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Research of the Relation between Preptin, Leptin and Insulin Resistance in Gestational Diabetes Mellitus Diagnosis Situations

Uncu U
Elazig Public Health Laboratory, Elazig, Turkey

Derin AO
Elazig Fethi Sekin City Hospital, Blood Center, Elazig, Turkey

Mahmut Bozkurt
Elazig Fethi Sekin City Hospital, Biochemistry Laboratory, Elazig, Turkey

Nazan Celik
Elazig Fethi Sekin City Hospital, Obstetrics and Gynecology Clinics, Elazig, Turkey

Fatos Uncu
Firat Univercity, Faculty of Health Sciences, Elazig, Turkey

Ihsan Halifeoglu
Firat Univercity, Faculty of Medicine, Elazig, Turkey
halifeoglu@hotmail.com

Abstract
In this work, it is aimed to research the applicability of Leptin and Preptin tests who are known to have an effect on insulin and glucose metabolism on Gestational Diabetes Mellitus (GDM) diagnosed pregnant patients, the insulin resistance, the parameters related to it and their correlation. Our work consists of volunteers who have filled out the application form. Among those who have volunteered by filling the participation form and became our test subjects, 41 of them form the healthy pregnant control group while 38 of them forms the GDM diagnosed group. From the blood samples taken while the test subject has an empty stomach for routine pregnancy tests, 4mL of the samples has been taken into test tubes with aprotinin and their preptin and leptin parameters have been studied. In our work, for the GDM and control groups, age, BMI and the family's diabetical history factors have been found to be significant according to the $p<0.05$ significance level. Leptin parameters have been found to be significant according to the $p<0.05$ significance level while preptin parameters has been found to be in significant $p>0.05$. Leptin parameter has been found to be significant in GDM diagnosed pregnant patients according to the $p<0.05$ significance level while preptin parameters has been found to be in significant.

Keywords: Gestasyonel Diabetes Mellitus, Preptin, Leptin.

1. Introduction

Diabetes, which is a very important problem all over the world, is also a serious health issue due to the frequency of detection and the problems it creates (Cho et al., 2018). "Gestational Diabetes" is defined as the "Glucose Tolerance Disorder" that occurs during first pregnancy. It is seen in approximately 7% of all pregnancies (Beksaç et al., 2001; Bakanlığı T.S., 2014). The GDM is physiopathologically similar to a Type 2 diabetes. Increasing insulin resistance and impaired β-cell function play an important role in GDM physiopathology. This is due to the effects of changing hormones during pregnancy (WHO, 2004; Green et al., 1996). In the second half of the pregnancy, the increasing release of hormones that cause diabetogenic effect results in increased fatty acids and glycerol levels in the maternal plasma (ADA, 2014; Management of Diabetes Mellitus Update Working Group, 2010). In the third trimester, which is the last stage of pregnancy, the need for insulin increases. The insulin resistance develops due to the increasing insulin insensitivity in tissues (Stumvoll et al., 2005; Yanıkkerem and Mutlu, 2012).

Insulin is a polipeptide structured hormone which is produced by the β-cells of Langerhans islets, which are in the form of clustered cells in the exocrine part of the pancreas (Pamela et al., 2005). Insulin resistance is defined as a dysregulated response to exogenous or endogenous insulin. This definition also encompasses the metabolic effects of insulin as a biological response to insulin (Gildal Altunoglu, 2012). The insulin molecule and C-peptide are released in equal amounts from the β cells of the langerhans islets of the pancreas and stored together. Although released in equal amounts, the half-life of C-peptide and insulin are not equal and the duration of C-peptide half-life is longer than that of insulin. In addition, while insulin is broken down in the liver the C-peptide is broken down by the kidneys. It takes a longer time for the C-peptide to be broken down because it is done in the kidneys. Because of the negligibility of the liver metabolism and the fact that it reflects the endogen insulin level, C-peptide measurement is a better indicator of β-cell function than insulin measurement (Metzger et al., 2007; Alberti et al., 2006; Catalano et al., 1991).

Leptin is a hormone discovered in 1994 by Friedman that weighs 16-kDa and containis 167 amino acids (Ray et al., 2001; Yogev and Visser, 2009; Cypryk et al., 2004). It is synthesized in the main body fat. It is also synthesized in placenta and fetus in small amounts (De Muylder, 1984). The primary purpose of leptin is to prevent the brain from developing obesity by regulating food intake and energy metabolism by having a negative effect (feedback) on the hypothalamus (Di Cianni et al., 2007; Kim et al., 2002). Leptin concentration is even higher in pregnancy. It peaks at the second trimester and remains at high concentrations till birth. It is known to decrease just before birth (Catalano et al., 2003).

Preptin is a hormone detected in experiments on mice in 2001. Prepin contains 34 aminoacids and is released from pancreatic β cells together with insulin. A pro-insulin alike preptin is a derivative of Pro-IGF2 and it increases insulin secration. Insulin-like factor 2 (IGF-2) is produced from Pro-IGF2. Pro-IGF2 is also the precursor to preptin (Buchanan et al., 2001; Mecacci et al., 2003).

2. Material and Methods

The individuals in our study were composed of 2 groups, 41 healthy pregnant women (as the control group) and 38 pregnant women with GDM who applied to the Elazığ Education and Research Hospital - Birth Policlinic between August 2014 and January 2015. This study was initiated with the approval of the Ethics Committee of the Faculty of Medicine of Fırat University (date 03.03.2013, meeting #8, verdict #10). The demographic information of the individuals participating in our work was recorded by filling in the Participant / Patient Demographic and Medical Information Form. Patients who have Type 1 and Type 2 diabetes, had multiple pregnancies, have kidney and liver diseases, are under the age of 18 and pregnant women using drugs that may have an effect on insulin metabolism were not included in the study.

Blood samples were taken after 8-12 hours of fasting from both control group and the patient group and these samples were stored in vials with gels, aprotinin and K3-EDTA to separate serum and plasma. On the blood serum, fasted blood glucose, triglyceride, HDL cholestrol, insulin and C-Peptide parameters, on K3-EDTA vials glycolated hemoglobin (HbA1c) and on the aprotinated vials isepreptin veleptin were studied The Body Mass Index (BMI) is calculated by dividing the weight of the participants by the square meter of their height (kg/m²).

HOMA-IR was calculated using the formula.

HOMA-IR= Fasted Insulin (μU / mL) X Fasted Glucose (mg/dL)/405. According to this formula, insulin resistance was evaluated as positive if the results were ≥2.5 and above.

3. Results

The age average was 26.8 ± 4.9 in the control group and 32.7 ± 6.0 in the GDM group. A statistically significant age-average difference was found when compared with control and GDM groups. ($p<0.05$).

The average body mass index (BMI) was found to be significantly increased compared to the control group (25.9 ± 3.8) and in the GDM (28.7 ± 4.7) group ($p <0.05$).

When inspected based on their family history of GDM, a significant difference was found in our study. ($p<0.05$).

DM is a genetically transmitted disease. A significant relation was found between the DM groups whose families had a DM history ($p<0.05$). While there was no significant relation in between in terms of preptin levels when the GDM group was compared to the control group ($p>0.05$); there was a significant difference between leptin levels ($p<0.05$) (Table 1).

There was a significant positive correlation between leptin and fasted glucose ($r = 0.326$; $p= 0.046$).

A statistically significant difference was found between the GDM pregnancies who has a negative and a positive insulin resistance in terms of their leptin, Insulin and C-Peptide parameters as a result of an analysis between leptin, preptin, insulin, C-Peptide ($p<0.05$).

There was no statistically significant difference between leptin and preptin (p>0.005).
Based on their the body mass index (BMI) of GDM pregnancies, in their preptin levels, there was no statistically significant difference among normal overweight, overweight and obese subjects (p>0.05). A statistically significant difference was found at leptin level (p<0.05). This difference was found to be due to the fact that leptin levels in normal overweight pregnancies were lower than overweight and obese pregnancies.

4. Discussion

The probability of having GDM was found to be statistically significant as the ages of the participants increased (p<0.05). In the thesis study conducted by Sefika Aydın Selcuk, the probability of having GDM was found to be significant in older patients. (p<0.05) (Alanbay et al., 2011).
Blood samples were taken from the pregnancies with a time difference of approximately ± 1.5 weeks, who were within approximately 25.5 weeks of gestation. As a result of the analysis, the likelihood of GDM was increased with increasing VKI (p<0.05). Whether the cause of this increase is due to progressing gestational week or fetal development is not known.
The likelihood of having GDM in those with family history of GDM was found to be statistically significant (p<0.05). No information was found in the literature whether having a GDM diagnosis in the family has a hereditary GDM risk that would affect pregnancies.
Although there is a known GDM risk factor for pregnancies that have GDM diagnoses in previous pregnancies and for those who have a family history of DM, there is no answer in the literature about whether pregnancies that have GDM diagnosis in their family are at risk for GDM or not.
In our study, the physiopathological effects of GDM were investigated by determining the levels of leptin and Preptin hormones that are known to have effects on insulin and glucose metabolism in healthy and fasted individuals with GDM.
In our study, leptin levels were found to be statistically significantly (p<0.05) higher in the GDM group than in the healthy pregnancies.
In other studies; Vitorates and his colleagues found that leptin levels were higher in the GDM cases compared to the healthy ones (Vitoratos et al., 2001). Ateybo and his colleagues also reported that leptin levels were high in the GDM group (Ategbo et al., 2006).
Alterations in fat deposits and glucose metabolism in pregnancy are linked to an increase in leptin levels (Schubring et al., 1998). Insulin resistance in the second trimester of pregnancy suggests that the cause of resistance and hyperinsulinemia is due to an increase in leptin levels (Laivuori et al., 2000). It has not yet been determined whether the changes in leptin levels in the GDM patients are causal or not (Qiu et al., 2004).
In our study, there was no statistically significant difference in the preptin levels in the GDM group compared to the healthy pregnancies in the control group (p>0.05). In other studies;
It is estimated that preptin-derived findings are a physiological enhancer of glucose-induced insulin release. Preptin was higher in Type II diabetes patients compared to the healthy control group (Yang et al., 2009).
Aslan and his colleagues reported that maternal serum and cord blood preptin levels were higher in women with GDM than in healthy pregnancies (Aslan et al., 2011).
In a study conducted by Aydin and colleagues, women with GDM were reported to have higher plasma and colostrum preptin concentrations than healthy breastfeeding women (Aydin et al., 2013).
In the thesis study performed by Baykuş, there was no statistically significant difference between the plasma preptin levels in control group and the GDM group (Baykuş, 2010).
While leptin levels were found to be statistically significant in GDM cases (p <0.05), there was no statistically significant difference in preptin levels in GDM cases (p> 0.05).
Based on insulin resistance, leptin levels were found to be statistically significant in GDM cases (p <0.05) while it was not statistically significant in healthy gestations (p> 0.05).
The leptin levels we obtained in our study were found to be statistically significantly higher in GDM cases compared to healthy pregnancies. Leptin levels, in GDM cases with positive insulin resistance were found to be statistically significantly higher than those in non-insulin resistant GDM cases, while there was no statistically significant difference between leptin levels in insulin resistant and noninsulin resistant cases in healthy gestations. These results suggest that the leptin parameter has a statistically significant relation between GDM-positive gestations and GDM gestations with positive insulin resistance. This made us think that leptin parameter may be used in the diagnosis and screening of GDM and should be supported by studying more samples.
Regarding preptin, there was no statistically significant difference between GDM and healthy pregnancies. There was no statistically significant difference among GDM cases with positive insulin

resistance, healthy gestations and non-insulin resistant GDM cases. While there is not enough literature on this subject, contradictory results have been found in those limited studies. There is a need for more studies on this topic.

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