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Original Article

U-shaped relationship between BMI and cardiometabolic risk: a six-group cross-sectional study

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ABSTRACT

Aims: Body-mass index (BMI) is a major determinant of cardiometabolic risk, yet the risk patterns in both low and high BMI categories remain incompletely characterized. This study aimed to investigate cardiometabolic risk markers across six BMI-based groups and to identify independent predictors of risk.

Methods: A total of 120 participants were stratified into six BMI groups. Anthropometric measurements, blood pressure, and laboratory parameters, including hsCRP, lipid profile, fasting glucose, insulin, HOMA-IR, and complete blood count, were collected. Comparisons among groups were performed using one-way ANOVA or Kruskal-Wallis tests as appropriate. Pearson or Spearman correlation analyses assessed associations between hsCRP and other laboratory markers. Multinomial logistic regression was used to identify independent predictors of group status, with BMI groups collapsed into three categories for model stability.

Results: Age and height did not differ significantly among BMI groups, while body weight and waist circumference differed as expected ($p<0.001$). hsCRP demonstrated a U-shaped association across BMI groups, with the lowest levels in the moderate BMI range and elevated levels observed in both the lowest and highest BMI groups. Correlation analyses revealed significant positive associations of hsCRP with triglycerides, TG/HDL ratio, fasting insulin, HOMA-IR, and MPV (all $p<0.001$). Multinomial logistic regression confirmed hsCRP as an independent predictor of BMI group status ($p=0.001$)..

Conclusion: Cardiometabolic risk markers exhibit a non-linear, U-shaped relationship with BMI. Importantly, elevated risk was detected not only in the high BMI groups but also in participants with low BMI, which emphasizes the need to consider underweight individuals in cardiometabolic risk assessment. hsCRP emerged as a robust independent predictor of BMI-associated risk, reinforcing its potential role in early detection strategies.

Keywords: Body-mass index, cardiometabolic risk, high-sensitivity C-reactive protein (hsCRP), underweight, obesity

INTRODUCTION

Body-mass index (BMI) is a simple and practical anthropometric measurement commonly used in assessing nutritional status. Increased BMI has been well documented in the literature to increase the risk of hypertension, dyslipidemia, insulin resistance, and cardiovascular disease (CVD).[1,2] On the other hand, it is increasingly emphasized that not only an elevated BMI but also a low BMI may be associated with adverse health outcomes.[3,4] Recent large-scale studies have reported a U-shaped or J-shaped relationship between BMI and cardiovascular mortality, suggesting that individuals with low BMI may have metabolic or inflammatory vulnerabilities that cannot be explained by traditional risk factors.[3,5,6]

Inflammation plays a central role in the development of cardiometabolic diseases, and high-sensitivity C-reactive protein (hsCRP) is one of the most commonly used biomarkers of low-grade systemic inflammation.[7] Elevated hsCRP levels are associated with endothelial dysfunction, atherogenesis, plaque instability, and future cardiovascular events.[8,9] Although it is known that hsCRP levels are elevated in obese individuals, how hsCRP behaves across the entire BMI spectrum-particularly in lean individuals-has not been sufficiently elucidated.[10] Understanding the inflammatory profile at extreme BMI values may shed light on the biological basis of the U-shaped risk pattern observed in epidemiological studies.

In addition to inflammation, insulin resistance, dyslipidemia, and changes in platelet activity are also important components of cardiometabolic risk.[11,12] The triglyceride/HDL ratio (TG/HDL), along with indicators such as the HOMA-IR scoring system and mean platelet volume (MPV), are considered early biochemical markers of atherogenic and proinflammatory conditions.[11-13] These markers may provide additional information about subclinical cardiometabolic disorders that occur in individuals with low or high weight. However, the number of studies that evaluate inflammatory and metabolic

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parameters together, divide BMI into multiple categories, and specifically evaluate the low BMI group is limited.[14,15]

The limited evidence on how inflammatory and metabolic cardiometabolic markers change across the broad spectrum of BMI highlights the need to clarify the risk profile of lean individuals in particular. This study aims to compare inflammatory and cardiometabolic risk indicators across six different BMI categories and to assess whether lean individuals exhibit adverse biomarker patterns similar to those seen in obese individuals. The combined consideration of hsCRP and basic metabolic parameters will contribute to a more comprehensive understanding of subclinical cardiometabolic risk across BMI groups.

METHODS

Ethics

Prior to the initiation of the study, all participants were informed about the study procedures and signed an informed consent form. Ethical approval was obtained from the Etlik City Hospital Clinical Researches Ethics Committee (Date: 06.08.2025, Decision No: 2025-243). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection and Inclusion/Exclusion Criteria

This study was designed as a cross-sectional study at the Internal Medicine Department of Kırıkkale University Faculty of Medicine, between September 2025 and November 2025. The sample size was calculated using the G*Power 3.1.9.7 software. For a one-way analysis of variance (ANOVA), assuming a significance level (α) of 0.05, a statistical power (1-β) of 0.95, and an effect size (Cohen's f) of 0.498, the required minimum sample size was determined to be 90 participants across six groups. In the present study, a total of 120 participants were included, thereby increasing the statistical power beyond the initially targeted level.

The study was designed to include 6 groups and a total of 120 patients. Individuals aged 18 to 80 who had no acute or chronic illnesses, were not taking any medication, and were visiting the hospital for routine check-ups were included in the study. The individuals included in the study were divided into 6 groups of 20 people each according to their BMI (kg/m2). Individuals with a BMI below 18.5 (Underweight) were assigned to group 1, individuals between 18.5 and 25 to group 2, individuals between 25 and 30 (Overweight) to group 3, individuals between 30 and 35 (Obese Class I) to group 4, individuals between 35 and 40 (Obese Class II) group 5, and individuals with a BMI over 40 are classified as group 6 (Obese Class III). The exclusion criteria for all groups were defined as the presence of any acute or chronic disease determined by detailed medical history, physical examination, blood pressure measurement, and comprehensive laboratory evaluation; fasting plasma glucose ≥126 mg/dl; blood pressure ≥140/90 mmHg; clinically significant hyperlipidemia (including markedly elevated LDL-cholesterol requiring medical treatment); abnormal hepatic or renal function tests; hsCRP levels >10 mg/L; use of any medication; pregnancy or breastfeeding; and current or past smoking. Participants were assigned to six BMI-based groups, with an equal number of males and females (10/10) in each group to ensure balanced sex distribution across all groups.

Study Design

Venous blood samples were collected from the individuals included in the study at the time of admission, following an 8-hour fasting period. Blood samples obtained for serum-based tests were drawn into serum separation tubes, allowed to clot at room temperature for 1 hour, and then centrifuged at 1000×g for 20 minutes. After serum separation, biochemical and hormonal parameters were analyzed immediately using an automated analyzer. For complete blood count (CBC) analyses, samples were collected into EDTA tubes. All blood samples were analyzed in the Biochemistry Laboratory of Kırıkkale University.

In our study, serum levels of 25-hydroxyvitamin D, ferritin, fasting insulin, thyroid-stimulating hormone (TSH), and free thyroxine (free T4) were measured using the electrochemiluminescence immunoassay (ECLIA) method on the Cobas 8000 e801 analyzer (Roche Diagnostics, Japan, 2019). C-reactive protein (CRP), hs-CRP, fasting plasma glucose (FPG), blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, phosphorus, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured photometrically using the Cobas 8000 c702 analyzer (Roche Diagnostics, Japan, 2018). The triglyceride-to–high-density lipoprotein cholesterol (TG/HDL-C) ratio was calculated and included in the analysis as an additional cardiometabolic risk marker. The CBC was performed using the BC-6800 Auto Hematology Analyzer (Mindray, Hong Kong, 2018) based on the SF Cube method for white blood cells and subtypes, DC impedance for platelet count, and the colorimetric method for hemoglobin. HbA1c was measured using the high-performance liquid chromatography (HPLC) method on the Premier Hb9210 device (Trinity Biotech, USA, 2020). The HOMA-IR index (homeostatic model assessment for insulin resistance) for each participant was calculated by multiplying the FPG level by the fasting insulin level and dividing the result by 405.[16]

The erythrocyte sedimentation rate (ESR) was determined using the Sistat ESR-40 analyzer (Sistat Diagnostics, Turkiye, 2018), which operates based on an automated photometric reading principle. Measurements were conducted in accordance with a procedure compliant with the Westergren method.

In the study, the patients' age (years), height (cm), and body weight (kg) were measured. Based on these data, the BMI (kg/m^2) was calculated. BMI was calculated by dividing the participants' body weight in kilograms by the square of their height in meters. Additionally, the participants' waist circumference (cm) was recorded. Waist circumference measurement was taken while standing upright on a flat surface by measuring the circumference at the level of the midline, just above both anterior superior iliac spines and aligned with the umbilicus. Systolic (SBP) and diastolic blood pressure (DBP) measurements were obtained in the seated position using a validated automatic device. Mean arterial pressure (MAP) was calculated for each patient using the standard formula: MAP=DBP+(SBP-DBP)/3.[17] The data were recorded on patient forms.

Statistical Analysis

All data collected in the study were analyzed using SPSS version 27.0. For numerical variables, mean and standard deviation were calculated. Normality analysis was performed to determine the appropriate statistical method. Comparisons among the BMI groups were performed using ANOVA when the data were normally distributed and the homogeneity of variances assumption was satisfied; otherwise, the non-parametric Kruskal-Wallis test was applied. Post hoc analyses were conducted following significant ANOVA or Kruskal-Wallis results to identify pairwise group differences, using Tukey's test or Dunn's test with Bonferroni correction, respectively. Categorical variables between groups were compared using the chi-square test. Pearson and Spearman correlation tests were used for correlation analyses depending on data distribution and were performed separately within groups as appropriate. Fisher's z transformation was applied to compare correlation coefficients between two groups.

To identify independent predictors of BMI group status, multinomial logistic regression was performed, initially including hsCRP, HOMA-IR, TRIG/HDL ratio, MPV, and other relevant laboratory and anthropometric parameters as predictors. Stepwise selection was applied to retain only statistically significant variables in the final model. Trend analysis was conducted to assess the presence of linear and non-linear (U-shaped) relationships between BMI categories and hsCRP levels. A p-value of <0.05 was considered statistically significant.

RESULTS

Groups consisted of individuals without chronic comorbidities and not on any long-term medication for any reason. In addition, all participants in all groups were non-smokers with no history of smoking,

Groups were compared in terms of age, height, waist circumference, and body weight. No significant differences were observed between the groups in terms of age and height. Each study group included an equal number of males and females (10/10). As expected, body weight and waist circumference differed significantly among the groups (both p<0.001), given that the groups were defined based on BMI ranges. The distribution of participants by sex, age, and anthropometric measurements is presented in **Table 1**.

The systemic blood pressure parameters systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were calculated for each patient according to BMI categories and compared between groups. The mean±standard deviation values for the groups are presented in **Table 2**.

Table 2. Comparison of systolic, diastolic, and mean arterial pressure values between groups

BMI group (kg/m²)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)
Group 1: underweight (<18.5) (n=20)	96.00±4.91	60.15 ± 3.50	72.10 ± 3.48
Group 2: normal (18.5-24.9) (n=20)	99.50±7.70	61.40±5.12	74.10±5.72
Group 3: overweight (25-29.9) (n=20)	114.30±7.47	77.35±4.28	89.67±5.29
Group 4: obese class I (30-34.9) (n=20)	119.70±5.38	79.35±3.13	92.80±3.78
Group 5: obese class II (35-39.9) (n=20)	119.75±4.47	83.75±3.34	95.75±3.57
Group 6: obese class III (≥40) (n=20)	124.25±2.94	93.65±3.01	103.85±2.89
p value	<0.001	<0.001	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Blood pressure and MAP differed significantly among BMI groups (one-way ANOVA, p<0.001 for all parameters). Post-hoc analyses revealed a consistent trend across all variables: groups 1 and 2 exhibited significantly lower systolic blood pressure, diastolic blood pressure, and MAP values compared with the other groups. groups 3 and 4 generally showed intermediate values with no significant differences between them for diastolic blood pressure and MAP, while group 5 displayed slightly higher values than groups 3 and 4 for diastolic blood pressure and MAP. group 6 demonstrated the highest systolic and diastolic blood pressure, as well as MAP values, and was significantly different from all other groups (p<0.05).

Groups were compared in terms of hematological parameters (white blood cell count, hemoglobin, platelet count, neutrophil count, and MPV), biochemical parameters (urea, creatinine, eGFR, sodium, potassium, calcium, phosphorus, albumin, FPG, ALT, and AST), lipid profiles (total cholesterol, LDL, HDL, triglycerides, and TG/HDL ratio), hormonal and vitamin levels (fasting insulin, TSH, free T4, and 25-OH Vitamin D), as well as inflammatory and tumor markers (CRP, hsCRP, ESR, and HOMA-IR). Statistically significant differences between the groups were observed in CRP, FPG, HbA1c, HOMA-IR, fasting insulin, total cholesterol, LDL, HDL, triglycerides, TG/HDL ratio, MPV, 25-OH Vitamin D, and ESR (p<0.05 for all). These results are summarized in **Table 3**.

Parameters found to be statistically significant in the table were evaluated using post-hoc analysis.

Post-hoc Tukey HSD analysis for CRP levels indicated that group 6 had significantly higher CRP compared with groups 2 and 3 (p<0.05). No other group comparisons reached

Table 1. Distribution of groups in terms of age, sex, height, body weight and waist circumference

BMI group (kg/m²)	Age (years)	Sex (M/F), n	Height (cm)	Body weight (kg)	Waist circumference (cm)
Group 1: underweight (<18.5) (n=20)	28.0±2.6	10/10	165.5±10.2	48.9±7.0	63.7±2.0
Group 2: normal (18.5–24.9) (n=20)	28.1±2.6	10/10	169.0±7.9	65.3±7.6	65.5±1.7
Group 3: overweight (25–29.9) (n=20)	27.8±3.6	10/10	168.3±9.1	79.0±10.6	69.3±1.5
Group 4: obese class I (30–34.9) (n=20)	27.5±3.3	10/10	162.3±6.4	85.0±6.6	71.0±1.1
Group 5: obese class II (35–39.9) (n=20)	28.2±3.5	10/10	162.8±11.3	97.7±15.1	73.1±4.0
Group 6: obese class III (≥40) (n=20)	27.4±3.3	10/10	162.5±8.9	118.2±18.7	76.5±5.1
p value	0.956	-	0.089	<0.001	<0.001

All groups were matched for sex (10 males and 10 females per group), and p values were not calculated due to equal distribution by study design

Table 3. Distribution of groups in terms of hemogram and biochemical parameters

Parameter	Group 1 underweight (n=20)	Group 2 normal (n=20)	Group 3 overweight (n=20)	Group 4 obese class I (n=20)	Group 5 obese class II (n=20)	Group 6 obese class III (n=20)	p value
Urea (mg/dl)	24.85±8.57	27.05±6.75	25.30±7.23	21.55±6.48	26.00±6.74	23.25±5.50	0.158
Creatinine (mg/dl)	0.70±0.11	0.70±0.08	0.66±0.12	0.66±0.10	0.71±0.11	0.64±0.07	0.166
eGFR	99.6±11.2	101.3±8.1	104.9±12.7	109.1±12.4	103.9±11.7	105.5±11.1	0.132
Sodium (mEq/L)	141.0±2.6	140.8±1.4	140.6±2.2	140.1±1.4	140.3±1.7	140.9±1.5	0.571
Potassium (mEq/L)	4.45±0.40	4.66±0.34	4.68±0.45	4.62±0.38	4.65±0.41	4.61±0.40	0.476
Calcium (mg/dl)	9.37±0.45	9.67±0.39	9.56±0.40	9.56±0.33	9.56±0.55	9.55±0.31	0.349
Phosphorus (mg/dl)	3.74±0.60	3.66±0.42	3.63±0.53	3.66±0.41	3.95±0.45	3.89±0.41	0.179
Albumin (g/dl)	4.44±0.26	4.56±0.21	4.55±0.26	4.50±0.34	4.51±0.39	4.58±0.27	0.714
Fasting plasma glucose (mg/dl)	92.80±10.48	95.40±11.32	91.70±13.62	89.25±3.85	97.55±10.50	99.95±12.48	0.026
CRP (mg/dl)	3.75±0.73	3.17±0.94	3.34±0.82	3.65±0.68	3.79±0.67	4.15±0.66	<0.001
ALT (U/L)	16.40±6.29	24.15±11.88	22.70±8.78	19.95±7.42	21.85±10.57	20.40±8.49	0.130
AST (U/L)	17.30±3.59	18.65±6.12	18.15±6.29	15.60±3.15	18.10±5.40	20.60±6.48	0.102
Hemoglobin A1c (%)	5.47±0.24	5.54±0.28	5.58±0.25	5.57±0.19	5.56±0.24	5.72±0.13	0.027
Total cholesterol (mg/dl)	175.9±8.0	171.6±9.2	193.0±12.8	215.1±9.4	237.9±10.7	250.3±10.6	<0.001
LDL (mg/dl)	121.8±10.7	98.3±11.5	121.3±14.5	146.3±11.9	169.8±13.9	189.2±14.2	<0.001
HDL (mg/dl)	38.5±4.68	56.5±3.44	48.5±3.59	44.8±3.48	40.3±3.65	32.5±3.63	<0.001
Triglycerides (mg/dl)	77.9±9.6	84.2±5.8	115.6±9.8	119.4±9.4	138.7±12.9	142.3±21.2	<0.001
TG/HDL ratio	2.04±0.26	1.49±0.10	2.39±0.24	2.67±0.22	3.45±0.30	4.39±0.61	<0.001
25-OH vitamin D (ng/ml)	11.4±2.0	13.1±1.8	13.1±1.9	11.6±1.9	10.5±2.5	11.8±2.6	<0.001
Ferritin (ng/ml)	35.85±17.28	39.06±11.63	32.20±8.25	36.52±7.64	38.02±8.04	39.99±6.84	0.235
Fasting insulin (µU/ml)	7.31±1.52	6.43±1.05	7.38±1.67	13.13±1.75	20.15±3.69	26.43±4.73	<0.001
TSH (mIU/L)	1.98±0.90	2.17±1.03	1.92±0.90	2.06±1.04	2.30±0.97	2.42±1.00	0.574
Free T4 (ng/dl)	1.20±0.16	1.24±0.32	1.16±0.17	1.21±0.13	1.21±0.15	1.29±0.17	0.489
White blood Cells (x10^3/µL)	7.05±1.53	6.93±1.04	7.16±1.16	7.33±1.00	7.53±0.97	7.81±0.94	0.140
MPV (fL)	10.65±0.18	9.91±0.14	10.30±0.13	10.53±0.11	10.63±0.11	10.94±0.11	<0.001
Hemoglobin (g/dl)	13.33±1.11	13.71±1.05	13.68±1.15	13.50±0.64	13.34±0.81	13.38±0.68	0.643
Platelet (10^3/µL)	238.80±50.74	241.45±39.77	227.67±47.25	239.00±42.37	211.98±21.83	225.45±27.94	0.160
Neutrophil (10^3/µL)	4.16±1.43	4.45±1.76	3.97±1.18	4.38±1.48	4.35±1.78	4.20±1.46	0.930
ESR (mm/h)	19.15±3.91	17.35±8.29	18.70±6.30	19.15±4.73	19.45±4.81	24.00±3.67	<0.001
HOMA IR	1.65±0.25	1.50±0.24	1.63±0.25	2.89±0.38	4.78±0.52	6.46±1.16	<0.001

Egfr: Estimated glomerular filtration rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG/HDL ratio: Triglyceride to high-density lipoprotein cholesterol ratio, 25-OH vitamin D, 25-hydroxyvitamin D, TSH: Thyroid-stimulating hormone, Free T4: Free thyroxine, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, HOMA-IR: Homeostasis model assessment of insulin resistance

statistical significance (p≥0.05), suggesting that systemic inflammation, as reflected by CRP, was particularly elevated in group 6 relative to some of the earlier groups.

Post-hoc Games–Howell analysis for ESR revealed that group 6 had significantly higher ESR values compared with groups 1, 2, 3, 4, and 5 (p<0.05). No significant differences were observed between groups 1, 2, 3, 4, and 5 (p≥0.05).

ANOVA revealed a weakly significant difference in FPG levels among the groups (p=0.026). Post-hoc Tukey HSD analysis indicated that group 6 had significantly higher FPG levels compared with group 1 (p=0.009). No other significant differences were observed between the remaining groups (p≥0.05).

One-way ANOVA analysis showed a marginally significant difference in HbA1c levels among the groups (p=0.027). Post-hoc Tukey HSD analysis revealed that group 6 had significantly higher HbA1c levels compared with group 1 (p=0.009). No significant differences were observed between the other groups (p≥0.05).

Post-hoc Games–Howell analysis revealed that insulin levels in groups 4, 5, and 6 were significantly higher compared with groups 1, 2, and 3 (p<0.05). Additionally, insulin levels in group 5 were significantly higher than in group 4 (p<0.05), and insulin levels in group 6 were significantly higher than in groups 4 and 5 (p≤0.001). No other significant differences were observed between the remaining groups (p≥0.05).

Post-hoc Games–Howell analysis revealed that HOMA-IR values in groups 4, 5, and 6 were significantly higher compared with groups 1, 2, and 3 (p<0.05). Additionally, HOMA-IR values in groups 5 and 6 were also significantly higher than in group 4 (p<0.05). No significant differences were observed in all other group comparisons (p≥0.05).

Post-hoc Games-Howell analysis demonstrated that triglyceride levels were significantly higher in groups 3-6 compared with groups 1 and 2 (p<0.05). No statistically significant differences were observed between groups 3 and 4 or between groups 5 and 6 (p≥0.05).

Post-hoc Tukey HSD analysis for HDL cholesterol levels showed that Group 1 had significantly lower HDL levels

compared with groups 2, 3, 4, and 6 (p<0.05), while no significant difference was observed with groups 5 (p≥0.05). Group 2 exhibited significantly higher HDL levels than all other groups (p<0.05). Group 3 had significantly higher HDL levels than groups 1, 5, and 6, but significantly lower levels than group 2 and higher levels than group 4 (p<0.05). Group 4 showed significantly higher HDL levels than groups 1, 5, and 6, but lower levels than groups 2 and 3 (p<0.05). Group 5 had significantly lower HDL levels than groups 2, 3, and 4, but higher levels than group 6, with no significant difference compared with groups 1 (p<0.05).

Post-hoc Tukey HSD analysis for total cholesterol levels indicated that group 1 had significantly lower total cholesterol compared with groups 3, 4, 5, and 6 (p < 0.05), while the difference with group 2 was not significant (p≥0.05). Group 2 also showed significantly lower total cholesterol levels than groups 3-6 (p<0.05). Group 3 had significantly higher total cholesterol compared with groups 1 and 2, but lower levels than groups 4, 5, and 6 (p<0.05). group 4 showed significantly higher total cholesterol than groups 1-3, but lower levels than groups 5 and 6 (p<0.05). Group 5 had significantly higher total cholesterol compared with groups 1-4, but lower levels than group 6 (p<0.05).

Post-hoc Tukey HSD analysis revealed significant differences in total cholesterol levels among most groups. Group 1 had significantly higher levels than group 2 (p<0.05), but did not differ from group 3 (p≥0.05); however, it had significantly lower levels compared with groups 4, 5, and 6 (p<0.05). Group 2 had significantly lower levels than all other groups (p<0.05). Group 3 did not differ from group 1 but showed significantly lower levels than groups 4, 5, and 6 (p<0.05). Group 4 had significantly higher levels than groups 1, 2, and 3, but lower levels than groups 5 and 6 (p<0.05). Group 5 showed significantly higher levels than groups 1-4, but lower levels than group 6 (p<0.05). Finally, group 6 had the highest total cholesterol levels compared with all other groups (p<0.05).

Post-hoc analysis using the Games-Howell test revealed significant differences in the TG/HDL ratio among the six groups. Group 1 had a significantly higher TG/HDL ratio than group 2 (p<0.05), but significantly lower ratios compared with groups 3-6 (p<0.05). Group 2 exhibited significantly lower TG/HDL ratios than groups 3-6 (p<0.05). Group 3 differed significantly from groups 4-6, while group 4 showed significantly lower values than groups 5 and 6 (p<0.05). Group 5 also differed significantly from group 6 (p<0.05). Overall, the TG/HDL ratio demonstrated an increasing trend across the groups, indicating progressively higher cardiometabolic risk in the later groups.

Post-hoc Tukey HSD analysis for MPV demonstrated that group 1 had significantly higher MPV values compared with groups 2 and 3, but significantly lower values than group 6 (p<0.05). No significant differences were observed between group 1 and groups 4 or 5 (p≥0.05). Group 2 exhibited significantly lower MPV values than all other groups (p<0.05). Group 3 had significantly lower MPV values than groups 4, 5, and 6 (p<0.05). No significant difference was observed between groups 4 and 5, whereas groups 6 showed significantly higher MPV values compared with all other groups (p<0.05).

Post-hoc Tukey HSD analysis for 25-OH Vitamin D levels revealed that group 2 and group 3 had significantly higher 25-OH Vitamin D levels compared with group 5 (p=0.004). No other pairwise comparisons between groups reached statistical significance (p≥0.05).

Evaluation of hsCRP Results

The mean hsCRP levels of the groups were 1.82±0.06, 1.65±0.16, 1.66±0.23, 1.71±0.15, 1.88±0.19, and 2.00±0.22 mg/L, respectively, from group 1 to group 6. The mean hsCRP levels of the groups are shown in **Figure**.

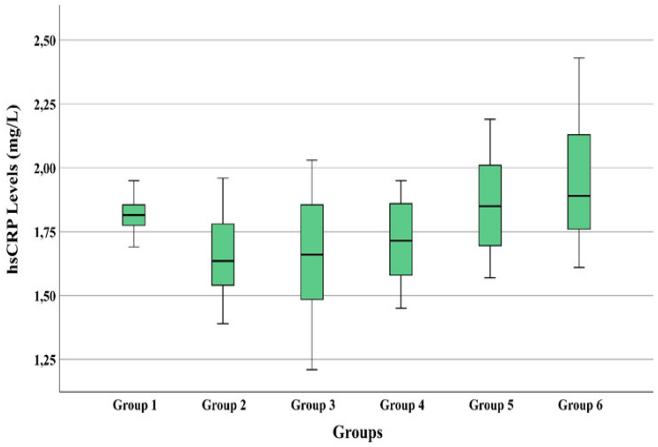

Figure. Distribution of hsCRP levels in the groups

HsCRP levels were evaluated among the six groups using one-way ANOVA, and statistically significant differences were found between the groups (p<0.001). The Games-Howell post hoc test was applied to determine which groups showed significant differences. The mean differences and p-values for statistically significant data, obtained by comparing all groups, are presented in **Table 4**.

Table 4. Games-howell post hoc results for differences in hsCRP levels between groups

Groups	Mean difference	p (games-howell)	Significance
1 vs 2	0.164	<0.001	Significant
1 vs 6	-0.187	0.015	Significant
2 vs 5	-0.229	0.003	Significant
2 vs 6	-0.350	<0.001	Significant
3 vs 5	-0.227	0.021	Significant
3 vs 6	-0.348	<0.001	Significant
4 vs 5	-0.173	0.038	Significant
4 vs 6	-0.294	<0.001	Significant

Only group comparisons with p<0.05 are shown

The relationships between hsCRP levels and other laboratory parameters were evaluated using Pearson or Spearman correlation analysis. When evaluated in all patients, hsCRP was positively correlated with CRP (r=0.31, p<0.001), total cholesterol (r=0.36, p<0.001), LDL (r=0.40, p<0.001), HDL (r=-0.41, p<0.001), triglycerides (r=0.24, p<0.001), TG/HDL ratio (r=0.37, p<0.001), fasting insulin (r=0.39, p<0.001), MPV (r=0.41, p<0.001), and HOMA-IR (r=0.40, p<0.001). No significant correlation was found between hsCRP and other parameters (p>0.05).

In different BMI groups, significant correlations between hsCRP and parameters were limited, and no strong relationship was observed, especially outside of lipid profile and insulin resistance parameters. All correlation results are presented in **Table 5**.

Table 5. Correlation between hsCRP levels and hemogram and biochemical parameters

Parameter	Group 1: underweight (n=20)	Group 2: normal (n=20)	Group 3: overweight (n=20)	Group 4: obese class I (n=20)	Group 5: obese class II (n=20)	Group 6: obese class III (n=20)	Total (n=120)
Urea (mg/dl)	-0.07 (0.756)	-0.31 (0.182)	0.07 (0.741)	0.00 (0.994)	-0.07 (0.766)	0.29 (0.213)	-0.03 (0.729)
Creatinine (mg/dl)	0.15 (0.513)	0.23 (0.312)	0.19 (0.421)	0.06 (0.781)	-0.12 (0.610)	0.21 (0.356)	0.06 (0.460)
eGFR	-0.29 (0.210)	0.29 (0.206)	0.07 (0.749)	0.03 (0.901)	0.07 (0.749)	0.04 (0.866)	0.04 (0.615)
Sodium (mEq/L)	0.05 (0.819)	0.16 (0.498)	-0.42 (0.065)	-0.34 (0.133)	0.10 (0.646)	0.12 (0.612)	-0.04 (0.662)
Potassium (mEq/L)	0.21 (0.357)	0.05 (0.813)	-0.24 (0.301)	-0.09 (0.690)	-0.14 (0.549)	0.13 (0.573)	-0.08 (0.379)
Calcium (mg/dl)	-0.00 (0.974)	-0.06 (0.778)	-0.09 (0.679)	-0.05 (0.814)	-0.10 (0.651)	0.38 (0.096)	-0.04 (0.606)
Phosphorus (mg/dl)	-0.26 (0.259)	-0.18 (0.432)	-0.23 (0.315)	0.13 (0.564)	-0.00 (0.972)	0.07 (0.758)	0.05 (0.537)
Albumin (g/dl)	0.02 (0.907)	-0.12 (0.591)	0.16 (0.494)	0.12 (0.588)	0.11 (0.634)	0.52 (0.017)*	0.14 (0.125)
Fasting plasma glucose (mg/dl)	-0.10 (0.674)	0.01 (0.957)	0.07 (0.754)	-0.15 (0.523)	0.24 (0.291)	-0.12 (0.592)	0.13 (0.136)
CRP (mg/dl)	0.04 (0.855)	0.32 (0.168)	-0.08 (0.708)	0.11 (0.646)	0.28 (0.223)	0.25 (0.287)	0.31 (<0.001)*
ALT (U/L)	-0.02 (0.927)	0.03 (0.879)	0.14 (0.530)	-0.05 (0.810)	0.07 (0.750)	0.00 (0.971)	-0.02 (0.775)
AST (U/L)	0.22 (0.340)	-0.13 (0.559)	-0.30 (0.191)	0.14 (0.553)	0.27 (0.236)	-0.18 (0.428)	0.00 (0.929)
Hemoglobin A1c (%)	-0.37 (0.105)	-0.40 (0.074)	-0.02 (0.904)	0.11 (0.631)	-0.09 (0.701)	0.20 (0.387)	0.01 (0.911)
Total cholesterol (mg/dl)	0.05 (0.810)	0.09 (0.679)	-0.10 (0.659)	0.02 (0.921)	0.34 (0.140)	-0.18 (0.425)	0.36 (<0.001)*
LDL (mg/dl)	0.01 (0.944)	0.03 (0.874)	-0.07 (0.762)	0.01 (0.937)	0.33 (0.145)	-0.25 (0.285)	0.40 (<0.001)*
HDL (mg/dl)	0.06 (0.783)	0.03 (0.894)	-0.10 (0.665)	-0.00 (0.989)	-0.17 (0.468)	0.44 (0.049)*	-0.41 (<0.001)*
Triglycerides (mg/dl)	-0.01 (0.956)	0.31 (0.181)	0.03 (0.877)	0.00 (0.983)	-0.16 (0.497)	-0.01 (0.961)	0.24 (<0.001)*
TG/HDL ratio	-0.07 (0.747)	0.32 (0.167)	0.11 (0.617)	0.00 (0.988)	0.00 (0.985)	-0.35 (0.126)	0.37 (<0.001)*
25-OH Vitamin D (ng/ml)	0.10 (0.658)	-0.16 (0.489)	-0.31 (0.175)	-0.07 (0.753)	0.01 (0.967)	0.34 (0.140)	-0.14 (0.099)
Ferritin (ng/ml)	-0.09 (0.705)	0.22 (0.350)	-0.27 (0.248)	0.30 (0.197)	0.00 (0.997)	0.04 (0.846)	0.08 (0.099)
Fasting insulin (µU/ml)	0.34 (0.141)	-0.00 (0.985)	0.18 (0.939)	0.03 (0.895)	-0.19 (0.402)	-0.06 (0.786)	0.39 (<0.001)*
TSH (mIU/L)	0.13 (0.565)	-0.19 (0.404)	-0.14 (0.539)	0.10 (0.652)	-0.03 (0.884)	0.08 (0.738)	0.04 (0.446)
Free T4 (ng/dl)	-0.27 (0.249)	0.15 (0.510)	0.17 (0.466)	0.21 (0.358)	-0.19 (0.420)	-0.27 (0.243)	0.06 (0.514)
White blood cells (x10³/µL)	0.04 (0.860)	0.01 (0.958)	0.50 (0.023)*	-0.28 (0.219)	0.19 (0.419)	-0.15 (0.518)	0.17 (0.053)
MPV (fL)	-0.17 (0.468)	-0.11 (0.644)	-0.25 (0.278)	0.03 (0.870)	0.31 (0.184)	-0.02 (0.908)	0.41 (<0.001)*
Hemoglobin (g/dl)	0.30 (0.197)	0.18 (0.448)	0.00 (0.975)	-0.17 (0.456)	0.35 (0.121)	0.24 (0.302)	0.03 (0.735)
Platelet (10³/µL)	0.18 (0.448)	-0.43 (0.058)	-0.02 (0.925)	0.09 (0.688)	0.05 (0.833)	-0.13 (0.559)	-0.11 (0.197)
Neutrophil (10³/µL)	-0.06 (0.794)	0.06 (0.787)	-0.54 (0.013)*	0.05 (0.821)	0.38 (0.098)	-0.22 (0.331)	0.11 (0.209)
ESR (mm/h)	-0.24 (0.298)	-0.17 (0.450)	-0.15 (0.509)	0.03 (0.885)	-0.12 (0.600)	0.31 (0.176)	0.10 (0.235)
HOMA IR	0.38 (0.098)	-0.00 (0.976)	0.10 (0.670)	-0.00 (0.985)	-0.06 (0.798)	-0.19 (0.419)	0.40 (<0.001)*

eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG/HDL ratio: Triglyceride to high-density lipoprotein cholesterol ratio, 25-OH vitamin D: 25-hydroxyvitamin D, TSH: Thyroid-stimulating hormone, Free T4: Free thyroxine, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, HOMA-IR: Homeostasis model assessment of insulin resistance. Correlation coefficients (r) and corresponding p-values are shown in parentheses; statistically significant correlations are denoted by an asterisk (*)

Results showed a significant quadratic association between BMI and hsCRP (cBMI²: B=0.000, p=0.030), indicating a U-shaped pattern, with higher hsCRP levels observed at both low and high BMI ranges, and lower levels at intermediate BMI. Linear cBMI was not significant (B=-0.006, p=0.114), and all covariates showed no statistically significant effects, confirming the minimal adjustment approach. This approach provides a stable and robust analysis, avoiding multicollinearity and outlier issues encountered in previous multinomial logistic regression models. These data are presented in **Table 6**.

These findings indicate that the relationship between BMI and inflammatory burden is not solely a linear increase but rather exhibits a non-linear (U-shaped) pattern that varies across different BMI levels. Trend analysis defines the shape of the relationship, and group-based comparisons were

Table 6. Association between BMI and hsCRP: linear quadratic regression

Variable	B	Std. error	Beta	t	p	95% CI	VIF
Constant	1.293	0.193	–	6.703	0.000	0.911-1.676	–
cBMI	-0.006	0.004	-0.263	-1.591	0.114	-0.013-0.001	4.038
cBMI²	0.000	0.000	0.194	2.202	0.030	0.000-0.001	1.141
FPG	0.001	0.002	0.049	0.566	0.573	-0.002-0.004	1.104
LDL	0.002	0.001	0.305	1.819	0.072	0.000-0.004	4.157
HOMA-IR	0.031	0.020	0.291	1.511	0.133	-0.010-0.071	5.449

B: Unstandardized regression coefficient, Beta: Standardized regression coefficient, SE: Standard error, CI: Confidence interval, VIF: Variance inflation factor, Cbmi: BMI centered by subtracting the mean, cBMI²: Quadratic term of centered BMI, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, LDL: Low-density lipoprotein cholesterol, FPG: Fasting plasma glucose. Dependent variable: natural logarithm of hsCRP (ln_hsCRP). The model includes minimal metabolic covariates (fasting glucose, LDL, HOMA-IR) to adjust for potential confounding. VIF values <5 indicate acceptable multicollinearity. cBMI² significance demonstrates a U-shaped association between BMI and hsCRP. Linear cBMI term represents deviation from mean BMI

used to assess which BMI group exhibited the minimum inflammatory burden. In previous analyses and post-hoc comparisons, the middle BMI group (group 2) was found to have the lowest significant values in terms of inflammatory burden, while the low BMI group (group 1) showed increased cardiometabolic risk indicators.

DISCUSSION

Our study found that hsCRP levels were 1.82±0.06, 1.65±0.16, 1.66±0.23, 1.71±0.15, 1.88±0.19, and 2.00±0.22 mg/L, respectively, from group 1 to group 6. In light of this data, the most important result of our study is that the relationship between BMI and hs-CRP, one of the inflammatory and cardiometabolic markers, exhibits a U-shaped distribution rather than a linear one, and that increased inflammatory and metabolic risk is revealed in the low BMI group. A review of the literature reveals that a study by Liqiang et al.[18] demonstrated that the relationship between inflammatory parameters such as hsCRP and BMI is non-linear and parallels the increase in obesity levels. Similarly, the study by Zhang et al.[19] emphasized the non-linear relationship between hsCRP and BMI and demonstrated a U-shaped or J-shaped distribution, revealing that hsCRP levels were high, particularly in the low BMI group. The study by Baek and Yoon emphasized that hsCRP levels increase as the degree of obesity increases and showed that hsCRP levels increase even more in patients who are both obese and have inflammatory findings.[20] In contrast, a study by Ghiasi Hafezi et al.[21] found a perfectly linear relationship between BMI and hsCRP levels. Similarly, in the study conducted by Tassone et al.,[22] the relationship between BMI and hsCRP was found to be linear. The possible difference between the results of our study and those of the two other studies can be attributed to sample selection. Furthermore, the small number of patients with extreme BMI values in both studies suggests that this is the fundamental reason for the emergence of a linear structure. However, in these studies, BMI data was used as a linear variable rather than a categorical variable, and we believe that the resulting analytical models directly revealing linear trends may be the probable cause of this outcome.

In our study, a quadratic linear regression model revealed a significant U-shaped association between BMI and hsCRP levels ($cBMI^2$: B=0.000, p=0.030), indicating that inflammatory burden is higher at both low and high BMI values and lower in the middle BMI range. This pattern was observed after adjusting for minimal metabolic covariates (fasting glucose, LDL, HOMA-IR), supporting the robustness of the U-shaped relationship between BMI and cardiometabolic risk. The study by Liu-Galvin et al.[23] reported that individuals within the normal BMI range may also carry a significant risk of inflammatory burden and metabolic impairment, emphasizing that BMI alone does not fully reflect cardiometabolic health. The study by Park et al.[24] emphasized that individuals with a normal BMI may be cardiometabolically unhealthy due to a high body fat percentage, and that BMI data alone is not sufficient to indicate cardiometabolic risk. In a meta-analysis conducted by Mohammadian Khonsar et al.,[25] it was demonstrated that cardiometabolic parameters were elevated in patients with normal BMI but high body fat percentage, emphasizing that BMI data alone is insufficient. Similar to the literature, our study also demonstrated that BMI should not be considered solely as an index reflecting body weight; when evaluated alongside inflammatory and metabolic risk markers, it can reveal different risk profiles. However, it also shows that a low BMI does not always offer a protective metabolic profile and that inflammatory and cardiometabolic risk is lower within the normal BMI range. This result shows that cardiometabolic risk is not limited to increases in obesity levels but can also be significant at low BMI levels, emphasizing that low BMI should not be considered a metabolically safe profile.

Our study revealed a significant relationship between increased BMI and cardiometabolic risk parameters. The study by Zhang et al.[26] showed that both inflammatory markers and cardiometabolic risk were higher, particularly in individuals with high BMI. The study by Ramos-Arellano et al.[27] specifically examined individuals with high BMI; it revealed that cardiometabolic indicators such as hsCRP, fasting insulin levels, lipid levels, and MAP were significantly elevated. The study by Fujii et al.[28] also found that as BMI increases, blood pressure rises and cardiometabolic parameters deteriorate. However, a study by Palatini et al.[29] showed that there was no deterioration in cardiometabolic risk parameters in young patients with high BMI. In a prospective cohort analysis conducted by Li et al.,[30] no significant deterioration in cardiometabolic risk parameters was observed in overweight and obese individuals compared to those of normal weight. It is anticipated that the inconsistent results between our study and the two other studies stem from the patient population. The fact that the individuals included in both studies were young or middle-aged may explain why there was no significant deterioration in cardiometabolic risk parameters.

Our study demonstrated a U-shaped association between BMI and hsCRP levels using a quadratic linear regression model, showing that inflammatory burden and cardiometabolic risk were relatively low in the middle BMI range, while risk increased at both low and high BMI values. These results are consistent with previously reported high BMI-related risks in the literature and additionally highlight an elevated risk in the low BMI group. Numerous clinical studies have been conducted on the possible biochemical mechanism underlying this finding. A study by Ellulu et al.[31] showed that increased adipokine production in the high BMI group increased hsCRP synthesis in the liver and that this effect was associated with risk factors such as insulin resistance, dyslipidemia, and blood pressure. In a study by Buchmann et al.[32] investigating inflammation, metabolic syndrome, and muscle mass loss, elevated hsCRP levels were shown to be associated with metabolic and muscle metabolism impairment. Although similar studies in the low BMI group are limited, a study by Nakajima et al.[33] observed impaired inflammatory parameters in elderly patients. Similarly, Li et al.[34] reported that inflammatory parameters worsened in elderly patients. Although the authors did not demonstrate the existence of a directly measured biological mechanism linking low body weight to inflammation, conceptual frameworks such as the malnutrition-inflammation complex provide an explanation for the elevation of inflammatory markers in low BMI. These findings suggest that the detection of increased inflammation in the low BMI group in our study has a reasonable basis in the literature.

The clinical significance of this study is that it emphasizes that BMI may be limited in assessing cardiometabolic risk and should be supported by additional biomarkers. The study

by Coral et al.[35] emphasized that BMI data alone may not be a sufficient indicator for assessing cardiometabolic risk. The study by Liu-Galvin et al.[36] also supports the current findings, emphasizing that individuals with low BMI do not always have a protective metabolic profile and may carry a risk in terms of inflammatory burden. Our findings suggest that BMI alone may not be a sufficient indicator for assessing cardiometabolic risk, consistent with the literature. However, it is thought that evaluations based solely on anthropometric measurements may be insufficient in the clinical follow-up of individuals with extreme BMI values and that a more comprehensive approach incorporating inflammatory/metabolic markers may be beneficial. In this context, our study highlights the potential importance of considering inflammatory parameters in addition to BMI in the assessment of cardiometabolic risk, as easily accessible inflammatory markers such as hsCRP show significant differences across BMI categories.

Overall, the findings indicate that BMI is not the sole determinant of cardiometabolic risk and that individuals with low BMI should also be carefully monitored for inflammatory burden and metabolic risk. These results emphasize the importance of considering inflammatory parameters in addition to BMI in clinical practice and shed light on the development of risk assessment strategies targeting the low BMI group.

Strengths of the Study

The analysis of BMI in multiple categories and the use of readily accessible inflammatory markers such as hsCRP have enabled a detailed examination of cardiometabolic risk in low and high BMI groups. Demonstrating that inflammatory parameters are significantly elevated, particularly in the low BMI group, constitutes the most important and original contribution of this study, as this is a topic rarely addressed in the literature. This finding emphasizes that individuals with low BMI do not always have a protective metabolic profile and may carry risk in terms of inflammatory burden.

Limitations

This study has some limitations. First, due to its cross-sectional design, causal inferences cannot be made regarding the relationships between BMI and inflammatory and cardiometabolic markers. Additionally, the relatively limited number of patients in the groups formed according to BMI categories may have restricted the detection of within-group variation and smaller effect sizes. Although BMI is a practical and widely used measure, it may not reflect body composition and fat distribution alone; waist circumference measurements, which we used in this study, may contribute to a more accurate assessment of cardiometabolic risk. Furthermore, hsCRP measurements were taken at a single time point, and temporal changes in inflammatory load could not be evaluated. The absence of other inflammatory cytokines, such as IL-6 and TNF-α, or detailed nutrition and physical activity data in the study, limits the in-depth investigation of possible mechanisms.

CONCLUSION

In this study, the relationship between BMI and cardiometabolic risk markers was not observed to be solely linear. Our analyses showed that even in the low BMI group, the inflammatory burden (hsCRP) increased and cardiometabolic risk rose. In the moderate BMI group, the risk was relatively low, while in the high BMI group, the risk increased again, thus revealing a U-shaped trend. The findings support that not only obesity but also low BMI may be an important determinant of cardiometabolic risk. These results emphasize the need to monitor individuals with low BMI for cardiometabolic risk in clinical evaluations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Etlik City Hospital Clinical Researches Ethics Committee (Date: 05.07.2023, Decision No: 2023-25).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: A.H., A.Ç.; Design: A.H., A.Ç.; Control: A.H., A.Ç.; Data Collection and/or Processing: A.H.; Analysis an/or Interpretation: A.H., A.Ç.; Literature Review: A.H.; Article Writing: A.H., A.Ç.; Critical Review: A.H., A.Ç.

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