

The effect of pioglitazone on circulating interleukin-10 and tumor necrosis factor-alpha levels in a patient with metabolic syndrome: A randomized, double-blind controlled trial

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Original Article

Abstract

BACKGROUND: This study aimed to evaluate the effect of pioglitazone as an insulin sensitizer on circulating interleukin-10 (IL-10) as an anti-inflammatory factor and tumor necrosis factor-alpha (TNF- α) as main proinflammatory factor in non-diabetic metabolic syndrome (MetS) patients in Caucasians race of Middle East area in Iran.

METHODS: We conducted a randomized double-blind controlled study of 68 non-diabetic patients with MetS. Patients were randomly divided into two groups including intervention group received pioglitazone 30 mg daily for 24 weeks, and the control group received placebo pills for the same duration. Circulating levels of TNF- α and IL-10 were assessed as a primary goal. Lipid profile, liver enzymes, blood pressure (BP), waist circumference, and body mass index (BMI) also were measured.

RESULTS: Lipid profile and fasting blood sugar had non-significant changes after treatment by pioglitazone, but BMI was increased significantly ($P = 0.002$). BP and waist circumference had a significant decrease in both groups ($P < 0.050$). Aspartate transaminase and alanine transaminase were decreased significantly in the pioglitazone group ($P = 0.002$). TNF- α decreased non-significantly in both groups ($P > 0.050$). IL-10 increased in intervention group non-significantly ($P = 0.971$); whereas in placebo group decreased to a little extent ($P = 0.401$). C-reactive protein was also decreased insignificant after receive pioglitazone ($P = 0.333$). There was no significant difference in all variables between the two groups ($P > 0.050$) except liver enzymes ($P < 0.050$).

CONCLUSION: This study indicates that the pioglitazone has no positive effect on improving inflammatory status in the non-diabetes patients with MetS.

Keywords: Pioglitazone, Interleukin-10, Tumor Necrosis Factor Alpha

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Introduction

Metabolic syndrome (MetS) with increasing prevalence is one of the most important health and medical problems in developed and developing countries.¹ Metabolic or X syndrome includes a set of metabolic risk factors such as abdominal obesity, dyslipidemia, impaired glucose homeostasis and hypertension associated with an increase of cardiovascular disease and its resulting mortality. In fact, cardiovascular disease is the most important consequence of X syndrome and mortality factor among this population.²

Recently, several studies propose elevated serum levels of inflammatory biomarkers as an emerging risk factor for many chronic diseases such as diabetes and MetS and consider inflammatory processes as the overt factor leading to cardiovascular diseases progression.³ In fact, systemic inflammation plays the main role in the pathogenesis of MetS and the role of intermediary in development of cardiovascular events in these patients.^{4,5} The production of proinflammatory factors such as interleukin-1 (IL-1), IL-6, tumor

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necrosis factor- α (TNF- α) and C-reactive protein (CRP) due to homeostasis in adipose tissue in MetS plays an important role in atherosclerotic disturbances and diabetes by affecting endothelial function of vessels and making resistance against insulin.^{6,7} Thus, overcoming insulin resistance could be a main step in prevention and treatment of patients suffering from MetS. Having agonist effect on peroxisome proliferator-activated receptor-gamma (PPAR- γ) and reducing inflammatory biomarker, thiazolidine (TZD) improves insulin sensitivity and has a little effect on the function of beta cells and liver.⁸⁻¹¹ Furthermore, TZD improves endothelial function, reduces vascular inflammation, free fatty acids and low-density lipoprotein cholesterol (LDL-C).¹² Among these, various studies have also investigated the effect of this drug category on the level of inflammatory biomarkers and vascular function of diabetic and non-diabetic patients, which besides anti-inflammatory effect of drug; they show contradictory results especially in various ethnicities.¹³⁻¹⁶ On the other hand, there are a few studies investigating the effect of this drug on plasma level of anti-inflammatory cytokines like IL-10.¹⁷ As far as we know, this study investigates the effect of pioglitazone (as a TZD) on plasma level of IL-10 as an anti-inflammatory factor and TNF- α as main proinflammatory factor in nondiabetic patients with MetS in Caucasians race of Middle East area in Iran, for the first time. The main reason for selection of patients suffering from MetS rather than one of its components like hypertension is that the resistance against insulin is a common pathophysiology between all different parts of MetS. The presence of all these components severely increases the cardiovascular risks. Hence, we assessed the effects of Pioglitazone as an insulin sensitizer on circulating IL-10 and TNF- α in the noted population (primary aim); and also we evaluated the metabolic risk factor including lipid profile, glucose serum level, body weight, blood pressure (BP) and other inflammatory makers like CRP as secondary aim.

Materials and Methods

This is a randomized; double-blind controlled trial study that approved by the Ethics Committee of the Isfahan University of Medical Sciences, Iran. The study was carried out on 89 men and women referring to Sedigheh Tahereh Medical Clinic (Isfahan Cardiovascular Research Institute) in 2012 to 2013. Inclusion criteria include age range of 35-65 years with non-diabetic MetS criteria. The updated Adult

Treatment Panel III guideline of the National Cholesterol Education Program definition was used for MetS detection. It was defined as the presence of 3 or more of the following components: (1) serum triglycerides (TG) \geq 150 mg/dl; (2) high-density lipoprotein-cholesterol (HDL-C) $<$ 40 mg/dl for men and $<$ 50 mg/dl for women; (3) glucose \geq 100 mg/dl fasting or on treatment; (4) BP \geq 130/85 mmHg or antihypertensive medication use, and (5) waist circumference \geq 102 cm in men and \geq 88 cm in women.¹⁸

Taking TZD medicine in the past 6 months, consumption of immunosuppression or anti-inflammatory drugs at the time of entrance to study, approved autoimmune disease, major cardiovascular events (like myocardial infarction), cerebrovascular disorders (stroke, transient ischemic attack), heart failure (Grade III or IV), liver enzyme abnormalities (liver enzymes level more than 2.5 times of normal), kidney dysfunction (creatinine higher than 1.8 mg/dl), pregnant women, breastfeeding women or women in childbearing age who do not have a good method of contraception were the exclusion criteria. Furthermore, in case of severe side effects associated with drugs that may require to stop drug consumption such as increased hepatic enzymes (2.5 times more than the base amount or higher), causing jaundice, making symptoms associated with heart failure, impaired vision, etc. the patients were excluded from the study. Conscious consent forms were completed by all participants.

Patients were divided into two 34-member groups receiving pioglitazone and placebo drugs by the use of table of randomized numbers. For the intervention group one tablet of 30 mg pioglitazone (Sajad Darou Pharmaceutical Co., Iran) per day was used.^{19,20} Patients in the placebo group consumed placebo pills daily (produced by Isfahan School of Pharmacy) similar to pioglitazone pills in terms of shape, size, and color. The treatment period was 24 weeks and in this period, patients were given advises on diet and physical activity based on the available guidelines.²¹ Patients were visited by residents of cardiovascular diseases within 6 weeks with the interval of every 2 weeks at the beginning and then monthly. In these visits, vital signs and drug side-effects were investigated and drugs were replaced by new one (Figure 1).

A volume of 10 cc venous blood sample was taken in the fasting state (12 h, between 8 and 9 AM) and serum was isolated by centrifugation 3000 $\times g$ for 20 min at a temperature of around 4 $^{\circ}C$. Circulating levels of IL-10 and TNF- α were measured using enzyme-linked immunosorbent

assay kit (Boster Biological Technology, China) in all patients before and after intervention. Fasting blood glucose, levels of total cholesterol, TG and HDL-C were measured through enzymatic method (Pars Azmoon Inc., Iran) by autoanalyzer (Hitachi 902, Japan). Concentrations of LDL-C was determined by Friedwald equation in individuals whose TG < 400 mg/dl. Complete blood count (CBC) was done by Sysmex KX-21N (Japan) counter. High sensitive CRP, alanine transaminase (ALT) and aspartate transaminase (AST) levels were also measured by Hitachi 902 autoanalyzer using Pars Azmoon analytical kits. All tests were conducted in a laboratory (laboratory of Isfahan Cardiovascular Research Institute) with the same laboratorial kits. BP, waist circumference were

measured before and after intervention. Demographic data including age, sex, hypertension and obesity were also recorded.

According to previous studies via inflammatory factors values and TNF- α standard deviation¹⁵ with first type error $\alpha = 0.05$ and study power = 0.8 the sample size was calculated as 27 individuals for each group. To compare the variables between two groups independent t-test was used. To compare the changes in quantitative variables in each group, Paired t-test was used. All data had a normal distribution by Shapiro–Wilk test. Analysis was performed through SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). Data are in the form of mean \pm standard deviation, and a significant level was considered as < 0.05.

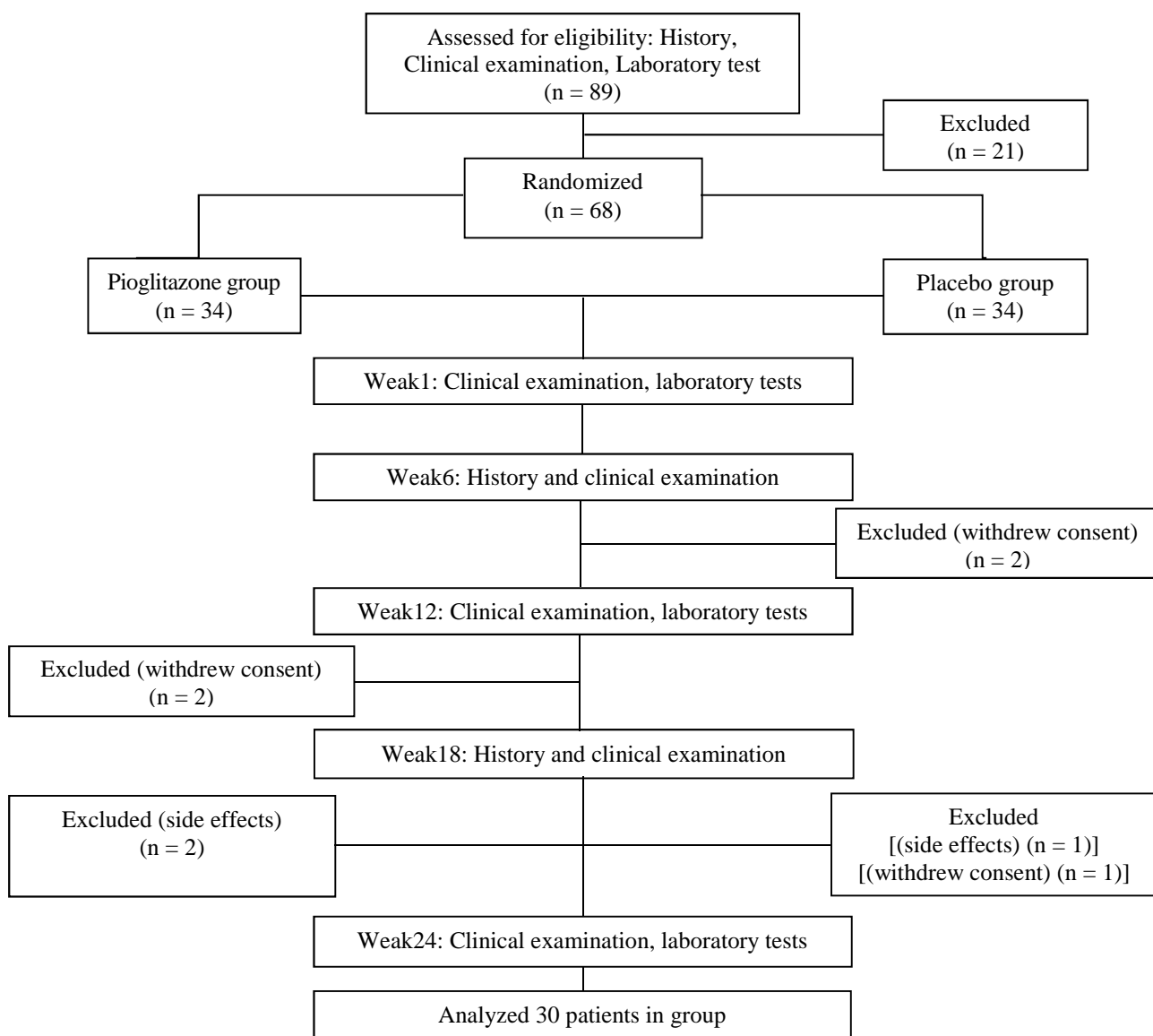


Figure 1. The chart of study process

Results

Eighty-nine patients participant in the study initially. Twenty-one of them excluded, and 68 patients including 32 female (54%) and age between 20 and 70 were eligible and randomized between to group (each one 34 patients). There were no significant differences between groups in demographic and primary metabolic information of patients that summarized in table 1. After 24 weeks of receiving pioglitazone, we saw different non-significant changes in lipid profile and fasting blood sugar. Total cholesterol, LDL-C, and HDL-C were increased

non-significantly in the intervention group, while decreased in the placebo group. Serum TG level decreased in both groups non-significantly too (Table 2). Our patients had meaningfully higher increase of body mass index (BMI) after treatment by pioglitazone versus placebo ($P = 0.002$) (Table 2). In both group waist circumference decreased significantly ($P = 0.003$). Fasting blood glucose had no meaningful change within and between groups.

Both systolic and diastolic BP showed significant improvement in the pioglitazone and placebo group (Table 2).

Table 1. Demographic and primary metabolic data

Variable	Pioglitazone group (n = 30)	Placebo group (n = 30)	P
Age (mean ± SD)	47.7 ± 7.2	47.4 ± 7.6	0.904
Gender (male) [n (%)]	17 (56)	11 (36)	0.121
Hypertension and Prehypertension [n (%)]	27 (90)	27 (90)	0.932
Dyslipidemia [n (%)]	21 (70)	23 (76)	0.771
Obesity [n (%)]	19 (63)	17 (56)	0.601

SD: Standard deviation

Table 2. Changes and comparison in metabolic factors and cytokines levels after 24 weeks treatment within and between groups

Variable	Pioglitazone group (n = 30)			Placebo group (n = 30)			Between groups	
	Baseline	After treatment	P*	Baseline	After treatment	P*	Corrected difference (95% CI)	P**
FBS (mg/dl)	98.03 ± 13.26	95.60 ± 18.52	0.484	95.53 ± 10.87	96.42 ± 11.71	0.673	+3.32 (-4.72-11.36)	0.411
Total cholesterol (mg/dl)	202.92 ± 34.46	210.17 ± 36.85	0.252	226.48 ± 61.41	211.40 ± 40.56	0.172	46.93 (-2.28-22.32)	0.075
Triglyceride (mg/dl)	241.42 ± 173.78	200.53 ± 117.54	0.093	231.53 ± 155.29	228.92 ± 112.86	0.927	+38.28 (-35.06-111.63)	0.300
HDL-cholesterol (mg/dl)	41.89 ± 10.64	44.03 ± 11.28	0.168	42.71 ± 9.50	42.85 ± 11.47	0.916	-2.00 (-6.05-2.05)	0.327
LDL-cholesterol (mg/dl)	107.10 ± 21.78	116.96 ± 25.41	0.074	119.29 ± 35.22	119.33 ± 31.36	0.995	-9.82 (-25.62-5.98)	0.218
Systolic BP (mmHg)	128.89 ± 14.55	117.43 ± 10.35	0.001	140.22 ± 20.11	123.78 ± 14.56	0.001	-3.83 (-10.63-2.96)	0.263
Diastolic BP (mmHg)	82.12 ± 8.31	78.01 ± 4.13	0.002	85.44 ± 10.10	81.12 ± 7.35	0.004	-0.61 (-4.81-3.58)	0.770
BMI (kg/m ²)	30.16 ± 3.30	31.13 ± 4.05	0.002	30.20 ± 4.10	30.63 ± 4.20	0.091	-0.53 (-1.28-0.21)	0.160
Waist circumference (cm)	102.44 ± 9.01	101.95 ± 10.23	0.003	101.55 ± 10.11	99.32 ± 10.20	0.003	1.31 (-4.03-1.41)	0.340
AST (U/l)	27.89 ± 7.72	22.60 ± 5.10	0.002	25.25 ± 6.10	24.37 ± 6.93	0.497	+4.39 (0.31-8.48)	0.035
ALT (U/l)	29.78 ± 11.94	24.57 ± 9.60	0.032	26.92 ± 13.30	30.96 ± 15.91	0.033	+9.25 (3.37-15.12)	0.003
White blood cell (10 ³ /ml)	6.11 ± 1.54	5.80 ± 1.02	0.23	10.59 ± 16.60	6.56 ± 1.42	0.330	-3.71 (-11.91-4.47)	0.361
hs-CRP (mg/l)	2.50 ± 1.54	2.00 ± 1.03	0.333	1.88 ± 0.96	2.61 ± 1.53	0.120	+1.22 (-0.13-2.57)	0.075
TNF-α (pg/ml)	12.10 ± 11.81	10.70 ± 4.82	0.581	10.43 ± 6.12	10.24 ± 5.23	0.901	+1.55 (-4.05-7.17)	0.580
IL-10 (pg/ml)	14.21 ± 12.01	14.30 ± 10.52	0.971	14.82 ± 5.01	13.72 ± 5.63	0.401	-1.10 (-7.05-4.85)	0.713

Data presented by mean ± SD; Significant level was considered as < 0.05 ; * Paired t-test for compare variables in each group; ** Independent t-test for compare variables between groups; CI: Confidence interval; SD: Standard deviation; FBS: Fasting blood sugar; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; BP: Blood pressure; BMI: Body mass index; AST: Aspartate transaminase; ALT: Alanine transaminase; hs-CRP: High-sensitivity-C reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-10: Interleukin-10

In the investigation of inflammatory status, there was not prominent change after treatment of pioglitazone, although we observed a non-significant decrease of hs-CRP and TNF- α serum levels in pioglitazone group versus placebo. IL-10 increased in the intervention group; however, this increase was not significant. This is while this anti-inflammatory cytokine in the placebo group decreased to a little extent. WBC count was decreased in both group, but no significant (Table 2). There was no significant difference in all variables between the two groups ($P > 0.050$) except liver enzymes (Table 2). Generalized edema and rise in liver enzyme (more than 2.5 times of the upper limit of normal) was seen in pioglitazone group and excluded from study (one of each cases); but on the average, ALT serum levels were significantly decreased in pioglitazone group ($P = 0.032$) and increased in placebo group ($P = 0.033$) (Table 2). Serum AST levels only decreased significantly in the pioglitazone group ($P = 0.002$). Changes in serum level of liver enzymes were in normal range. One patient discontinued the study of severe headache complaint in the placebo group.

Discussion

This study indicated that the treatment with pioglitazone has no positive impact on improving inflammatory status in non-diabetic MetS patients. Despite most previous studies, pioglitazone has no significant impact on the reduction of TNF- α in blood circulation. Martens et al. also found the changes in TNF- α plasma levels due to pioglitazone as insignificant.¹⁶ Plasma IL-10 level showed no significant increase in the pioglitazone group. In another study, the reverse effect of TZD (rosiglitazone) on the inflammation trend was seen with a decrease of this anti-inflammatory cytokine and effect on IL-1 function.¹⁷ The previous studies (without consideration of glycemic control) obtained different results concerning lipid profile and obesity status the same as inflammatory cytokines. Moreover, most studies didn't report a positive effect of TZD on lipid profile status.¹⁴⁻¹⁶ We showed non-significant increasing of total cholesterol, HDL-C, LDL-C and decreased in TG level after 24 weeks consumption of PPAR- γ agonist. Although the result of a meta-analysis study have shown an improving effect of pioglitazone on serum HDL-C and TG levels.²² BMI was increased significantly in patients receiving pioglitazone due to increasing appetite and body fat and fluid retention

mechanism probably.²³ In this trial, the improvement of BP in both group patients was significant that it is attributed to the regular blood pressure management and lifestyle modification advice given to the participants.²⁴ Liver enzyme had a significant decrease in the pioglitazone group in our non-diabetic patients, which it unexpected effect needed more detailed studies. In comparison to previous studies, McCoy et al. showed that there is strong relation between sensitivity to insulin and plasma level of inflammatory and coagulation cytokines like CRP, TNF- α and plasminogen activator inhibitor type 1 (PAI-1) as risk factors for cardiovascular diseases in diabetic and pre-diabetic patients. However, this change was not significant concerning IL-6 and fibrinogen level. In this study, sensitivity to insulin had no effect on weight and blood pressure of individuals; however it leads to 10% increase in HDL-C and 11.9% decrease in TG. The final result of this study indicated that combined treatment of metformin and pioglitazone (metformin 1000 mg/d + pioglitazone 45 mg/d, for 12 weeks) can lead to improvement of inflammatory and coagulation factors in groups at high risk like Asian-Indians race by creating sensitivity to insulin and at the end leads to reduction of occurrence and mortality of cardiovascular disease in these individuals.¹³

Raji et al. study showed that the resistance to insulin is more in Asian-Indian race rather than European Caucasians in non-diabetics. Furthermore, in this study, 16 weeks treatment with pioglitazone (30 mg/d) significantly improved insulin sensitivity and insulin-dependent vasodilation in the Asian-Indian race. At this intervention, CRP and PAI-1 plasma level meaningfully decreased in Asian-Indian group and Adiponectin level increased which lead to risk reduction of cardiovascular disease emergence in this population. Lipid profiles in both populations did not change; however, increase of BMI in Caucasian individuals was significant after treatment.¹⁴ Shimizu et al. showed that in poor control Japanese diabetic patients, pioglitazone (pioglitazone 15-30 mg/d vs. voglibose 0.6-0.9 mg/d, for 12 weeks) significantly increases adiponectin level and decreases TNF- α level in addition to control of blood glucose. Reduction of systolic and diastolic pressure and weight reduction was the other findings of treatment with pioglitazone.¹⁵ In a 4 weeks study, Martens et al. showed that pioglitazone (pioglitazone 30 mg/d vs. placebo) can reduce cardiovascular disease in

diabetic patients by blocking direct effect of TNF- α on vascular endothelial, however, CRP, IL-6 and TNF- α plasma level and lipid profile didn't significantly decreased in this study.¹⁶ On the other hand, Halvorsen et al. showed that treatment with rosiglitazone (rosiglitazone 4-8 mg/d vs. placebo, for 12 weeks) leads to meaningful reduction of IL-10 level and IL-1 antagonist receptor in individuals suffering from MetS which indicates the inflammatory effects of this drug. This finding contradicts with anti-inflammatory effect of this drug in reduction of CRP, IL-6 and monocyte chemoattractant protein-1 and uric acid in this study or comparing with other studies.¹⁷

As seen, TZD and especially pioglitazone leads to increase of sensitivity to insulin in most studies, however, their effects on reduction of level and type of inflammatory cytokine differed in various races and populations. It is obvious that the effect difference of treatment with TZD in blood circulation of inflammatory and anti-inflammatory cytokines in most studies and this study can be due to investigated population and race, method and duration of intervention and the type of patients. Furthermore, concerning different findings, it is not possible to definitely speak of the positive role of these drugs in improving of the effect of lipid profile, obesity status and blood pressure of individuals.

Failure to assess the response to insulin sensitivity and the lack of measurement of other inflammatory and anti-inflammatory cytokines in the population can be regarded as limitations of this study. Furthermore, it is also suggested that future studies with larger sample focus on reassessment of anti-inflammatory cytokines, particularly IL-10 in various population of races.

Conclusion

This study showed that pioglitazone has no effect on reduction of TNF- α as a proinflammatory cytokine and increase of IL-10 as an anti-inflammatory cytokine in non-diabetic individuals with MetS in Caucasians race of Middle East in Iran.

Conflict of Interests

Authors have no conflict of interests.

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