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Original Article

The significance of blood and salivary oxidative stress markers and chemerin in gestational diabetes mellitus

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ABSTRACT

Objective: Gestational diabetes mellitus (GDM) is a medical complication of pregnancy. The aim of this study was to evaluate the correlations between the salivary and blood levels of oxidative stress markers and an adipokine chemerin, which play a role in the pathogenesis of GDM.
Materials and methods: Study groups (Control (n = 29), GDM (n = 22)) had been assessed clinically healthy oral hygiene, according to the age range between 25 and 40 years, BMI<30 kg/m2, who were non-smokers and who were not having systemic diseases. GDM was diagnosed using a 100 g OGTT. Saliva samples were collected without stimulation between 08.30 and 10.00 a.m.. Chemerin and TrxR levels were measured by ELISA. Malondialdehyde, sulfhydryl and NO levels were determined by spectrophotometric analysis. Statistical analysis were performed by Shapiro Wilk, Mann Whitney U, Student's t test.
Results: Blood pressure, BMI, and plasma chemerin, salivary chemerin, fasting glucose, LDL, triglyceride, CRP levels in GDM were not different when compared to Control. There were significant differences between Plasma TrxR and HDL levels. Also, significant differences between salivary TrxR and Malondialdehyde levels were observed in GDM.
Conclusion: It was concluded that the optimal cut-off points for oxidative stress parameters and chemerin level can be used to distinguish between healthy pregnant and GDM.

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy. Insulin resistance (IR) can be developed resulting in higher maternal post-prandial glucose levels during the second trimester in pregnancy [1]. Hyperglycaemia can lead to enhanced production of reactive oxygen species, reactive nitrogen species, and promotes oxidative stress in diabetes. Pregnancy is associated with developing oxidative stress accompanied by hyperglycaemia and IR result in an increased circulating lipid levels (e.g., triglycerides (TG), free fatty acid (FFA), total cholesterol (TC) and low-density lipoprotein (LDL)). Increased plasma FFA concentrations are associated with IR. GDM is associated with an elevated level of oxidative stress due to both the overproduction of free radicals and a deficiency in the antioxidant defense [2–4].

The adipose tissue is the origin of IR that contribute to, or are affected by, GDM. Adipose tissue actively secretes adipokines which have metabolic effects [5]. Chemerin is an adipokine which may regulate insulin sensitivity [6]. On the contrary, Yu et al. reported that high levels of chemerin may improve IR [7]. Mamali et al. showed that there was positive correlation between serum and salivary adipokine levels [8]. Previous studies reported that circulating chemerin levels increased in the third trimester or no differences were found between GDM and healthy pregnancy [9,10]. Hare et al. showed that circulating chemerin level decreased in GDM [11]. It was demonstrated that chemerin could also correlate negatively with total oxidative response, which suggested that dysregulation of oxidative stress might be induced by chemerin [12].

Thiols contain a sulfhydryl group and play a significant role in defense against reactive oxygen species. Decreased levels of thiols have been considered in diabetes mellitus [13]. Thioredoxin (Trx) is an antioxidant thiol protein and controls cellular redox balance. Trx is reduced by Thioredoxin Reductase (TrxR), which is known to be the only physiological reductant. The Trx/TrxR system plays an important role in the cellular defense against oxidative stress,

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physiology of the adipose tissue, insulin sensitivity, metabolic syndrome and obesity. Activity of TrxR maintains Trx redox cycling which is required for counteraction of oxidative stress [14–16]. Trx system is stimulated when Reactive Oxygen Species are generated. TrxR is overexpressed upon oxidative stress [17,18].

Saliva can be collected easily and painless. Therefore, saliva can be a preferable diagnostic material than blood analysis [19]. The parameters that evaluated in this study were examined in either blood or saliva in previous studies.

The aim of this study was to examine the relationship between the 2nd and 3rd trimesters in the study groups of blood and salivary malondialdehyde (MDA), nitric oxide (NO), sulfhydryl (RSH), TrxR, chemerin levels and to determine whether there is any correlation by examining both the saliva and blood levels of the relevant parameters.

Materials and methods

General information and subjects grouping

The subjects were 51 pregnant women (Control (n = 29), GDM (n = 22)) who were selected from the outpatient clinic of obstetrics and gynaecology department at the Faculty of Medicine. They were routinely screened between 2nd-3rd trimester of gestation for GDM. The Ethical approval were taken from the Ethics Committee of Gazi University with an accession number: 10.02.2014/78. All participants provided informed consent.

Inclusion and exclusion criteria

GDM was diagnosed if two or more plasma glucose levels were elevated during a 100 g, 3 h oral glucose tolerance test [20]. After diagnosis, 22 women with GDM were clinically managed by diet alone. A certified clinical nutritionist provided GDM women with nutritional guidance. GDM are recommended to be fed with bodyweight x 30 kcal/per day (58% carbohydrate, 16% protein, 27% lipid, 1500 mg calcium, 30 gr fibre). All participants had been assessed clinically healthy oral hygiene by the principle dental researcher, according to the age range between 25 and 40 years, the body mass index (BMI) < 30 kg/m2, who were non-smokers and who were not having systemic diseases. The exclusion criteria were the following: Women with a pre-gestational BMI>30 kg/m^2; diagnosis of pre-gestational diabetes; chronic underlying systemic disease; smoking; gestation number >3; age >40 years; periodontal disease and deep caries, and exposure to cancer treatment.

Assays

Blood and unstimulated saliva samples were prepared simultaneously after overnight fasting. Two hours prior to the saliva collection, all participants were instructed to brush their teeth. The collection was carried out at the same time of day (between 08:30–10:00 a.m.). Unstimulated whole saliva (about 3 ml) was collected over 5 min from each subject. During the saliva collection, the participants sat in a relaxed position with their heads bent forward, allowed to drain into a plastic container. Blood samples were collected into vacutainer tubes. The blood and saliva samples were centrifuged at 2500 g for 5 min, and stored at −80 °C until analysis.

Plasma and salivary chemerin concentrations were measured using ELISA according to the manufacturers' guidelines spectrophotometrically (BosterBio, USA, Catalog Nr: EK1329). The sensitivity of the chemerin ELISA was <20 pg/ml, while the intra-assay and inter-assay coefficients of variation were between 4.7–7.6% and 6–9.3%, respectively with a detection range for chemerin of 0.78–50 ng/ml. Plasma and salivary TrxR levels (μmol/min/mL) were measured using ELISA (Cayman's Thioredoxin Reductase (TrxR) Assay Kit, USA, Catalog Nr:10007892) according to the manufacturers' guidelines spectrophotometrically. The intra-assay and inter-assay coefficients of variation were 2.3% and 6.1%, respectively with a detection range of the assay is from 0.013 to 0.063 μmol/min/ml of TrxR activity, which is equivalent to an absorbance increase of 0.01–0.05 per minute under the standardized conditions of the assay. All serum and salivary samples were tested in duplicated in the same assay plate. Serum and salivary chemerin or TrxR were expressed in terms of their respective standards.

Plasma and salivary MDA (nM/MDA/mL), RSH (nM/RSH/mL) and NO (μM/L) levels were determined by spectrophotometric analysis [21].

Statistical analysis

Data analysis was performed using the IBM Statistical Package for Social Sciences (SPSS), version 25 (IBM SPSS Statistics, Armonk, NY, USA). While the mean differences between groups were compared by Student's t test, otherwise, Mann Whitney U test was applied for comparisons of the medians. Categorical data were analysed by Pearson's chi-square or Fisher's exact test, where appropriate. Degrees of association between continuous variables were evaluated by Spearman's Rank Correlation analysis. The optimal cut-off points for laboratory measurements distinguish between Control and GDM were evaluated by ROC analysis as giving the maximum sum of sensitivity and specificity for the significant test. Diagnostic performance (i.e. sensitivity, specificity, positive and negative predictive values) for each clinical measurement were also calculated. A p value of less than 0.05 was considered statistically significant. But, all possible multiple comparisons, the Bonferroni Correction was applied for controlling Type I error.

Results

The demographics, clinical characteristics and selected laboratory parameters of the study participants are summarized at Table 1.

The plasma and salivary laboratory measurements are shown in Table 2. The salivary MDA (p = 0.001) and TrxR levels (p = 0.001) in GDM were significantly increased, plasma TrxR levels in GDM were significantly decreased compared to Control (p = 0.041). There were not statistically significant in other measurements between Control and GDM.

The salivary MDA (AUC = 0.812, 95% confidence interval: 0.694–0.929, p < 0.001), plasma TrxR (AUC = 0.680, 95% confidence interval: 0.517–0.843, p = 0.041) and salivary TrxR (AUC = 0.813, 95% confidence interval: 0.681–0.945, p < 0.001) measurements regarding AUC were found statistically significant to distinguish between Control and GDM (Table 3). The optimal cut-off points for plasma TrxR (<6.82), salivary TrxR (>3.599) and salivary MDA (>11.7) measurements distinguish between two groups which are shown in Table 4.

Salivary TrxR and MDA were significantly elevated in GDM during 2nd trimester when compared to Control (p < 0.025). There were not statistically significant in other measurements during 2nd and 3rd trimester between Control and GDM (Table 5).

Plasma chemerin levels positively correlated with plasma TrxR (r = 0.324, p = 0.032) for all participants. Salivary TrxR levels positively correlated with salivary chemerin (r = 0.307, p = 0.043), salivary RSH (r = 0.333, p = 0.027), and salivary MDA (r = 0.355, p = 0,018) for all participants. Salivary chemerin levels positively

Table 1
Demographic, clinical characteristics, selected routine laboratory parameters and blood pressures of Control and GDM.

	Control (n = 29)	GDM (n = 22)	p
Age[years][a]	30.2 ± 4.1	32.1 ± 4.3	0.134
Gestational age, weeks[b]	25 (24–28)	28.5 (17–39)	**0.001***
Gestational age, weeks[c]			**0.001***
2nd Trimester	24 (82,8%)	7 (31.8%)	
3rd Trimester	5 (17,2%)	15 (68.2%)	
Number of gestations[b]	2 (1–3)	3 (1–3)	0.144
BMI[kg/m^2][a]	24.2 ± 2.9	25.7 ± 2.5	0.058
GDM history[d]	0 (0.0%)	3 (13.6%)	0.074
Cesarean section history[d]	6 (20.7%)	0 (0.0%)	**0.031***
Birthweight[g][b]	3160 (940–3800)	3420 (2600–4670)	0.486
Fasting plasma glucose[mg/dL][a]	91.1 (67.1–125.3)	84.0 (70.0–106.0)	0.058
Triglyceride[mg/dL][a]	172.8 ± 51.7	202.7 ± 57.6	0.063
LDL-C[mg/dL][a]	135.9 ± 33.7	142.9 ± 32.1	0.470
HDL-C[mg/dL][a]	82.5 ± 18.7	70.8 ± 11.8	**0.016** *
Total cholesterol[mg/dL][a]	253.0 ± 46.0	254.2 ± 36.6	0.920
CRP[mg/L][b]	5.2 (0.7–18.4)	5.4 (1.1–14.4)	0.896
Urine density[b]	1015 (1005–1020)	1012.5 (1004–1025)	0.551
Urine ketone[mg/dL][d]	0 (0.0%)	2 (10.0%)	0.168
Urine glucose[mg/dL][d]	0 (0.0%)	2 (10.0%)	0.168
SBP[mmHg][b]	100 (80–120)	100 (90–120)	0.736
DBP[mmHg][b]	60 (50–80)	60 (60–80)	0.116

*: Statistically significant (p < 0.05) (bold).
[a] Student's t test
[b] Mann Whitney U test
[c] Pearson's chi-square test
[d] Fisher's exact test.

Table 2
The oxidative stress and insulin resistance parameters of two groups.

	Control	GDM	p[a]
Plasma			
NO[μM/L]	6.1 (2.8)	7.2 (5.0)	0.214
Chemerin[ng/mL]	2.7 (6.4)	2.9 (2.4)	0.412
TrxR[μM/min/mL]	6.8 (1.0)	6.6 (0.5)	**0.041***
Sulfhydryl[nM/mL]	131.6 (30.7)	138.8 (48.8)	0.914
MDA[nM/mL]	7.9 (3.0)	10.5 (7.5)	0.211
Saliva			
NO[μM/L]	25.7 (58.4)	22.6 (52.8)	0.976
Chemerin[ng/mL]	0.36 (0.11)	0.37 (0.15)	0.693
TrxR[μM/min/mL]	3.5 (0.1)	3.6 (0.1)	**0.001***
Sulfhydryl[nM/mL]	14.0 (4.4)	18.7 (14.8)	0.102
MDA[nM/mL]	10.5 (8.8)	16.2 (7.7)	**0.001***

*: Statistically significant (p < 0.05).
[a] Mann Whitney U test.

Table 3
AUC and 95% confidence intervals for laboratory measurements distinguish between Control and GDM.

	AUC	95% Confidence Interval		p
		Min	Max	
Plasma				
NO[μM/L]	0.605	0.440	0.770	0.214
Chemerin[ng/mL]	0.570	0.401	0.739	0.412
TrxR[μM/min/mL]	0.680	0.517	0.843	**0.041**
Sulfhydryl[nM/mL]	0.509	0.330	0.689	0.914
MDA[nM/mL]	0.604	0.428	0.780	0.211
Saliva				
NO[μM/L]	0.507	0.343	0.670	0.936
Chemerin[ng/mL]	0.534	0.364	0.704	0.693
TrxR[μM/min/mL]	0.813	0.681	0.945	**0.001**
Sulfhydryl[nM/mL]	0.635	0.473	0.797	0.102
MDA[nM/mL]	0.812	0.694	0.929	**0.001**

Statistically significant (bold).

correlated with salivary RSH (r = 0.336, p = 0,021) assessed by Spearman's correlation method (p < 0.05) for all participants. Plasma chemerin levels positively correlated with plasma TrxR (r = 0,501 ve p = 0,108) in Control assessed by Spearman's correlation method (p < 0.025). There were no significant correlations between any of the other parameters.

Discussion

Obesity and GDM are the extensive metabolic abnormalities due to decrease in maternal pregravid insulin sensitivity or increased IR [22].

The chemerin exacerbates glucose intolerance and disrupts glucose tolerance [23]. Yang et al. reported a significantly increased level of plasma chemerin level in patients with type 2 diabetes with hypertension than patients with type 2 diabetes mellitus and normal controls. The circulating levels of chemerin were significantly associated with key markers of metabolic syndrome, especially high blood pressure [24]. Previous studies reported that, serum chemerin levels and CRP were not significantly different between GDM and Control, and serum chemerin levels positively correlated with blood pressure and CRP are consistent with the present study [25,26]. No difference was observed in blood pressure between GDM and Control in present study. Plasma chemerin level was significantly associated with maternal BMI, TG and blood pressure [23]. In our study there were no statistically significant differences in plasma and salivary chemerin levels between Control and GDM. This may be due to the GDM women having their diabetes well controlled with a very strict diet and adjusted for pre-pregnancy BMI<30. Up today, no report could be found the comparison of the salivary chemerin levels between GDM and healthy pregnancy.

Thioredoxin reductase plays a role in maintaining the cellular redox balance. Ghanem et al. demonstrated that serum thioredoxin reductase level was decrease in Type 2 DM [14,27]. In present study, TrxR levels of Control and GDM were not different in the second and third trimester. The plasma TrxR value in GDM was significantly decreased, and the salivary TrxR value in GDM was significantly increased when compared to Control. The salivary TrxR level of GDM

Table 4
The optimal cut-off points for laboratory measurements distinguish between Control and GDM, and diagnostic performance of plasma TrxR, salivary TrxR and MDA.

	Cut-off points	Sensitivity	Specificity	PPV	NPV
Plasma TrxR	<6.82	90.9%	50.0%	64.5%	84.6%
Salivary TrxR	>3.599	68.2%	86.4%	83.3%	73.1%
Salivary MDA	>11.7	81.8%	69.0%	66.7%	83.3%

PPV: Positive predictive values, NPV: Negative predictive values.

Table 5
Salivary laboratory measurements of two groups during gestational 2nd-3rd trimesters.

	Control	GDM	p*
NO[μM/L]			
2nd Trimester	23.9 (60.2)	10.3 (92.4)	0.945
3rd Trimester	34.4 (48.7)	28.2 (47.5)	0.893
p#	0.933	0.799	
Chemerin[ng/mL]			
2nd Trimester	0.35 (0.10)	0.38 (0.09)	0.466
3rd Trimester	0.41 (0.09)	0.35 (0.20)	0.530
p#	0.132	0.837	
TrxR[μM/min/mL]			
2nd Trimester	3.5 (0.08)	3.6 (0.08)	**0.010**
3rd Trimester	3.6 (0.05)	3.6 (0.06)	0.360
p#	0.308	0.368	
Sulfhydryl[nM/mL]			
2nd Trimester	14.7 (5.4)	22.4 (19.4)	0.199
3rd Trimester	13.3 (2.8)	17.3 (13.3)	0.098
p#	0.114	0.581	
MDA[nM/mL]			
2nd Trimester	9.9 (10.5)	15.9 (7.2)	**0.004**
3rd Trimester	11.0 (6.7)	16.2 (8.4)	0.081
p#	0.382	1.000	

*: Bonferroni-corrected Mann Whitney U test was used for the comparisons between two groups in 2nd and 3rd trimesters and $p < 0.025$ were accepted statistically significant, #: Bonferroni-corrected Mann Whitney U test was used for the comparisons between 2nd and 3rd trimesters of two groups separately and $p < 0.025$ were accepted statistically significant (bold).

was significantly increased than Control in the second trimester. This may be because of diet composition which was given to GDM.

Todoroki et al. reported that Trx level in the breast milk was found higher than in plasma level [28]. Content of the Trx may vary depending on the type of tissue examined and the salivary glands which have the highest value. Increased diameters of duct cells of salivary glands showed increased levels of TrxR [29,30]. These findings that obtained in previous studies may be an explanatory for the salivary TrxR levels in our study. No report could be found the comparison of the salivary TrxR levels in GDM. The best cut-off points for plasma and salivary TrxR levels distinguish between Control and GDM may be important in follow up the pregnancy.

There was statistically significant and positive correlation between plasma chemerin and TrxR level in Control. Plasma chemerin levels positively correlated with plasma TrxR for all participants. Salivary TrxR levels positively correlated with salivary chemerin, salivary RSH, and salivary MDA levels for all participants. Salivary chemerin levels positively correlated with salivary RSH levels for all participants.

Insulin resistance are associated with oxidative stress. Oxidative stress may be a major regulator of the development of insulin resistance.

In this study, there was no statistically significant difference the plasma and salivary NO levels between two groups. Salivary NO levels increased in type 1 and type 2 DM. NO levels may depend on diet and pH in gingival tissues [31,32]. Carbohydrate prescriptions for lunch and dinner may have to remain <45% for low postprandial glucose levels in GDM [33]. In the present study, the diet prescription with calories from carbohydrate 58% may have an additive effect in reducing the concentrations of maternal glucose in GDM. Regulated of maternal glucose levels with diet in GDM may be considered to explain that there is no difference plasma and salivary NO values between two groups. Such a diet strategy may have important implications to prevent fetal complications and improve maternal health outcomes.

Serum HDL levels were significantly lower in GDM. There were no statistically significant difference the fasting blood glucose levels, TG, LDL and TC, CRP, urine density, urine ketone, urine glucose and blood pressure levels between two groups. Plasma HDL, TG, LDL, TC, and CRP values between two groups were consistent with the previous studies and were attributed to the effect of diet intervention to GDM [9,25,34]. Lower HDL levels in GDM may be related to the country where the data were collected and fat accumulation stop due to decreased lipoprotein lipase (LPL) activity in the last three months of pregnancy [35]. Urine ketone value of two groups was consistent with Major's study [36].

Three times more free radicals can be neutralized by plasma compared to the same saliva volume. Free MDA can pass from blood to saliva. GDM treated with diet may have high antioxidant enzyme activity and high salivary MDA concentration [37]. The increase in plasma MDA levels in GDM was not statistically significant. The salivary MDA levels in GDM were significantly higher than Control in the second trimester. There was no statistically significant difference in salivary MDA levels between two groups in the third trimester. Salivary MDA levels may be affected prior to the plasma level by the oxidative stress. The optimal cut-off point for salivary MDA distinguish between two groups is 11.7. The sensitivity of the salivary MDA is significantly higher in differentiating between two groups. According to these results, it can be preferred to follow up the pregnancy by the help of salivary MDA levels when compared to plasma levels.

Consistent with study by Zygula et al. we found that plasma RSH levels were ~10 times higher than salivary levels in GDM and Control [37].

Conclusion

In conclusion, some features in pregnancy such as BMI<30, a good glycaemic control, no diabetic complication, no blood pressure difference, proper lipid profile, non-smoking and healthy oral hygiene describe the similarity of oxidative stress and insulin resistance markers between GDM and Control.

The optimal cut-off points for oxidative stress parameters and chemerin level can be used to distinguish between healthy pregnant and GDM.

Besides that, the development of the fetus and its complications can be more easily followed up with the assignment of these parameters just in saliva without venopuncturing.

Ethical approval

All procedures performed in the study involving human participants were in accordance with ethical standards of the Ethics Committee of Gazi University.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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References

[1] Hornnes P, Lauenborg J. Screening for gestational diabetes. In: Mahmood TA, Arulkumaran S, editors. Obesity. 1st ed. London: Elsevier; 2013. p. 271–9.
[2] Sesti G. Pathophysiology of insulin resistance. Best Pract Res Clin Endocrinol Metabol 2006;20:665–79.
[3] Lappas M, Hiden U, Desoye G, Froehlich J, Hauguel-de Mouzon S, Jawerbaum A. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxidants Redox Signal 2011;15:3061–100.
[4] Fülöp P, Seres I, Lőrincz H, Harangi M, Somodi S, Paragh G. Association of chemerin with oxidative stress, inflammation and classical adipokines in non-diabetic obese patients. J Cell Mol Med 2014;18:1313–20.
[5] Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The pathophysiology of gestational diabetes mellitus. Int J Mol Sci 2018;19:3342.
[6] Takahashi M, Takahashi Y, Takahashi K, Zolotaryov FN, Hong KS, Kitazawa R, et al. Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. FEBS Lett 2008;582:573–8.
[7] Yu S, Zhang Y, Li MZ, Xu H, Wang Q, Song J, et al. Chemerin and apelin are positively correlated with inflammation in obese type 2 diabetic patients. Chin Med J 2012;125(19):3440–4.
[8] Mamali I, Roupas ND, Armeni AK, Theodoropoulou A, Markou KB, Georgopoulos NA. Measurement of salivary resistin, visfatin and adiponectin levels. Peptides 2012;33:120–4.
[9] Garces MF, Sanchez E, Ruíz-Parra AI, Rubio-Romero JA, Angel-Müller E, Suarez MA, et al. Serum chemerin levels during normal human pregnancy. Peptides 2013;42:138–43.
[10] Kasher-Meron M, Mazaki-Tovi S, Barhod E, Hemi R, Haas J, Gat I, et al. Chemerin concentrations in maternal and fetal compartments: implications for metabolic adaptations to normal human pregnancy. J Perinat Med 2014;42:371–8.
[11] Hare KJ, Bonde L, Svare JA, Randeva HS, Asmar M, Larsen S, et al. Decreased plasma chemerin levels in women with gestational diabetes mellitus. Diabet Med 2014;31(8):936–40.
[12] Cătoi AF, Suciu Ş, Pârvu AE, Copăescu C, Galea RF, Buzoianu AD, et al. Increased chemerin and decreased omentin-1 levels in morbidly obese patients are correlated with insulin resistance, oxidative stress and chronic inflammation. Clujul Med 2014;87:19–26.
[13] Prakash M, Shetty MS, Tilak P, Anwar N. Total thiols: biomedical importance and their alteration in various disorders. OJHAS 2009;8:1–9.
[14] Burke-Gaffney A, Callister ME, Nakamura H. Thioredoxin: friend or foe in human disease? Trends Pharmacol Sci 2005;26:398–404.
[15] Lu J, Holmgren A. The thioredoxin antioxidant system. Free Radic Biol Med 2014;66:75–87.
[16] Tinkov AA, Bjørklund G, Skalny AV, Holmgren A, Skalnaya MG, Chirumbolo S, et al. The role of the thioredoxin/thioredoxin reductase system in the metabolic syndrome: Towards a possible prognostic marker? Cell Mol Life Sci 2018;75(9):1567–86.
[17] Chang CH, Han ML, Teng NC, Lee CY, Huang WT, Lin CT, et al. Cigarette smoking aggravates the activity of periodontal disease by disrupting redox homeostasis- an observational study. Sci Rep 2018;8:11055.
[18] Jekell A, Hossain A, Alehagen U, Dahlström U, Roseń A. Elevated circulating levels of thioredoxin and stress in chronic heart failure. Eur J Heart Fail 2004;6:883–90.
[19] Chojnowska S, Baran T, Wilińska I, Sienicka P, Cabaj-Wiater I, Knaś M. Human saliva as a diagnostic material. Adv Med Sci 2018;63:185–91.
[20] Mishra S, Rao CR, Shetty A. Trends in the diagnosis of gestational diabetes mellitus. Scientifica (Cairo) 2016;2016:5489015.
[21] Kurtel H, Granger DN, Tso P, Grisham MB. Vulnerability of intestinal interstitial fluid to oxidant stress. Am J Physiol 1992;263:G573–8.
[22] Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: role in short- and long-term implications for mother and fetus. J Nutr 2003;133:1674–83.
[23] Li XM, Ji H, Li CJ, Wang PH, Yu P, Yu DM. Chemerin expression in Chinese pregnant women with and without gestational diabetes mellitus. Ann Endocrinol 2015;76:19–24.
[24] Yang M, Yang G, Dong J, Liu Y, Zong H, Liu H, et al. Elevated plasma levels of chemerin in newly diagnosed type 2 diabetes mellitus with hypertension. J Invest Med 2010;58(7):883–6.
[25] Pfau D, Stepan H, Kratzsch J, Verlohren M, Verlohren HJ, Drynda K, et al. Circulating levels of the adipokine chemerin in gestational diabetes mellitus. Horm Res Paediatr 2010;74:56–61.
[26] Görkem Ü, Küçükler FK, Togrul C, Güngör T. Are adipokines associated with gestational diabetes mellitus? J Turk Ger Gynecol Assoc 2016;17:186–90.
[27] Ghanem HB, Elsheikh M, El-Benhawy SA, Shahba A. Adipocytokines, inflammatory, epigenetic instability & angiogenesis biomarkers in type 2 diabetic Egyptian women with breast cancer. Diabetes Metab Syndr 2019;13:24–9.
[28] Todoroki Y, Tsukahara H, Ohshima Y, Shukunami K, Nishijima K, Kotsuji F, et al. Concentrations of thioredoxin, a redox-regulating protein, in umbilical cord blood and breast milk. Free Radic Res 2005;39:291–7.
[29] Martínez-Galisteo E, Padilla CA, Holmgren A, Bárcena JA. Characterization of mammalian thioredoxin reductase, thioredoxin and glutaredoxin by immunochemical methods. Comp Biochem Physiol B Biochem Mol Biol 1995;111:17–25.
[30] Gromer S, Urig S, Becker K. The thioredoxin system–from science to clinic. Med Res Rev 2004;24:40–89.
[31] Abdolsamadi HR, Rezaei F, Goodarzi MT, Moghimbeigi A, Jazaeri M, Asadi S, et al. Comparison of salivary nitric oxide and epidermal growth factor level between diabetic patients and healthy individuals. Int J Diabetes Dev Ctries 2015;35:477–82.
[32] Sánchez GA, Miozza VA, Delgado A, Busch L. Total salivary nitrates and nitrites in oral health and periodontal disease. Nitric Oxide 2014;36:31–5.
[33] Peterson CM, Peterson JL. Percentage of carbohydrate and glycemic response to breakfast, lunch, and dinner in women with gestational diabetes. Diabetes 1991;40:172–4.
[34] Miyazaki Y, Kawano H, Yoshida T, Miyamoto S, Hokamaki J, Nagayoshi Y, et al. Pancreatic B-cell function is altered by oxidative stres induced by acute hyperglycaemia. Diabet Med 2007;24:154–60.
[35] Ryckman KK, Spracklen CN, Smith CJ, Robinson JG, Saftlas AF. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. BJOG 2015;122:643–51.
[36] Major CA, Henry MJ, De Veciana M, Morgan MA. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. Obstet Gynecol 1998;91:600–4.
[37] Zygula A, Kosinski P, Zwierzchowska A, Sochacka M, Wroczynski P, Makarewicz-Wujec M, et al. Oxidative stress markers in saliva and plasma differ between diet-controlled and insulin-controlled gestational diabetes mellitus. Diabetes Res Clin Pract 2019;148:72–80.