Original Article

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Does Glucagon-Like Peptide-1 Have a Role in the Etiopathogenesis of Gestational Diabetes?

Glukagon Benzeri Peptit-1 Gestasyonel Diyabet Etiyopatogenezinde Bir Role Sahip mi?

Mustafa Demirpençe, Nur Demirpençe*, Pelin Tütüncüoğlu, Gonca Örük, Nesil Atalay, Ahmet Görgel, Hamiyet Yılmaz**, Banu Arslan***, Mitat Bahçeci

İzmir Katip Çelebi University Atatürk Training and Research Hospital, Clinic of Endocrinology and Metabolism, İzmir, Turkey
*Dokuz Eylül University Faculty of Medicine, Department of Public Health, İzmir, Turkey
**Tepecik Training and Research Hospital, Clinic of Endocrinology and Metabolism, İzmir, Turkey
***Atatürk Training and Research Hospital, Clinic of Clinical Biochemistry, İzmir, Turkey

Abstract

Purpose: The aim of this study was to evaluate glucagon-like peptide-1 (GLP-1) levels, lipid parameters, thyroid-stimulating hormone (TSH), c peptide and glycated hemoglobin (A1C) values in pregnant women at high-risk for gestational diabetes mellitus (GDM).
Material and Method: In this cross-sectional study, we included pregnant women at high-risk for GDM who attended the endocrinology and metabolic diseases outpatient clinics at İzmir Katip Çelebi University Atatürk Training and Research Hospital between January 2013 and April 2013. Twenty pregnant women with GDM and eleven without GDM participated in the study. The dependent variable in the study was GDM that was evaluated by 75 mg oral glucose tolerance test (OGTT). Independent variables were the levels of glucose, A1C, insulin, c-peptide, GLP-1, TSH, and lipid parameters, all evaluated in fasting blood samples. Besides, glucose, insulin, c-peptide, GLP-1 levels during OGTT were also evaluated in blood samples collected at 60 and 120 minutes.
Results: While fasting insulin levels were statistically significantly higher among women with GDM, there was no statistically significant difference in the levels at 60 and 120 minutes between the two groups. There was no significant difference in fasting c-peptide levels and c-peptide levels at 60 minutes during OGTT between the two groups, however, c-peptide levels at 120 minutes were higher in women with GDM. The women with GDM was found to have lower fasting GLP-1 levels than women without GDM. Although it was not significant, GLP-1 levels at 60 and 120 minutes were also lower among women with GDM.
Discussion: A decrease in GLP-1 levels may have a role in the etiopathogenesis of GDM and type 2 diabetes mellitus.
Keywords: Gestational diabetes, glucagon-like peptide 1, type 2 diabetes mellitus

Öz

Amaç: Bu çalışmanın amacı gestasyonel diyabet mellitus (GDM) açısından yüksek riskli gebelerde glukagon benzeri peptit (GLP-1) seviyelerini, lipit parametrelerini, tiroid stimüle edici hormon (TSH), c peptid, insülin ve glikolize hemoglobin (A1C) düzeylerini değerlendirmektir.
Gereç ve Yöntem: Bu kesitsel çalışmadaki olguları Ocak-Nisan 2013 tarihlerinde İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi Endokrinoloji ve Metabolizma Hastalıkları Polikliniği'ne başvuran GDM riski yüksek olan gebeler oluşturmaktadır. Çalışmaya GDM olan 20 ve GDM olmayan 11 gebe kabul edilmiştir. Çalışmanın bağımlı değişkeni GDM'ye sahip olmaktır ve 75 mg oral glukoz tolerans testi (OGTT) ile değerlendirilmiştir. Bağımsız değişkenler glukoz, A1C, insülin, c-peptit, GLP-1, lipit parametreleri ve tiroid stimule edici hormon düzeyleridir. Bağımsız değişkenlerin tümü açlık kan örneğinde çalışılırken insülin, c-peptit ve GLP-1 düzeyleri ayrıca oral glukoz yükleme testinin 60. ve 120. dakikalarında da değerlendirilmiştir.
Bulgular: Açlık insülin düzeyleri GDM'li gebelerde daha yüksek iken OGTT'nin 60. ve 120. dakikalarında farklılık gözlenmedi. GDM'si olan ve olmayan gebelerde açlık ve 60. dakika c-peptit düzeyleri arasında fark gözlenmemesine karşın 120. dakika değeri GDM'si olan kadınlarda daha yüksekti. Lipid düzeyleri açısından GDM olan ve olmayan gebeler arasında farklılık izlenmedi. A1C düzeyleri GDM'li olanlarda daha düşük saptandı. Açlık GLP-1 düzeyleri GDM'li kadınlarda anlamlı olarak daha düşük saptandı. Bu düşüklük 60. ve 120. dakikalarda da devam etmesine karşın istatistiksel olarak anlamlı değildi.
Tartışma: GLP-1 seviyelerindeki azalma tip 2 diyabette olduğu gibi GDM etiyopatogenezinde de rol oynuyor olabilir.
Anahtar kelimeler: Gestasyonel diyabet, glukagon benzeri peptit-1, tip 2 diyabet

Address for Correspondence: Mustafa Demirpençe MD, Atatürk Training and Research Hospital, Clinic of Endocrinology and Metabolism, İzmir, Turkey
Phone: +90 505 525 23 37 E-mail: demirpencemustafa@gmail.com **Received:** 17/03/2015 **Accepted:** 15/01/2016

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy (1,2). Women with known diabetes mellitus before conception are not classified as having GDM (3). The prevalence of GDM has increased over the past decades in parallel with the increase in the rates of obesity and type 2 diabetes mellitus (T2D), and this trend is expected to continue. Although it has been reported that GDM affects at least 7% of pregnancies in the United States (3), depending on the diagnostic criteria used and the population screened, the prevalence of GDM ranges between 1.1% and 25.5 (4). Women with GDM are at increased risk for urinary tract infections, pyelonephritis, asymptomatic bacteriuria, preeclampsia (2), and cesarean delivery (5). Fetal risks of poor glucose control include stillbirths, macrosomia (2), birth trauma and neonatal hypoglycemia (5). Of having both high prevalence and important complications, GDM is one of the major metabolic disorders during pregnancy. GDM usually resolve postpartum, but commonly recur in subsequent pregnancies (4) and causes an increased risk for T2D later in life (5).

In the pathogenesis of GDM and T2D, beta cells responsible for insulin secretion are destroyed, thus, insulin secretion diminishes, glucagon secretion increases and insulin resistance occurs. In T2D, glucagon-like peptide-1 (GLP-1) levels also decrease.

GLP-1 is an incretin hormone that is released rapidly into the circulation after oral nutrient ingestion (6). GLP-1 stimulates insulin secretion, inhibits glucagon secretion and gastric emptying (7). It induces weight loss by reducing food intake (8,9). Some studies have indicated that GLP-1 might inhibit beta cell apoptosis and stimulate beta cell proliferation (10).

As they decrease in T2D (11), it is uncertain how GLP-1 levels change in GDM. While one study has shown that GLP-1 levels decrease (12), another has shown that GLP-1 levels remain the same in GDM (13).

In our study, we have evaluated GLP-1 secretion in response to oral glucose load in pregnant women at a high risk for GDM.

The aims of this study were to evaluate

1. How GLP-1 levels change in pregnant women at a high risk for GDM.
2. How lipid parameters, thyroid-stimulating hormone (TSH) and glycosylated hemoglobin (A1C) levels change in GDM.

Materials and Methods

Study Population

This cross-sectional study was conducted on pregnant women at a high risk for GDM who attended İzmir Katip Çelebi University Atatürk Training and Research Hospital Endocrinology and Metabolic Diseases outpatient clinics between January 2013 and April 2013. Risk factors for GDM were determined as advanced maternal age (above 37), high pregnancy weight (above 80 kg or body mass index above 28 kg/m^2), polycystic ovarian syndrome, history of previous macrosomia, polyhydramnios, unexplained stillbirths, GDM history, family history of T2D in first-degree relatives, being a member of an ethnic group at an increased risk for the development of T2D (including Mediterraneans) (2). Thirty-one patients having one of these risk factors were randomly selected. Patients having T2D or impaired glucose intolerance before pregnancy were excluded from the study. The dependent variable in the study was GDM diagnosed by 75-gram oral glucose tolerance test (OGTT). The diagnosis of GDM was established according to the International Association of the Diabetes in Pregnancy Study Groups (IADPSG) criteria. Subjects meeting at least two criteria-fasting blood glucose ≥95 mg/dL, a blood glucose level of ≥180 mg/dL and ≥153 mg/dL during OGTT at 60 minutes and 120 minutes, respectively-were diagnosed as having GDM. Independent variables of the study were the levels of glucose, A1C, insulin, c-peptide, GLP-1, TSH, lipid parameters [total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)]. All of them were evaluated in fasting blood samples. Besides, glucose, insulin, c-peptide, and GLP-1 levels during OGTT were also evaluated in blood samples collected at 60 and 120 minutes.

This study was approved by the Institutional Review Board of İzmir Atatürk Training and Research Hospital, Department of Endocrinology and followed the Declaration of Helsinki ethical principles for medical research involving human subjects. The patients were informed verbally about the study and written informed consent was obtained from all participants.

Biochemical Analysis

Glucose concentrations were measured in blood samples by the hexokinase method, TG, LDL and HDL levels (mg/dL) were measured by enzymatic methods using commercial kits and a Abbott Architect C8000 auto-analyzer (Abbott Laboratories, USA). Total cholesterol (mg/dL), TSH (uIU/mL), insulin (mlU/mL) and c-peptide (mlU/mL) concentrations were measured by the electrochemiluminescence method with commercial kits by Siemens ACS CENTAUR auto analyzer (Siemens Corporation, USA). A1C analysis was performed by affinity chromatography HPLC on a Primus Ultra 2 analyzer (Primus Corporation, Kansas City, Kansas, USA). GLP-1 was determined using commercial kits by Labotect microelisa device (YK160 GLP-1 EIA; Yanaihara Inst. Inc., Awakura, Japan).

Statistical Analysis

Data analysis was performed by SPSS 15.0 package programme. Continuous variables were presented as mean, median and standard deviation, and minimum-maximum values. The Shapiro-Wilk test was performed to determine the distribution ($p<0.05$). The Mann-Whitney U test was used to evaluate the statistical significance between two different medians. A p value of less than 0.05 was considered statistically significant. The total sample size of 31 gives 80% of power with 95% of confidence level and effect size as 1.1 for the Mann-Whitney U test.

Results

After performing 75-gram OGTT in 31 pregnant women at a high risk for GDM, 64.5% (20) of them were diagnosed with GDM.

There was no statistically significant difference in fasting blood glucose levels between women with or without GDM ($p=0.051$). The women with GDM had statistically higher glucose levels at 60

and 120 minutes during OGTT than women without GDM (p=0.002 and p=0.017, respectively) (Table 1).

The median age of women with GDM and without GDM was 31 years (19-41) and 28 years (20-35), respectively (p=0.046). There was no difference in gestational age between women with GDM and without GDM (p=0.765) (Table 2).

There was no difference in fasting LDL, HDL, TG, and total cholesterol levels between women with or without GDM (p=0.163, p=0.949, p=0.157, and p=0.190, respectively) (Table 3).

TSH levels were similar between the two groups (p=0.363). The median level of A1C was 5.7 (5.1-6.3) in women with GDM and 5.5 (5.1-6.3) in women without GDM (p=0.039). While fasting insulin levels were statistically significantly higher in women with GDM than in those without GDM (p=0.024), there was no statistically significant difference in insulin levels at 60 and 120 minutes during OGTT between the two groups (p=0.151 and p=0.237, respectively). There was no significant difference between the two groups in fasting c-peptide levels and c-peptide levels at 60

Table 1. Fasting and post oral glucose tolerance test glucose levels of women with and without gestational diabetes mellitus

Glucose	GDM+(n=20)		GDM-(n=11)		p*
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	
Fasting	88.6 (11.4)	86.0 (74.0-112.0)	80.5 (7.3)	81.0 (72.0-93.0)	0.051
60. minute	177.5 (33.3)	184.0 (67.0-240.0)	147.8 (23.8)	157.0 (110.0-179.0)	0.002
120. minute	147.0 (36.5)	159.0 (81.0-199.0)	113.3 (21.4)	108.0 (87.0-146.0)	0.017

*Mann Whitney U test was performed, SD: Standard deviation, GDM: Gestational diabetes mellitus

Table 2. Age and pregnancy period properties of women with and without gestational diabetes mellitus

	GDM+(n=20)		GDM-(n=11)		p*
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	
Age (year)	31.4 (5.4)	31.0 (19.0-41.0)	27.8 (3.8)	28.0 (20.0-35.0)	0.046
Pregnancy period (week)	25.1 (7.1)	27.0 (10.0-32.0)	26.8 (4.8)	25.5 (18.0-32.0)	0.765

*Mann Whitney U test was performed, SD: Standard deviation, GDM: Gestational diabetes mellitus

Table 3. Properties of hormone and biochemical parameters for women with and without gestational diabetes mellitus

	GDM+(n=20)		GDM-(n=11)		p*
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	
LDL	128.5 (36.4)	126.0 (75.0-198.0)	157.1 (61.9)	138.5 (90.0-321.0)	0.163
HDL	60.8 (12.0)	58.0 (43.0-83.0)	61.5 (19.9)	55.0 (29.0-101.0)	0.949
TG	180.1 (61.6)	180.0 (49.0-309.0)	221.5 (71.4)	209.0 (125.0-341.0)	0.157
T.CHOL	225.4 (46.0)	226.0 (131.0-313.0)	262.9 (70.1)	242.5 (169.0-432.0)	0.190
TSH	1.4 (1.0)	0.98 (0.01-3.47)	1.8 (1.4)	2.0 (0.01-4.72)	0.363
A1C	5.7 (0.3)	5.7 (5.1-6.3)	5.4 (0.4)	5.5 (5.1-6.3)	0.039
Insulin					
Fasting	14.8 (4.9)	14.7 (6.5-26.4)	10.5 (3.7)	11.6 (5.2-21.9)	0.024
60. minute	122.4 (62.1)	105.3 (18.8-220.5)	87.1 (48.0)	78.8 (46.7-194.9)	0.151
120. minute	105.4 (65.4)	81.8 (27.8-257.6)	66.8 (29.1)	64.9 (21.4-208.7)	0.237
C-Peptide					
Fasting	2.3 (0.8)	2.1 (1.2-3.6)	1.8 (1.6)	1.7 (0.9-3.4)	0.091
60. minute	10.9 (4.0)	10.0 (4.1-17.9)	8.6 (2.9)	8.7 (6.1-16.4)	0.076
120. minute	11.7 (4.1)	10.0 (5.0-20.0)	8.1 (2.3)	8.6 (4,9-15,0)	0.016
GLP-1					
Fasting	5.5 (1.8)	4.9 (2.7-9.9)	16.0 (18.3)	6.3 (3.8-50.0)	0.028
60. minute	5.9 (1.9)	5.5 (3.4-10.5)	11.5 (13.9)	5.6 (3.7-50.0)	0.237
120. minute	7.7 (9.8)	5.0 (4.0-50.0)	10.1 (9.8)	5.6 (3.1-36.6)	0.434

*Mann Whitney U test was performed, SD: Standard deviation, GDM: Gestational diabetes mellitus, LDL: Low-density lipoprotein, HDL: High-density, lipoprotein, TG: Triglyceride, T.CHOL: Total cholesterol, TSH: Thyroid-stimulating hormone, GLP-1: Glucagon-like peptide, A1C: Glycosylated hemoglobin

minutes during OGTT (p=0.091, p=0.076 respectively), however, the mean levels at 120 minutes were 10.0 (5.0-20.0) and 8.6 (4.9-15.0) in women with GDM and in those women without GDM, respectively (p=0.016). The mean fasting GLP-1 level was found to be lower in women with GDM than in women without GDM [4.9 (2.7-9.9) vs. 6.3 (3.8-50.0)] (p=0.028). Low GLP-1 levels were found not to be statistically significant at 60 and 120 minutes of OGTT in women with GDM (p=0.237, p=0.434, respectively) (Table 3).

Discussion

The prevalence of GDM among pregnant women at high risk for GDM was 65.4%. Women with GDM were older than those without GDM (p=0.046). Levels of A1C were higher, fasting GLP-1 levels were lower in women with GDM (p=0.039 and p=0.028, respectively). Although it was not significant, GLP-1 levels at 60 and 120 minutes during 75-gram OGTT were also lower in women with GDM.

Although there have been studies showing decreased GLP-1 levels in T2D (11,14), the number of studies evaluating the levels of GLP-1 in GDM are limited.

However, in one study, there was also no significant change in GLP-1 concentration during OGTT (15) fasting GLP-1, decreased significantly in women with GDM.

Lencioni et al. (14) also determined decreased GLP-1 secretion in response to OGTT in GDM and normal glucose tolerance during and after pregnancy.

Kosinski et al. (15) have investigated the incretin effect during third trimester and 3 to 4 months postpartum in women with and without GDM. In women with GDM, the incretin effect increased significantly postpartum (31±6 vs. 56±6%, p=0.02), whereas the increment in women with NGT was insignificant (16).

Bonde et al. (17) have investigated GLP-1 response in pregnant women with and without GDM and compared with that after delivery when normal glucose tolerance was reestablished. The levels of GLP-1 during pregnancy were lower than the levels after pregnancy (18).

In our study, we found significantly higher levels of A1C in women with GDM than in those without GDM. Significantly elevated levels of A1C in GDM have also been reported in other studies (19,20).

Although elevated TG levels in GDM have been reported (20,21), Sobki et al. (21) have reported lower levels of TG in patients with GDM when compared to that in subjects without GDM (22). In our study, we found no significant difference in TG levels between women with and without GDM.

Insulin and c-peptide levels should be parallel to each other. However, in our study, while fasting insulin levels were statistically higher in women with GDM, fasting c-peptide levels were not higher than in those without GDM. In addition, c-peptide levels at 120 minutes during OGTT were higher in women with GDM, but there was no statistically significant difference in insulin levels. This may be due to searching on a small sample size because huge differences from median level may affect the p value. Fasting GLP-1 levels were lower in women with GDM. As decreased GLP-1 levels play a part in the etiopathogenesis of T2D, decreased GLP-1 levels may also play a role in the etiopathogenesis of GDM.

Conclusion

Women with GDM were found to have lower fasting GLP-1 levels than women without GDM (p=0.028). Although it was not significant, GLP-1 levels at 60 and 120 minutes were also lower in women with GDM compared to those without GDM.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.
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Ethics

Ethics Committee Approval: This study has been approved by the Institutional Review Board of İzmir Katip Çelebi University Atatürk Training and Research Hospital, Informed Consent: Patients were informed verbally and they consented to the study.
Peer-review: Internally peer-reviewed.

Authorship Contributions

Patient Selection and Assessment: Mustafa Demirpençe, Ahmet Görgel, Pelin Tütüncüoğlu, Gonca Örük, Nesil Atalay, Mitat Bahçeci, Biochemical Evaluations: Banu Arslan, Design: Mustafa Demirpençe, Ahmet Görgel, Pelin Tütüncüoğlu, Gonca Örük, Mitat Bahçeci, Data Collection or Processing: Mustafa Demirpençe, Ahmet Görgel, Pelin Tütüncüoğlu, Gonca Örük, Analysis or Interpretation: Mustafa Demirpençe, Nur Demirpençe, Mitat Bahçeci, Literature Search: Mustafa Demirpençe, Writing: Mustafa Demirpençe, Nur Demirpençe, Hamiyet Yılmaz.
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