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Evaluation of serum antioxidant status and dietary antioxidants in patient with gestational diabetes mellitus

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Abstract
Background: Diabetes mellitus is the most common metabolic disease complicating pregnancy which leads to maternal and foetal morbidity. Gestational diabetes mellitus (GDM) is described as glucose intolerance diagnosed during pregnancy. Increased oxidative stress has implicated in diabetic problems. The aim of the current study was to evaluate serum antioxidant status and dietary antioxidants in gestational diabetes mellitus.
Material and Methods: The study was conducted in the Department of Obstetrics and Gynaecology, University College of Medical Sciences and Guru Teg Bahadur hospital, Delhi from November 2017 to April 2019. 300 Antenatal women were recruited from the ANC OPD of the Department of Obstetrics and Gynaecology with the period of gestation upto 28 weeks diagnosed with GDM as per DIPSI criteria. Preconceptional dietary intakes of nutrients including antioxidants by using a food frequency questionnaire (FFQ). Unpaired student t test was used to compare serum Total Antioxidant Capacity (TAC) levels; dietary antioxidants i.e. Vitamin E, Zinc, Vitamin C & ß-carotene and mitochondrial DNA copy number between GDM and non GDM women. Logistic regression was used for categorical outcome to find the association of serum TAC levels with risk of GDM. A p value of <0.05 was taken as significant. Software used for statistical analysis was SPSS.
Results: This was a case control study conducted among 300 antenatal women presenting to the ANC OPD upto 20-22 weeks were recruited and were subjected to a 75 gram OGTT at their first visit. Those with OGTT ≥140 mg/dl were diagnosed as GDM as per DIPSI guidelines and day matched controls with a OGTT <140mg/dl were recruited as controls. Controls were again subjected to a repeat OGTT at 24 to 28 weeks and the OGTT value ≥140 mg/dl were taken as Gestational diabetes (cases) whereas OGTT value <140mg/dl still remained as controls. The average age of women with GDM in the present study was 28.2 years compared to 24.4 years of women without GDM. Over 40% of women with GDM were of age thirty years and over, while only around 10% of women without GDM fell in this age group. The total antioxidant capacity (TAC) of serum was assessed by double-antibody sandwich enzyme-linked immune-sorbent assay (ELISA) method. Multivariate logistic regression was performed to compare independent variables and other potential risk factors between 2 groups. The results showed that TAC concentration of serum in women with GDM was significantly with in healthy pregnant women. Intakes of vitamin E (18.33±2.00, p<0.001), vitamin C (220.45±3.55, p<0.001) β carotene (912.83±11.17, p<0.001) and zinc (11.63±0.75, p<0.001) were highly significantly with women with GDM as compared to healthy pregnant women. The groups showed significant difference in vitamin C, vitamin E, β-carotene, and zinc (p<0.05).
Conclusion: Our findings showed that Preconceptional dietary intake of antioxidants Vitamin E, Vitamin C, Zinc and ß-carotene was significantly less in women with GDM as compared to women without GDM. Antioxidant status could be enhanced by consumption of food rich in antioxidant and high dietary intake of fruit and vegetables and other rich antioxidant sources in GDM, which may be ultimately beneficial in the prevention and management of GDM.

Keywords: gestational diabetes mellitus, serum antioxidant status, dietary antioxidants, TAC

Introduction
Diabetes mellitus is the most common metabolic disease complicating pregnancy which leads to maternal and foetal morbidity. Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy (American College of Obstetrics and Gynaecologists, 2013). The prevalence worldwide is on a rising trend due to lifestyle changes and obesity. Depending on the population and diagnostic criteria used, the prevalence of gestational diabetes mellitus varies. The WHO estimates 10-25% pregnancies to be affected by diabetes mellitus [1].

Pregnancy itself is a physiological state, accompanied by high energy demand and an increased oxygen utilisation, both of which may lead to increased oxidative stress. Imbalance between the free-radical production and radical-scavenging capacity leads to oxidative stress. 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. A single hyperglycaemia-induced process of overproduction of superoxide by mitochondrial electron-transport chain seems to be the first and key event in the activation of all the pathways involved in the pathogenesis of diabetes complications. Total antioxidant capacity (TAC) is the balance between antioxidants (neutralizing systems) and the oxidants (oxidative stress) and is a biomarker which is used to measure the antioxidant potential of the body. Due to the combined effects of antioxidants, the total antioxidant capacity (TAC) or the combined activity of all the antioxidants is recommended instead of measuring each agent separately. However, studies about the maternal nutrition status, antioxidant nutrients and TAC in women with GDM are limited. The exact pro-oxidant and antioxidant status in gestational diabetes mellitus is still not clear. This study aims to compare TAC and preconceptional maternal nutrition status of dietary antioxidants in women with gestational diabetes mellitus presenting to a tertiary care hospital in the capital of the country. It also aims to find the correlation between pregnancy outcomes and the antioxidant capacity of the women. This study will help validate the role of oxidative stress in the causation of the condition, appropriate use of antioxidants for prevention of the same and prompt further research into diagnostic and therapeutic options for the optimum management of women with gestational diabetes mellitus.

Material and Methods

The study was conducted in the Department of Obstetrics and Gynaecology, Department of Biochemistry and Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur hospital, Delhi from November 2017 to April 2019.

Type of study: The study was a Nested case control study.

Subjects: 300 Antenatal women were recruited from the ANC OPD of the Department of Obstetrics and Gynaecology of UCMS and GTB Hospital, Delhi.

Sample size: Based on a previous study [11], considering a SD of 0.7 in GDM and 0.1 in Non GDM women to estimate an absolute difference of 1.4 in TAC levels at 90% power and 5% level of significance a sample size of 10 is required in each group. Similarly for SD of 3.1 in GDM and non GDM women to estimate an absolute difference of 4.4 in Vitamin E levels and for SD of 1.9 in GDM and 1.7 in non GDM women to estimate an absolute difference of 1.7 in Zinc levels at 90% power and 5% level of significance sample size of 12 and 24 is required respectively in each group. So, a sample size of 24 in each group was sufficient for the study. Adding 5% loss to follow up, sample size is taken as 30 for each group. Considering the prevalence of GDM about 11% in GTB hospital, to obtain 30 cases of GDM women, we required a sample of 300 antenatal women. No studies were available for sample size of mitochondrial DNA damage assessment in GDM, because of financial constraints sample size of 30 cases and controls were taken for the study.

Inclusion criteria for cases

All antenatal women with period of gestation upto 28 weeks diagnosed with GDM as per DIPSI criteria.

Inclusion criteria for controls

All antenatal women with period of gestation upto 28 weeks with OGTT values <140mg/dl as per DIPSI criteria.

Exclusion criteria for cases and controls

1. Antenatal women with previous history of Type 2 diabetes mellitus, chronic hypertension. 2. Multiple pregnancies. 3. History of any acute medical illness, fever, infection or any evidence of ongoing inflammation. 4. History of past chronic medical illness for example previous renal disease, liver disease, jaundice, epilepsy, cancer. 5. Patients on chronic medications for example steroids, anti-epileptic drugs.

Methodology

Ethical clearance was obtained from the Institutional Ethics committee. Informed written consent was taken from the recruited antenatal women. 300 Antenatal women upto 20-22weeks were recruited voluntarily for the study from the ANC OPD. A detailed history was taken and examination conducted. Routine investigations were carried out and noted. They were also subjected to OGTT at their first antenatal visit. 75g glucose was administered irrespective of last meal time. Those women with 2hours OGTT values ≥140mg/dl were taken as gestational diabetes mellitus (cases) as per DIPSI criteria. Controls were chosen from women with 2hour glucose after 75g OGTT <140mg/dl. Controls were again subjected to a repeat OGTT at 24 to 28 weeks of gestation, and the OGTT value ≥140 mg/dl were taken as gestational diabetes mellitus (cases) whereas OGTT values <140mg/dl still remained as control.

Dietary Antioxidants estimation

Preconceptional dietary intake of nutrients including antioxidants during last 1 year was taken from cases and controls. Participants were asked to report the frequency and consumption of portion size for each food item using a detailed proforma which included food frequency questionnaire (FFQ) prepared by the Dietician of our hospital. FFQ is a checklist of food and beverages with a frequency response section for subjects to report how often each item was consumed over a specified period of time. The analytic strategy used in food frequency questionnaire is that the frequency of consumption is multiplied by portion size and these are summed up to obtain nutrient totals. The approximate daily intake of antioxidants Vitamin E (mg), Zinc (mg), Vitamin C (mg) and ß-carotene (mcg) was then calculated using the values provided in nutritive values of Indian Food Composition table (IFCT), 2017 given by National institute of nutrition (NIN).

1. Sample collection

At 24 to 28 weeks gestation, blood samples for estimation of maternal serum total antioxidant capacity (TAC) levels and mitochondrial DNA copy number (damage) were taken from cases and day matched controls.

- Under all aseptic precautions, 4ml maternal blood was drawn from the cases and controls.
- 1ml of maternal blood was collected in a plain vial and allowed to stand for 20minutes to clot. Supernatant serum was separated and stored in aliquots at -20 °C for estimation of Total antioxidant capacity (TAC) levels.
- 3ml blood was collected in an EDTA vial and was stored in aliquots at -20 °C before proceeding for mitochondrial DNA copy number assessment by mtDNA copy number by real

time PCR method.

2. Total antioxidant Capacity (TAC) estimation
Kit for the estimation of Total Antioxidant Capacity (TAC) in millimoles was used (Cayman Chemicals) based on the principle- Aqueous and lipid-soluble antioxidants are not separated in this kit protocol, thus the combined antioxidant activities of all its constituents including vitamins, proteins, lipids, glutathione, uric acid etc. are assessed. The assay relies on the ability of the antioxidants in the sample to inhibit the oxidation of ABTS (2,2'-Azino-di-[3-ethylbenzthiazoline sulphonate]) to ABTS by metmyoglobin. The amount of ABTS produced can be monitored by reading the absorbance at 750 nm or 405 nm. Under the reaction conditions used, the antioxidants in the sample cause suppression of the absorbance at 750 nm or 405 nm to a degree which is proportional to their concentration. The capacity of the antioxidants in the sample to prevent ABTS oxidation is compared with that of Trolox, a water-soluble tocopherol analogue, and is quantified in millimolar trolox equivalents.

3. Estimation of mtDNA copy number: The relative mitochondrial DNA copy number was estimated by real time PCR (dye based chemistry) from extracted DNA by using mitochondrial specific primers and nuclear specific primers. The ratio of Ct values gave the relative mitochondrial DNA content which in turn reflects the mitochondrial copy number and hence mitochondrial DNA damage.
To determine the mitochondrial DNA content, relative to nuclear DNA use, the following equation was used: ΔCT = (nucDNA CT – mtDNA CT) and Relative mitochondrial DNA content = $2 \times 2^{\Delta CT}$.

mtDNA primer

Mitochondrial primers:	Nuclear primers B2-microglobulin
Forward primer: CAC CCA AGA ACA GGG TTT GT	Forward primer: TGC TGT CTC CAT GTT TGA TGT ATC T
Reverse primer; TGG CCA TGG GTA TGT TGT TA	Reverse primer; TCT CTG CTC CCC ACC TCT AAG T

1. Samples were discarded once measurement of the markers is complete.
2. All cases were managed by medical nutrition therapy (as advised by dietician of our hospital) and insulin therapy as per hospital protocol.
3. 1 ml of maternal blood was collected at 37-38 weeks in a plain vial from cases for Total antioxidant capacity (TAC) levels by the method described above to study changes in its level with treatment.
4. Maternal and neonatal outcomes were noted in both the groups.

Follow up
1. The subjects were called up for regular ANC follow up as per the number of antenatal visits given by WHO i.e. once every four weeks till 28weeks of gestation, fortnightly till 32 weeks and weekly thereafter.
2. The subjects were also followed up in case they report in the emergency to the labour room.
3. Adherence to regular follow up in the ANC was ensured by regular telephonic contact.

Statistical Analysis: Unpaired student t test was used to compare serum TAC levels, dietary antioxidants i.e. Vitamin E, Zinc, Vitamin C & ß-carotene and mitochondrial DNA copy number between GDM and non GDM women. Chi square test/ Fisher's test was used to compare history of stillbirth, macrosomia, family history of DM in women with and without gestational diabetes mellitus. It was also used to compare adverse maternal and neonatal outcomes between GDM and non GDM women. Logistic regression was used for categorical outcome to find the association of serum TAC levels with risk of GDM. A p value of <0.05 was taken as significant. Software used for statistical analysis was SPSS.

Results
In present study out of 300 Antenatal women upto 20-22 weeks. They were recruited voluntarily for the study from the ANC OPD. After obtaining written informed consent, preconceptional average dietary intake including antioxidants was taken from cases and controls and dietary intake of antioxidants vitamin E(mg), Zinc(mg), Vitamin C(mg) and ß-carotene(mcg) was calculated from Food Frequency questionnaire. Results of vitamin E, zinc, and beta carotene were found statistically significant (p<0.05).

Table 1: Total Antioxidant Capacity levels (mM) in GDM and non GDM women at 24-28 weeks

Total Antioxidant Capacity (mM) at 24-28 weeks	Mean±SD	p value
GDM	3.82 ± 0.65	0.013
Non-GDM	3.35 ± 0.78	

Table 2: Total Antioxidant Capacity levels (mM) in GDM women at 24-28 weeks & 37 weeks

GDM women	Mean ± SD	p value
TAC at 24-28 weeks	3.82±0.78	0.047
TAC at 37 weeks	4.20±1.15	

Table 3: Calculation of Odds ratio (OR) for Total Antioxidant Capacity at 24-28 weeks

GDM women (N=30)	Regression coefficient (Standard error)	Odds ratio (95% CI)	p value
TAC at 24-28 weeks	0.933(0.395)	2.542(1.171-5.517)	0.018

Table 4: Preconceptional dietary intake of Vitamin E (mg) in GDM and non GDM women

Dietary intake of Vitamin E(mg)	Mean±SD	p value
GDM	18.33±2.00	<0.001
Non-GDM	34.36±2.10	

Table 5: Preconceptional dietary intake of Zinc (mg) in GDM and non GDM women

Dietary intake of Zinc (mg)	Mean ± SD	p value
GDM	11.63±0.75	<0.001
Non GDM	20.49±0.95	

Table 6: Preconceptional dietary intake of Vitamin C(mg) in GDM and non GDM women

Dietary intake of Vitamin C (mg)	Mean ± SD	p value
GDM	220.45±3.55	<0.001
Non GDM	231.1±4.31	

Table 7: Preconceptional dietary intake of ß-carotene(mcg) **in** GDM and non GDM women

Dietary intake of ß-carotene (mcg)	Mean ± SD	p value
GDM	912.83±11.17	<0.001
Non GDM	977.27±21.69	

Table 8: Mitochondrial DNA copy number in GDM and non GDM women

Mitochondrial DNA copy number	Mean ± SD	p value
GDM	263.56±100.99	0.252
Non-GDM	232.21±108.86	

The mean Mitochondrial DNA copy number in GDM women was 263.56±100.99 and in non GDM group was 232.21±108.86. No statistically significant difference was found between the two groups (p=0.252).

Discussion

This was a case control study comparing the levels of serum antioxidant status (Total antioxidant capacity), preconceptional dietary antioxidants (Vitamin E, Zinc, Vitamin C & ß-carotene) and mitochondrial DNA copy number(marker of oxidative stress) in women with and without gestational diabetes at 24 to 28 weeks period of gestation presenting to the antenatal clinic of Department of Obstetrics and Gynaecology in University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi from November 2017 to April 2019. The average age of women with GDM in the present study was 28.23 years compared to 24.40 years of women without GDM. Over 40% of women with GDM were of age thirty years and over, while only around 10% of women without GDM fell in this age group. Makgoba *et al* found a strong positive association between increasing maternal age and the risk of developing GDM[3]. Khalil *et al* made similar observations while studying the association of increasing maternal age and adverse outcome(OR, 1.88 (95% CI, 1.55-2.29); *P*<0.001) [4]. Xu and colleagues found the incidence of GDM at 18-25 years, 25-35 years and 36-45 years to be 1.8%,4% and 9.5% respectively [6]. In our study, 56.6% of women with GDM were parous, while only around 43.3% normoglycemic women were parous. Only 43% of the women with GDM were in their first pregnancy whereas more than half of women without GDM were primigravidae. This difference was found to be statistically insignificant (p=0.389). For higher order pregnancies, the findings of our study were in accordance with the findings of Bener *et al* who conducted a large study involving over 2000 women and found that increasing parity is associated with increased incidence of Gestational diabetes (p=0.004) [5].

In the current study, the mean BMI in GDM group was 23.58±2.67 kg/m^2 compared to 21.39±1.66 kg/m^2 in non GDM group, a statistically significant difference (*p*<0.001). Several studies validate this finding. Xu *et al* observed that obese women were more likely to develop GDM than women with normal weight(OR = 2.89, 95% CI (1.42, 5.90) [6]. In the current study, we found no significant association between family history of diabetes and incidence of GDM (p=0.237). Probably the lack of proper access to healthcare in the family members or the failure to diagnose diabetes in all of the population led to this finding this is similar with study done by Schwartz *et al*, and they found no association between family history of diabetes and recurrence of GDM [7].

In the current study, it was observed that the mean serum Total Antioxidant Capacity (TAC) in women with GDM (3.82±0.65) was higher as compared to healthy pregnant women (3.35±0.78). The result was found to be statistically significant (p=0.013). Similar results were observed by Al Shebly MM *et al* [8] who evaluated oxidative stress and antioxidant capacity in diabetic, hypertensive and healthy control women during labour, and observed total antioxidants significantly increased in GDM(1.5±0.38) than healthy control group(0.59±0.04) (*p*<0.05). In the present study, the TAC levels at 37 weeks were higher in GDM women than the levels of TAC at 24-28 weeks in women with GDM. This probably indicates the increased activity of antioxidants defence system by the treatment provided to the GDM women in the form of Medical Nutrition Therapy (MNT) ± Insulin. The preconceptional dietary intake of antioxidant nutrient, Vitamin E was significantly lower in women with GDM as compared to non GDM women in the current study. This difference was found to be statistically significant (*p*<0.001). The pre-conceptional intake of Zinc, an important antioxidant was significantly lower in women with GDM than non GDM women in the current study (*p*<0.001). This was similar to the results observed in the study conducted by Bo S *et al* [9], who noticed that intake of dietary zinc was negatively associated with development of gestational diabetes mellitus and daily zinc intake of 1mg/day resulted in 11% reduction in the risk of gestational hyperglycemia. It could be explained by the fact that zinc could limit oxidant-induced damage with protection against vitamin E depletion, hence increasing the stabilisation of membrane structure. In the current study the mean value of preconceptional dietary intake of Vitamin C in GDM women (220.45 ± 3.55) was lower than that in non GDM women (231.1 ± 4.31). The difference between the two groups was statistically significant (*p*<0.001). Similar results were found in a previous study, in which the dietary intake of Vitamin C was inversely associated with risk of development of GDM conducted by Liu C, *et al*. Women with dietary intake of vitamin C more than 200mg/day, experienced lower odds of GDM (OR 0.68, 955 CI: 0.49-0.95) than those with intake 115-200mg/day. This data suggested that higher dietary vitamin C intake during pregnancy lowers the risk of GDM [10]. The mean value of preconceptional dietary intake of ß-carotene, in the present study was lower in GDM women (220.45 ± 3.55) than non GDM women (231.1 ± 4.31). The difference between the two groups was statistically significant (*p*<0.001). The results were in concordance with the study by Gao Q, *et al* who noted dietary carotenoids intake in GDM women and found that women in the highest quartile had a lower risk of GDM (OR 0.50; 95% CI 0.29, 0.86).

Conclusion

The present study concludes that: Levels of serum Total Antioxidant Capacity (TAC) at 24-28 weeks was significantly higher in women with GDM than in women without GDM, depicting a compensatory rise of antioxidants in response to the oxidative stress of GDM. Levels of serum Total Antioxidant Capacity (TAC) in women with GDM was significantly higher at 37 weeks of gestation compared to their levels at 24-28 weeks of gestation. Preconceptional dietary intake of antioxidants Vitamin E, Vitamin C, Zinc and ß-carotene was significantly less in women with GDM as compared to women without GDM. The mitochondrial DNA copy number, marker of oxidative stress was higher in GDM women as compared to non GDM women. No definitive correlation of dietary antioxidants and mitochondrial DNA copy number estimation was established with adverse pregnancy outcomes.

Recommendations

Estimating TAC levels early in pregnancy can help in predicting development of gestational diabetes mellitus. The association of low preconceptional dietary intake of antioxidants in women with gestational diabetes mellitus indicates a definitive role of use of preconceptional antioxidants supplementation in women at high risk of GDM. Dietary counselling regarding inclusion of fruits and vegetables rich in antioxidants to reproductive age group females can be considered beneficial for disease prevention/ better pregnancy outcomes. Further studies to validate the above findings on a larger scale are needed.

Limitations

The serum levels of micronutrient antioxidants were not evaluated. A larger sample size is needed to establish the correlation of antioxidants with GDM and adverse pregnancy outcomes.

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