The Predictive Value of Selenium in Diagnosis of Gestational Diabetes: A Nested Case-Control Study

Aim: The present study was conducted to determine the predictive value of Selenium (Se) in the diagnosis of Gestational diabetes Mellitus (GDM).

Methods: This is a nested case-control study with 636 normal pregnant mothers in their 11th-13th weeks. Gestational diabetes screening was done in weeks 24–28. Twenty-five individuals were detected as GDM, and for every GDM two gestational age-matched normal pregnant women were selected. The blood selenium level was measured in both groups.

Results: The serum Se level in the case group was lower than that of the control group (50.60 ± 10.88 versus 66.02 ± 10.57) in the first trimester. Also, in the second trimester, Se was lower in the case group (39.87 ± 10.23 versus 63.17 ± 10.22). The best cut-off point for selenium in order to predict the incidence of gestational diabetes in our study was 48.2. Pregnant women with selenium levels below 48.2 were more likely to develop gestational diabetes.

Conclusion: Serum selenium was lower in the GDM subjects compared with age-matched control group; the clinical concept and mechanism of this finding need to be investigated through further studies.

Keywords: diabetes mellitus, gestational, prenatal, pregnancy, selenium

Introduction

Gestational Diabetes mellitus (GDM) is referred to as having various degrees of glucose intolerance with onset or recognition during pregnancy.1–4 1–14% of all pregnancies are accompanied with GDM, inducing short- and long-term maternal and prenatal complications.1,5 During natural pregnancy, Insulin resistance increases parallel with the rise in oxidative stress. It, eventually, results in antioxidant level reduction.6,7

The aforesaid conditions are more observed in the GDM affected women. Glucose oxidation, protein glycation, as well as lipid peroxidation in women suffering from GDM cause free radical accumulation.6,8 It is argued that there is a positive correlation between erythrocyte glutathione peroxidase activities and Insulin resistance. This correlation reveals that oxidative stress decreases the insulin secretion and increases the insulin resistance. Accordingly, this correlation is connected to Type 2 diabetes.6,7

Selenium (Se), an essential trace element, is considered a key component of numerous selenoproteins in an antioxidant defense system. Glutathione peroxides consist of a group of enzymes supporting the body against oxidative stress. Glutathione peroxides have selenium in the form of selenocysteine in the catalytic site.9 It is also assumed that selenium with properties like insulin can have anti-diabetic function.6

Reference

1. Sayadi M, Akbarzadeh M, Dabbaghmanesh MH, Bashiri K, Asadi N, Sayadi M. Gestational Diabetes: A Nested Case-Control Study. Int J Gen Med 2020:13;53–60.
Recently, the result of a review article and meta-analysis carried out by Asgari et al revealed that Se concentration of women with gestational diabetes is substantially lower than that of the normal pregnant women. Kilinc et al’s research showed that serum selenium level in women with gestational diabetes and those with glucose intolerance is lower than that of the normal pregnant women. Han reached the conclusion that there was a link between low Se level and gestational diabetes. Asemi in a clinical trial indicated that Se supplementation among pregnant women with gestational diabetes resulted in improved glucose homeostasis as well as reduced inflammation and improved oxidative stress.

The above-mentioned surveys showed that low level of selenium in women is related to gestational diabetes. It should be noted that none of these studies has looked into the casual relationship of gestational diabetes and selenium. This study is an attempt to evaluate the predictive value of selenium in gestational diabetes. Such research has not been conducted, as far as the authors know, in the last 20 years.

Method

Setting

This study is a nested case-control study. First, 636 gestational age cohorts were enrolled in the study and at the first pregnancy visit, the required samples were obtained. Then, the study sample was followed up until the outcome, which is gestational diabetes. After the outcome, the case group and those who were negative for gestational diabetes were included in the main phase of the study. The case is called a nested witness. This study was performed to compare the plasma levels of selenium in healthy primiparous women with gestational diabetes who referred to selected clinics Hafez educational and therapeutic center and Comprehensive Medical Genetic Center (CMGC) affiliated to Shiraz University of Medical Sciences in 2013–2014.

Study Population

On the basis of the former results, the sample size of gestational diabetes and normal groups was 25 and 50 subjects, respectively. The number of the subjects was calculated using the following formula:

\[ n = \left( \frac{z_{1-\alpha/2} + z_{1-\beta}}{\delta} \right)^2 \]

where \( n \) is the sample size, \( z_{1-\alpha/2} = 1.96 \) for \( \alpha = 0.05 \), \( z_{1-\beta} = 1.282 \) for \( \beta = 0.2 \), \( \delta = 0.093 \) (difference), d=2, \( \alpha = 5\% \), \( z_{1-\alpha/2} = 1.96 \), 1 -\( \beta = 80\% \), \( z_{1-\beta} = 0.85 \).

In a prospective study design, the required sample size in the case group with a confidence level of 95%, \( p=5\% \) (incidence rate of Diabetes), for the purpose of \( n \) numbers using the formula, \( n = \left( \frac{A + \sqrt{A^2 + \frac{n}{p}}}{\frac{d}{\sqrt{p(1-p)}}} \right)^2 \) ; 636 was obtained. In this formula, \( A = \frac{z_{1-\alpha/2}}{\frac{d}{\sqrt{p(1-p)}}} \) .

Therefore, 636 eligible primigravida women were included in this study from March 2014 to January 2015, with the following inclusion (placement) criteria: singleton pregnancy, age lower than 30 years old (because age is associated with the incidence of diabetes, we have to control the role of the age. In the onset of gestational diabetes, women under the age of 30 were studied., gestational age less than 14 weeks based on the first trimester ultrasound exam, none-smokers, no history of recognized internal diseases such as hypertension, diabetes, kidney disease, cardiovascular disease, etc., no personal history of glucose intolerance, no personal and family history of diabetes, neither personal nor family history of deep venous thrombosis, with BMI < 30 (kg/m²), no history of chronic disease or vitamin deficiency, lack of taking any medication (except for iron supplementation) or any types of multivitamins containing selenium during the previous year, and living in Shiraz during the previous 2 years. All participants had gestational age under 14 weeks at the beginning of the study and were followed until 24–28 weeks of pregnancy. The study group was requested to fill out a questionnaire to get their demographic data and their physical activities before pregnancy. Exclusion criteria included use of multivitamin supplementation containing Se during the study; lack of correlation between gestational age based on the last menstrual period and sonographic exam of first trimester; no chronic disease such as kidney, thyroid, hypertension and cardiovascular diseases; preterm labor or abortion or any complication prior to 28 gestational weeks; no presentation to prenatal care unit; and withdrawal from the study. The gestational age of the subjects was lower than 14 weeks. Their cases were followed up till 24–28 gestational week. All research units were asked to fill out the questionnaires to obtain their demographic information as well as physical activities prior to gestation.

Matching Process Between the Case and Control Subjects

Sampling was done by using a convenience sampling method; then, out of 636 patients who were included in
the study, about 25 subjects were diagnosed as gestational diabetes mellitus, which was considered as the case group. For the control group, we selected the gestational age of the case and healthy mothers. Then, for each case based on gestational age, we arranged the healthy groups and randomly selected one of them to match the gestational age according to the selected control group.

Variable Considerations
Anthropometric parameters including weight, height, and body mass index were measured. Weight was measured using a standard scale while the subjects were in light clothing. Body mass index was calculated as weight (in kilograms) divided by the squared height (in meters). The height was measured by using tape measure.

Outcome
Blood Sample Collection and Analysis
For the first phase of the study, 5-mL venous blood was taken from each subject in the first trimester. The serum was separated within 1 hr after blood sampling by centrifugation. Then, all the samples were coded and transferred to Endocrine and Metabolism Research Center of Shiraz University of Medical Sciences. The serum was frozen at −70°C and remained intact in the site until the end of the second phase of sampling. All the subjects between 24 and 28 weeks of pregnancy received 50g oral glucose challenge test. If glucose was ≥140 mg/dL, the participants underwent a 100 g OGTT. GDM was diagnosed if two glucose values were above the thresholds defined by Carpenter and Coustan (fasting plasma glucose > 95 mg/dL, 1-h post load glucose (PLG) >180 mg/dL, 2-h PLG >155 mg/dL and 3-h PLG>140 mg/dL). 25 women were diagnosed with GDM and for each GDM patient 2 matched gestational age pregnant women were selected from healthy pregnant women. Then, the second stage of blood samples from gestational diabetes and selected healthy individuals were taken.

Serum Selenium Levels
The third phase of survey was launched by measuring the selenium of the first and second phases of the case and control groups. The experiments were performed by using a GBC atomic absorption spectrometer (AAS 932 - HG3000-AUS) equipped by hydride generation module. The operated parameters for the metal of interest were set as recommended by the manufacturer. Selenium was determined by hydride generation atomic absorption spectrometry (HG-AAS) and selenium (Si) hollow cathode lamp operating at the current of 4 mA, the wavelength of 196 nm, and the spectral bandwidth of 2 nm.

Statistical Analysis
In the present study, statistical analysis was performed using SPSS, version 20. Values were expressed as mean ± standard deviation. An independent-samples t-test was used to compare the quantitative variables including age, height, weight, BMI, gestational age at the beginning of the study, mean of the glucose challenges and selenium level. Chi-square test was applied for the qualitative variables including the jobs, education and physical activities between the patient and control groups. Kolmogorov Smirnov Test was used for data normality assessment. Pearson Correlation Test was applied for evaluation of the correlation of variables (the mean of GCT and BMI). Logistic Regression Analysis was conducted to find the relationship between the selenium level and gestational diabetes with BMI control variables. ROC curve was used to determine the best cut-off point. A p-value <0.05 was considered significant.

Result
Six hundred and thirty-six women were included in this study. Twenty-five pregnant women underwent abortion and 6 people had preterm labor. No significant difference was detected between the two groups concerning the mean age, education level, pre-pregnancy physical activity and gestational age, whereas there was a significant difference between the groups in job (p-value <0.046) Pre-pregnancy mean weight was more in the GDM group in comparison with the normal group and a statistically significant difference was observed between the two groups regarding BMI (Table 1).

The mean 1 hr glucose level (with 50 g glucose) in the 28–24 weeks of gestation in the case and control groups was statistically significant (p=0.001) (Table 2). Table 3 shows the mean fasting blood glucose and glucose tolerance of 3 hrs (1 hr, 2 hrs and 3 hrs) in the case group (Table 3).

Serum Se concentration in the case group was significantly lower than that of the normal group during both first (50.60 ± 10.88 versus 66.02 ± 10.57) and second trimesters (39.87 ± 10.23 versus 63.17 ± 10.22). Moreover, Se level in the second trimester was significantly lower than that of the first trimester in the case and control groups. Se level decreased in the second trimester in the case and control groups (10.68±3.61, 2.84±1.88), respectively, in comparison to the first trimester (Tables 4 and 5). Besides, pre-pregnancy
The reasons for reduction may
Heilan
in women affected with GDM, the over-
A lower level
*P values are signiﬁcant.
GDM
0.259
25.36 5.31 22.77 2.85 0.029*
25.76 3.65 25.66 3.52 0.909
0.46*
0.44 *
161.52 7.04 162.3 5.28 0.592
*Glucose challenge test; **Gestational diabetes mellitus.
Mean Blood Glucose 1 hr (50 g Glucose) in 24–28
28
125.52
22.12
24.5
GTT 2 hrs
163.44
24.5
GTT 3 hrs
125.52
22.12
Table 3 Mean of Fasting Blood Glucose and 3 hrs’ Glucose Tolerance (1 hr, 2 hrs and 3 hrs) in the Case Group
Variables
FBS
GTT 1 hr
GTT 2 hrs
GTT 3 hrs
Mean
95.40
201.48
163.44
125.52
SD
24.54
17.55
24.5
22.12
Table 1 Demographic Characteristics of the Patients and Control Groups
Variables
Age
Gestational Age At entry
Length
Weight
BMI
Table 2 Mean Blood Glucose 1 hr (50 g Glucose) in 24–28
Weeks in Both Groups
Variables
GDM** (n = 25)
Normal (n = 50)
P value
GCT*
163.48
14.84
105.30
14.49
0.001 <
Notes: *Glucose challenge test; **Gestational diabetes mellitus.
weight in the case group was more than the control group and
body mass index was higher in the case group than in the
control group (Table 1). The relationship between body mass
index and GCT was calculated using Pearson correlation
coefficient that was not statistically significant (Table 6).
By using ROC curve, the best cut-off point for prediction of
gestational diabetes was obtained 48.2. Sensitivity and
specificity of this point were 0.83, 0.94, respectively,
being statistically signiﬁcant. The area under the curve
was 0.93 which was statistically signiﬁcant (Figure 1).
Pearson correlation showed that BMI and GCT means
were not statistically signiﬁcant between the two groups.
Logistic Regression Analysis was used to evaluate the
effect of Se and BMI on the outbreak of gestational diabe-
tes. According to the result of this analysis, the effect of
BMI on the outbreak of diabetes was not statistically
signiﬁcant.
Discussion
According to our results, serum Se level decreased during
pregnancy, and its reduction was signiﬁcant in the gesta-
tional diabetes women. Se level in the ﬁrst trimester of
pregnancy was lower in those individuals who later had
gestational diabetes than the normal group. Se level in
diabetic women was lower than that of the normal group in
the 24–28 weeks.
Selenium is an antioxidant material helping to prevent
the adverse effects of free radicals. Glutathione peroxidase
(GP) which holds about 60% of the selenium in the body
is an antioxidant enzyme helping to detoxify the body and
protecting the cell against oxidative impairment.10
Evidence shows that serum selenium level reduces
during pregnancy.6,13,14 The reasons for reduction may
be hemodilutional phenomenon in pregnancy, the rise of
fetal requirements, and deposition in the placenta.6,10,11,15
Furthermore, owing to the rise of lipid peroxidation during
pregnancy, the activity of antioxidants such as glutathione
and erythrocyte glutathione peroxidase increases; there-
fore, the level of serum Se decreases, especially in the
third trimester.6,7 In women affected with GDM, the over-
production of free radicals induces the impairment of
radical scavenger function mechanisms.16 A lower level
of selenium has been explained in GDM, and it has been
indicated that there was an inverse relationship with this
trace element status and glucose tolerance.10,11,17-19
In numerous researches, Se level was measured during
the 24–28 weeks. Kilinc et al showed that Se level in women
with gestational diabetes and glucose intolerance is lower
than that of the control group. The mean level of Se in
gestational diabetes, glucose intolerance and control group
was 34.7±8.7, 39.9±6.5, and 50.7±6.5, respectively.10 Heilan
et al. reached the conclusion that Glutathione peroxides activity and level of Se may contribute to the pathogenesis of gestational diabetes. The Se levels in gestational diabetes and control group were 0.0620± 0.0224, and 0.0783 ± 0.0209, respectively. Furthermore, Glutathione peroxides activity in the case group was higher than that of the control group. Other studies revealed that Se level in gestational diabetic women was lower than that of the control group. The result of our research confirms other researcher’s achievements. The result of Hawke’s study revealed that the Se level diminished at 12–34 weeks of gestation. However, this reduction was not statistically significant, whereas in our research, the Se level in both case and control groups decreased and this reduction was significant in the control group. In Hawke’s research, 22 pregnant women were included in 12th week, one of whom was suffering from glucose intolerance and the rest of the subjects were healthy. Five subjects were found to have glucose intolerance and 1 had gestational diabetes. The sample size in the Hawke’s study was lower than that of the present study; furthermore, every subject was considered as her own control. However, in our study, 636 eligible primigravida women were included. All participants had gestational age under 14 weeks at the beginnings of the study and were followed until 24–28 weeks of pregnancy.

Twenty-five people were known as GDM and 50 normal pregnant women were the control group. Moreover, mean Se level (111±12,126±15) in 12, 34 weeks was higher than our mean; this can be due to the difference of selenium in the soil in different areas. Askari et al. found a negative correlation between selenium and gestational diabetes, especially in the third trimester. They could not detect a causal relationship between Se and GDM due to the design of the research (case-control or cross-sectional). On the basis of this meta-analysis, it is unknown that decrease in the serum Se is a predictive value of gestational diabetes and glucose intolerance or pregnant women with hyperglycemia have low Se level.

### Table 4: Bio-Variable and Multivariable Logistic Regression on Selenium and Other Covariates

| Variables  | Bio Variable (Unadjusted) | (Adjusted) Multivariable |
|------------|--------------------------|-------------------------|
|            | Coefficient | P value | OR (95% CI) | Coefficient | P value | OR (95% CI) |
| Age        | −0.008       | 0.908   | 0.992 (0.865–1.137) | 0.059       | 0.568   | 1.061 (0.866–0.299) |
| BMI        | −0.172       | 0.016   | 0.842 (0.732–0.968) | −0.150      | 0.115   | 0.860 (0.714–1.037) |
| Selenium   | 0.146        | <0.001  | 1.157 (1.0179–1.242) | 0.140       | <0.001  | 1.151 (1.071–1.236) |

Note: The bold values represent the significant difference in p values.

### Table 5: Changes of Serum Selenium Level in Gestational Diabetes and Normal Pregnant Women in the First and Second Trimester

| Selenium  | GDM (n = 25) | Normal (n = 50) | P value |
|-----------|--------------|-----------------|---------|
| First trimester | 50.60 ± 10.88 | 66.02 ± 10.57 | <0.001 |
| 24–28 week    | 39.87 ± 10.23 | 63.17 ± 10.22 | <0.001 |
| Mean change   | −10.68±3.61 | −2.84±1.88 | <0.001 |
| P value       | <0.001       | <0.001          |        |

### Table 6: Correlation Between GCT and BMI in the Case and Control Groups

| Group           | Case | Control |
|-----------------|------|---------|
| Pearson correlation | −0.285 | 0.072   |
| P-value         | 0.167 | 0.619   |
same line with our study. However, some studies have shown that the level of diabetes in diabetic patients is greater than the control group, which is in contrast to our study. And in some studies, the serum levels of selenium in diabetic patients and control group did not differ. And these differences may be due to racial differences and other interfering factors that require more studies. Selenium content also varies in different geographic regions, which is effective in altering the selenium levels. Besides, in the study of Liu X and colleagues, 14 Serum Trace Elements including selenium in pregnancy were studied in Chinese women as to their health and nutrition. The results showed that serum Fe, Zn, and Se concentrations were significantly reduced, but this study has not examined the association between this decline and the incidence of diabetes.

The cut-off points for gestational diabetes were obtained 48.2 µg/L with a sensitivity of 83.3% and specificity of 94%. In previous studies, only the Se value was compared in the case and control groups and the cutoff point was not reported. Two studies were done in Iran, reporting the cut-off points for preeclampsia. Ghaemi in a research conducted in Shiraz in 2013 reported that 62.2µg/L has been determined as the Se cut-off point. Maleki et al obtained 60 µg/L as the cutoff point. The difference of our cut-off point from the mentioned studies can indicate that Se level decreases significantly in GDM, in comparison with preeclampsia.

Implications for Practice
If further studies on selenium and gestational diabetes are carried out and the findings of this study are confirmed, the incidence of gestational diabetes can be reduced by administration of selenium supplement to pregnant women. In addition, selenium supplements can be used to treat pregnant women with gestational diabetes.

The strength of this study is that, unlike other cross-sectional or case-control studies, we designed a Nested Case-Control study of serum selenium level. Furthermore, the present research made a comparison between the Se level of the first trimester compared to the control group and more significant reduction of selenium in women with GDM during pregnancy, it can be concluded that the serum selenium was lower in GDM subjects compared with age-matched control group; also, the clinical concept and mechanism of this finding need to be investigated through further studies. The reduced serum levels may be effective in prediction of GDM. Due to the cut-off point obtained in this study, it can be said that pregnant women who have serum selenium levels less than 48/2 µg/L in the first trimester are more likely to be diagnosed with gestational diabetes. By applying Se to the routine tests at the first prenatal care, we can identify the individuals with low levels of selenium; moreover, by prescribing selenium supplements we can prevent these women from gestational diabetes. Further studies with larger sample sizes are needed to examine the role of selenium in the onset of gestational diabetes and support our findings.

Conclusion
Due to the low serum selenium levels in the case group in the first trimester compared to the control group and more significant reduction of selenium in women with GDM during pregnancy, it can be concluded that the serum selenium was lower in GDM subjects compared with age-matched control group; also, the clinical concept and mechanism of this finding need to be investigated through further studies. The reduced serum levels may be effective in prediction of GDM. Due to the cut-off point obtained in this study, it can be said that pregnant women who have serum selenium levels less than 48/2 µg/L in the first trimester are more likely to be diagnosed with gestational diabetes. By applying Se to the routine tests at the first prenatal care, we can identify the individuals with low levels of selenium; moreover, by prescribing selenium supplements we can prevent these women from gestational diabetes. Further studies with larger sample sizes are needed to examine the role of selenium in the onset of gestational diabetes and support our findings.

Ethical Approval
The present research was approved by the ethics committee of Shiraz University of Medical Sciences and written informed consents were obtained from all participants (proposal No: 6905 ethical code: IR. sums. REC S6905). This study was conducted in accordance with the Declaration of Helsinki.

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Disclosure
The authors report no conflicts of interest in this work.

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