RESEARCH ARTICLE

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The Relationship of Body Mass Index with Insulin Resistance, hs-CRP, and Lp(a) Levels in Female Gender

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Abstract

Background and Aim: Chronic obesity causes adipose tissue to produce mediators that promote atherogenesis and vascular inflammation, contributing to hyperlipidemia, diabetes, hypertension, and cardiovascular disease (CVD). This study aimed to examine the relationship between body mass index (BMI) with homeostatic model assessment for insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), and lipoprotein(a) [Lp(a)] levels in females.

Materials and Methods: One hundred thirty-one females participated in the study: 46 morbidly obese, 38 obese, 25 overweight, and 22 normal BMI. To determine insulin resistance, all participants had their HOMA-IR values assessed. As an inflammatory marker, hs-CRP and as a lipid biomarker, Lp(a) were checked.

Results: A significant difference in the HOMA-IR was found between the normal and the obese ($P = 0.001$) and morbidly obese ($P = 0.0001$) participants. There was also a significant difference in terms of HOMA-IR between the overweight and morbidly obese ($P = 0.001$) groups. In paired-group comparisons, hs-CRP was found to be significantly different between the normal group and obese ($P = 0.001$) and morbidly obese ($P = 0.0001$). Additionally, a significant difference in terms of hs-CRP between the overweight and morbidly obese participants ($P = 0.003$) was found. When Lp(a) values were compared, there was a significant difference between the normal group and those who were overweight ($P = 0.0001$), obese ($P = 0.0001$), and morbidly obese ($P = 0.0001$). A significant positive correlation of BMI was shown with HOMA-IR, hs-CRP, and Lp(a) levels.

Conclusion: Elevated BMI in females is related to insulin resistance, elevated hs-CRP, and Lp(a), which confer a residual risk for CVD.

Keywords: Body mass index, hs-CRP, insulin resistance, lipoprotein(a)

INTRODUCTION

The prevalence of overweight, obesity, and morbid obesity is on the rise in today's society.[1,2] Accumulating evidence backs up the claim that body mass index (BMI) over the normal range is an independent risk factor for a variety of illnesses[3-5] including atherosclerosis. Low grade inflammation related to inflammatory mediators released from adipose tissue is called obesity-related inflammation.[6] Inflammation brought on by obesity increases the risk of a systemic inflammatory response, which may lead to several metabolic dysregulations. It has long drawn attention because atherosclerosis is a chronic inflammatory event and that inflammation has a part in every

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stage of the pathogenesis of atherosclerosis. In overweight and obesity, metabolic problems such as reduced peripheral glucose absorption, insulin resistance, and glucotoxicity may ultimately result in increased blood glucose.[7,8] The argument at which a rise in BMI is associated with an increase in overall mortality is, however, constant, although its precise value varies between studies and populations.[9]

Various inflammatory mediators, including interleukin-1 (IL-1), tumor necrosis factor-a (TNF-a), and IL-6, are released by adipocytes and are key players in the liver's production of high-sensitivity C-reactive protein (hs-CRP).[10,11] Several studies have demonstrated that inflammatory biomarkers, such as CRP, might increase risk estimation and the capacity to predict associated illnesses[12], considering the expanding evidence linking inflammation to various chronic health disorders, including diabetes, metabolic syndrome, and CVD.[13] On the other hand, lipoprotein(a) [Lp(a)], a lipid biomarker, is thought to promote atherosclerotic conditions by pro-atherogenic, pro-inflammatory, and/or pro-thrombotic processes, despite a lack of consensus.[14] Furthermore, various prospective studies have demonstrated that higher plasma levels of Lp(a) are a potential risk for stroke and CVD. [15,16]

The relationship between inflammatory markers and BMI appears to have conflicting results among studies.[17,18] Considering all mentioned above, we assessed the relationship between insulin resistance, inflammation, lipid biomarkers, and BMI by the using of measurements of homeostatic model assessment for insulin resistance (HOMA-IR), hs-CRP, and Lp(a) levels.

MATERIALS AND METHODS

Study population

In this cross-sectional study, 131 female participants between the ages of 18 and 65 with 46 morbidly obese, 38 obese, 25 overweight, and 22 normal BMI were included from October 2012 to January 2014. The individuals' age, height, and weight values were noted. The individuals' weight in kilos was determined using a calibrated digital balance. The height was taken in cm using a wall-mounted, transportable measuring tape. By dividing an individual's weight in kilos by their height in meters squared, the BMI is obtained [weight (kg)/height (m^2)]. Those with a BMI of 18.5-24.9 kg/m^2 were categorized as normal, 25-29.9 kg/m^2 as overweight, 30-39.9 kg/m^2 as obese, and ≥40 kg/m^2 as morbidly obese.[19,20]

Blood was taken from the participants after 12 hours of fasting for evaluating blood glucose, hemoglobin, creatinine, lipid parameters, insulin, and HbAIc and was immediately studied. HOMA-IR value was computed using the following equation: (fasting blood glucose x fasting insulin) / 405. [21] Plasma samples were separated and maintained at -80 °C in order to analyze hs-CRP and Lp(a). Before processing, the samples were brought to room temperature. For hs-CRP, a BioCheck kit was used, and for Lp(a), an ASSAYPRO brand kit was employed. Patients with known coronary artery disease, heart failure, valve disease, prosthetic valves, atrial fibrillation/flatter rhythm, known diabetes, and patients with indications for coronary angiography were excluded from the study. Additionally, because they may affect the levels of inflammatory parameters to be assessed, patients with acute infections, asthma, rheumatological conditions, renal failure, pulmonary emboli, a history of cerebrovascular disease, malignancy, and patients who had undergone trauma or surgery was also eliminated from the study.

Kit support was given by the Pamukkale University Scientific Research Projects Unit as part of the Scientific Research Project with the project number 2012TPF033. The study protocol was accepted by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (decision no: 12.06.2012-11). Good Clinical Practices were followed in the design of the study, the Declaration of Helsinki was adhered to, and all individuals gave their written informed permission.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) 20 for Windows was used for the study's statistical analysis. Continuous variables were represented by mean ± standard deviation, median (minimum-maximum values), and categorical variables by numbers (percentage). In independent group comparisons, when parametric test assumptions are provided, analysis of variance and significance test of difference between two means; when parametric test assumptions were not met, Kruskal-Wallis analysis of variance and Mann-Whitney U test are used. Using the chi-square test, differences between qualitative data were analyzed. The Pearson correlation coefficient was used to examine the relationship between variables. $P < 0.05$ was used to determine statistical significance.

RESULTS

Of the female individuals included in the study according to the BMI value, 22 were in the normal group, 25 were in the overweight, 38 were obese, and 46 were in the morbidly obese group. The baseline characteristics of the study groups are shown in Table 1. While the mean age of the females in the normal group was 33.72 ± 7.47 years, this value was 48.20 ± 15.48 years in the overweight group, 48.31 ± 15.83 years in the obese group and 39.69 ± 12.10 years in the morbidly obese group. Age differences between the groups were observed to be statistically significant (p=0.0001). The comparison both HOMA-IR and inflammatory parameters between groups are shown in Table 2. While the HOMA-IR value was 2.08 ± 1.49 in individuals with normal group, it was 2.84 ± 3.00 in the

overweight group, 3.86 ± 2.59 in the obese group, and 3.81 ± 2.60 in the morbidly obese group. HOMA-IR value differences between the groups were observed to be statistically significant ($P = 0.0001$). In paired group analysis, a significant difference in terms of HOMA-IR was observed in the normal group and the obese ($P = 0.001$) and morbidly obese ($P = 0.0001$) groups. Additionally, HOMA-IR value was observed to be significantly different between the overweight and morbidly obese ($P = 0.001$) groups. The mean hs-CRP value was 0.07 ± 0.05 mg/L in participants with normal BMI, 0.87 ± 1.36 mg/L in the overweight group, 1.44 ± 1.30 mg/L in the obese group, and 2.12 ± 1.22 mg/L in the morbidly obese group. Hs-CRP value differences between the groups were observed to be statistically significant ($P = 0.0001$). In paired-group comparisons, it was found that there were significant differences in hs-CRP levels between the normal BMI group and obese ($P = 0.001$) and morbidly obese ($P = 0.0001$) groups. Additionally, a significant difference in hs-CRP levels between the overweight and morbidly obese groups was observed ($P = 0.003$). The mean Lp(a) value of females included in the normal group was 26.67 ± 4.73 mg/dL, for overweight it was 53.25 ± 12.78 mg/dL, for obese, it was 55.72 ± 6.09 mg/dL, and for morbid obese it was 56.13 ± 7.12 mg/dL. Lp(a) value differences between the groups were observed to be statistically significant ($P = 0.0001$). In paired-group comparisons, a significant difference was found between the normal group and the overweight ($P = 0.0001$), obese ($P = 0.0001$) and morbidly obese ($P = 0.0001$) groups. There were also significant positive correlations of BMI with HOMA-IR, hs-CRP, and Lp(a) ($P = 0.0001$, $r = 0.288$ vs $P = 0.0001$, $r = 0.480$ vs $P = 0.0001$, $r = 0.528$), respectively [Table 3].

DISCUSSION

In addition to the treatment of conventional risk factors that induce ischemia processes, primary preventive approaches are crucial for controlling the epidemic growth of cardiovascular illnesses. To obtain a true risk estimation and the individuals who would benefit from therapy, it is necessary to identify all possible risk variables. In our study, we observed that insulin resistance, was measured by HOMA-IR, increased among

Table 1: Baseline characteristics of the study population

	Normal (*n*=22)	Overweight (*n*=25)	Obese (*n*=38)	Morbidly obese (*n*=46)	*p*-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age	33.72±7.47	48.20±15.48	48.31±15.83	39.69±12.10	0.0001*
Weight, kg	57.89±8.98	70.56±6.74	88.63±10.42	121.53±17.74	0.0001*
Height, cm	163.09±7.34	159.40±6.17	159.78±6.32	161.84±7.29	0.292
BMI, kg/m^2	21.59±2.06	27.59±1.31	34.60±2.88	46.24±6.29	0.0001*
Glucose, mg/dL	89.21±12.52	94.23±10.29	96.52±11.44	98.14±12.56	0.115
Insulin, µIU/mL	9.07±5.62	11.33±9.55	15.38±9.43	15.50±10.52	0.0001*
Hb, g/dL	12.87±0.79	13.49±1.14	13.16±1.17	12.99±1.11	0.205
Cre, mg/dL	0.60±0.06	0.69±0.08	0.66±0.09	0.62±0.09	0.003*
T.chol, mg/dL	172.40±33.7	193.72±41.58	192.50±29.84	192.26±26.59	0.018*
TG, mg/dL	76.50±32.30	131.64±65.53	151.23±72.11	143.04±69.35	0.0001*
LDL-C, mg/dL	95.09±27.52	112.68±41.71	117.78±24.45	115.28±26.49	0.005*
HDL-C, mg/dL	62.00±11.32	54.68±14.14	47.18±11.38	48.30±8.40	0.0001*

BMI: Body mass index, Cre: Creatinine, Hb: Hemoglobine, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SD: Standard deviation, T.chol: Total cholesterol, TG: Triglyceride, *Statistically significant

Table 2: Comparison of HOMA-IR, hs-CRP, and Lp(a) between groups

	Normal (*n*=22)	Overweight (*n*=25)	Obese (*n*=38)	Morbidly obese (*n*=46)				
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	p†	p‡	p§	p‖
HOMA-IR	2.08±1.49	2.84±3.00	3.86±2.59	3.81±2.60	NS	**0.001***	**0.0001***	0.012*
hs-CRP	0.07±0.05	0.87±1.36	1.44±1.30	2.12±1.22	NS	**0.0001***	**0.0001***	0.0001*
Lp(a)	26.67±4.73	53.25±12.78	55.72±6.09	56.13±7.12	**0.0001***	**0.0001***	**0.0001***	NS

P†: P-value comparing normal and overweight individuals, p‡: P-value comparing normal and obese individuals, p§: P-value comparing normal and morbidly obese individuals, p‖: P-value comparing overweight and morbidly obese individuals, BMI: Body mass index, HOMA-IR: Homeostatic model assessment of insulin resistance, hs-CRP: High-sensitivity C-reactive protein, Lp(a): Lipoprotein(a), SD: Standard deviation, *Statistically significant

Table 3: Correlation of BMI with HOMA-IR, hs-CRP, and Lp(a)

	r	*p*-value
HOMA-IR	0.288	0.0001*
hs-CRP	0.480	0.0001*
Lp(a)	0.528	0.0001*

BMI: Body mass index, HOMA-IR: Homeostatic model assessment of insulin resistance, hs-CRP: High-sensitivity C-reactive protein, Lp(a): Lipoprotein(a), *Statistically significant

females with BMI over the normal range, and that inflammatory and lipid biomarkers such as hs-CRP and Lp(a) rose in tandem with the increase in BMI.

Revealing the association between BMI and HOMA-IR, may contribute to the implementation of strategies, dietary and lifestyle modifications that are required for the prevention or reduction of the onset of type 2 diabetes (T2DM), which is among the most important health concerns of today.[22] According to the our study results, we found that HOMA-IR rise progressively with increasing BMI, and in paired-group comparisons, the average HOMA-IR value of the control group was significantly lower compared to the obese and morbidly obese groups. Additionally, there was a significant difference in HOMA-IR between the overweight and morbidly obese females. The results of our study were in agreement with those of previous studies[23,24], the HOMA-IR values used to assess insulin resistance exhibited a linear association with BMI. In addition, consistent with our study results, two recent cross-sectional studies revealed that individuals with abnormal HOMA-IR values had significantly higher BMI. [25,26] Furthermore, in a study by Singh *et al*. [27], it was revealed that a HOMA-IR threshold of 2.5 was shown to be sufficient for the diagnosis of metabolic syndrome in terms of sensitivity and specificity. In our study, the HOMA-IR value in the overweight, obese, and morbidly obese groups were shown to be greater than this value. Therefore, managing body weight may be crucial in clinical practice, not just for obese and morbidly obese females but also for overweight females.

In this study, an important marker for assessing the risk of CVD, hs-CRP levels, was observed to rise with an increase in BMI. This might be the result of excessive adipose tissue, which causes systemic inflammation. [28,29] In a study by Kawamoto *et al*. [30], BMI was shown to be independently and significantly related to hs-CRP in participants aged <74 years. Similarly, Weinbrenner *et al*. [31] showed that elevated hs-CRP concentrations were related to increased abdominal fat. Additionally, our study's findings are supported by previous research that shows diet-induced weight reduction is related to reduced blood concentrations of IL-6, TNF alpha, and CRP. [32] Similar outcomes were seen in those who received gastric bypass surgery. [33-35] Our findings support the view that obesity is responsible for a low degree of systemic inflammation.

According to the findings of our study, Lp(a), a lipid biomarker known to carry residual risk and related to early accelerated atherosclerosis, ischemic CVD, and calcific aortic stenosis[36-38], increased concurrently with the rise in BMI. Similar to our study results, Bostan *et al*.[39] revealed that the Lp(a) levels were significantly higher in obese individuals than in overweight individuals. This is in accordance with the results of a previous study by Aaseth *et al*.[40], which showed that Lp(a) levels considerably decreased in obese individuals who underwent gastric bypass surgery. Additionally, Teng *et al*.[41] demonstrated that important risk variables for AMI include BMI and Lp(a) levels. In the instance of initial AMI, they observed an important additive interaction of Lp(a) and BMI, indicating that Lp(a) raises one's risk of initial AMI when BMI is high.

On the other hand, several studies have focused on the association of low Lp(a) levels and the higher risk of incident T2DM. A recent meta-analysis indicated that Lp(a) thresholds of 3 to 5 mg/dL are associated with a 38% increased risk of T2DM than thresholds of >27 to 55 mg/dL.[42] In contrast, Wang *et al*.[43] observed that Lp(a) values in individuals with diabetes in the Chinese population were significantly higher than in non-diabetic individuals. In another recent study, it was found that elevated Lp(a) levels of >28.72 mg/dL may reduce T2DM risk, but only in males and those aged above 60 years.[44] In our study, although all groups had Lp(a) levels that above those considered extremely low Lp(a) threshold values (e.g. <5 mg/dL), prospective studies must gain a deeper understanding and clarify the causal relationship in this topic.

Study limitations

We realize that our study has several limitations. Our study's sample size was quite small. We used a cross-sectional design, therefore, we were unable to gain predictive and prognostic information by following the patients. To verify our findings, we need a multicenter study with a greater number of participants and a prospective design. The incompatibility in terms of age between the control and patient groups seems to be another limitation of our study. In addition to being a risk factor for CVD, age is associated with an increased likelihood of additional cardiac risk factors. To reduce these effects of age, we excluded individuals with traditional risk factors from our study Additionally, since most types of CVD are more prevalent in older adults than in the general

population, we selected patients under the age of 65, which is defined as "young" by the World Health Organization. Moreover, the current studies do not indicate a relationship between HOMA-IR and age.[45] On the other hand, Lp(a) is frequently measured just once, on the assumption that it does not alter with age.[46] Of note, the results of studies on the relationship between age and hs-CRP are inconsistent.[47] Most studies comparing serum levels of hs-CRP and showing the reported rise in hs-CRP levels with increasing age, included elderly patients or compared participants aged ≥65 to <65 years.[48,49]

CONCLUSION

Given the direct relationship of HOMA-IR, hs-CRP, and Lp(a) levels with elevated levels of BMI, the assessment of these indices may pave the way for the implementation of measures that contribute to the diagnosis, management, and the course of CVDs and associated risk factors in female individuals.

Ethics

Ethics Committee Approval: The study protocol was accepted by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (decision no: 12.06.2012-11).

Informed Consent: All individuals gave their written informed permission.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.U., Y.İ.A., Concept: B.U., Y.İ.A., Design: B.U., Y.İ.A., İ.D.K., Data Collection and/or Processing: B.U., Y.İ.A., İ.D.K., Y.E., Analysis and/or Interpretation: B.U., Y.İ.A., Literature Search: H.S., Writing: B.U., H.S.

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