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The Role of Maternal Serum Adiponectin Levels in Screening and Diagnosis of Gestational Diabetes Mellitus

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Abstract

Objective: To evaluate the role of maternal serum adiponectin levels in screening and diagnosis of gestational diabetes mellitus (GDM).

Methods: Two hundred and seventy four pregnant patients which were followed-up in our clinic were enrolled in our study. Between the 24th and 28th gestational weeks we performed single step (75 g) OGTT to 125 pregnant patients and two steps (50/100 g) OGTT to 149 pregnant patients. Serum adiponectin levels were measured in all pregnant women. The results of the GDM group and the control group were compared.

Results: In the two steps OGTT we detected 31 (20,8%) GDM cases out of 149 patients. In the single step OGTT we detected 27 (21,6%) GDM cases out of 125 patients (p >0.05). GDM was detected in 58 of 274 pregnant women (21,1%). We have detected a statistical significance between the maternal serum adiponectin levels of patients with GDM and healthy patients between 24-28 gestational weeks. The mean maternal adiponectin level was detected as 12.1±5.6 µg/ml in patients with GDM whereas in healthy patients mean maternal adiponectin level was 17,1±6.6 µg/ml [0.70, Confidence interval (CI) %95, 0,62-0,78 p:0,0001].

Conclusion: Adiponectin levels are significantly lower in patients with GDM when compared with healthy pregnant women.

Keywords: Gestational diabetes mellitus, adiponectin, oral glucose tolerance test.

Gestasyonel diabetes mellitus tanı ve taramasında maternal serum adiponektinin yeri

Amaç: Gestasyonel diabetes mellitus (GDM) tanı ve taramasında maternal serum adiponektin seviyesinin öneminin irdelenmesi.

Yöntem: Çalışmamıza kliniğimizde takipleri yapılan 274 gebe dahil edildi. 24-28 gebelik haftasında 125 gebeye tek aşamalı 75 gr OGTT ve 149 gebeye de iki aşamalı gebelik diyabeti tarama testi uygulandı. Tüm gebelerde aynı zamanda serum adiponektin düzeylerine bakıldı. Uygulanan testler sonucu GDM tanısı koyulan gebelerle kontrol grubunun verileri karşılaştırıldı.

Bulgular: 149 hastadan oluşan iki aşamalı test grubunun 31'inde (%20,8) GDM tespit edilirken, 125 gebeden oluşan tek aşamalı test grubunun 27'sinde (%21,6) GDM tespit edildi (p >0.05). Toplam 274 hastanın 58'inde (%21,1) GDM olduğu görüldü. Yapılan testler sonucunda GDM tespit edilen ve edilmeyen gebeler arasında 24-28. GH arasında bakılan serum adiponektin düzeylerinde istatistiksel olarak ileri derecede anlamlı fark saptandı. GDM'li gebelerin ortalama adiponektin düzeyi 12.1±5.6 µg/ml iken, GDM olmayanların ortalama adiponektin düzeyi 17,1±6.6 µg/ml olarak bulundu [0.70, Confidence interval (CI) %95, 0,62-0,78 p:0,0001].

Sonuç: GDM'li gebelerde serum adiponektin düzeyleri anlamlı olarak sağlıklı gebelerden düşük bulunmuştur.

Anahtar Sözcükler: Gestasyonel diabetes mellitus, adiponektin, oral glukoz tolerans testi.

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Introduction

Gestational diabetes mellitus (GDM) is defined as a carbonhydrate intolerance which either begins or is diagnosed during pregnancy.[1] Another definition is hyperglycemia seen after the 20th gestational week. GDM is seen approximately in 3-5% of all pregnancies, although this ratio may change between 1-14% depending on the population or the test used.[2,3,4]

It's still controversial how to screen and diagnose GDM. Formerly it has been suggested to screen all pregnant patients, then screening high risk patients only or performing the diagnostic test directly in high risk patients have been found to be more appropriate. But it's reported that only 50% of GDM cases can be diagnosed by screening high risk patients.[5]

Today, we use 50 g oral glucose tolerance test (OGTT) for screening and 100 g OGTT for diagnosis of GDM.[2,3,6] Recently, considering the cost effectiveness, 75 g OGTT was proposed as a screening and diagnostic test performed in a single step. World Health Organisation (WHO) recommends 2 hours 75 g OGTT and this test is accepted in some European countries. Two-steps test is used in United States.[2,3] See table 1 for the diagnostic criteria used in GDM.

Adiponectin is secreted from the adipose tissue and is the most abundant adipokine in circulation and it plays a key role in metabolic syndrome.[9] The plasma level is 2-30 μg/ml. Adiponectin has anti-inflammatory, anti-atherosclerotic and anti-diabetogenic effects. Insulin is the main regulator of its secretion from the adipocytes. The most well-known effect of adiponectin is regulation of the insulin sensitivity. Adiponectin has globular and collagen components. After the secretion it's transformed to trimer form, and finally it becomes a polymer which is composed of 4-6 trimers. Both trimer and polymer forms are found in the circulation, whereas monomer form is not. The globular part of adiponectin is similar to TNF-α, except the sequence. Both globular and complete forms of adiponectin is accepted to be biologically active but controversies still continue. Leukocyte elastase separates the globular structure from the molecule. This part may be retrimerized but it cannot polimerize back. Therefore, the active leukocytes are thought to regulate the bioactivity of adiponectin by an unknown mechanism. Although the adipocytes are the main source of adiponectin, there is no increase in adiponectin as well as leptin levels in obese patients. In contrast, adiponectin levels are found to be decreased in obese patients and increased in patients with anorexia nervosa. Adiponectin levels are significantly decreased in patients with diabetes mellitus type 2. The relationship between insulin sensitivity status and adiponectin levels is not clear. However in obese patients, TNF-a secreted from white adipose tissue (WAT) is found to supress production and secretion of adiponectin.[10]

On the other hand, adiponectin decreases the production and activity of TNF-α. The TNF-a originating from macrophages have been supressed by adiponectin in rats induced by endotoxin. Reduction of IL-6, induction of IL-10 and antagonization of IL-1 receptors are other anti-inflammatory effects of adiponectin. These effects of adiponectin can be explained by NF-kB inhibition. It binds to collagen I, III and V but spares II and IV. It interferes with the opposition of endothelial adhesion molecules and VCAM-1, ICAM-1 and E-selectin. Adiponectin significantly reduces the activities

Table 1. The diagnostic criteria used in GDM.[7,8]

Organization	(OGTT)	Modified criteria	Plasma glucose levels (mg/dl) Fasting	1. hour	2. hour	3. hour
ADA	100 g	Carpenter and Coustan	≥95	≥180	≥155	≥140
	75 g		≥95	≥180	≥155	-
ACOG	100 g	NDDG or Carpenter and Coustan	≥105	≥190	≥165	≥145
WHO	75 g		≥126	-	≥140	-

Two or more values above treshold are required for ACOG or ADA criteria. One or more value(s) above treshold is/are required for WHO criteria.[6,10]

DM: Diabetes Mellitus; **GDM:** Gestational Diabetes Mellitus; **ADA:** American Diabetes Association; **ACOG:** American College of Obstetricians and Gynecologists; **WHO:** World Health Organization; **OGTT:** Oral Glucose Tolerance Test; **NDDG:** National Diabetes Data Group

of ICAM-1 and VCAM-1. Besides adiponectin regulates activities of resistin and visfatin which are secreted from the WAT and effects on insulin.[11]

The collagen part of the adiponectin is similar to the complement factor C1q, surfactant protein A, surfactant protein D and mannose binding protein. It can bind endotoxin with high affinity which is a lipopolysaccharide (LPS). Therefore the role of adiponectin in endotoxemia is attributed to its interaction with LPS rather than its anti-inflammatory effect.

Methods

Two hundred and seventy four pregnant patients admitted to Cerrahpasa Medical Faculty Department of Obstetrics and Gynecology pregnancy outpatient clinic and perinatology clinic, March 2005 and February 2006 inclusive were enrolled. Our study is designed as a descriptive study.

The gestational ages were calculated according to the last menstrual period (LMP) and early pregnancy ultrasound measurements. Age, height, weight, body mass index (BMI), personal history, family history, gravidity, parity and OGTT test results were recorded.

10 cc of venous blood samples from all patients in the study group were collected in dry tubes before performing the diabetes screening tests between 24-28 GWs. Serum parts were separated and preserved in -80°C till target patient population is reached to be evaluated at once. Serum adiponectin levels were measured.

GDM screening and diagnosis tests were performed between 24-28 GWs in all 274 patients. Single step 2 hours 75 g OGTT was performed in 125 patients. The test results were interpreted according to the ADA criteria (?2 values above treshold, fasting glucose levels: 95 mg/dl, 1 hour: 180 mg/dl, 2 hours 155 mg/dl). Two steps 50 g OGTT was performed in 149 patients. The patients with 1 hour blood glucose levels of ?140 mg/dl were accepted as screening test positive according to ADA and ACOG criteria. The diagnostic test was performed in screening test positive patients after a 3 days standard diet (at least 250 g of daily carbonhydrate). After a fasting period of 12-16 hours, the blood samples were collected at 8 am and then in the 1st, 2nd and 3rd hours.

Carpenter and Coustan criteria were considered in the interpretation of 100 g OGTT and ?2 levels above treshold (fasting: 95 mg/dl, 1 hour 180 mg/dl, 2 hour 155 mg/dl, 3 hour 155 mg/dl) were accepted to have GDM.

Serum adiponectin levels were measured by a kit which is based on ELISA (Human adiponectin assaypro catalog no: EA2500-1). Adiponectin levels were recorded in microgram/ml (μg/ml).

Statistical Package for Social Sciences (SPSS Release 11.5, SPSS inc., Chicago, IL, USA) was used during statistical calculations. Student's t test was used for parametric variables. 0.05 was accepted as treshold for statistical significance. Sensitivity, specificity and area under curve values were calculated ROC (Receiver operating characteristic) curves.

Results

Two hundred and seventy four patients were included into the study. GDM was observed in 58 (21.1%) patients and not observed in 216 patients. Two steps and single step tests were performed in 149 and 125 women, respectively. These two groups were similar in respect to age, gravidity, parity, maternal weight and BMI, gestational week at screening.

Among 149 patients who underwent two steps OGTT, GDM was found in 31 (20.8%) patients. Among 125 patients who underwent single step OGTT, GDM was found in 27 (21.6%) patients. GDM was detected in 58 (21.1%) of 274 patients.

The serum adiponectin levels of patients with GDM and without GDM were significantly different. Mean serum adiponectin levels were 12.1±5.6 μg/ml and 17.1±6.6 μg/ml in patients with GDM and without GDM, respectively. (p:0.0001) (Table 2, Graphic 1).

Area under curve (AUC) was calculated from the ROC curve drown which was based on the adiponectin levels of the OGTT results of 274 women and found to be 0.706. [0.70, Confidence interval (CI) 95%, 0.62-0.78 p:0.0001] The treshold for adiponectin was set as 10.4 μg/ml. Sensitivity, specificity and PPV are found to be 86%, 50% and 63.2% respectively.

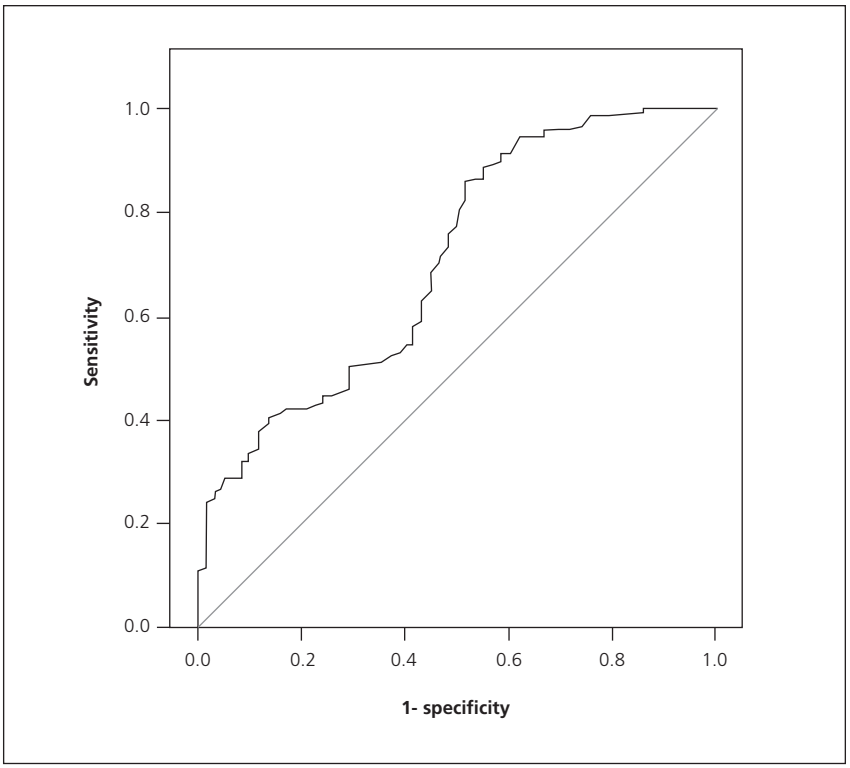
If cut-off value of adiponectin is taken as 5,6 μg/ml, sensitivity is 100% and specificity is 14% in general means. If cut-off value is taken as 27μg/ml, sensitivity is 11% and specificity is 100% (Table 3).

There were 38 women which were 50 gr OGTT positive and 100 gr OGTT negative. The mean adiponectin level of this group were compared with non-GDM group and there was no significant difference between two groups (p>0.05).

Table 2. Serum adiponectin levels of normal pregnant women and women with GDM.

	Normal	GDM	p
Number of patients (n)	216	58	
Adiponectin (microg/ml)	16.6±6.6	12.4±5.7	**0.0001**
HbA1c	4.86±0.54	5.39±0.52	**0.0001**

p< 0,05 significant
GDM: gestational diabetes mellitus.



Graphic 1. ROC curve for adiponectin levels in women with GDM.

Discussion

It's controversial not only whether screening for GDM in all patients or only in the risk groups, and also the screening method of choice. Screening for GDM in most population groups may seem unnecessary regarding that its prevalence is below 5%, but if the 4 folds increase in perinatal mortality is considered it's a reasonable effort.[12] Although the average prevalence of GDM is 3-5%, it may vary between 1-14% depending on the method used.[13,14]

GDM incidence in Turkey is reported as 1.23-6,6%. In our study, GDM incidence was found as 21.1% and this high ratio is attributed to the fact that our clinic is a tertiary (reference) center.

Table 3. Sensitivity and specificity rates in various adiponectin levels in women with GDM.

Adiponectin level	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
5.6 µg/ml	100	14	54	100
10.4 µg/ml	86	50	63	92
15 µg/ml	54	59	25	82
20 µg/ml	28	48	12	71
27 µg/ml	11	100	100	80

GDM: Gestational diabetes mellitus, **PPV:** positive predictive value, **NPV:** negative predictive value.

In our study there was no statistical significance between 75 g and 50/100 g OGTTs in detecting GDM (21.6% vs %20,8).

The most significant fetal complication in GDM was macrosomia. Sereday et al.[15] have chosen macrosomia as reference complication and compared sensitivity and specificity levels of 50 g, 75 g and 100 g OGTTs, and they found that the highest sensitivity was observed in 50 g whereas the highest specificity was observed in 75 g OGTT followed by 100 g OGTT. It has also been suggested that considering that some patients may miss the second step, 75 g OGTT is more reliable than 50/100 g OGTT.[15]

Adiponectin (Acrp 30, AdipoQ, apM-1 or GBP28) is a protein hormone which plays a role in a series of metabolic reactions including glucose regulation and fatty acid catabolism. Adiponectin is secreted into the blood mainly from adipose tissue. The blood levels of adiponectin are inversely proportional with the amount of fat in the body.

Maternal serum adiponectin levels are not correlated with maternal weight and BMI. Total liquid amount is increased during pregnancy and that's why body weight and BMI are weak parameters to assess adiposity in early postpartum period. Maternal serum adiponectin concentrations do not correlate with serum glucose and insulin levels. However, the negative correlation between the maternal serum adiponectin levels and maternal fasting glucose/insulin ratio may indicate that adiponectin has a role in glucose regulation. It's possible that adiponectin levels increase if effective glucose management is maintained and this may make adiponectin a good marker of insulin sensitivity.

It's not clearly stated so far that changes in maternal adiponectin levels in GDM are the cause or the result of GDM. In our study mean maternal adiponectin levels of patients with GDM are found as 12.4 μg/ml compared to 16.6 μg/ml in women without GDM. (p: 0.0001)

If the treshold for adiponectin was set as 10.4 μg/ml, sensitivity, specificity and PPV were found to be 86%, 50% and 63.2% respectively.

If cut-off value of adiponectin is taken as 5.6 μg/ml, sensitivity is 100% and specificity is 14% in general means. If cut-off value is taken as 27 μg/ml, sensitivity is 11% and specificity is 100%. Therefore depending on the results we gathered from our study, we may conclude that GDM can be diagnosed in all patients with an adiponectin value of ≤5.6 μg/ml and GDM can be ruled out in all patients with an adiponectin value of ?27 μg/ml. In our study, there are 8 patients whose adiponectin level is ≤5.6 μg/ml and 25 patients whose adiponectin level is ?27 μg/ml.

We may also make a qualitative, instead of quantitative, measurement, in other words test results may be given as positive or negative instead of numeric values. In this case, if cut-off value is taken as 10.4 μg/ml as we did in our study, considering that the sensitivity is 86%, 49 (18.2% of all) patients would have been diagnosed as GDM and would be spared from OGTT and 9 (4.2% of all) would be missed even if they have been GDM.

Finally, we must emphasize that adiponectin is too expensive and obviously cannot be used instead of OGTT.

Conclucion

Serum adiponectin levels are significantly lower in patients with GDM when compared with healthy pregnant women, supporting hitherto publications. We think that serum adiponectin levels can be used as a marker in screening and diagnosis of GDM.

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