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The Relationship Between Plasma Glucagon-Like Peptide-1, C-Reactive Protein and Adiponectin Levels in Obese Patients with Normal and Impaired Glucose Tolerance

Normal ve Bozulmuş Glukoz Toleransı Olan Obez Hastalarda Plazma Glukagon-Benzeri Peptit-1, C-Reaktif Protein ve Adiponektin Düzeyleri Arasındaki İlişki

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Abstract

Objective: One of the most important pathophysiological changes occurring in obese patients is systemic inflammation. This study aims to examine the relationship between C-reactive protein (an inflammatory marker), anti-inflammatory adiponectin, and glucagon-like peptide-1, which is an important incretin hormone involved in the pathogenesis of Type 2 diabetes mellitus, in obese patients having normal and impaired glucose tolerance.

Material and Methods: This study observed 60 obese patients having body mass index ≥30 kg/m^2. Out of the 60 obese patients, 30 patients showed normal glucose tolerance, while the remaining 30 had impaired glucose tolerance. Another group (control group) included 20 healthy individuals having normal body mass index. Plasma adiponectin, glucagon-like peptide-1, fasting insulin, lipid profile, hemoglobin a1c and C-reactive protein levels were examined in all the patients, including the control group.

Results: Obese patients with impaired glucose tolerance and normal glucose tolerance were compared to patients in the healthy control group. It was determined that both the categories of obese patients possessed significantly higher C-reactive protein levels and lower glucagon-like peptide-1 levels than those of the healthy control group (respectively p=0.001, p=0.001, p=0.001, p=0.001). Moreover, the adiponectin levels were observed to be lower in the impaired glucose tolerance group than that in the healthy control group (p=0.010). However, there was no significant difference within the impaired glucose tolerance group with regard to C-reactive protein, glucagon-like peptide-1, and adiponectin levels. The correlation analysis revealed a significant positive correlation between C-reactive protein, body mass index, and waist circumference in the normal glucose tolerance group (respectively, r=0.427, p=0.019 and r=0.407, p=0.026). On the other hand, no significant correlation was observed between glucagon-like peptide-1, adiponectin, and the other parameters in these subjects. Furthermore, a significantly negative correlation was observed in the impaired glucose tolerance group in terms of glucagon-like peptide-1 levels and waist circumference (r=-0.380, p=0.038). Nevertheless, no significant correlation was observed among C-reactive protein levels, adiponectin, and other parameters in this patient group.

Conclusion: The high C-reactive protein level observed among obese patients in this study may indicate the involvement of an inflammatory process in obese patients. The observation of high C-reactive protein and low glucagon-like peptide-1, as well as adiponectin levels among obese patients, can be used as a marker for tracking the progression of diabetes in impaired glucose tolerance patients during the follow-up examinations. Moreover, the positive correlation among C-reactive protein, body mass index, and waist circumference in normal glucose tolerance patients, as well as the negative correlation between glucagon-like peptide-1 levels and waist circumference in impaired glucose tolerance patients, supports this claim.

Keywords: Diabetes mellitus; obesity; adiponectin; GLP-1; CRP; impaired glucose intolerance

Özet

Amaç: Obez hastalarda en önemli patofizyolojik değişikliklerden biri sistemik inflamasyondur. Bu çalışmada, normal ve bozulmuş glukoz toleransı olan bez hastalarda Tip-2 diabetes mellitus patogenezinde rol oynayan önemli bir inkretin hormon olan glukogan-benzeri peptit-1 ile C-reaktif protein (inflamatuar belirteç) ve anti-inflamatuar adiponektin arasındaki ilişkinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya beden kitle indeksi ≥30 kg/m^2 olan 60 obez hasta alındı. Altmış obez hastanın 30'unda normal glukoz toleransı, geriye kalan 30 hastada bozulmuş glukoz toleransı mevcuttu. Kontrol grubu normal beden kitle indeksi olan 20 sağlıklı kişiyi içermektedir. Kontrol grubu da dâhil olmak üzere tüm hastalarda plazma adiponektin, glukogan-benzeri peptit-1, açlık insülini, lipid profili, hemoglobin a1c ve C-reaktif protein düzeyleri incelendi.

Bulgular: Bozulmuş glukoz toleransı ve normal glukoz toleransı olan obez hastalar, sağlıklı kontrol grubundaki hastalar ile karşılaştırıldı. Her iki obez hasta grubunun sağlıklı kontrol grubuna göre anlamlı olarak daha yüksek C-reaktif protein düzeyleri ve daha düşük glukogan-benzeri peptit-1 düzeyleri olduğu saptandı (sırasıyla p=0,001, p=0,001, p=0,001, p=0,001). Ayrıca, adiponektin düzeylerinin bozulmuş glukoz toleransı grubunda sağlıklı kontrol grubundan daha düşük olduğu gözlendi (p=0,010). Bununla birlikte, bozulmuş glukoz toleransı grubunda C-reaktif protein, glukogan-benzeri peptit-1 ve adiponektin düzeyleri açısından anlamlı bir fark belirtilmedi. Korelasyon analizinde normal glukoz toleransı grubundaki C-reaktif protein, beden kitle indeksi ve bel çevresi arasında anlamlı pozitif korelasyon saptandı (sırasıyla r=0,427, p=0,019 ve r=0,407, p=0,026). Diğer taraftan, bu hastalarda glukogan-benzeri peptit-1, adiponektin ve diğer parametreler arasında anlamlı bir ilişki gözlenmedi. Ayrıca, bozulmuş glukoz toleransı grubunda glukogan-benzeri peptit-1 düzeyleri ve bel çevresi açısından anlamlı negatif korelasyon gözlendi (r=-0,380, p=0,038). Bununla birlikte, bu hasta grubunda C-reaktif protein seviyeleri, adiponektin ve diğer parametreler arasında anlamlı bir ilişki saptanmadı.

Sonuç: Bu çalışmada, obez hastalar arasında gözlenen yüksek C-reaktif protein düzeyi, obez hastalarda inflamatuar bir sürecin varlığını gösterebilmektedir. Obez hastalar arasında yüksek C-reaktif protein ve düşük glukogan-benzeri peptit-1 ve adiponektin düzeylerinin gözlenmesi, bu parametrelerin bozulmuş glukoz toleransı hastalarında takip için kullanılabileceğini akla getirmektedir. Ayrıca normal glukoz toleranslı hastalardaki C-reaktif protein, beden kitle indeksi ve bel çevresi arasında pozitif korelasyon ve bozulmuş glukoz toleransı hastalarında glukogan-benzeri peptit-1 seviyeleri ve bel çevresi arasındaki negatif korelasyon bu iddiayı desteklemektedir.

Anahtar kelimeler: Diabetes mellitus; obezite; adiponektin; GLP-1; CRP; bozulmuş glukoz toleransı

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Introduction

Obesity is a growing public health concern affecting both, developed and developing countries. Moreover, the risk of T2DM is increasing among obese individuals. One of the most significant pathophysiological changes in obese individuals and patients with T2DM is the presence of chronic systemic inflammation. Studies have indicated that inflammatory markers are present in high amounts in obese patients while the anti-inflammatory markers are present in low numbers.

Earlier studies have revealed that the levels of CRP, a type of inflammatory marker, are directly related to body fat tissue levels; as the body fat texture increases, so does the CRP level (1). It has also been found that a large number of cytokines like adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1) are secreted by the fat cells. Adiponectin is an anti-diabetic and anti-atherogenic protein, the concentration of which is reduced in obese patients. Along with being involved in the pathogenesis of familial hyperlipidemia, it is also an anti-inflammatory cytokine, possessing an insulin-sensitizing effect and, lipid oxidation-enhancing effect (2). However, it is still not known as to which of the relative effects of adiponectin deficiency and pro-inflammatory mediator excess are predominant in pre-diabetic obese patients. Earlier investigations have indicated that decreased levels of adiponectin in patients with metabolic syndrome during follow-up examinations may be predictive of IGT (3). Glucagon-like Peptide-1 (GLP-1) is the most potent incretin hormone. Several studies have found that post-prandial GLP-1 levels are low in pre-diabetic obese patients as well as in patients with type 2 diabetes (4). GLP-1 is secreted from the L cells in small intestine and increases insulin secretion when plasma glucose rises above fasting levels. In addition, GLP-1 inhibits glucose uptake by inhibiting glucagon over-release. Apart from its effects on glucagon, GLP-1 also decreases appetite by delaying gastric emptying, especially during the postprandial period (5).

This study investigated the relationship between CRP, adiponectin, and GLP-1 levels within three groups of patients: obese patients with IGT, obese patients with NGT, and a control group consisting of healthy patients. A secondary goal of this study was to assess the contribution of these relationships in the development of T2DM.

Material and Methods

Consent for conducting the study was obtained from the Gaziantep University Medical Faculty Ethics Board data 18.05.2015. The participants were patients who had applied to the outpatient clinic of the Endocrinology and Metabolism Department in the Hospital of Gaziantep University, Faculty of Medicine. According to the inclusion criteria, age of the participants ranged from 18-65 years, BMI was ≥30 kg/m^2, and they did not have any other chronic disease. Patients were divided into three different groups according to results of the Oral Glucose Tolerance Test (OGTT). The first group consisted of 30 obese patients with NGT, the second included 30 obese patients with IGT, and third group comprised of healthy individuals with normal OGTT results. The waist circumference of participants in all the groups was measured at the midpoint of the distance between the lower edge of the costa and spina iliaca. Blood samples were obtained for biochemistry and hormone parameters (fasting insulin levels, lipid profiles, HbA1C, CRP). Three milliliters of venous blood samples were drawn in non-anticoagulated tubes and centrifuged for a total of 30 min at 3000 rpm. To measure adiponectin levels, 4 mL of venous blood was drawn without the addition of any anticoagulant and was centrifuged for 30 min at 3000 rpm. The samples were then placed in Eppendorf Tubes and stored at -80 °C in a deep freeze. For assessing GLP-1 levels, 3 mL of venous blood was obtained and placed into blood tubes with ethylenediaminetetraacetic acid (EDTA; an anticoagulant). The blood samples were then transferred, without any delay, to aprotinin-containing tubes and were centrifuged at 3000 rpm for 5 min. Subsequently, the blood samples were placed in Eppendorf Tubes and stored at -80°C in a deep freeze. Insulin resistance (IR) was determined using the Homeostasis Model Assessment (HOMA) index. A 75 g OGTT was conducted among all the participants. The Homeostasis Model Assessment

of Insulin Resistance (HOMA- IR) is the most widely used method for assessing IR in various studies (6). HOMA-IR and HOMA equations are as quoted below:
HOMA-IR= (FPI × FPG)/22.5; HOMA-%β = (20 × FPI)/(FPG-3.5)
Exclusion criteria for the participants included conditions that may cause inflammation (acute infectious diseases, malignancies, inflammatory rheumatic diseases, etc.); the presence of autoimmune diseases; pregnancy; patients with chronic renal failure; and patients with acute or chronic liver disease.

Measurement of Serum GLP-1 Levels

Serum samples collected from the patients were removed from the deep freeze and brought to room temperature. GLP-1 levels (Millipore EGLP-35K) in the serum samples were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method. The use of ELISA kits was based on the following principles:
1. Active GLP-1 is captured by monoclonal antibodies and immobilized on the microplate. The binding occurs particularly in the N-terminal region of the active GLP-1 molecules.
2. The binding of anti-GLP-1-alkaline-phosphatase reveals the conjugation of immobilized GLP-1.
3. Unbound compounds are removed by washing.
4. The amount of bound conjugates is determined by the addition of MUP (methyl-umbelliferyl-phosphate), a fluorescent product formed by the interaction of alkaline phosphatase in the medium.
As the amount of the fluorescent substance formed was directly proportional to the concentration of active GLP-1 in the sample, the resultant concentration of active GLP-1 was subsequently calculated using standard references (100; 100; 50; 50; 20; 20; 10; 10; 5; 5; 2) and obtained via proportionality. The plate was read by a fluorescent plate reader having excitation wavelength 355 nm and emission 460 nm.

Measurement of Serum Adiponectin Levels

The serum samples collected from the patients were removed from the deep freeze and brought to room temperature. Adiponectin (AssayPro EA2500-1) levels were measured using the ELISA method, which quantifies human adiponectin levels via a quantitative sandwich enzyme immunoassay technique within 3 h. A precoated microplate with a polyclonal antibody specific for adiponectin was utilized and, adiponectin standards (50.00, 25.00, 12.50, 6.250, 3.125, 1.563 and 0.781 ng/mL) and samples were intervened between the immobilized antibody and adiponectin- specific biotinylated polyclonal antibody. All non-bound materials were washed away and the peroxidase enzyme substrate was added to the remnant. The reaction ceased with exposure to darkness, for color formation, and the addition of an acid solution. Color intensity was read spectrophotometrically at 450 nm using an ELISA reader (BioTek Instruments, USA). The adiponectin levels of obese and control patients were calculated using standard graphics.

Statistical Analysis

The Shapiro-Wilk test was employed for the normally distributed numerical data, while Student's t-test was used to compare the variables that fit a normal distribution in the two groups. ANOVA tests were also employed among the three groups. The Kruskal-Wallis test and Dunn's multiple comparison test was used for comparing normal non-dispersive variables in the three groups. The relationships between categorical variables were tested using chi-square test, while correlations between numerical variables were tested via Spearman's rank correlation. SPSS Version 22.0 was utilized for the analyses. A p-value <0.05 was considered significant.

Results

Demographic and laboratory characteristics of all the patients are displayed in Table 1.
Significant differences were observed between the obese and control group in terms of CRP, GLP-1, and adiponectin levels. In comparison with the healthy control group, HOMA-IR and CRP were significantly higher (p=0.011, p=0.012, p=0.001, respectively) while the GLP-1 levels were significantly lower (p=0.001) in the NGT obese group. However, there was no significant difference between the two groups in terms of HbA1C

Table 1. Demographic and laboratory characteristics of all patients.

	IGT obese (n=30)	NGT obese (n=30)	Healthy control (n=20)	P
Gender†				
Female	17 (57)	18 (60)	12 (60)	0,958
Male	13 (43)	12 (40)	8 (40)	
Age (year)*	41,53 ±9,34	40,20 ±8,84	36,70 ±6,64	0,147
BMI (kg/m²)*	37,27 ±6,52	34,69 ±4,67	24,31 ±2,59	0,001
Waist Circumference (cm)*	121,10 ±11,89	117,30 ±16,17	86,50 ±13,24	0,001
Insulin (mU/mL)**	13,58 (9,26-22,67)	10,01 (7,15-14,4)	5,92 (5,22-8,39)	0,001
HbA1C (%)**	5,95 (5,37-6,4)	5,6 (5,3-5,9)	5,4 (5,2-5,7)	0,003
Homa IR**	3,42 (2,22-5,86)	2,27 (1,61-3,43)	1,31 (1,14-1,99)	0,001
T. Cholesterol (mg/dL)**	209,5 (173,75-245,0)	212,00 (185,00-236,5)	200,5 (180,0-220,75)	0,903
Triglyceride (mg/dL)**	157,5 (109,5-227,5)	179,5 (128,75-241,25)	120,0 (91,75-207,75)	0,129
HDL (mg/dL)**	49,5 (41,5-56)	44,0 (38,0-53,5)	51,5 (44,0-61,5)	0,06

* Numerical variables (mean ±SD) ** Numerical variables (median 25-75%)† Categorical variable number (%) P<0.05 significant.

and adiponectin (p=0.276, p=0.068, respectively). Likewise, in comparison with the control group, it was observed that insulin, HbA1C, HOMA-IR, and CRP levels were significantly higher (p=0.001, p=0.001, p=0.001, p=0.001, respectively) while the GLP-1 and adiponectin levels were significantly lower (p=0.001, p=0.010, respectively) in the IGT group. These findings are displayed in Table 2.

When the NGT and IGT groups were compared, HbA1C and HOMA-IR levels were determined to be significantly higher among IGT patients (respectively, p=0,015, p=0,046). However, no significant difference was observed between the two groups in terms of insulin, CRP, GLP-1, and adiponectin (p=0,091, p=0,221, p=0,739, p=0,392, respectively). These results are also presented in Table 2.

A significantly positive correlation was identified between GLP-1 and adiponectin (p=0.004, r=0.620). In the NGT group, a significantly positive correlation was observed between CRP and BMI, and waist circumference (p=0,019, r=0,427, p=0,026, r=0,407, respectively). There was no significant correlation between GLP-1 and adiponectin or other parameters.

In the IGT obese patient group, a significantly negative correlation was observed between GLP-1 and waist circumference (p=0.038, r=-0.380). However, no significant correlation was found between CRP and adiponectin.

Discussion

It is well known that insulin resistance is commonly observed in obese individuals and that higher BMI values are associated with an increase in the incidence and prevalence of T2DM (7). One study has proven that the risk of diabetes can increase eleven-fold when BMI increases from 20 to 30 mg/m²

Table 2. Comparison of insulin, HbA1C, HOMA-IR, CRP, GLP-1, and adiponectin levels Between NGT & IGT obese groups and control group.

	NGT Obese/Control Mean±SD	p value	IGT Obese/Control Mean±SD	p value	IGT Obese/NGT obese Mean±SD	p value
HbA1C	5.46±0.33/5.53±0.40	0.004	6.08±1.06/5.53±0.40	0.004	6.08±1.06/5.46±0.33	0.002
HOMA-IR	2.99±2.82/1.74±1.26	0.035	6.73±10.5/1.74±1.26	0.035	6.73±10.5/2.99±2.82	0.012
Insulin	12.2±7.88/8.01±5.59	0.037	21.4±25.6/8.01±5.59	0.030	21.4±25.6/12.2±7.88	0.007
Adiponectin	15.0±4.84/18.0±6.16	0.632	16.4±16.1/18.0±6.16	0.63	16.4±16.1/15.0±4.84	0.596
GLP-1	28.5±9.16/45.7±16.1	0.675	27.4±7.41/45.7±16.1	0.675	27.4±7.41/28.5±9.16	0.001
CRP	5.87±7.60/1.37±1.04	0.99	5.87±4.82/1.37±1.04	0.99	5.87±4.82/5.87±7.60	0.006

P <0.05 was considered statistically significant.

(8). In the current study, insulin resistance determined by HOMA-IR was observed to be significantly higher in IGT and NGT obese patients than that in the healthy individuals. On the other hand, there was no significant difference in terms of total cholesterol, triglycerides, HDL, and LDL values among these three groups. Similarly, some studies have reported no association between insulin resistance and LDL cholesterol levels at all (9-11).

Several studies on obesity have mentioned the presence of chronic systemic inflammation in the obese patients (12). Many cytokines, including adiponectin, leptin, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which are released from the fat cells, support this inflammatory presence. The presence of CRP is another indicator of high inflammation in obese individuals. Pickup et al. have demonstrated that an increase in the levels of IL-6 and CRP is a characteristic of metabolic syndrome in T2DM patients. (13) Although, in the NGT group, a significantly positive correlation between CRP and BMI, and waist circumference was observed, yet there was no significant correlation between CRP and other parameters in the IGT group. These results prompt the conclusion that obesity increases CRP values; however, it must be noted that there is no additional increase in CRP due to impaired glucose tolerance in obese patients.

Obesity causes an increase in the plasma levels of leptin, resistin, TNF-α, and IL-6 as well as a decrease in the adiponectin levels. A study by Venderel et al. has shown that plasma IL-6, leptin, adiponectin, and resistin levels may be higher and ghrelin levels may be lower in non-morbidly obese patients (14). They found that the plasma lipid levels, insulin resistance, leptin and IL-6 levels decreased with weight loss, while adiponectin and ghrelin levels increased as the patient lost weight. Similar to these findings, it was observed in the present study that the plasma adiponectin levels among obese patients were significantly lower than that in the control group.

In the past, researchers have asserted that glucose levels, in a narrow range of normal physiological conditions, are controlled by insulin and glucagon. Today, however, the presence of a more complex multihormonal system has changed this understanding (15). Studies concerning the use of GLP-1 agonists, an amylin analog (i.e., pramlintide), leptin, and GH-based drugs in the treatment of obesity are becoming increasingly prevalent (16). Therefore, it is necessary to clarify further, the roles of respective hormones in the pathogenesis of obesity. Some researchers have demonstrated that the cause of decreased GLP-1 levels in obesity is leptin resistance (17). Nevertheless, the mechanism of decreased GLP-1 secretion in obesity is not fully understood. In the studies conducted among rats, high-fat feeding has been shown to reduce GLP-1 and anorexic response by inducing leptin resistance (18, 19). In the present study, a significant difference in GLP-1 levels was observed among the three groups. In both, the NGT and IGT obese patient groups, GLP-1 values decreased significantly as compared to that in the control group. However, when the NGT and IGT groups were compared, no significant difference in GLP-1 levels was found. Nevertheless, in the IGT obese patient group, a significantly negative correlation between GLP-1 and waist circumference was observed. Based on these findings, it can be deduced that impaired glucose tolerance may not be significantly affected by fasting GLP-1 levels; however, fasting GLP-1 levels may affect waist circumference and, consequently, impaired glucose tolerance in obese patients. These findings can be clarified by examining more number of patients.

The presence of a significantly positive correlation between waist circumference and CRP in NGT patients as well as a significantly negative correlation between GLP-1 and waist circumference in IGT patients implies that GLP-1 and CRP levels may predict diabetic progression in obese individuals. Thus, further studies, if conducted in relation to these findings, may illuminate new ways of treating diabetes in obese patients.

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Authorship Contributions

Idea/Concept: Ersin Akarsu; Design: Ersin Akarsu; Control/Supervision: Ersin Akarsu; Data Collection and/or Processing: Ahmet Dündar; Analysis and/or Interpretation: Ersin Akarsu; Literature Review: Ahmet Dündar, Ersin Akarsu; Writing the Article: Zeynel Abidin Sayiner; Critical Review: Ersin Akarsu; References and Fundings: Ahmet Dündar; Materials: Ahmet Dündar.

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