Evaluation of the Inflammatory State in Healthy Obese and non-Obese Group According to Body Mass Index and Waist-Hip Ratio Using Procalcitonin and Neopterin

Vücut Kitle Indeksi ve Bel/Kalça Oranına Göre Sağlıklı Obez ve Non-obezlerde İnflamatuar Durumun Prokalsitonin ve NeopterinleDeğerlendirilmesi

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ABSTRACT

Objective: We aimed to evaluate the role of high sensitivity-CRP (hs-CRP), procalcitonin (PCT), and neopterin in the diagnosis of chronic low-grade inflammation in obesity according to waist-hip ratio and body mass index.
Materials and Methods: 67 obese, overweight, and healthy adults were included with a mean age of 41.1±10 years. All participants were divided into two groups according to the waist-hip ratio (WHR<0.9 group A, WHR≥ 0.9 group B) and into three groups according to body mass index (BMI) (BMI< 25kg/m^2 - group 1, BMI-25-29.9 kg/m^2 - group 2, BMI≥ 30 kg/m^2 – group 3). Hs-CRP, PCT, neopterin levels of the groups were compared. Lipid profile and blood glucose levels were also evaluated.
Results: There was no significant difference in Hs-CRP, neopterin, PCT between the groups based on the waist-hip ratio (p>0.05). In BMI groups, Hs-CRP levels were related to the degree of obesity, and the differences between group 1 and group 3, and group 2 and group 3 were significant (p<0.05). There was no difference in neopterin levels among the groups (p> 0.05). In the PCT levels, there were statistical significance between group1 and group3 and between group 2 and group 3, but no difference was found between group 1 and group 2 (p>0.05).
Conclusion: It was shown that the increase in total fat mass in the body may lead to an increase in inflammation markers. However, it was concluded that this difference is more closely related to the degree of obesity rather than fat distribution.

Key Words: Obesity, inflammation, high sensitivity-CRP, procalcitonin, neopterin

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ÖZET

Amaç: Biz bu çalışmada obezite ile ilişkili kronik düşük dereceli inflamasyonun tanısında, hs-CRP (yüksek sensiviteli-CRP), PCT (prokalsitonin) ve neopterinin rolünü vücut kitle indeksi (VKİ) ve bel kalça oranına (BKO) gore değerlendirmeyi amaçladık.
Yöntem: Yaşortalaması 41.1±10 yıl olan obez, aşırı kilolu ve sağlıklı 67 erişkin çalışmaya dahil edildi. Tüm katılımcılar BKO'na (BKO<0.9 grup A, BKO≥ 0.9 grup B) gore iki gruba ve VKİ'ne gore üç gruba (VKİ<25kg/m^2 grup 1, BMI=25-29.9kg/m^2 grup 2, BMI ≥30kg/m^2 grup 3) ayrıldı. Hs-CRP, PCT ve neopterin düzeyleri gruplar arasında karşılaştırıldı. Lipid profile ve kan şekeri seviyeleri de değerlendirildi.
Bulgular: BKO'na gore oluşturulan gruplar arasında Hs-CRP, NP, PCT arasında anlamlı
fark yoktu (p>0.05). BMI gruplarında Hs-CRP düzeyleri obeziteyle birlikte yükselmiş
bulundu. grup 1- grup 3 ve grup 2 - grup 3 arasındaki fark anlamlı düzeydeydi (p<0.05). NP düzeyleri arasında gruplar arasında fark yoktu (p>0.05). PCT düzeylerinde grup 1 ve grup 2 ve grup 1 ve grup3 arasında istatistiksel olarak anlamlı sonuçlar vardı, ancak grup 1 ile grup 2 arasında anlamlı fark bulunmadı (p>0.05).
Sonuç: Vücuttaki toplam yağ kütlesindeki artışın, inflamasyon belirteçlerinde bir artışa yol
açabileceği gösterilmiştir. Bununla birlikte, bu farkın yağ dağılımından ziyade obezite derecesi ile daha yakından ilişkili olduğu sonucuna varılmıştır.

Anahtar Sözcükler: Obezite, inflamasyon, yüksek sensiviteli-CRP, prokalsitonin, neopterin

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INTRODUCTION

Obesity is a worldwide health problem, especially in developed countries and its prevalence has almost tripled between 1975 and 2016. Therefore the World Health Organization (WHO) has been declared obesity as a global epidemic disorder (1). Abnormal and excessive fat accumulation in obesity causes a chronic energy metabolism disorder due to different cell types such as monocyte-derived macrophages and dendritic cells in adipose tissue. Consequently, adipose tissue has various autocrine, paracrine, and endocrine effects, and therefore accepted as an active endocrine organ (2, 3). Acting like an endocrine tissue, adipose tissue is a source of various pro-inflammatory cytokines, chemokines, growth factors, and complement proteins that are responsible for chronic low-grade inflammation in visceral obesity (3-5). The increase in these molecules triggers local effects on the endothelium that leads to increased production of vascular and intercellular cell adhesion molecules, (vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM)) as well as vascular permeability. This allows fluid (which contains molecules such as those in complement protein) and cells such as polymorphonuclear and mononuclear phagocytes and other cells to escape to the extravascular compartment (6). This chronic low-grade inflammation of the white fat tissue in obesity and overweight leads to chronic diseases such as insulin resistance, impaired glucose tolerance, and even diabetes (7-11). In addition, this is also crucial in "obesity-related cardiovascular diseases (CVD)", such as myocardial infarction (MI) and/or stroke (8, 11, 12, 13). The risk of these diseases in obesity is associated with the type of fat accumulation (14). Anthropometric measurements such as Body Mass Index (BMI) and Waist Hip Ratio (WHR) are commonly used parameters that evaluate the accumulation of body fat distribution (15). BMI does not have the ability to differentiate fatness as central or visceral whereas WHR is shown to be more reflective of visceral fat and central adiposity, as well as a better predictor of obesity-related disorders (8, 15, 16).

Since the adipose tissue has been attributed as an important source of pro-inflammatory mediators, there is increasing evidence that the fat tissue is majorly responsible for the production of C-reactive protein (CRP) from the liver, by synthesizing the tumor necrosis factor-alpha (TNF-α), interleukin–1 (IL–1), and interleukin–6 (IL–6) (17). Also, it has been shown that CRP levels are proportional to body fat tissue amount (17). Elevated serum CRP has been shown to predict the future risk of CVD. Another novel marker of inflammation neopterin (NP) is produced upon with the stimulation of Th1-type cytokine interferon γ (INF-γ), from human monocyte-derived macrophages in adipose tissue and released into cell fluids (18). So, cellular immune activation can easily and sensitively be evaluated by the measurement of NP levels in biological fluids. NP concentration reflects the oxidative stress level caused by immune system activation (19). Therefore, like CRP, NP is used as an early predictor of the presence of inflammation in obesity that was associated with diabetes and CVD (18). Another inflammation marker PCT especially known as an early predictor of infection and sepsis is also expressed and produced by adipose tissue (20, 21). In vitro excretion of PCT from adipocytes is triggered by activated macrophages and the presence of these macrophages in adipose tissue is reported to be related to the degree of obesity (5, 21). Considering the relationship between inflammation and obesity, this provides evidence for PCT to be a potential biomarker.

Since the adipose tissue is primarily responsible for the production of these inflammatory markers (such as CRP, NP, and PCT), several studies have been published to show the association between chronic low-grade inflammation in obesity (9, 16, 22-26). In this study, we aimed to evaluate the predictive role of the high sensitivity-CRP (hs-CRP), NP, PCT levels of obese, overweight, and normal-weight healthy individuals according to BMI and WHR.

METHODS

Study design

The study was conducted in Abant İzzet Baysal University Faculty of Medicine, Education, and Research Hospital Clinical Chemistry Laboratory. 67 participants with a mean age of 41.1±10 years were included. The ethical committee of Abant Izzet Baysal University School of Medicine approved the study. The study group was chosen from individuals who did not have any systemic disease.

Smoking, alcohol use, drug therapy (anti-inflammatory and oral contraceptives, etc.), rapid weight gain, hypertension, diabetes mellitus (DM), presence of active infection, systemic inflammatory diseases, hepatitis, cardiovascular diseases, and malignancy were accepted as exclusion criterions. Written informed consent was obtained from each participant before included in the study. Normal weight individuals were taken as the control group.

Anthropometric Measurements

Height, weight, waist, and hip circumference measurements were performed by the same trained person in a standardized manner. WHR was calculated as waist measurement divided by hip measurement (W÷H). The measurements were categorized as WHR<0.90, group A (n=31), and WHR≥0.90, group B (n=36). BMI (kg/m^2) was calculated with the formula kg/m^2 where kg is a person's weight in kilograms and m^2 is the square-meter of the height. Likewise, BMI was also evaluated categorically, comparing BMI≥30 kg/m^2 (obese, group 3, n=24) and BMI was between 25–29.9 kg/m^2 (overweight, group 2, n=22) to BMI≤25 kg/m^2 (control, group 1, n=21). All parameters were also compared using both WHR and BMI as continuous variables.

Biochemical Analysis

Venous blood samples were drawn from the participants after 30 min of rest between 7.30 am and 9.30 am and after 12-hour overnight fasting. For serum, venous blood samples were stored at room temperature for 30 minutes and centrifuged at 1500g for 15 minutes. Glucose and lipid parameters (triglyceride (TG), total cholesterol, HDL (high-density lipoprotein) cholesterol were analyzed in Abbott C8000 (Chicago, IL, USA) analyzer. Hs-CRP levels were determined by the nephelometric method (BN prospec, Dade Behring Marburg, Germany). For PCT and NP measurements, serum samples were stored at -80°C, less than six months. PCT measurements were performed on the Kryptor device with the original Brahms PCT cryptor kit (Brahms Diagnostica, Berlin, Germany). The Kryptor method has a measuring range of 0.02–1000 ng/mL, a functional sensitivity of 0.06 ng/mL. NP measurements were performed using the DRG neopterin ELISA kit (Instruments GmbH, Germany). The kit controls have been found within the acceptable ranges as stated on the vial labels. Both intraassay and interassay coefficent variation (cv) values of the analytes were below 10%. Benchmark Plus BioRAD (Hercules, USA) ELISA reader and the Thermo Lab Systems Corp Well wash, 4-MK2 Model microplate washer (Denley Instruments, Billinghurst, UK) were used for the ELISA method. White blood cell (WBC) was measured with Cell-Dyn 3700 cell counter (Abbott Diagnostics Division, Abbott Laboratories, Illinois, USA). Erythrocyte sedimentation rate (ESR) measurements were performed using the Westergreen method with Sed Rate Screener 100 (SRS 100, Greiner Bio-one GmbH, Kremsmunster, Austria).

Statistical analysis

All data were given as mean ± standard deviation (SD). Distributions of all parameters were tested by the Shapiro-Wilk test. For the comparison between two group (group A, group B), the *t*-test was used for parametric distribution and the Mann-Whitney *U* test was used for the nonparametric distribution. For the groups based on BMI (group 1, group 2, group 3), the One-way ANOVA test, and then Bonferonni post hoc analysis was used for parametric distributions. For nonparametric distributions the Kruskal Wallis test was used among the three groups for the difference. There was no difference between these tests, so the all results were given with the One-Way ANOVA test. SPSS 15.0 program was used for statistics. Statistical significance was accepted as $p < 0.05$.

RESULTS

Sixty seven patients were assigned into three group according to BMI as; group 1 (n=21, BMI ≤25 kg/m^2), group 2 (n=22, BMI 25–29.9 kg/m^2) and, group 3 (n=24, BMI ≥30 kg/m^2). The demographic and laboratory characteristics of these groups were shown in Table 1. Inter-group WHR, T. Cholesterol, TG, HDL cholesterol, VLDL (very low density lipoprotein) cholesterol, ESR, CRP, and PCT levels were statistically significant whereas NP levels were not significantly different ($p > 0.05$). Multiple comparisons of these parameters between the groups according to BMI were shown in Table 2. Between group 1 and group 2, WHR, T.cholesterol, HDL cholesterol, VLDL cholesterol, TG, and PCT levels were statistically significant whereas there were no differences between group 2 and group 3. Between group 1 and group 3, CRP, HDL cholesterol, VLDL cholesterol, and WHR were significantly different.

The demographic and laboratory characteristics of the groups based on WHR (group A, group B) are shown in Table 3.

Mann-Whitney U test was used to compare glucose, TG, HDL cholesterol, VLDL cholesterol, CRP, ESR, and PCT values between the groups.

There was a significant difference between the groups in terms of TG, VLDL cholesterol, HDL cholesterol, while no significant difference was found in CRP, NP, PCT (Table 3).

For the comparison the One-way ANOVA test, and then Bonferonni post hoc analysis was used for parametric distributions and for nonparametric distributions the Kruskal Wallis test was used.

Table 1. Demographics and the comparison of the study group based on BMI.

	Total	Group 1	Group 2	Group 3	p
Age (Year)	41.1±10	38.5±10.4	42.3±9.4	42.1±10.3	**0.381**
BMI (kg/m²)	28.4 ±5.7	22.2±2.7	27.5±1.5	34.7±3.1	**<0.001**
WHR	0.88±0.8	0.82±0.08	0.92±0.04	0.9±0.09	**<0.001**
Glucose (mg/dl) *	93.3±8.5	92.2±10.7	92.8±6.8	94.7±7.8	**0.605**
T. Chol. (mg/dl)	193±32.8	179.2±29.4	205.9±33.3	193.4±28.1	**0.026**
TG (mg/dl) *	144.4±90.1	87.4±29.4	167.2±102.5	173.3±93	**0.010**
HDL cholesterol (mg/dl) *	44.7±9.8	51.8±12	43.2±6.9	40.0±6.0	**<0.01**
VLDL cholesterol (mg/d) *	28.9±18	17.5±5.9	33.45±20.4	34.6±18.6	**0.010**
WBC(*1000)	6.6±1.3	6.3±1.2	6.58±1.1	6.9±1.4	**0.292**
ESR (mm/h) *	8±6.9	4.6±3.1	7±5.3	12±1.4	**0.010**
CRP (mg/dl) *	3.1±3.57	1.4±1.9	2.8±0.6	4.8±4	**0.005**
NP (nmol/l)	1.8±0.48	1.7±0.5	1.9±0.5	1.8±0.5	**0.650**
PCT (ng/ml)*	0.27±0.18	0.18±0.14	0.3±0.2	0.3± 0.18	**0.011**
Male/Female (n)	43/24	16/5	17/5	10/14	-

*means that the distribution of the parameter was not normal

Table 2. Comparisons of the CRP, NP, and PCT between the groupscbased on BMI.

	Group 1-2 (p)	Group 1-3 (p)	Group 2-3 (p)
CRP (mg/l) *	0.34	0.003	0.126
NP (nmol/l)	0.625	0.848	0.914
PCT (ng/ml) *	0.013	0.05	0.825
Glucose (mg/dl) *	0.973	0.609	0.744
T. Cholesterol (mg/dl)	0.019	0.295	0.375
TG (mg/dl)*	0.007	0.003	0.966
HDL cholesterol (mg/dl) *	0.004	<0.001	0.435
VLDL cholesterol (mg/dl) *	0.006	0.003	0.968
WBC(x1000)	0.792	0.265	0.63
WHR	<0.001	0.002	0.798

*means that the distribution of the parameter was not normal.

Table 3. Demographics,and comparison of the groups based on WHR .

	Total	Group A	Group B	p
WHR	0.88±0.8	0.81±0.06	0.94±0.04	<0.001
Age (year)	41.1±10	38.9±9.2	43.4±10.6	0.108
Glucose (mg/dl)*	93.3±8.5	93.1±6.9	93.9±9.9	0.395
T. cholesterol**(mg/dl)**	193±32.8	186.6±34.1	200±31.2	0.139
TG (mg/dl)*	144.4±90.1	109.4±68.6	171.1±95.3	<0.001
HDL Cholesterol **(mg/dl)***	44.7±9.8	48.5±11.0	42±7	0.004
VLDL Cholesterol **(mg/dl)***	28.9±18	21.9±13.7	34.2±19	<0.001
WBC(*1000)	6.6±1.3	6.5±1.2	6.7 ± 1.3	0.605
ESR (mm/h)*	8.0±6.9	9.3±7.6	6.88 ± 6.2	0.083
CRP (mg/l)*	3.1±3.57	2.6±3.2	3.5±3.9	0.251
NP (nmol/l)	1.8±0.48	1.7±0.5	1.9±0.4	0.073
PCT (ng/ml)*	0.27±0.18	0.3 ± 0.2	0.3 ± 0.16	0.419
Male/Female (N)	**43/24**	**12/19**	**29/5**	-

***means that the distribution of the parameter was not normal andMann Whitney U test used for the comparison.

DISCUSSION

In this study, CRP, NP, and PCT levels were compared in obese, overweight, and control groups according to BMI and WHR. Based on BMI, inter-group CRP levels were related to the obesity degree. Additionly, with PCT levels statistically significant results were obtained between group 1 and group 2, and between group 1 and group 3, while no difference was found between group 2 and group 3. There was no difference in NP levels among the groups. When we evaluated the CRP, NP and PCT levels based on WHR, a significant difference was not seen between group A and group B.

Numerous studies in healthy obese have shown that obesity is associated with low-grade inflammation, characterized by high levels CRP (8, 10, 13). Similarly, in a study involving overweight and normal weight children between 8-16 years of age, CRP levels were significantly higher in the overweight group, which was associated with low-grade systemic inflammation (27). In our study, in accordance with these findings, the CRP levels were correlated with the BMI, and the statistically significant difference was seen especially between group 1 and group 3. On the other hand, we found a statistically insignificant elevation between the groups according to WHR reflecting abdominal obesity. However, Ford et al. found a statistically significant correlation between Hs–CRP and anthropometric measurements (BMI, and WHR) in adults aged 17–39 years (16). Chambers et al. studied CRP levels in 1025 healthy East Asian people aged 35-60 years and found that CRP levels were significantly higher in insulin resistance and abdominal obesity. They also stated that there might be a significant correlation between CRP level and CVD (11).

Bozdemir et al., classified 49 healthy adults (32 females, 17 males) according to BMI and WHR, and found a significant correlation between CRP levels and the anthropometric measurements especially between WHR and CRP (22).

NP levels were not statistically significant between the groups categorized according to BMI and WHR. However, Ledochowski et al. found a positive correlation and statistically significant difference between BMI and NP concentrations in healthy obese individuals (9). In the study of Ursavas et al., NP levels were studied in 22 newly diagnosed patients with obstructive sleep apnea and in 18 healthy subjects without obstructive sleep apnea, and an insignificant difference was found in serum NP levels. However, in the same study, a significant positive correlation was found between BMI and NP levels (r=0.320, p=0.044) (23). Bozdemiret al., also showed a statistically insignificant increase in NP levels with BMI while the NP levels were significantly higher and correlated with WHR (22).

According to BMI, between group 1 and group 2 the statistically significance was seen only in PCT levels. Although there was a difference between the PCT levels between the groups (group A and group B) based on WHR, this difference was not statistically significant. Several studies have shown that there is a strong correlation between plasma concentrations of PCT and the degree of the inflammatory response (10, 25, 22). In a study conducted by Abbasi et al., obesity, insulin resistance, and metabolic syndrome, plasma PCT levels were correlated with BMI, and emphasized that PCT levels can be used as a new marker for adipocyte dysfunction (24). In another similar study, PCT and Hs-CRP levels were found to be associated with obesity and insulin resistance in 106 type 2 diabetes patients and 44 controls (10).

In a study conducted by Hestiantoro et al., PCT levels were not correlated with BMI but were significantly correlated with body fat percentage (27). In the study of Hestiantoro et al., with 50 obese, 35 normal-weight children aged between 5-15 years, both PCT and Hs-CRP levels were significantly higher in the obese group (25).

In conclusion there were significant differences between CRP levels among the groups according to BMI and WHR. In addition, there were only significant differences in PCT levels in BMI groups while statistically insignificant increase in NP levels. It was shown that the increase in total fat mass in the body might lead to an increase in inflammation markers. It was thought that the increase in inflammation markers such as CRP and PCT could be considered as a possible predictor in the predetermination of clinical conditions such as insulin resistance, CVD caused due to the increased risk of obesity. The absence of a significant difference between the groups based on WHR, reflects the total body fat mass is more related than the fat distribution in the body on the inflammatory state. The outcome of this study was the correlation of BMI with the inflammation parameters was more predictive than WHR. In the light of these findings, we believe that studies with homogeneous gender distribution with more subjects should be support the evaluation of obesity and chronic low-grade inflammation.

Conflict of interest

No conflict of interest was declared by the authors.

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