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Antioxidant Enzymes in Gestational Diabetes: A Study on a Kuwaiti Population

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Abstract

Objectives: We hypothesize that enzymatic antioxidants are significant contributors to antioxidant status in gestational diabetes (GDM) through scavenging of free radicals. Methods: We evaluated total antioxidant activity and the activities of two major physiological antioxidant enzymes: glutathione peroxidase (GPX) and superoxide dismutase (SOD) in peripheral blood of 22 pregnant Kuwaiti women in second trimester afflicted with GDM, 28 healthy pregnant women (also in 2nd trimester) and 27 healthy non-pregnant women. Enzyme activities were measured using spectrophotometric assays.

Results: No significant differences were noted in total antioxidant activity in peripheral blood in the three cohorts; however, serum SOD activity was significantly decreased in blood of both GDM women ($p<0.05$) and healthy pregnant subjects ($p<0.05$) relative to the non-pregnant cohort. Conversely, the activity of GPX was significantly elevated in blood of GDM-afflicted women relative to non-pregnant ($p<0.001$); and healthy pregnant women ($p<0.001$). GPX/SOD ratio was significantly higher in the GDM group compared to normal pregnancy and non-pregnant control ($P<0.01$).

Conclusion: The activity of GPX /SOD ratio may be a marker of glycemic control in women with gestational diabetes. It is reasonable to conclude that the pathogenesis of GDM may involve the release of substantial quantities of mediators. This phenomenon suggest further investigation in the management of GDM which may involve other therapeutic targets for pharmacological intervention.

Keywords: Pregnancy; Diabetes; Antioxidant enzymes; Lipid metabolism

Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance of varying degree of severity with onset or first recognition during pregnancy [1]. This definition makes it difficult to distinguish between undiagnosed diabetes existing before pregnancy and hyperglycemia induced by pregnancy.

Increasing Prevalence of Gestational Diabetes Mellitus (GDM)

The prevalence of GDM and Type 2 diabetes in pregnancy are increasing with the epidemic of obesity [2]. Gestational diabetes is complicates 0.15% to 12.3% of pregnancies [3] with wide variation in the incidence of gestational diabetes reported among ethnic groups. The prevalence of GDM among Kaiser Permanente Colorado (KPCO) members doubled from 1994 to 2002 (2.1-4.1%, P <0.001), with significant increases in all racial/ethnic groups [4]. The trend toward older maternal age, the epidemic of obesity and diabetes, and the decrease in physical activity and the adoption of modern lifestyles in developing countries have all contributed to an increase in the prevalence of GDM [1,5]. GDM is associated with significant future risk of permanent diabetes in the mother, obesity and diabetes in the offspring [6], in gestational diabetes there are health implications for both the mother and infant who remain at risk for a number of complications, especially adverse fetal outcome such as embryopathy, spontaneous miscarriages, macrosomia, shoulder dystocia and stillbirth [7]. There is a strong association between maternal diabetes in pregnancy and impaired cognitive outcome [8].

Oxidative Stress and hyperglycaemia (GDM) in Pregnancy

Oxidative stress plays an important role in the development of complications of diabetes in pregnancy. Oxygen free radicals produced during aerobic metabolism may be involved in severe damage of cellular structure [9,10]. The involvement of reactive oxygen species in diabetic pregnancy has been reported by a number of authors [11-13]. It has been severally demonstrated that a single hyperglycemia-induced process of overproduction of superoxide by the mitochondrial electron-transport chain seems to be the first and key event in the activation of allthe pathways involved in the pathogenesis of diabetic complications [14]. They include increased polyol pathway flux, increased advanced glycosylation end product formation, activation of protein kinase C, and increased hexosamine pathway flux. Superoxide overproduction is accompanied by increased nitric oxide generation, due to an endothelial NOS and inducible NOS uncoupled state, a phenomenon favoring the formation of the strong oxidant peroxynitrite, which in turn damages DNA. DNA damage is an obligatory stimulus for the activation of the nuclear enzyme

poly(ADP-ribose) polymerase. Poly(ADP-ribose) polymerase activation in turn depletes the intracellular concentration of its substrate NAD(+), slowing the rate of glycolysis, electron transport, and ATP formation, and produces an ADP-ribosylation of the GAPDH [15]. These processes result in acute endothelial dysfunction in diabetic blood vessels that, convincingly, also contributes to the development of diabetic complications [13,16]. Recent studies showed association of GD with impaired SOD activities and enhanced circulating lipid metabolite levels [17]. Of the many biological targets of oxidative stress, lipids are the most involved class of biomolecules. Lipid oxidation gives rise to a number of secondary products. Malondialdehyde (MDA) is the principal and most studied product of polyunsaturated fatty acid peroxidation. This aldehyde is a highly toxic molecule and should be considered as more than just a marker of lipid peroxidation. Its interaction with DNA and proteins has often been referred to as potentially mutagenic and atherogenic [18].

Antioxidant Defense system

To prevent free radical damage the body has a defense system of antioxidants. Unfortunately, controversial information has been reported on the intervention by antioxidant defense system. Carine et al. [19] and Zachara et al. [20] found no difference in GPX levels between pregnant women at third trimester and non-pregnant women. Conversely, Hchne and Walters [21] found increased GPX throughout pregnancy. The activity of superoxide dismutase was reported to be elevated in erythrocytes and blood plasma in late uncomplicated pregnancy [22], which may reflect a normal response to restore the oxidative system balance. Low levels of plasma SOD and GPX were shown in pregnancy-induced hypertension [23]; reduced placental level of these enzymes was also reported [24]. Increased lipid peroxidation and lack of compensatory mechanisms (increase in antioxidant enzyme activity) were reported in pregnant type I diabetics; the activity of superoxide dismutase and glutathione peroxidase in erythrocyte were reduced during the first and second trimesters [25].

The aim of this study was to evaluate the levels of scavenging enzymes in GD with a view to identify one that may serve as a useful marker of increased risk of fetal distress.

Materials and methods

Subjects

Participation in this study was voluntary and conducted with informed consent of all participants. The study has been approved by Kuwait University, Faculty of Medicine Review Board.This study included 22 multiparous pregnant women (mean age 33.4 ± SE, 0.9 year) in their second trimester of pregnancy diagnosed with gestational diabetes. Diabetes was diagnosed first time during pregnancy on the basis of standard glucose tolerance test (GTT) using the IADPSG guidelines for diagnosis of GDM [26].The consensus recommends a one-step 75 g oral glucose tolerance test for all women not already known to be diabetic at 24–28 weeks of gestation. Gestational Diabetes is diagnosed where one or more threshold value is exceeded (fasting ≥ 5.1 mmol/l, 1-hour ≥ 10.0 mmol/l, 2-hour ≥ 8.5 mmol/l). All patients managed their diabetic condition solely through dieting or insulin and diet were in good metabolic control, defined as tested glucose level between 3.3 –6.1 mmol/l (glucose oxidase method), evaluated by 4 hourly determinations.Matched control cohorts included 28 healthy women (mean age 31.5 ± 0.9 years) also in the second trimester of pregnancy, none of whom had a history of diabetes, preeclampsia, hypertension or renal disease; and 28 healthy pregnant women matched for age and parity and gestation and 27 healthy non-pregnant multiparous women (mean age 32.5 ± 1.0 years) served as control.

Methods

Whole blood was collected in heparinized tubes. Plasma was separated and stored at –20°C for measurement of total antioxidant activity within two weeks. Whole blood was centrifuged at 1000 X g for 10 min, and supernatant was discarded. Red blood cells were washed twice with a double volume of 0.9% NaCl solution and finally haemolyzed by adding 10 volumes of double distilled water and left to stand at 4°C for 15 min. The haemolysate was centrifuged at 3000 X g for 10 min and portions of the supernatant were taken for determination of SOD and GPX. Randox kits (Randox labs, Armore, UK) containing buffer, chromogen, substrate and standard were used to determine the activities of antioxidant enzymes as was previously reported [27,28].

Total antioxidant assay

ABT was incubated with a peroxidase and H2O2 to produce the radical cation ABTS. This has relatively stable blue green color at 600 nm. Antioxidants in the added plasma cause suppression of this color proportional to their concentration. Both positive and negative controls were used.

Superoxide dismutase assay

Xanthine and xanthine oxidase were used to generate superoxide radicals in the whole blood lysate samples, with resultant red formazen dye. The superoxide dismutase activity was then measured by the degree of inhibition of this reaction.

Glutathione peroxidase assay

The oxidation of NADPH was followed at 340nm in a mixture containing reduced glutathione and glutathione reductase. The decrease in absorbance was measured.

Statistical analysis

Analysis was performed using multiple comparison analysis of variance (ANOVA) with a post-hoc Tukey test. All statistical analysis were performed using the SPSS for Windows statistical package version 17 (Norusis/SPSS, Inc.). A value of $p < 0.05$ was considered statistically significant.

Results

Table 1 summarizes the characteristics of the women included in the three study groups. Differences in activities of selected antioxidant enzymes emerged when the three study groups were compared.

As shown in Table 2, there is a significant decrease in serum SOD activity in blood of GD (150.5 ± 15.9 U/ml) and healthy pregnant subjects (129.9 ± 13.1) relative to the non-pregnant cohort (198.3 ± 11.6 U/ml) ($p < 0.05$ respectively). The activity of GPX was found to be elevated almost 2 fold in the blood of GD-afflicted women (12128.3 ± SE, 1244.6 U/l) compared to non-pregnant (5814.1 ± 1027.5 U/l) and healthy pregnant women (6694.6 ± 957.1 U/l) ($p<0.001$ respectively).

	Non-Pregnant Control N= 27	Gestational Diabetes N= 22	Control pregnancy N=28
Age (years)	32.5 ± 1.0	32.75 ± 1.2	31.5 ± 0.9
Weight (Kg)	82.4 ± 2.9	81.7 ± 3.0	84.3 ± 3.5
parity	2.6 ± 0.8	2.9 ± 0.6	1.9 ± 0.3
abortion	0.84 ± 0.26	0.73 ± 0.22	0.95 ± 0.27
Live birth	2.4 ± 0.6	2.8 ± 0.6	1.9 ± 0.3

Table 1: Demographic data of gestational diabetes patients and control pregnancy at 2nd trimester

On the other hand, no significant differences were noted in total antioxidant activity when this parameter was compared in peripheral blood of non-pregnant (1.11 ± 0.04 mmol/L), healthy pregnant (1.12 ± 0.04mmol/L) and GD-afflicted cohorts (1.09 ± 0.05 mmol/L).

Enzyme	Non-Pregnant control N=27	Control normal Pregnancy N=28	Gestational Diabetes N= 22
Total antioxidant(mmol/L)	1.11 ± 0.04	1.12 ± 0.04	1.09 ± 0.05
GPX (U/L)	5814.1 ± 1027.5	6694.6 ± 957.1	12128.3 ± 1244.6**##
SOD (U/ml)	198.3 ± 11.6	129.9 ± 13.1*	150.5 ± 15.9*
GPX/ SOD ratio	49.0 ± 12.4	51.7 ± 7.13	117.9 ± 34.9*#

Table 2: Levels of antioxidant enzymes in gestational diabetes in late second trimester.* p<0.05, ** p<0.01 vs non-pregnant control, # p< 0.05, ## p< 0.01 vs cont-Preg 2nd trimester

As shown in table 2, GPX/SOD ratio, was significantly higher in the gestational diabetes study group compared to non-pregnant control (P<0), and normal pregnancy control (P<0.05). Among the two control groups, there was no significant difference in the GPX/SOD ratio.

Discussion

In this study, the activity of antioxidant enzymes superoxide dismutase (Cu, Zn-SOD), glutathione peroxidase (GPX) and total antioxidant capacity (TAC) were investigated in hemolysate of erythrocytes. TAC was formulated as the "cumulative action of all the antioxidants present in plasma and body fluids, thus providing an integrated parameter rather than the simple sum of measurable antioxidants" [29]. There were no significant differences in the expression of TAC between gestational diabetes and the normal pregnant and non-pregnant controls. This is hardly surprising. The role and use of total antioxidant activity has been criticized and direct assay of urate, ascorbate and tocopherol the major small molecules that contribute to TAC, has been recommended [30].

Superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT), together with glutathione (GSH), form the first-line of defense against ROS in irradiated tissues. SOD converts superoxide anion (O_2•−) to H_2O_2, which is then detoxified to water by GPX and CAT. If not removed, H_2O_2 itself causes oxidative damage to biomolecules, or it can be converted to a more damaging hydroxyl radical (•OH) species. Reduced glutathione, GSH, is involved in the non-enzymatic removal of ROS and also serves as the hydrogen donor in GPX-mediated reaction. The oxidized glutathione (GSSG) is either reduced back to GSH *via* glutathione reductase-mediated reaction, or exported out of the cells. Therefore, the GSH equivalent to the sum of GSH + 2GSSG, serves as a measure of the total glutathione capacity of cells at any given time in response to oxidative stress [31]. The various parameters of the antioxidant defense system such as the total antioxidant status, vitamins C and E, selenium and activities of scavenging enzymes, e.g. catalase, SOD and GPX reflect counteraction of the influx of potentially damaging free radical species [32].

Contrary to a previous report [33] on cord blood of newborn delivered to diabetic mothers, we found no change in serum total antioxidant level in any of the pregnant groups relative to the non-pregnant controls. The SOD activity, on the other hand, was significantly reduced in both pregnant groups (35.6% in control pregnancy and 24.1% in gestational diabetes); diabetes did not seem to have an obvious impact on the magnitude of this change. Further scrutiny of the metabolic status of the control pregnant group may provide an explanation for this apparent anomaly. The suppression of SOD we found in the gestational diabetic group is consistent with the previous reports on the subject and the current views on the role of this enzyme in diabetes [17,34,35]. The GPX activities in our study were elevated in the gestational diabetes groups, compared to the control pregnant (p<0.01) and the healthy non-pregnant controls (p<0.01). On the other hand, the antioxidant scavenging efficiency was assessed by the ratio of GPX activity/SOD activity (Table 2). Bonfigli et al. [36] have shown that the efficiency of ROS scavenging in the system was associated with increased values of this ratio in rats.

It is interesting to note that unlike the SOD activities in these groups, GPX was markedly influenced by gestational diabetes. These observations are in contrast to some previous reports on GPX in

diabetes where GPX showed either no change or paralleled SOD, both showed a reciprocal relationship with MDA or RBARS levels [19,32,37,38]. The unexpected increase in the GPX activities here can only be evaluated in the context of a full spectrum of the levels of antioxidant components. These results reflect a positive adaptive response able to assure an efficient protection not only against chronic, diabetes-mediated reactive oxygen species (ROS) overproduction, but also versus further oxidative damage. Further investigations may suggest modified treatment program for GDM patients at early pregnancy. Park and Associates [39] found striking differences in the anti-oxidant activities of RBC with respect to the pneumonitis development. Those who developed pneumonitis showed higher SOD and lower GPX activities at baseline compared to those who did not (3.7 *vs.* 6.8 unit/mg for median SOD, 16.5 *vs.* 10.7 nmol/min/mg for median GPX). These results show a strong rationale to monitor SOD and GPX activities of RBC to identify patients who are at risk of developing pneumonitis, and to implement a strategy of increasing the GPX/SOD ratio in order to lower the risk. In a recent study, women with previous GDM have high catalase levels which correlate positively with glucose intolerance, indicating the potential effect of oxidative stress on postpartum dysglycemic status [40].

In summary, our study shows an elevation in GPX/SOD ratio in GDM. This may be used as an index of glycemic control after further evaluation of this phenomenon.

Conflict of interest

The authors have no conflict of interest.

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