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Markers of Non-alcoholic Fatty Liver Disease Among Metabolically Healthy and Unhealthy Obese Individuals

Metabolik Olarak Sağlıklı ve Sağlıksız Obez Bireylerde Non-Alkolik Yağlı Karaciğer Hastalığının Belirteçleri

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ABSTRACT

Objectives: Obesity, which is defined as excessive and abnormal accumulation of adipose tissue, can lead to various systemic diseases beyond the deterioration of the quality of life of individuals. In this study, we aimed to compare the biochemical parameters, the presence of hepatosteatosis, non-invasive liver fibrous scores (NAFLD), and common carotid artery (CCA) media thickness in metabolically healthy obese (MHO) and metabolically unhealthy obese (MUHO).

Methods: Charts of patients who were admitted to the internal medicine outpatient clinic between June 2018 and June 2019 were retrospectively evaluated. Patients with body mass index ≥30 kg/m2 were evaluated for inclusion in the study. Participants were divided into two groups as MHO and MUHO, according to the Third National Health and Nutrition Examination Survey III criteria. The presence of liver fibrosis was calculated using NAFLD fibrosis score (NFS) and Fib-4 score. Patients categorized as MHO and MUHO were compared according to demographic characteristics, biochemical parameters, and radiological findings.

Results: Totally, 123 obese patients were enrolled into the study, and 95 patients were classified as MUHO. CCA was measured as 0.6 mm in MHO and 0.7 mm in MHUO, and the difference was statically significant in favor of MHO ($p<0.001$). Homeostatic model assessment of insulin resistance (HOMA-IR), insulin level, and triglyceride/glucose index (TyG) index were significantly higher in MUHO. The difference of Fib-4 indexes in MHO and MUHO was not statistically significant ($p=0.100$). However, NFS was significantly better in MHO ($p<0.001$).

Conclusion: The present study showed that almost four out of five obese patients were classified as MUHO. In addition, levels of glutamyl transferase, HOMA-IR, insulin, and TyG index were significantly higher in MUHO in comparison with MHO. Moreover, MUHO cases had significantly higher CCA media thickness levels, liver size, and worse NFS.

Keywords: Healthy obesity; homeostatic model assessment of insulin resistance; non-alcoholic fatty liver disease; non-invasive liver fibrous scores; triglyceride/glucose index.

ÖZET

Amaç: Aşırı ve anormal yağ dokusu birikimi olarak tanımlanan obezite kişilerin yaşam kalitesinin bozulmasının ötesinde çeşitli sistemik hastalıklara da yol açabilmektedir. Bu çalışmada, metabolik olarak sağlıklı obez (MHO) ve metabolik olarak sağlıksız obezde (MUHO) biyokimyasal parametrelerin, hepatosteatoz varlığının, invaziv olmayan karaciğer fibröz skorlarının (NAFLD) ve ana karotid arter (CCA) media kalınlıklarının karşılaştırılmaysı amaçlandı.

Yöntem: Haziran 2018-Haziran 2019 tarihleri arasında dahiliye polikliniğine başvuran hastaların dosyaları retrospektif olarak incelendi. Beden kitle indeksi ≥30 kg/m2 olan hastalar çalışmaya dahil edildi. Katılımcılar, 3. Ulusal Sağlık ve Beslenme Sınavı Anketi III kriterlerine göre MHO ve MUHO olarak iki gruba ayrıldı. Karaciğer fibrozu varlığı NAFLD fibroz skoru (NFS) ve Fib-4 skoru kullanılarak hesaplandı. MHO ve MUHO olarak sınıflandırılan hastalar demografik özellikler, biyokimyasal parametreler ve radyolojik bulgular açısından karşılaştırıldı.

Bulgular: Çalışmaya toplam 123 obez hasta alındı ve 95 hasta MUHO olarak sınıflandırıldı. CCA, MHO'da 0,6 mm, MUHO'da 0,7 mm olarak ölçüldü ve aradaki fark MHO lehine istatistiksel olarak anlamlıydı (p<0,001). İnsülin direnci (HOMA-IR), insülin seviyesi ve trigliserit/glukoz indeksinin (TyG) homeostatik model değerlendirmesi MUHO'da anlamlı derecede yüksekti. MHO ve MUHO'daki Fib-4 indekslerinin farkı istatistiksel olarak anlamlı değildi (p=0,10). Ancak NFS, MHO'da anlamlı olarak daha iyiydi (p<0,001).

Sonuç: Bu çalışma, beş obez hastadan yaklaşık dördünün MUHO olarak sınıflandırıldığını gösterdi. Ek olarak, GGT, HOMA-IR, insülin ve TyG indeksi seviyeleri, MHO'ya kıyasla MUHO'da anlamlı derecede yüksekti. Ayrıca, MUHO olgularında önemli ölçüde daha yüksek CCA media kalınlığı, karaciğer boyutu ve daha kötü NFS vardı.

Anahtar sözcükler: Sağlıklı obez; HOMA-IR; NAFLD fibrozis skoru; non-alkolik yağlı karaciğer hastalığı; trigliserit/glukoz indeksi.

Obesity is simply defined as an accumulation of excessive and abnormal adipose tissue that may deteriorate human health. The World Health Organization uses the body mass index (BMI) scale for the definition of obesity and qualifies adults with BMI ≥30 kg/m^2 as obese.[1] Due to changes in dietary habits and increases in sedentary lifestyles, obesity has become a pandemic disease and 40% of the world population will be obese in 2050 according to estimates.[2] Beyond the economic burden on the health system and the deterioration of the person's quality of life, numerous studies stated there were significant correlations between obesity with hypertension, diabetes mellitus, cardiac diseases, malignancies, and liver diseases.[3,4]

Interestingly, some studies found that some obese patients with similar BMI were more resistant to obesity-related diseases. Despite the increased body fat rate of these individuals compared to individuals with normal BMI, metabolic factors such as insulin sensitivity, blood lipid levels, blood pressure, and inflammation markers were observed to be less or not as impaired as expected, and they were named metabolically "healthy" obese (MHO).[5] One of the most common liver diseases associated with obesity is non-alcoholic fatty liver disease non-invasive liver fibrous scores (NAFLD). Untreated NAFLD may remain stable but result in cirrhosis and hepatocellular carcinoma formation.[6] Previous studies emphasized the importance of imaging techniques and laboratory biomarkers for the identification of liver fibrosis.

Differences in biochemical and radiological parameters in MHO and metabolically unhealthy obese (MUHO) are still under investigation. In the present study, we compared the biochemical parameters, presence of hepatic steatosis, non-invasive liver fibrosis scores, and common carotid artery (CCA) thickness in MHO and MUHO.

Methods

This study has been conducted in accordance with the Helsinki Declaration, ensuring the adherence to its ethical principles and the respect for privacy rights throughout the research process.

Charts of patients who were admitted to the internal medicine outpatient clinic between June 2018 and June 2019 were retrospectively evaluated. Local ethics committee approval was obtained with ID number 128–2021 and informed consent was obtained from all patients for the use of their data. Patients with BMI ≥30 kg/m^2 were evaluated for inclusion in the study. Patients over 30 years of age, whose CCA was measured by color Doppler USG and the presence of hepatic steatosis was evaluated by abdominal ultrasonography were included in the study. Systolic and diastolic blood pressures were measured in the sitting position and after resting for at least 5 min. Blood pressure measurements were made twice for each individual and the mean value was recorded. Waist circumference was measured based on the midpoint of the distance between the arch costa and the anterior superior iliac spine. Furthermore, biochemical parameters such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), glomerular filtration rate (GFR), uric acid, C reactive protein (CRP), ferritin, insulin level, homeostatic model assessment of insulin resistance (HOMA-IR), triglyceride/glucose (TyG) index and complete blood count were examined in all patients. NAFLD fibrosis score (NFS) and Fib-4 score were used to calculate the presence of liver fibrosis. Exclusion criteria were patients with BMI ≤30 kg/m^2, patients with incomplete data and patients with a history of liver and/or carotid artery surgery, patients with metastasized cancer in the liver, and patients with primary liver cancer. Patients were divided into two groups as MHO and MUHO, according to the Third National Health and Nutrition Examination Survey (NHANES) III criteria and were compared according to demographic characteristics, biochemical parameters, and radiological findings.

Homeostatic Model Evaluation of HOMA-IR and TyG Index

Homeostatic model evaluation of HOMA-IR was calculated as fasting glucose (mg/dL) x fasting insulin (μU/mL)/405. HOMA-IR over 2.5 was considered high.[7] To define the

TyG index, the formula TyG= Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2] formula.[8]

Evaluation of Hepatic Fibrosis with Liver NFS and Fib-4 Score

While calculating NFS, the following formula was used; NFS=–1.675 + (0.037×age) + (0.094×BMI) + (1.13×hyperglycemia) + (0.99×AST/ALT ratio) – (0.013×platelet count) – (0.66×albumin). Patients were classified as having low, moderate, or high probability of fibrosis according to scores < –1.455, –1.455 ≤ score ≤0.676, and score >0.676, respectively.[9] In addition, the Fib-4 scoring system including patient age, platelet count, AST, and ALT was used (Fib-4=Age (years) × AST (U/L)/[PLT (109/L) × ALT 1/2 (U/L)]. Patients were categorized as low, moderate, or high probability of fibrosis according to scores <1.45, 1.45 ≤ score ≤3.25, and score >3.25, respectively.[10]

Statistical Analysis

Categorical variables are presented as numbers and percentages. Study data are summarized as mean±standard deviation. The statistical analysis was performed using the SPSS 16.0 for Windows. The distributions of the variables were evaluated using the Kolmogorov–Smirnov z-test. The Mann–Whitney U test was used to analyze non-normally distributed variables, whereas T-tests were used to analyze normally distributed variables. P<0.05 was considered statistically significant.

Results

In total, 123 obese patients were enrolled in the study, and 95 patients were classified as MUHO. The mean age of MHO and MUHO was 49.5 years and 55.7 years, respectively (p=0.003). The gender, mean Achilles diameter and mean liver size were comparable between groups (p=0.120, p=0.423, and p=0.450, respectively). However, CCA was measured as 0.6 in MHO and 0.7 in MHUO, and the difference was statistically significant in favor of MHO (p<0.001). In addition, the mean liver size was 140.8 mm in MHO and 154.1 mm in MUHO (p=0.001) (Table 1).

The GGT level was significantly higher in MUHO (31.2 IU/L vs. 21.8 IU/L, p=0.040), but levels of ALP, LDH, AST, ALT, creatinine, e-GFR and uric acid were similar between the groups (p=0.450, p=0.330, p=0.540, p=0.680, p=0.290, p=0.610 and p=0.370, respectively). In contrast, HOMA-IR (2.1 vs. 3.7, p=0.005), insulin level (8.7 IU/L vs. 12.9 IU/L, p=0.028), and TyG index (8.7 vs. 9.4, p<0.001) were significantly higher in MUHO. Furthermore, the mean neutrophil count was 3766.1 in MHO and 4249.5 in MUHO (p=0.030). The fib-4 index was 0.9 and 1.1 in MHO and MUHO and the difference was not statically significant (p=0.100). However, NFS was –1.5 in MHO and –0.4 in MUHO, and NFS was significantly better in MHO (p<0.001) (Table 2).

Table 1. Comparison of demographic characteristics and radiological parameters between metabolically healthy and unhealthy obese patients

	Healthy obese (n=28)		Unhealthy obese (n=95)		p
	n	%	n	%	
Age (years)	49.5±9.4		55.7±9.4		**0.003**
Gender					0.120
Female	16	57.1	69	72.6	
Male	12	42.9	26	27.4	
CCA (mm)	0.6±0.1		0.7±0.2		**<0.001**
Achilles diameter (cm)	3.4±0.6		4.1±0.9		0.423
Liver size (mm)	140.8±13.6		154.1±18.9		**0.001**
Liver median (mm)	61.8±55.5		53.0±47.5		0.450

CCA: Common carotid artery media thickness

The distribution of NFS between MHO and MUHO was significantly different (p<0.001). A total of 15 patients in MHO and 16 patients in MHUO were classified as F0-F2, whereas 13 patients in MHO and 61 patients in MUHO were classified as indeterminate. Finally, no MHO patient was categorized as F3- F4, but 18 patients in MUHO were categorized as F3-F4 according to NFS. Contrarily, the distribution of Fib-4 indexes according to MHO and MUHO was similar (p=0.304). Distributions of NFS and Fib-4 according to MHO and MUHO indexes are summarized in Table 3.

Discussion

The incidence of obesity is increasing, and understanding the impact of obesity subtypes (MHO and MUHO) on human health will provide the opportunity for early diagnosis and treatment in these patients. We aimed to clarify differences in biochemical, radiological, and non-invasive liver fibrosis scores in MHO and MUHO in this study. We found a significantly increment in GGT, HOMA-IR, insulin, TyG index, and neutrophil count levels in MUHO. In addition, MUHO had significantly higher CCA, liver size, and worse NFS.

Table 2. Comparison of biochemical parameters and non-invasive liver fibrosis scores between metabolically healthy and unhealthy obese patients

	Healthy obese (n=28)	Unhealthy obese (n=95)	p
GGT (IU/L)	21.8±16.8	31.2±22.3	**0.040**
ALP (IU/L)	83.9±25.5	88.6±28.7	0.450
LDH (IU/L)	197.2±28.5	189.1±36.1	0.330
AST (IU/L)	21.5±6.2	23.2±13.9	0.540
ALT (IU/L)	22.3±12.2	23.6±16.0	0.680
Creatinine (mg/dL)	0.7±0.1	0.7±0.2	0.290
eGFR (mL/dk/1.73 m^2)	100.9±22.1	94.8±19.2	0.610
Uric acid (mg/dL)	5.1±1.0	5.3±1.3	0.370
HOMA-IR	2.1±0.9	3.7±3.2	**0.005**
Insulin (mIU/L)	8.7±3.1	12.9±9.8	**0.028**
TyG index	8.7±0.5	9.4±0.6	**<0.001**
CRP (mg/L)	6.4±6.0	5.6±4.3	0.460
Ferritin (ng/mL)	44.5±33.6	46.3±40.0	0.830
Neutrophil (uL)	3766.1±848.8	4249.5±1427.2	**0.030**
Lymphocyte (uL)	2428.6±638.9	2666.3±824.1	0.220
Platelet (uL)	279000.0±53723.6	270178.9±62757.4	
NAFLD fibrosis score	−1.5±1.2	−0.4±1.2	**<0.001**
Fib 4 index	0.9±0.3	1.1±0.7	0.100
AST/ALT	1.1±0.3	1.1±0.4	0.710

GGT: Glutamyl transferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GFR: Glomerular filtration rate; HOMA-IR: Homeostatic model assessment of insulin resistance; TyG: Triglyceride/glucose; CRP: C reactive protein; NAFLD: Non-alcoholic fatty liver disease; Fib 4: Fibrosis 4.

Table 3. Comparison of NAFLD fibrosis score and Fib-4 score between healthy and unhealthy obese patients

	Healthy obese (n=28)		Unhealthy obese (n=95)		p
	n	%	n	%	
NAFLD score					
F0-F2 n=31	15	48.4	16	51.6	**<0.001**
Indeterminate n=74	13	17.6	61	82.4	
F3-F4 n=18	0	0	18	100	
Fib-4 score					
<1.45 n=108	26	24.1	82	75.9	0.304
1.45–3.25 n=13	2	15.4	11	84.6	
>3.25 n=2	0	0	2	100	

NAFLD: Non-alcoholic fatty liver disease; Fib-4: Fibrosis-4.

The NFS was developed to evaluate the stabilization or progression risk of NAFLD to advanced liver cirrhosis and end-stage liver disease. Furthermore, previous reports demonstrated that worse NFS was associated with systemic diseases apart from liver pathologies. Zuo et al.[11] analyzed the relationship between NFS and chronic kidney disease in 4042 patients, and the authors concluded that worse NFS was related with a high risk of chronic kidney disease. In another study, Treeprasertsuk et al.[12] studied the effect of NFS on the survival of patients with coronary artery disease, and the authors stated that higher NFS at baseline was a predictive factor for death in patients with coronary artery disease. In this study, we found significantly worse NFS in MUHO, so these patients are more likely to experience liver disease and general health problems throughout their lifetime.

Insulin and HOMA-IR levels are important parameters to define cardiologic and metabolic risks in the adult population. Salgado et al.[13] compared patients with NAFLD and healthy individuals with regard to insulin and HOMA-IR levels, and both insulin and HOMA-IR levels were significantly higher in patients with NAFLD. In addition, Salgado et al.[13] stated that HOMA-IR values ≥2.0 or 2.5 had diagnostic value in distinguishing patients with NAFLD from the control group. In another study, Fujii et al.[14] found significantly higher levels of insulin and HOMA-IR in diabetic patients with NAFLD and emphasized that insulin levels≥12.0 µU/mL, and HOMA-IR ≥2.90 were associated with advanced liver fibrosis. In accordance with the literature, we found significantly higher levels of insulin and HOMA-IR in MUHO.

The TyG index is a practical marker that significantly increases in metabolic syndrome, and previous reports showed a higher TyG index in patients with coronary artery disease, stroke, and NAFLD. Kitae et al.[15] analyzed 16,093 individuals, and the authors divided the study population into three subgroups according to TyG index. Kitae et al.[15] found that 8.48 ≤ TyG in men and 7.97 ≤ TyG in women significantly increased the NAFLD risk in comparison with TyG < 8.00 in men and TyG < 7.53 in women. Moreover, Zheng et al.[16] stated that TyG >8.52 was a useful tool to predict the incidence of NAFLD. In the present study, we found significantly higher levels of TyG in MUHO.

Glutamyl–transferase has an important role as a pro-oxidant and is a direct marker of liver damage and liver size, which could be a direct finding of hepatic steatosis and liver pathologies. Tahan et al.[17] compared NAFLD patients with normal GGT levels and patients with 2 times the upper limit of normal GGT levels, and stated that the fibrosis stage was significantly associated with higher GGT level. Furthermore,

Ballestri et al.[18] emphasized the increased liver size in patients with NAFLD. We found significant increases in GGT level and liver size in MUHO compared with MHO. However, we did not use sonoelastography while evaluating the liver in NAFLD patients, which may be a subject for another study.

CCA has become an important parameter for the evaluation of patients with metabolic syndrome and NAFLD. Farcas et al.[19] analyzed the relationship between NAFLD and CCA in 100 individuals, and the authors found that increased CCA media thickness was a risk factor for hepatic fat accumulation. In another study by Demircioglu et al.,[20] the CCA of 80 obese patients was evaluated and they found a significant correlation between increased CCA thickness and hepatic steatosis grade. Similarly, we found increased CCA in MUHO.

The present study has some limitations. The retrospective nature of our study and the relatively small patient number can be considered the two main limitations. In addition, we performed a cross-sectional study and did not investigate the long-term effect of MUHO on the parameters studied. Moreover, we had no data about how long patients had been MHO or MUHO. The effect of obesity duration on biochemical parameters and radiological findings may be a subject of further studies.

Conclusion

In conclusion, the present study showed that almost four out of five obese patients were classified as MUHO. In addition, levels of GGT, HOMA-IR, insulin, and TyG index were significantly higher in MUHO in comparison with MHO. Moreover, MUHO cases had significantly higher CCA level, liver size, and worse NFS. The findings of the present study should be confirmed by prospective randomized studies with larger patient numbers.

Disclosures

Ethics Committee Approval: The study was approved by Haseki Training and Research Hospital Clinical Research Ethics Committee, Date: 01.12.2021, decision number: 128–2021.

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Conflict of Interest: None declared.

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