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Correlations between biomarkers of oxidative stress, glycemic control and insulin resistance in women with type 2 diabetes

ABSTRACT

Background. The main characteristic of type 2 diabetes mellitus (T2DM) is hyperglycemia due to insulin resistance. Enhanced oxidative stress owing to increased oxygen free radicals and/or reduced antioxidant defense has very important roles in T2DM development and also most of its complications. The aim of the current study was to evaluate correlations between biomarkers of oxidative stress, glycemic control and insulin resistance in women with T2DM.

Materials and methods. Seventy nine women with T2DM were included in the current study and fasting blood samples were collected. Hemoglobin A_{1c} (HbA_{1c}); glucose; oxidative stress biomarkers including malodialdehyde, 8-isoprostane, catalase and total antioxidant capacity (TAC) were measured. The adiponectin/leptin (A/L) ratio and the homeostasis model assessment of beta-cell function (HOMA-B) were calculated. The results were considered significant when the p-value was less than 0.05.

Results. Serum levels of TAC showed a significant positive correlation with the A/L ratio ($r = 0.261$, $p = 0.02$). A significant negative correlation was observed between values of HbA_{1c} and TAC ($r = –0.300$, $p = 0.007$). However, HbA_{1c} correlated positively with 8-isoprostane ($r = 0.236$, $p = 0.036$). Values of HOMA-B correlated negatively with values of HbA_{1c} ($r = –0.327$, $p = 0.003$). Serum levels of 8-isoprostane were significantly higher in obese (BMI > 30 kg/m^2) women than in non-obese (BMI < 30 kg/m^2) women ($p = 0.032$). Values of catalase ($p = 0.022$) and HOMA-B ($p = 0.009$) were significantly lower in women with $HbA_{1c} \geq 7.6\%$ compared with women with $HbA_{1c} < 7.6\%$.

Conclusions. In summary, chronic hyperglycemia results in oxidative stress. This situation might lead to less beta cells function. In addition, low levels of the A/L ratio were associated with increased oxidative stress.
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Key words: type 2 diabetes, oxidative stress, hyperglycemia, insulin resistance, reactive oxygen species

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Introduction

The main characteristic of type 2 diabetes mellitus (T2DM) is hyperglycemia due to insulin resistance. In-

sulin resistance also can lead to metabolic impairment of other biomolecules such as lipids and proteins [1]. Enhanced oxidative stress owing to increased oxygen free radicals and/or reduced antioxidant defense has very important roles in T2DM development and also most of its complications [2]. Studies have shown that oxidative stress has a central role in insulin resistance development [3].

Increased circulating levels of glucose can cause oxidative stress via overproduction of reactive oxygen species [4]. On the other hand, beta cells function is impaired during chronic hyperglycemia because of increased oxidative stress which damages the cells [5].

Since antioxidant enzymes activities are low in beta cells, they are very sensitive to destructive effects of oxidative stress. On the other hand, lipotoxicity induced in beta cells by means of oxidative stress might be a central mechanism of destructive effects of reactive oxygen species in these insulin-secreting cells [6]. Current literature shows that oxidant/antioxidant balance is disrupted in people with obesity that leads to increased oxygen free radicals production which means an oxidative stress condition [4].

The current study was designed to evaluate correlations between biomarkers of oxidative stress, glycemic control and insulin resistance in women with T2DM.

Materials and methods

The current study was performed after approving by the Ethics Committee of the University. Eighty Persian women with T2DM were selected using convenience sampling method according to World Health Organization (WHO) [7] criteria after signing an informed consent form. One of the patients was excluded from the study. Therefore, the final sample size became 79 women with T2DM. Among the patients 54% were in premenopausal status and 46% were in postmenopausal status ($p = 0.574$). Age range of the patients was 40–65 years.

No more than 2 years of T2DM duration and not taking antioxidants supplements during the last three months were inclusion criteria of the current study. Patients under treatment with insulin and other hormone, anticoagulants, diuretics and β-blockers were excluded from the study. Other exclusion criteria were alcoholism, smoking, pregnancy, lactation and any chronic renal, hepatic, thyroid, haematic and gastrointestinal disorders.

Systolic and diastolic blood pressures, waist circumference (WC) and weight were measured and body mass index (BMI) was calculated and reported as kg/m^2.

Subjects were divided into two groups including obese (BMI > 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) [8]. Subjects were also divided into two groups according to hemoglobin A_{1c} (HbA_{1c}) values (HbA_{1c} < 7.6% and $HbA_{1c} \geq 7.6\%$) [9]. As glucose-lowering drugs, all patients were under treatment with metformin or a combination of metformin and glibenclamide.

After 12 hours of overnight fasting, blood samples were collected. Hemoglobin A_{1c} was assessed using column chromatography method (Biosistem, Spain). Serum values of glucose and Gamma-glutamyltransferase enzyme (GGT) were evaluated using commercially available colorimetric methods (Parsazmun, Iran). Other assays were included activity of catalase using spectrophotometric method [10], the ferric reducing ability of plasma (FRAP) assay for evaluating total antioxidant capacity (TAC) [11] and the thiobarbituric acid (TBA) assay for determining malodialdehyde (MDA) [12]. Other assays included insulin (Monobind Inc., USA), leptin and total adiponectin (BioVendor Laboratory Medicine, Inc. Czech Republic) and free 8-isoprostane (Cayman Chemical, Ann Arbor, MI, USA) using enzyme-linked immunosorbent assay (ELISA) on a microplate reader (STAT FAX 4200, USA).

The homeostasis model assessment of insulin resistance (HOMA-IR) [13], the quantitative insulin sensitivity check index (QUICKI) [14], the homeostasis model assessment of β-cell function (HOMA-B) [5], the leptin/adiponectin ratio (L/A) [13] and the adiponectin/leptin ratio (A/L) [15] were calculated.

Statistical analysis were done using Kolmogorov–Smirnov test for exploring normal and skewed distributed variables, independent-samples t-test and Mann-Whitney U-test for analyzing differences in demographic and biochemical data in Tables 1 and 2 and Pearson's and Spearman's correlation analyses for exploring correlations between biochemical variables in SPSS 19 software (SPSS Inc, Chicago, IL). Chi-square test was used for qualitative analysis. The mean ± SEM was used for expressing the variables and were considered statistically significant at a p-value less than 0.05.

Results

Demographic and biochemical characteristics of women with T2DM are presented in Table 1. Correlations were assessed in whole of the subjects. Serum levels of malodialdehyde correlated negatively with levels of adiponectin ($r = –0.30$, $p = 0.007$) (Figure 1). A negative correlation was observed between serum levels of 8-isoprostane and activities of catalase ($r = –0.24$, $p = 0.032$). A significant positive correlation was observed between serum activities of GGT and values of waist circumference ($r = 0.23$, $p = 0.041$). Serum levels of TAC showed a significant positive correlation with the A/L ratio ($r = 0.261$, $p = 0.02$) (Figure 2).

Table 1. Demographic and biochemical characteristics of women with type 2 diabetes mellitus (T2DM)

Variables	T2DM (n = 79)
Age (years)	53.09 ± 0.73
Duration of diabetes (year)	4.94 ± 0.30
Waist [cm]	103.68 ± 0.99
Weight [kg]	72.98 ± 1.05
BMI [kg/m^2]	28.53 ± 0.38
SBP [mm Hg]	12.59 ± 0.17
DBP [mm Hg]	8.03 ± 0.08
FBG [mg/dl]	139.86 ± 5.41
HbA_{1c} (%)	8.68 ± 0.24
Insulin [mIU/l]	13.99 ± 0.50
Adiponectin [μg/ml]	6.71 ± 0.33
Leptin [μg/ml]	21.92 ± 1.35
A/L ratio	0.43 ± 0.04
L/A ratio	3.94 ± 0.38
MDA [nmol/ml]	11.37 ± 0.39
8-isoprostane [pg/ml]	401.19 ± 9.96
Catalase [KU]	2.05 ± 0.11
GGT [U/L]	32.94 ± 2.50
TAC [mmol/L]	0.30 ± 0.01
HOMA-IR	4.82 ± 0.25
HOMA-B	99.84 ± 12.50
QUICKI	0.31 ± 0.002

Results are presented as mean ± SEM. BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; FBG — fasting blood glucose; HbA_{1c} — hemoglobin A_{1c}; A/L — the adiponectin/leptin ratio; L/A — the leptin/adiponectin ratio; MDA — malodialdehyde; GGT — gamma-glutamyl transferase; TAC — total antioxidant capacity; HOMA-IR — homeostasis model assessment of insulin resistance; HOMA-B — homeostasis model assessment of beta-cell function; QUICKI — quantitative insulin sensitivity check index

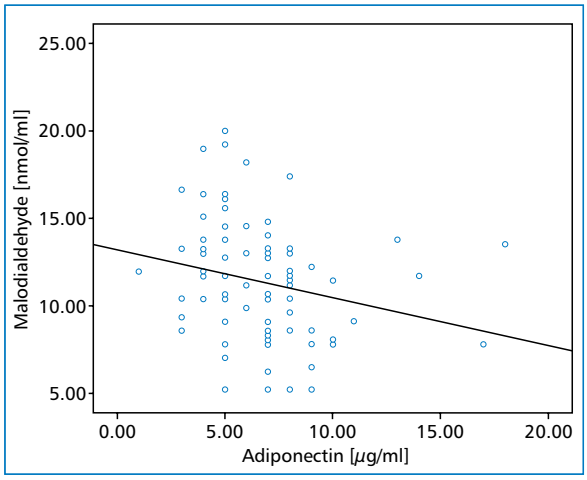

Figure 1. Correlation between serum levels of malodialdehyde and levels of adiponectin in women with type 2 diabetes mellitus (r = –0.30, p = 0.007)

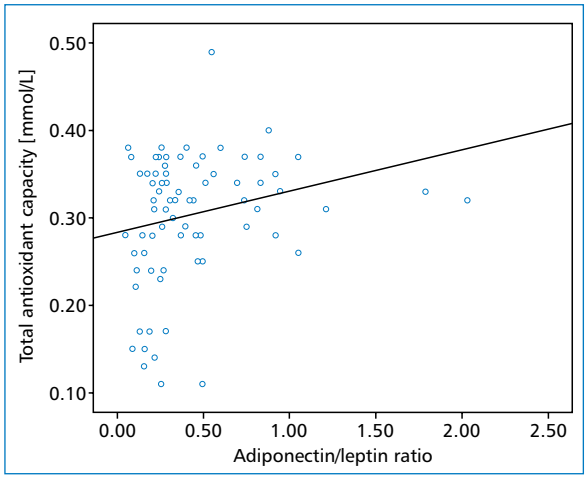

Figure 2. Correlation between serum values of total antioxidant capacity and the adiponectin/leptin ratio in women with type 2 diabetes mellitus (r = 0.261, p = 0.02)

However, TAC correlated negatively with the L/A ratio (r = –0.262, p = 0.02). A significant negative correlation was observed between values of HbA_{1c} and TAC (r = –0.300, p = 0.007). However, HbA_{1c} correlated positively with 8-isoprostane (r = 0.236, p = 0.036) (Figure 3). Values of HOMA-B correlated negatively with values of HbA_{1c} (r = –0.327, p = 0.003) (Figure 4). A significant positive correlation was observed between values of FBS and HbA_{1c} (r = 0.32, p = 0.004). Serum activities of GGT showed a slightly positive correlation with levels of malodialdehyde (r = 0.219, p = 0.051).

Comparison of demographic and biochemical characteristics of obese and non-obese women with T2DM was presented in Table 2. Obese women had higher values of waist circumference (p < 0.001), weight (p < 0.001) and BMI (p < 0.001) than non-obese women. Serum levels of 8-isoprostane were significantly higher in obese women than in non-obese women (p = 0.032). Marginally decreases were observed in values of HOMA-B (p = 0.091) and TAC (p = 0.087) in obese women compared with non-obese women. HOMA-IR was nonsignificantly higher in obese women compared with non-obese women.

Table 3 shows comparison of demographic and biochemical characteristics of women with T2DM according to HbA_{1c} values. Women with $HbA_{1c} \geq 7.6\%$ had higher values of FPG (p = 0.006), HbA_{1c} (p < 0.001), SBP (p = 0.006) and HOMA-IR (p = 0.027) than women with $HbA_{1c} < 7.6\%$. However, values of catalase (p = 0.022)

Table 2. Comparison of demographic and biochemical characteristics of obese (BMI > 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) women with type 2 diabetes mellitus

Variables	Non-obese (n = 50)	Obese (n = 29)	p
Age (years)	52.80 ± 0.93	53.59 ± 1.20	0.609
Duration of diabetes (year)	5.06 ± 0.36	4.72 ± 0.54	0.598
Waist [cm[	100.84 ± 1.09	108.59 ± 1.57	< 0.001
Weight [kg]	68.02 ± 1.06	81.53 ± 0.89	< 0.001
BMI [kg/m^2]	26.31 ± 0.28	32.35 ± 0.25	< 0.001
SBP [mm Hg]	12.54 ± 0.22	12.67 ± 0.27	0.881
DBP [mm Hg]	7.93 ± 0.10	8.21 ± 0.13	0.188
FBG [mg/dl]	134.04 ± 6.43	149.90 ± 9.56	0.154
HbA_{1c} (%)	8.57 ± 0.31	8.86 ± 0.37	0.319
Insulin [mIU/l]	14.16 ± 0.62	13.69 ± 0.87	0.652
Adiponectin [μg/ml]	6.60 ± 0.41	6.90 ± 0.54	0.906
Leptin [μg/ml]	22.16 ± 1.69	21.51 ± 2.29	0.818
A/L ratio	0.44 ± 0.06	0.42 ± 0.05	0.428
L/A ratio	4.27 ± 0.55	3.39 ± 0.41	0.428
MDA [nmol/ml]	11.20 ± 0.51	11.65 ± 0.60	0.585
8-isoprostane [pg/ml]	385.03 ± 13.21	429.05 ± 13.53	0.032
Catalase [KU]	2.02 ± 0.14	2.10 ± 0.18	0.744
GGT [U/L]	32.51 ± 3.30	33.67 ± 3.80	0.473
TAC [mmol/L]	0.31 ± 0.01	0.29 ± 0.01	0.087
HOMA-IR	4.63 ± 0.27	5.16 ± 0.51	0.316
HOMA-B	107.69 ± 15.98	86.31 ± 20.13	0.091
QUICKI	0.31 ± 0.002	0.31 ± 0.003	0.677

Results are presented as mean ± SEM. Abbreviations are given in Table 1

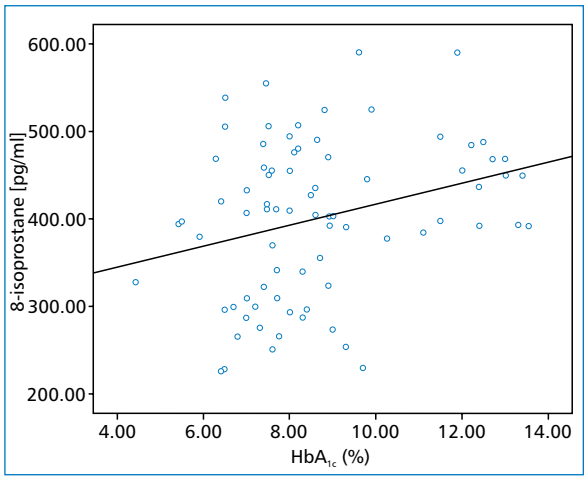

Figure 3. Correlation between values of HbA_{1c} and 8-isoprostane in women with type 2 diabetes mellitus (r = 0.236, p = 0.036)

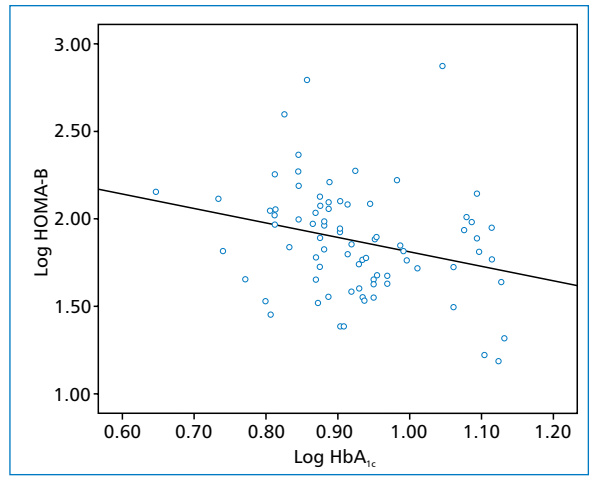

Figure 4. Correlation between values of HbA_{1c} and the homeostasis model assessment of beta-cell function (HOMA-B) in women with type 2 diabetes mellitus (r = –0.327, p = 0.003)

Table 3. Comparison of demographic and biochemical characteristics of women with type 2 diabetes mellitus according to HbA_{1c} values

Variables	HbA_{1c} < 7.6% (n = 27)	HbA_{1c} ≥ 7.6% (n = 52)	p
Age (years)	53.44 ± 1.02	52.90 ± 0.99	0.730
Duration of diabetes (year)	5.15 ± 0.43	4.83 ± 0.41	0.620
Waist [cm]	102.56 ± 1.94	104.27 ± 1.11	0.413
Weight [kg]	71.41 ± 1.76	73.80 ± 1.30	0.282
BMI [kg/m^2]	27.89 ± 0.58	28.86 ± 0.50	0.233
SBP [mm Hg]	11.92 ± 0.24	12.93 ± 0.21	0.006
DBP [mm Hg]	7.91 ± 0.14	8.10 ± 0.10	0.605
FBG [mg/dl]	120.48 ± 6.16	149.92 ± 7.22	0.006
HbA_{1c} (%)	6.74 ± 0.14	9.68 ± 0.26	< 0.001
Insulin [mIU/l]	14.12 ± 0.76	13.92 ± 0.66	0.852
Adiponectin [μg/ml]	6.59 ± 0.59	6.77 ± 0.39	0.619
Leptin [μg/ml]	23.23 ± 2.43	21.24 ± 1.63	0.487
A/L ratio	0.38 ± 0.05	0.46 ± 0.05	0.451
L/A ratio	4.09 ± 0.59	3.87 ± 0.49	0.451
MDA [nmol/ml]	11.94 ± 0.71	11.07 ± 0.46	0.290
8-isoprostane [pg/ml]	383.81 ± 18.31	410.21 ± 11.71	0.211
Catalase [KU]	2.40 ± 0.23	1.86 ± 0.12	0.022
GGT [U/L]	35.28 ± 5.69	31.72 ± 2.42	0.687
TAC [mmol/L]	0.32 ± 0.01	0.30 ± 0.01	0.120
HOMA-IR	4.15 ± 0.29	5.17 ± 0.34	0.027
HOMA-B	130.24 ± 23.86	84.06 ± 14.08	0.009
QUICKI	0.31 ± 0.003	0.31 ± 0.003	0.137

Results are presented as mean ± SEM. Abbreviations are given in Table 1

and HOMA-B (p = 0.009) (Figure 5) were significantly lower in women with HbA_{1c} ≥ 7.6% compared with women with HbA_{1c} < 7.6%.

Discussion

In the current study some important correlations were observed including negative correlation between values of HbA_{1c} and TAC, negative correlation between values of HOMA-B and HbA_{1c}, positive correlation between values of HbA_{1c} and 8-isoprostane and positive correlation between values of the A/L ratio and TAC.

A study conducted by Picu et al. [4] has shown a positive correlation between total oxidant status (TOS) and HbA_{1c} in patients with T2DM. Therefore, it has been hypothesized that prolonged hyperglycemia results in overproduction of reactive oxygen species which leads to oxidative stress. In the current study,

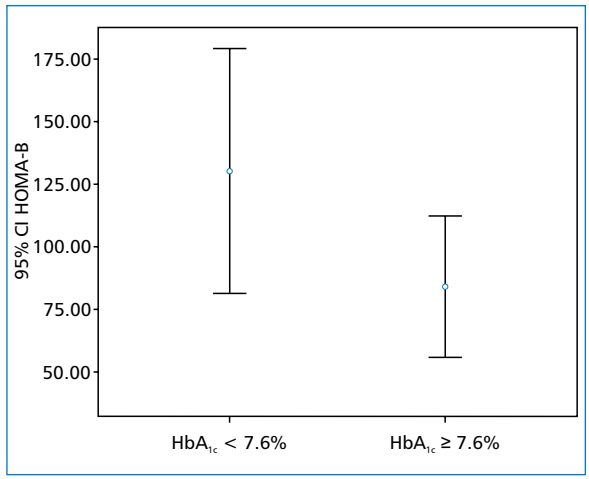

Figure 5. Comparison of the homeostasis model assessment of β-cell function (HOMA-B) of women with type 2 diabetes mellitus according to HbA_{1c} values (p = 0.009)

a significant negative correlation was observed between values of HbA_{1c} and TAC. On the other hand, current study showed a significant positive correlation between values of HbA_{1c} and 8-isoprostane. These results could support the hypothesis.

Hou et al. [5] and Al-Hakeim et al. [9] divided patients with T2DM according to HbA_{1c} values. They observed that patients with higher values of HbA_{1c} have lower values of HOMA-B. Therefore, beta cells function is affected by glycemic control. A negative correlation has shown between values of HOMA-B and HbA_{1c} in males with T2DM [16]. In the current study, Values of HOMA-B correlated negatively with values of HbA_{1c} in the whole patients. In addition, values of catalase and HOMA-B were significantly lower in women with $HbA_{1c} \geq 7.6\%$ compared with women with $HbA_{1c} < 7.6\%$. Increased circulating levels of glucose can cause oxidative stress via overproduction of reactive oxygen species [4]. On the other hand, beta cells function is impaired during chronic hyperglycemia because of increased oxidative stress which damages the cells [5]. Since antioxidant enzymes activities are low in beta cells, they are very sensitive to destructive effects of oxidative stress. On the other hand, lipotoxicity induced in beta cells by means of oxidative stress might be a central mechanism of destructive effects of reactive oxygen species in these insulin-secreting cells [6].

Gamma-glutamyltransferase (GGT) is an enzyme which is well known as a biomarker of fatty liver and alcohol consumption. However, it has been shown that GGT shows a direct relationship with incidence of diabetes independent of popular risk factors such as alcohol consumption. Current literature shows that GGT can also be used as a biomarker of oxidative stress condition in which its activity increases. GGT activity in serum shows a negative correlation with serum levels of antioxidants [17, 18]. In the current study, serum activities of GGT showed a slightly positive correlation with levels of malodialdehyde. On the other hand, plasma GGT activity is also related to obesity with the risk for T2DM [18]. In the current study, a significant positive correlation was observed between serum activities of GGT and values of waist circumference.

Leptin and adiponectin are adipokines that are secreted by white adipose tissue. The principal known role of leptin is energy homeostasis regulation. On the other hand, pro-inflammatory property of leptin has been demonstrated that causes proliferation of monocytes. This property of leptin can cause an increase in activity of enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which leads to an increase in oxygen free radicals production. In other words, leptin can induce oxidative stress [4]. On the other hand, adiponectin has been suggested as the strongest anti-inflammatory cytokine and can promote insulin sensitization effect. Moreover, some antioxidant effects of adiponectin has been reported that can prevent mitochondrial depolarization and dysfunction [19, 20]. It has been reported that in individuals with metabolic syndrome levels of total adiponectin correlates negatively with values of malodialdehyde. Therefore, it has been concluded that lower values of the A/L ratio can cause increased oxygen free radicals which leads to oxidative stress in patients with metabolic syndrome [21]. In the current study, serum levels of adiponectin correlated negatively with levels of malodialdehyde. On the other hand, serum levels of TAC showed a significant positive correlation with the A/L ratio and a significant negative correlation with the L/A ratio. Therefore, low levels of the A/L ratio or high levels of the L/A ratio were associated with increased oxidative stress in subjects of the current study.

Study of Picu et al. [4] has shown a positive correlation between total oxidant status and the percentage of total body fat in patients with T2DM. Therefore, it has been proposed that in obesity oxidant/antioxidant balance is disrupted that leads to increased oxygen free radicals production which means an oxidative stress condition. In the current study, women with BMI > 30 kg/m^2 had higher values of 8-isoprostane and marginally decreased TAC values than women with BMI < 30 kg/m^2 that might indicate an oxidative stress condition.

The current study had some limitations. The most important of them were small sample size and not using a normal group. Other limitation was that the data were not analyzed according to the history of nulli and multiparity pregnancy, gestational diabetes mellitus (GDM), macrosomia and polycystic ovary syndrome (PCOS).

Conclusions

In conclusion, chronic hyperglycemia results in oxidative stress. This situation might lead to less beta cells function. The current study showed that obesity was associated with increased oxidative stress and disrupted oxidant/antioxidant balance. In addition, low levels of the A/L ratio or high levels of the L/A ratio were associated with increased oxidative stress.

Conflict of interest

The authors declared that they have no conflict of interest.

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