 0.71 (ns)	****-1.61 ± 1.71 (ns)	-2.12 ± 0.67	-6.8 ± 0.71
HbA1c	0.09 ± 0.01	0.02 ± 0.02 (ns)	•± 0.02 (ns)	-0.09 ± 0.01
HOMA-IR	0.35 ± 0.15(0.02)	-1.22 ± 0.16	-1.19 ± 0.12	-1.58 ± 0.15
Fasting insulin (µu/ml) I000	0.88 ± 0.53 (ns)	-4.06 ± 0.58	-3.60 ± 0.41	-5.24 ± 0.53
Fasting glucose (mg/dl)	0.28 ± 0.44 (ns)	-4.10 ± 0.52	-4.52 ± 0.34	-5.29 ± 0.35
Triglycerides mg/dL	-8.75 ± 2.34	-27.28 ± 3.88	-5.34 ± 2.16(0.01)	-25.78 ± 2.29
CLDL mg/dL	-1.97 ± 0.78	1.10 ± 1.07 (ns)	-4.52 ± 0.75	-6.13 ± 0.75
cholesterol	-3.70 ± 0.85	-2.61 ± 1.2 (0.03)	-5.0 ± 0.82	-9.84 ± 0.83
SCr	0.05 ± 0.004	**0.003 ± 0.01 (ns)	0.06 ± 0.04	*0.02 ± 0.01 (ns)

All p values are < 0.01 except when indicated in parenthesis [a] weight differences at 1 year from 6 months after randomization [b] waist circumference was taken at run-in visits (visits taking place after screening visit and prior to randomization n number of participants, * n = 165, ** n = 285, *** n=218, and **** n = 274
W Cir= Waist circumference

Table 2. Partial spearman correlation coefficients of baseline values (p-values) of CRP, tPA, and fibrinogen with selected metabolic and anthropometric variables (troglitazone arm)

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CHOL	CLDL	UCRE	UALB	SCr	eGFR
tPA	0.04 (NS)		0.13 (0.04)	0.20 (0.001)	0.22 (<0.001)	0.16 (0.006)	0.23 (<0.001)	0.12 (0.040)	0.22 (<0.001)	0.13 (0.030)	0.4 (NS)	0.04 (NS)	0.09 (NS)	0.14 (0.20)	0.01 (NS)	0.01 (NS)
Fibr	0.53 (<0.001)	0.13 (0.04)		0.31 (<0.001)	0.16 (0.006)	0.11 (NS)	0.18 (0.003)	0.22 (<0.001)	0.26 (<0.001)	-0.03 (NS)	0.08 (NS)	0.10 (NS)	0.02 (NS)	0.09 (NS)	0.16 (0.007)	0.01 (NS)

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen (mg/dL), 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 (mg/dL), CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate

* Waist Circumference was measured at run-in visits per DPP study

** weight was measured at 6 months visits

Table 3. Partial spearman correlation coefficients of baseline (p-values) for CRP, tPA, and fibrinogen with selected metabolic and anthropometric variables adjusted for age, sex, and ethnicity

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CHOL	CLDL	UCRE	UALB	CREA	eGFR
tPA	0.07 (NS)		0.17 (0.005)	0.21 (<0.001)	0.24 (<0.001)	0.16 (<0.001)	0.26 (<0.001)	0.12 (0.05)	0.25 (<0.001)	0.13 (0.04)	0.17 (0.004)	0.03 (NS)	0.08 (NS)	0.13 (0.03)	0.07 (NS)	-0.01 (NS)
Fibr	0.49 (<0.001)	0.17 (0.005)		0.35 (<0.001)	0.14 (0.02)	0.12 (0.05)	0.15 (0.01)	0.25 (<0.001)	0.28 (<0.001)	0.003 (NS)	0.08 (NS)	0.11 (NS)	0.06 (NS)	0.11 (NS)	0.01 (NS)	0.02 (NS)

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen (mg/dL), 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 (mg/dL), CLDL = Low Density Lipoprotein Subfraction (mg/dL), UALB = Urine Albumin (mg/dL), SCr = Serum Creatinine (mg/dL), eGFR = Estimated Glomerular Filtration Rate

* Waist Circumference was measured at run-in visits per DPP study

** weight was measured at 6 months visits

Table 4. Partial spearman correlations of the changes of year 1 change from baseline (P values) in the coagulation markers with select metabolic and renal variables (troglitazone intervention

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight**	TRIG	CLDL	CREA	eGFR	ACR
	-0.05	1.0	-0.13	0.41	0.52	0.62	0.55 (0.04)	0.34	0.53	0.08	-0.19	0.54	0.42	0.06
tPA	(NS)		(NS)	(NS)	(0.05)	(0.01)		(NS)	(0.04)	(NS)	NS)	(0.04)	(NS)	NS)
Fibr	0.53	-0.13	1.0	-0.09	-0.23	-0.31	-0.23 (NS)	0.34	0.09 (NS)	-0.65	0.3	0.19	0.06	0.66
	(0.04)	(NS)		(NS)	(NS)	(NS)		NS)		(0.009)	(NS)	(NS)	(NS)	(0.008)

CRP = C-Reactive Protein (mg/dL),), Fibr= Fibrinogen (mg/dL), 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 5. Partial spearman correlations of the changes of year 1 change from baseline (P values) in the coagulation markers with select metabolic and renal variables, adjusted for age, sex, and ethnicity

	CRP	tPA	Fibr	W Cir*	FSG	FSI	HOMA-IR	HBA1c	Weight*	TRIG	CLDL	SCr	eGFR	ACR
tPA	0.04	1.0	-0.01	0.23	0.49	0.58	0.5 (NS)	0.49	0.35	0.04	0.49	-0.69	0.58	0.04
	(NS)		(NS)	(NS)	(NS)	(0.05)		(NS)	(NS)	(NS)	(NS)	(0.01)	(0.05)	(NS)
Fibr	0.3 (NS)	-0.01 (NS)	1.0	-0.17	-0.33	-0.30	-0.33 (NS)	0.037	0.12	-0.59	0.14	0.6	0.27	0.75
				(NS)	(NS)	(NS)		(NS)	(NS)	(0.04)	(NS)	(NS)	(NS)	(0.005)

CRP = C-Reactive Protein (mg/dL), Fibr= Fibrinogen (mg/dL), 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

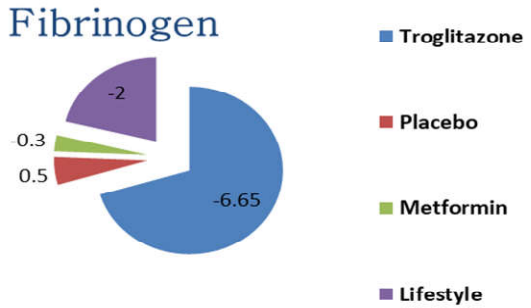

Figure 1a. Median percent values of troglitazone main effect on fibrinogen levels (Data for placebo, metformin and lifestyle were already published by Haffner *et al*., 2005, and were reproduced in this analysis)

Correlation analysis between the changes in selected metabolic and anthropometric variables with changes in coagulation markers at 1 year from base line are shown in Tables 4 and 5, before and after adjusting for age, sex, and ethnicity. Changes in weight showed significant correlation only with changes in tPA, the correlation was positive and strong in magnitude (r= 0.53, P= 0.04), after adjustment for demographic variables this correlation became statistically non-significant. Similar pattern appeared in the correlation with changes in tPA and changes in fasting glucose and HOMA-IR showed significantly strong and positive correlation, these correlations became nonsignificant after adjusting for age, sex, and ethnicity. Correlation of changes in tPA and changes in fasting insulin levels remained significant after adjustment.

DISCUSSION

The analysis demonstrated significant reduction in fibrinogen levels due to treatment with troglitazone for 12 months. The percentage change shown by troglitazone exceeded the results produced in the other three interventions according to what have already been reported by Haffner *et al*., in a previous DPP study performed in the same population analyzed in this report. Haffner *et al*., studied the effects of the metformin, placebo, and lifestyle interventions on fibrinogen, troglitazone was not included in their study. While our study reported a 6.65% reduction in fibrinogen levels, only 2% and 0.3% reductions were shown by lifestyle and metformin after 12 months of intervention, respectively, placebo rather showed an increase (Haffner *et al*., 2005). Current findings also demonstrated a significant reduction in tPA levels by all four interventions. Troglitazone produced the highest percentage change in tPA levels, followed by lifestyle, then metformin, with placebo achieving the lowest percentage. Results for the change in coagulation markers due to treatment with troglitazone was supported by previous research. A small study by Sidhu *et al*. reported a significant decrease in fibrinogen levels from 3.81gm/L ± 1.12 to 3.38 gm/L ± 0.65 in the eighty-four non-diabetic individuals included in this study, the length of treatment was 12 weeks (Sidhu *et al*., 2003). A significant reduction from 297.9 ± 55.7 to 250.0 ± 41.4 mg/dl in fibrinogen levels after 12 weeks of treatment with troglitazone was also reported by another study, a total of 21 diabetic individuals were included, a sulfonyl urea was used as a comparator (Kubo, 1998). Few other studies showed no significant reduction in fibrinogen because of troglitazone treatment (Fonseca *et al*., 1998).

Previous literature reported quite more on PAI-1 rather than tPA levels when studying the effects of TZDs on fibrinolysis and coagulation. Both tPA and uPA, Urokinase plasminogen activator, are proven to be crucial components of the blood coagulation and fibrinolysis, they work primarily by producing plasmin, the primary fibrinolytic protein, from plasminogen (Collen, 1999; Furie, 2009; Senior *et al*., 1986; and Richardson *et al*., 1976). The activity of tPA and uPA is dependent on PAI-1 (Wiman, Hamsten, 1990; Sprengers *et al*., 1987; Chapin *et al*., 2015; and Bu *et al*., 1994). Plasmin generation is therefore the net result of the activity of the plasminogen activators, tPA and uPA, and the PAIs. This underscores the importance of studying these coagulation factors especially in prediabetic populations ~~which~~ are already at an increased risk for morbidity and mortality due to higher thrombotic events because of the disease state itself (Calles-Escandon *et al*., 1999; Sacco R.L, 1995).

Diabetic population usually report higher tPA levels, most of which is usually found in its inactive forms bound to PAI-1 (Auwerx *et al*., 1988). Activation of tPA is fundamentally controlled by PAI-1 (Hu *et al*., 2008; Eddy, 1997; Kitching *et al*., 1997; and Haraguchi *et al*., 2001). Diabetes is associated with two folds increase in the risks for vascular complications resulting in increased mortality (Booth *et al*., 2006; and Smith *et al*., 2016); this was in part due to enhanced thrombotic conditions and decreased fibrinolysis (yden *et al*., 2013; and Grant, 2007). Abnormalities in coagulation markers, such as fibrinogen and tPA, are associated with increased risks of thrombosis resembling hypercoagulable defects (Schafer, 1985). Insulin resistance was reported to be closely associated with inflammatory and coagulation markers, in turn, these markers were shown to be correlated with multiple CV events including ischemic heart disease and MI (Gruzdeva *et al*., 2013; Fernández *et al*., 2003; and Smit *et al*., 2006).

Several animal and human studies reported on the ability of the TZDs to decrease the production of PAI-1 and affect their circulating levels (Gottschling-Zeller *et al*, 2000; Hanefeld *et al*., 2011; and Tripathy *et al*., 2013). Human research has also supported our findings regarding the reduction in tPA levels by the TZDs. Davidson *et al*. studied the effect of a combination of rosiglitazone and a sulfonylurea in a total of 245 African American and Hispanic American patients with type 2 diabetes and followed them for 24 weeks. They found significant reduction in tPA percentage levels in the rosiglitazone combination intervention, which amounted to more than 17 percent (Davidson *et al*., 2007). The magnitude of the outcome from Davidson *et al*. study was comparable to our findings. However, our analysis showed a greater percentage reduction with troglitazone after 12 months of treatment. Another study also reported similar reductions in tPA results with troglitazone as ours, although their results did not reach a statistical significance. The study included 48 diabetic patients comparing the effect of troglitazone with a sulfonylurea for a period of four weeks (Kato *et al*, 2000). The inconsistency of the outcome from previous research on the effect of treatment with troglitazone on tPA and fibrinogen levels, only stresses the need for more structured research addressing these critical markers. Mechanistically, there is no clear explanation for the effects of troglitazone on coagulation markers. Hyperglycemia was suggested as a reason behind the decreased coagulation activity of tPA, glycosylation of these proteins may lead to their impaired activity (Almer *et al*., 1975). Similar glycosylation theories were suggested regarding the impact of TZDs on fibrinogen (Brownlee *et al*., 1983; Carr and Alving, 1995; Mirshah *et al*., 1987). The clinical significance of these proposals has not yet been fully recognized. Clearly, further studies are needed to determine the actual mechanisms which precisely explain the effect of TZDs on markers of coagulation.

As previously indicated, our study showed marked elevation in the overall mean CRP and fibrinogen levels (0.58 ± 0.03 v. 383.15 ± 3.41), respectively, compared with healthy individuals, similar to what was reported in previous research. Ganda *et al*., reported values of fibrinogen in the range of 339 ± 7.3 mg/dL in diabetic subjects to be considered substantial elevation, especially when compared to the levels in the control subjects,

248 ± 9.1 mg/dL (Ganda *et al*., 1992), clearly the values reported in our analysis exceeded what was reported in this previous report. Elevated fibrinogen values shown in our studied population at baseline agreed with previous reports

(McMillan, 1981; Festa and D'Agostino *et al*., 2000; and Festa and D'Agostino *et al*., 1999). Elevated fibrinogen levels were suggested to be contributing factors in the underlying disease process in diabetic vascular disorders, rather than simply signals for atherosclerosis (Smith *et al*., 1979; and Velican *et al*., 1980). The overall increase in levels of inflammatory and coagulation markers were reported to be associated with increased CVD risks, especially MI (Tousoulis *et al*., 2007). Our results as well as others may lead to the suggestion that improved vascular function brought by TZDs could possibly be related to their ability to suppress inflammation and coagulation markers, as suggested by previous reporting (Tousoulis *et al*., 2007; Gada *et al*., 2013).

Elevated CRP and fibrinogen levels in African Americans at baseline were also observed by our analysis. This pattern agrees with what was shown in preceding research (Carroll *et al*., 2009; Lin *et al*., 2007; and Wee *et al*., 2008). In fact, different reports considered the elevation in the levels of CRP and fibrinogen among African Americans to be a possible explanation for the increased risk for CVD in this specific population (Anuura *et al*., 2008). Our findings, regarding the reduction in coagulation markers, further support the assumption that TZDs exerts their benefits on CVD by reducing these specific markers, this extends to such at risk population as the African Americans. African American and Hispanic American are also reported to have higher rates of insulin resistance and obesity than other ethnicities, this elevates the risks for CVDs (Cossrow *et al*., 2004). Results from our analysis displayed significant reductions in measures of insulin sensitivity, HOMA-IR and fasting glucose levels, brought by troglitazone treatment for 1 year, our results showed higher reductions in comparison to metformin and placebo. These findings resembled multiple previous documentations in which troglitazone has proven to be a powerful insulin sensitizer, exceeding the effect of metformin which is considered the only other known class of antidiabetics which is thought to work, at least partially, on insulin resistance (Chu *et al*., 2002). Insulin resistance is a major player in the etiology of prediabetes and diabetes along with insulin deficiency (ADA, 2012; Morris *et al*., 2012; FB HU *et al*., 2001; Ferrannini *et al*., 2011 and Chen *et al*., 1988), which emphasizes the importance of the TZDs as the only antidiabetic class currently available that predominantly target insulin resistance (Natali and Ferrannini, 2006; Hallsten *et al*., 2002; and Yki-Jarvinen, 2004).

The significant reduction in triglycerides levels due to troglitazone treatment as described in this current study, is supported by previous research, both animal and human. Animal research have reported on the triglycerides lowering effect of TZDs, suggesting some different pathways for this benefit than their effect on glycemia (Day, 1999; and Reginato *et al*., 1999; and Burant *et al*., 1997). In humans, the impact of the TZD members on other lipid variables including LDL and total cholesterol was diverse depending on the particular agent utilized. While troglitazone and pioglitazone demonstrated improvement, rosiglitazone did not (Gegick *et al*., 2001; and Olansky *et al*., 2003). Lifestyle modification, on the other hand was shown to produce significant reduction on these markers compared to placebo or multiple other pharmacological agents, consistent with our current findings (Salimi *et al*., 2017; Kseneva *et al*., 2016; and Takahashi *et al*., 2013).

The close association between dyslipidemia, presented in elevated triglycerides, total cholesterol, low density lipoprotein C (LDL-C), and CVDs have been demonstrated by several studies, which lead to the recommendation by many guidelines to affirm the demands for the reduction of the levels of these products as a preventative measure for CV risks (Ray *et al*., 2014; and Stone *et al*., 2014). Partial spearman correlation analysis between inflammatory and coagulation markers revealed some significant correlation between these CV surrogate markers. Strong correlation of CRP and fibrinogen shown by this present analysis indicates a strong association between the process of inflammation and coagulation. This comes in close alignment with previous investigations which suggests similar association between these two variables and with the component of insulin resistance (Festa and D'Agostino *et al*., 2000; Han *et al*., 2002; Juhan-Vague *et al*., 1993; and Ndumele *et al*., 2006). Elevated fibrinogen levels have been considered an independent risk factor for CVDs, and were also found to be in close association with traditional CV risk factors (Stec *et al*., 2000; Barasch *et al*., 1995; and Krobot *et al*., 1992), this may in part explains the underlying benefits of the TZDs on CVDs. Furthermore, this analysis has displayed a close correlation between HOMA-IR, a measure for insulin resistance, and markers for coagulation. These results may possibly confirm previous reports on the impact of the levels of coagulation markers on CV events through modifying insulin resistance components (Gruzdeva *et al*., 2013; Fernández *et al*., 2003; and Smit *et al*., 2006). The important role of chronic inflammation as a triggering factor of insulin resistance has long been predicted (Pickup *et al*., 1998). Large trials, including the Framingham Offspring Study and the Insulin Resistance Atherosclerosis Study (IRAS), have underscored the correlation between defective fibrinolysis and insulin resistance in diabetic and non-diabetic subjects (Bastard *et al*., 2000; Festa and D'Agostino *et al*., 1999 and Meigs *et al*., 2000).

The significant results shown by this present study regarding the correlation of weigh and waist circumference with tPA, although modest in value, may stress the importance of adiposity as an important factor in the process of coagulation and fibrinolysis. This suggestion was supported by previous findings indicating direct contribution of adipose tissues in the elevation o PAI-1 levels in obese subjects (Loskutoff *et al*., 1998; and Alessi *et al*., 1997), which in turn may directly affect the activity of tPA. Partial spearman correlation analysis was performed to study whether the changes produced by troglitazone on fibrinogen or tPA are affected by changes in metabolic, anthropometric, or demographic measures. Correlational analyses were conducted to examine the relationship between the differences in the coagulation markers in relation to the differences in HBA1c from baseline to 1 year in each intervention. These results revealed a negative relationship between changes in HBA1c and changes in fibrinogen and tPA.

Even though, the magnitude of the correlation was moderate, and statistically nonsignificant in few instances, it may still suggest an association between the effect of TZDs on glycemic control and their effect in these coagulation markers, especially tPA. Based on the observed results, it seemed like the decreases in the levels of fibrinogen did not correlate with improvement shown by troglitazone in insulin sensitivity and glycemia, nor with the changes in weight and waist circumference, although the changes in the two latter variables

did not reach statistical significance. The change in fibrinogen due to troglitazone treatment demonstrated a strong correlation with the decrease in triglycerides, although the magnitude was negative in value. On the other hand, tPA displayed a significant correlation with changes in weight, HOMA-IR, fasting insulin, and fasting glucose. Together, these observations, especially the presented results for the correlation of fibrinogen, suggest that troglitazone exerts its action, at least partially, via different mechanism apart from its effects on insulin resistance and glycemic control, these suggestions were supported by a small study done on prediabetic individuals. This study showed similar results from troglitazone on the reduction in CRP and tPA (van Tits *et al*., 2005). Similarly, the effect of troglitazone on tPA seems to be closely associated with changes in glycemia and in measures for insulin resistance including HOMA-IR and fasting insulin levels.

Multiple linear regression analysis was performed to explain whether the effect of troglitazone on tPA or fibrinogen could possibly be explained by changes in selected demographic, anthropometric, or metabolic variables. Results from our regression analysis produced statistically non-significant models. Accordingly, neither of the changes in HOMA-IR, fasting insulin, fasting glucose, or HbA1c at 1 year from baseline, nor changes in weight at 1 year from 6 months or changes in waist circumference at 1 year from run-in visits were suitable to explain this relationship. Based on the results from the effect of TZDs on lipid and metabolic markers, in addition to the correlation analysis performed between the main effect of troglitazone on coagulation markers with changes in measures for insulin resistance including fasting insulin levels and HOMA-IR and measures of glycemia including HbA1c and fasting glucose levels, we may be able to address the concern regarding the effect of changes in these measures on the main effect of troglitazone. Therefore, we may assume that our finding regarding the effect of troglitazone on fibrinogen were not affected by changes in these selected metabolic and anthropometric measures studied. On the other hand, change in tPA could possibly be influenced by the effect of troglitazone on these other measures. Furthermore, and as shown from the unadjusted and adjusted correlational analysis, demographic measure including age, sex, or ethnicity played a role in changes on tPA. These suggestions were supported by our results from regression analysis discussed earlier. These conclusions appeared in contradiction with the suggestion drawn earlier from the results of the main findings in which troglitazone significantly changed the levels of inflammatory and coagulation markers, especially when the analysis was stratified based on sex or ethnicity. It appears from our findings that multiple conclusions can be drawn regarding the impact of metabolic and anthropometric changes, or the demographic variabilities on the main effect of troglitazone on coagulation markers.

LIMITATIONS

Among the 528 participants included in the original DPP study who were on troglitazone, we obtained access to coagulation variables at 1 year for about only a half. Another limitation is the fact that troglitazone is no longer available as a drug for human treatment, due to documented hepatotoxicity, this may limit the ability to reproduce the results expected from our study. Nevertheless, the availability of data on troglitazone presents a unique opportunity to expand on the characteristics of the TZDs as a class, especially since all TZDs exert their actions through the same mechanism and share multiple similarities.

African American population were the only specific ethnic group selected to study the effects of troglitazone on coagulation markers when the analysis was performed based on ethnicity. Other races, especially Asian American and Indian Americans also deserved a careful consideration since they are also disproportionally affected by obesity and insulin resistance more than other ethnicities. Finally, while our analysis studied the effect of troglitazone on the markers mentioned above on prediabetic subjects, the study failed to control for the concurrent medications used, especially agents which may have an additive effect on these markers.

CONCLUSION

Although troglitazone has already been withdrawn from U.S markets due to claims of liver toxicities, which was proven to be agent specific rather the class, two other agents from the TZD class are still available. These agents, in addition to their unique mechanism of action through their ability to target insulin resistance, they may as well act as a valuable alternative to the currently available antidiabetic agents, especially due to their ability to act on coagulation risks in the face of documented reports of an increase in both cardiovascular and renal problems in the prediabetic and diabetic populations. In addition to their superlative role in the prevention of prediabetes and preserving pancreatic beta cell function, TZDs have emerged as potential therapeutic agents in the treatment of cancer, Alzheimer's, and disorders associated with inflammation such as rheumatoid arthritis and ulcerative colitis, and many other disease states through their role in the activation of Peroxisome proliferator-activated receptor gamma (PPARγ) receptors, nuclear receptors which affect and regulate gene expression. The safety of the pharmacological agents used for the prevention and the treatment of type 2 diabetes mellitus is very important, especially CV safety considering the high risk of such disorders due to the disease state itself. And in the face of the many claims doubting the CV safety of the TZDs. Our study demonstrated the benefits of the TZDs, resembled by the troglitazone, in reducing certain CV surrogate risk markers due to the treatment with troglitazone for 12 months. These benefits appeared as a decrease in the levels of coagulation markers including fibrinogen and tPA. These benefits are of special value especially in such a population which is already at increased risk for CV morbidity and mortality. The effects of troglitazone on these markers exceeded that of metformin, which is the only other available agent from different class of antidiabetic to work on insulin resistance. We also examined the extent of the impact of the changes in weight and waist circumference, and of the changes in measures of glycemia and insulin resistance on the action of the troglitazone on the main markers investigated by this analysis. Our analysis was unable to associate the effect of these changes with the main effect of troglitazone. The design and scope of our analysis did not allow us to establish mechanistic explanation behind the significant effects of troglitazone on coagulation 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. Although, multiple suggestions were made in this regard,

which were supported by previous research, indeed, further research is still needed to determine the actual mechanisms which can precisely explain the variety of effects shown by troglitazone.

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