ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2024;(4):442-453 // 10.5505/amj.2024.43778

THE RELATIONSHIP BETWEEN HEPATIC STEATOSIS INDEX (HSI) AND CORTISOL METABOLISM IN OBESE PATIENTS

Rahime Evra Karakaya[1], Abbas Ali Tam[2], Sevgul Fakı[3], Gülsüm Karaahmetli[3], Pervin Demir[4], Oya Topaloglu[2], Didem Ozdemir[2], Reyhan Ersoy[2]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

[2]Department of Endocrinology and Metabolism, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

[3]Department of Endocrinology and Metabolism, Ankara Bilkent City Hospital, Ankara, Türkiye

[4]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

Correspondence:
Rahime Evra Karakaya (e-mail:evracakir1@gmail.com)

Submitted: 24.10.2024 // Accepted: 12.12.2024

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: This study aims to investigate the relationship between blood cortisol, 24-hour urinary cortisol, and cortisol levels after overnight administration of 1 mg dexamethasone with liver steatosis in obese subjects.

Materials and Methods: Blood cortisol, 24-hour urinary cortisol, 1 mg Dexamethasone suppression test (DST) cortisol levels, and anthropometric measurements of obese patients were retrospectively recorded. Liver steatosis was assessed using ultrasonography (USG) results and the Hepatic steatosis index (HSI) was calculated from the recorded data.

Results: The mean blood cortisol of the 296 patients included in the study was 13.51±4.74 µg/dL (median=12.9; min= 3.3; max=35.8), the mean 24-hour urinary cortisol was 22.9±27.65 µg/dL (median=16.22; min=3.08; max=350.28), the mean 1 mg DST cortisol was 0.76±0.29 µg/dL (median=0.7; min=0.5; max=2), and the mean HSI was 56.96±8.12. No significant relationship was found between cortisol levels and HSI ($p>0.05$). After adjustment for age, sex, and comorbidities, the correlation between HSI and 1 mg DST cortisol was higher in the group without fatty liver ($rs=0.355$) than in the group with fatty liver ($rs=0.060$) ($p=0.032$).

Conclusion: Further research is needed to better understand the complex relationship between HSI and cortisol in obese individuals.

Keywords: Cortisol, obesity, liver steatosis, hepatic steatosis index.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a group of liver diseases ranging from cirrhosis, characterised by varying degrees of liver necrosis and fibrosis, to advanced liver disease and hepatocellular carcinoma.[1] About 2% of people with simple steatosis may progress to end-stage cirrhosis over 20 years. People with steatohepatitis or fibrosis have a 50% chance of developing cirrhosis within two years.[2]

NAFLD is the most common chronic liver disease in the world, with an estimated prevalence of between 25% and 45% in the general population[3], but its prevalence is even higher, affecting up to 70% of people with obesity and type 2 diabetes.[4]

The underlying mechanisms of NAFLD are complex and not fully understood, although insulin resistance is widely recognised as a key factor in its onset and progression.[5] Insulin resistance leads to liver fat accumulation by promoting de novo lipogenesis, reducing fatty acid beta-oxidation and increasing the breakdown of very-low-density lipoprotein (VLDL). It also increases the release of fat from adipose tissue, leading to a greater influx of fatty acids into the liver.[6]

NAFLD is strongly associated with visceral obesity, dyslipidaemia, insulin resistance and type 2 diabetes, suggesting a significant role in the metabolic syndrome.[7] While it is prevalent in up to 80% of obese individuals, it can also be observed in 16% of individuals with a normal body mass index (BMI) who have no metabolic risk factors.[8]

Previous research has linked high levels of both endogenous and exogenous glucocorticoids to central obesity and metabolic syndrome.[9-11] In overweight or obese individuals, plasma cortisol levels may be comparable or even lower than in non-obese individuals, suggesting possible alterations in cortisol metabolism in some cases.[12]

Glucocorticoids and their role in regulating glucocorticoid metabolism are critical in the development of NAFLD. Alterations in hepatic glucocorticoid metabolism may lead to increased cortisol production in individuals with NAFLD.[13] Understanding the relationship between cortisol metabolism, obesity and NAFLD may provide insights into how glucocorticoids influence these conditions and help to develop new approaches for prevention and treatment. This study aims to investigate the relationship between blood cortisol, 24-hour urinary cortisol and 1 mg DST cortisol levels with liver steatosis in obese individuals.

Materials and Methods

Study population

This study was conducted retrospectively between February 2019 and May 2022, with 296 obese patients who presented to the Endocrinology and Metabolic Diseases Outpatient Clinic of Ankara City Hospital for endocrine evaluation prior to bariatric surgery. Patients under 18 years of age, those who had undergone bariatric surgery, those who were pregnant or lactating, those with liver disease due to other causes (autoimmune diseases, Wilson's disease, hemochromatosis, hepatitis B, hepatitis C), those diagnosed with psychiatric diseases, female patients who consumed more than 20 mg of alcohol per day and male patients who consumed more than 30 mg of alcohol per day were excluded from the study. This study was conducted in accordance with the Declaration of Helsinki and ethical approval for the study was obtained from Number 1 Clinical Applications Ethics Committee of the Ankara Bilkent City Hospital with approval number E1-22-2725 and date 29/06/2022.

Descriptive characteristics and anthropometric measurements

Demographic and health-related data were collected from patient records, including comorbidities such as hypertension and type 2 diabetes, and measurements of body weight (kg), height (cm), body fat mass (kg), body fat percentage (%), waist circumference (cm), and hip circumference (cm). Waist to hip ratio was calculated as waist circumference / hip circumference.[14] BMI was calculated as body weight (kg) / (height in meters)^2 with a BMI of 30 kg/m^2 or higher classified as obesity.[15]

Biochemical parameters

Patients' biochemical parameters, including fasting blood glucose (FBG), insulin, blood cortisol, 24 hour urinary cortisol, 1 mg DST cortisol, adrenocorticotropic hormone (ACTH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count (PLT), and gamma glutamyl transferase (GGT) levels, were recorded from patient records. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated to assess insulin resistance using the formula FBG (mg/dL) x fasting insulin (µIU/mL) / 405, and patients with a HOMA score ≥ 2.7 were considered to have insulin resistance (IR).[16]

1 mg DST cortisol

The results of the standardised low-dose overnight DST were documented after administration of a single oral dose of 1 mg dexamethasone at 23:00 hrs. Serum cortisol levels were then measured between 8:00 and 9:00 the next morning.

Liver Steatosis

The presence of liver steatosis was recorded in patients who underwent liver USG. In addition, the HSI was used to assess NAFLD, calculated using the following equation

HSI = 8 × (ALT/AST ratio) + BMI (+2 if female; +2 if T2DM).

Based on this calculation, an HSI > 36 was considered positive.[17]

Statistical Analyses

In this study, descriptive statistics including mean ± standard deviation, median (minimum; maximum) and frequency (percentage) were presented as appropriate based on the type of variable and distribution characteristics. The Mann-Whitney U test was used to compare two independent groups. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic ability of the hepatic steatosis index (HSI) in predicting the reference outcome (USG). An area under the curve (AUC) closer to 1 indicates higher diagnostic accuracy, while values closer to 0.5 indicate no discrimination. The optimal cut-off points were identified using Youden's index, which optimises the balance between sensitivity and specificity. Spearman's rho correlation analysis was used to explore relationships between variables, with correlation strength categorised as follows: 0 (none), <0.30 (weak), 0.30-0.49 (moderate), 0.50-0.69 (fair), 0.70-0.89 (strong), and >0.89 (very strong).[18] The z-test was used to compare differences between correlations in the USG groups. A p-value of <0.05 was considered significant for all statistical tests. Analyses were performed with SPSS version 21.0 (Armonk, NY: IBM Corp.).

Results

A total of 296 patients were included in the study, of whom 240 (81.1%) were female. The mean age of the participants was 38.67±11.97 years (median=39; min=18; max=66). Of the 284 patients for whom USG records were available, 168 (59.2%) had hepatic steatosis and 70 of these individuals (41.7%) had grade 2 steatosis. The mean BMI of the patients was 44.25±6.76 kg/m^2 (median: 43.2; min=30.7; max=79.6). The prevalence of insulin resistance was 78.2% and 16.9% of the patients had diabetes. Among the biochemical parameters, the mean blood cortisol level was 13.51±4.74 µg/dL (median=12.9; min=3.3; max=35.8), and the mean 24-hour urinary cortisol level was 22. 9±27.65 µg/dL (median=16.22; min=3.08; max=350.28), and the mean 1 mg DST cortisol was 0.76±0.29 µg/dL (median: 0.7; min=0.5; max=2). The mean HSI was 56.96±8.12 (Table 1).

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Table 1. The demographic properties and clinical results of patients

Variable	n (%)	Variable	n	mean±SD or %	Median (min; max)
Sex		Age (years)	295	38.67±11.97	39 (18; 66)
Male	56 (18.9)	BMI (kg/m^2)	293	44.25±6.76	43.2 (30.7; 79.6)
Female	240 (81.1)	Body fat (%)	230	45.32±6.04	46.4 (28.8; 60.3)
USG		Body fat mass (kg)	229	53.36±12.89	52.2 (27.9; 102.2)
Without fatty liver	116 (40.8)	Waist circumference (cm)	278	125.16±14.23	125 (94; 170)
With fatty liver	168 (59.2)	Hip circumference (cm)	241	135.55±12.56	135 (111; 192)
Grade 1	48(28.6)	Waist-hip ratio	241	0.92±0.08	0.91 (0.68; 1.21)
Grade 2	70(41.7)	HOMA-IR	239	5.65±5.33	4.27 (0.85; 54.31)
Grade 3	50(29.7)	IR – (<2.7)	52	21.8	
Smoking		IR + (≥2.7)	187	78.2	
No	171 (58.4)	Blood cortisol (µg/dL)	296	13.51±4.74	12.9 (3.3; 35.8)
Yes	90 (30.7)	24 h urinary cortisol(µg/dL)	277	22.9±27.65	16.22 (3.08; 350.28)
Ex-smoker	32 (10.9)	1 mg DST cortisol (µg/dL)	205	0.76±0.29	0.7 (0.5; 2)
Comorbidities*		<1.8	202	98.5	
No	151 (51.0)	>1.8	3	1.5	
Yes	145 (49.0)	ACTH (pg/mL)	296	25.09±17.49	20.75 (4.5; 181)
Diabetes mellitus	50 (16.9)	AST (U/L)	293	23.82±11.83	21 (6; 126)
Prediabetes	17 (11.7)	ALT (U/L)	293	31.21±17.58	26 (7; 104)
Hypertension	81 (55.9)	AST/ALT	293	0.85±0.37	0.79 (0.18; 4.29)
CAD	15 (10.3)	≤0.8	153	52.2	
Hyperlipidemia	26 (17.9)	>0.8	140	47.8	
Medication*		PLT (10^9/L)	292	301.96±71.93	297.5 (135; 590)
Metformin	53 (36.6)	HSI	290	56.96±8.12	55.93 (40.7; 103.5)
Oral antidiabetic	25 (17.2)	>36	290	100.0	
Insulin	14 (9.7)	FBG (mg/dL)	291	100.86±31.24	93.5 (69; 376)
Antihypertensive	51 (35.2)	GGT (U/L)	296	29.83±26.79	24 (7; 288)
Antilipidemic	10 (6.9)				
Oral contraceptive	6 (4.1)				

**Multiple responses were given. USG: Ultrasonography, CAD: Coronary artery disease, BMI: Body mass index, HOMA-IR: Homeostatic Model Assessment- Insulin Resistance, DST: Dexamethasone suppression test, ACTH: Adrenocorticotropic hormone, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, PLT: Platelet count, HSI: Hepatic steatosis index, FBG: Fasting blood glucose, GGT: Gamma-glutamyl transferase*

24-hour urinary cortisol (µg/dL) value was significantly higher in males than in females, blood cortisol and 1 mg DST cortisol levels were similar between sexes (Table 2).

Table 2. Comparison of cortisol levels between males and females

	Male		Female		p-value
	mean±SD	**Median (min; max)**	**mean±SD**	**Median (min; max)**	
Blood cortisol (µg/dL)	14.11±4.26	13.80 (3.30; 25.90)	13.37±4.84	12.50 (3.60; 35.80)	0.090
24 h urinary cortisol (µg/dL)	32.90±51.71	21.51 (7.12; 350.28)	20.69±18.09	15.18 (3.08; 177.46)	**0.005**
1 mg DST cortisol (µg/dL)	0.84±0.33	0.80 (0.50; 1.77)	0.74±0.33	0.70 (0.50; 2.00)	0.137

DST: Dexamethasone suppression test

A small positive correlation was found between the HSI and USG results (rs = 0.168; p = 0.005). The ROC analysis performed on the HSI and USG results showed an AUC of 0.599 (95% CI: 0.532-0.666). Using a cut-off of ≥60.46, the sensitivity and specificity were 33.33% and 82.30%, respectively. When the cut-off was set at ≥52.99, the sensitivity increased to 73.81%, while the specificity decreased to 41.59% (Figure 1).

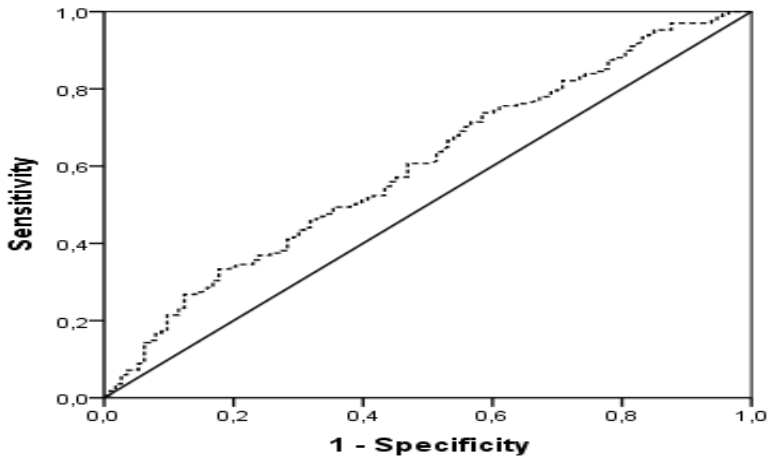

Figure 1. ROC curve for HSI based on USG reference.

USG: Ultrasonography, HSI: Hepatic steatosis index

When analyzing the relationship between HSI and waist circumference and hip circumference for the whole sample and within the USG groups, a moderate positive correlation was observed (p<0.001). No significant relationship was found between cortisol levels and HSI. According to the USG results, the correlation between hip circumference and HSI was significantly lower in subjects with fatty liver (rs = 0.674) than in subjects without fatty liver (rs = 0.804) (p = 0.014). In the whole sample, a significant positive relationship was found between HSI and HOMA-IR in individuals with and without fatty liver based on USG groups (Table 3).

Table 3. Correlation between HSI and some variables

	HSI						
	All sample		**USG**				**Comparison of r_s values**
			Without fatty liver		**With fatty liver**		
	r_s	**p-value**	**r_s**	**p-value**	**r_s**	**p-value**	**p-value**
Waist circumference	0.642	**<0.001**	0.679	**<0.001**	0.617	**<0.001**	0.197
Hip circumference	0.730	**<0.001**	0.804	**<0.001**	0.674	**<0.001**	**0.014**
Waist-hip ratio	0.118	0.069	0.150	0.121	0.052	0.566	0.229
Blood cortisol	0.047	0.428	0.197	**0.036**	0.001	0.994	0.053
24 h urinary cortisol	0.094	0.121	-0,078	0.430	0.107	0.182	0.073
1 mg DST cortisol	0.086	0.223	0.263	**0.040**	0.036	0.681	0.069
ACTH	0.042	0.474	0.089	0.349	0.034	0.660	0.324
HOMA-IR	0.392	**<0.001**	0.433	**<0.001**	0.324	**<0.001**	0.172

r_s: Spearman rho correlation coefficient, HSI: Hepatic steatosis index, USG: Ultrasonography, DST: Dexamethasone suppression test, ACTH: Adrenocorticotropic hormone, HOMA-IR: Homeostatic Model Assessment- Insulin Resistance

After adjustment for age, sex, and comorbidities, a significant correlation was found between HSI and 24-hour urinary cortisol in all subjects (r=0.196, p=0.007). The correlation between HSI and 1 mg DST cortisol in the group without fatty liver (rs=0.355) was higher than that in the group with fatty liver (rs=0.060) (p=0.032) (Table 4).

Table 4. Correlation between HSI and cortisol levels after adjustment for some variables

Adjusted for age, gender, and comorbidities	HSI						
	All sample		USG				Comparison of r_s values
			Without fatty liver		With fatty liver		
	r_s	p-value	r_s	p-value	r_s	p-value	p-value
Blood cortisol	-0.003	0.970	0.127	0.357	-0.027	0.769	0.179
24 h urinary cortisol	0.196	**0.007**	0.303	**0.024**	0.148	0.101	0.166
1 mg DST cortisol	0.123	0.094	0.355	**0.008**	0.060	0.506	**0.032**

r_s: Spearman rho correlation coefficient, HSI: Hepatic steatosis index, USG: Ultrasonography, DST: Dexamethasone suppression test

Discussion

According to the results of this study, cortisol levels were not related to HSI in obese individuals. However, after adjustment for age, sex, and comorbidities, the correlation between HSI and 1 mg DST cortisol was stronger in those without fatty liver.

Glucocorticoids affect key pathways involved in lipid and carbohydrate metabolism and their elevated levels are associated with a higher risk of developing NAFLD.[19] Hypercortisolism contributes to conditions such as insulin resistance, dyslipidemia, hypertension, visceral obesity, and hepatic steatosis, which are common features of metabolic syndrome. Cortisol is known to disrupt insulin sensitivity by directly acting on the insulin receptor pathway and increasing lipolysis and proteolysis, resulting in increased release of free fatty acids and amino acids.[20]

Targher et al.[21] investigated the relationship between cortisol secretion and NAFLD in patients with diet-controlled type 2 diabetes. 24-hour urinary-free cortisol and post-dexamethasone cortisol levels were significantly elevated in patients with NAFLD compared to those without. Regression analysis showed that these cortisol measures were independent predictors of liver steatosis. In a separate study, Targher et al.[7] also investigated the relationship between liver histology and cortisol secretion in NAFLD patients and found that urinary-free cortisol levels and post-dexamethasone cortisol concentrations were higher in NAFLD patients compared to controls. In addition, these cortisol levels significantly correlated with and could independently predict the degree of liver fibrosis. Conversely, another study reported no significant association between

plasma cortisol levels and NAFLD; instead, NAFLD was significantly correlated with age, BMI, waist-hip circumference, ALT, and triglyceride levels.[13]

In obese individuals, clinical studies investigating the relationship between NAFLD and cortisol levels remain limited. Zoppini et al.[22] investigated cortisol levels after overnight low-dose dexamethasone in obese patients with NAFLD and reported an approximately 50% reduction in circulating cortisol levels in those with NAFLD compared to those without steatosis. They also identified cortisol levels after overnight low-dose dexamethasone as an independent risk factor for NAFLD. In contrast to the previous study, our study did not find a significant relationship between cortisol levels and HSI in an obese population. However after adjustment for age, sex, and comorbidities, in individuals without liver steatosis (as determined by USG), the relationship between HSI and 1 mg DST cortisol levels was stronger compared to those with liver steatosis. In obese individuals, cortisol levels may vary; however, chronic stimulation of the hypothalamic-pituitary-adrenal (HPA) axis may lead to processes such as adaptation or desensitization, resulting in a suppressed cortisol response. In this case, low cortisol levels may be observed in obese individuals. In addition, factors such as insulin resistance, leptin levels, and inflammation that affect cortisol metabolism may influence the HPA axis and cortisol metabolism, and these factors may affect cortisol levels independently of fatty liver. Our results suggest that the absence of hepatic fat accumulation might allow for a more pronounced interaction between hepatic steatosis-related factors and cortisol metabolism. However, the severity of liver steatosis in our study population was predominantly in the early stages (grades 1 and 2), which may not be advanced enough to significantly alter cortisol metabolism.

Conditions such as non-alcoholic steatohepatitis (NASH) or advanced fibrosis, which are associated with more severe hepatic inflammation and systemic metabolic disturbances, may have a greater impact on cortisol levels. These findings highlight the need for further research to elucidate the mechanisms underlying these associations and to investigate whether more advanced stages of liver disease show stronger correlations with cortisol metabolism.

The positive correlation of HSI with waist circumference, hip circumference, and HOMA-IR confirms a strong association between liver steatosis, insulin resistance, and body fat distribution. In particular, the more pronounced relationships observed in individuals without USG-assessed liver steatosis may suggest that HSI better reflects metabolic risk in this group. While indicators of visceral fat, such as waist circumference, are more strongly associated with liver steatosis, hip circumference reflects subcutaneous fat and typically shows a weaker relationship with liver steatosis.[23] In this study, the lower correlation between HSI and hip circumference in individuals with liver steatosis compared to those without may indicate that subcutaneous tissue is less affected in those with liver steatosis.

The study has several limitations. Firstly, it is a retrospective and single-center study. Secondly, a non-invasive method was used to diagnose NAFLD. Although imaging techniques and various indices are currently used to diagnose NAFLD, the gold standard for diagnosis and staging of NAFLD is liver biopsy.[24] While liver steatosis was detected in all patients by HSI, only 59.2% of patients were found to have liver steatosis by ultrasound, suggesting that these two methods may have different sensitivities in assessing liver steatosis. The majority of patients with steatosis detected by USG were classified as grade 1 and 2, suggesting that HSI may be less sensitive in the early stages of liver steatosis. Thirdly, dexamethasone may be metabolized differently in individuals with chronic liver disease,[21] and it has been suggested that the pharmacokinetics of dexamethasone may differ in NAFLD.[7] In addition, blood dexamethasone levels were not measured in this study. Lastly, the small number of male participants in our study may limit the generalisability of the results across sexes. This situation is related to the retrospective nature of the data and the lower rates of males seeking bariatric surgery for obesity. However, to minimize this difference, we performed separate analyses for male and female participants.

In conclusion, the results of the study suggest that there is no direct relationship between HSI and cortisol in obese individuals and that cortisol metabolism may be independent of liver steatosis. Further research is needed in people with advanced liver disease or in different subgroups of obesity to better understand the relationship between cortisol metabolism and liver steatosis.

Ethical Considerations: This study was conducted following the Declaration of Helsinki and ethical approval for the study was obtained from the Ankara City Hospital with approval number E1-22-2725 and date 29.06.2022.

Conflict of Interest: The authors declare no conflict of interest.

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