European Review for Medical and Pharmacological Sciences 2024; 28: 4255-4263

Unlocking the secrets of metabolic syndrome: retroperitoneal fat area as a novel predictor

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ABSTRACT. – OBJECTIVE: Metabolic syndrome (MetS) affects about one-fourth of the global adult population and is characterized by hyperglycemia, abdominal obesity, low HDL (high-density lipoprotein cholesterol) cholesterol, and high triglycerides and blood pressure. Its emergence in developed nations is linked to energy intake imbalances and sedentary lifestyles. There is a parallel between MetS and conditions marked by glucocorticoid excess, such as Cushing's syndrome (CS), sharing features like central obesity, hypertension, dyslipidemia, and insulin resistance. This study aimed to investigate the association between retroperitoneal fat area (RFA) and MetS components in patients undergoing laparoscopic lateral transabdominal adrenalectomy. While intra-abdominal visceral fat's role in MetS has been studied, the significance of RFA needs further exploration.

PATIENTS AND METHODS: The research involved 88 patients categorized into three groups: adrenal-dependent CS, subclinical CS (SCS), and nonfunctional adrenal incidentaloma (NFA). Parameters, including body mass index (BMI), RFA, waist circumference, blood pressure, lipid profile, and fasting glucose levels, were measured. The study used hormonal hypersecretion assessments, criteria for SCS diagnosis, and biochemical analyses. MetS components were determined based on established criteria, and RFA quantification used advanced imaging software on computed tomography (CT) scans. Previous studies on intra-abdominal fat and MetS were reviewed to contextualize the findings.

RESULTS: Patients with MetS had significantly higher BMI, waist circumference, and RFA compared to those without MetS. Positive correlations were observed between BMI, RFA, central obesity, and MetS. ROC curve analysis showed a significant relationship between RFA and MetS, with a cutoff value of 36.6 cm² predicting MetS accurately in 95% of cases. The results were compared with existing literature on visceral fat's impact on MetS.

CONCLUSIONS: The study findings underscore the associations between anthropometric parameters, specifically RFA and MetS. RFA is a valuable tool for assessing metabolic risk, with implications for refining criteria for adrenalectomy in individuals with adrenal incidentalomas.

Key Words:
Retroperitoneal fat area, Metabolic syndrome, Laparoscopic lateral transabdominal adrenalectomy.

Introduction

Metabolic syndrome (MetS) stands as a prevalent cluster of interconnected health abnormalities, encompassing hyperglycemia, abdominal obesity, diminished high-density lipoprotein cholesterol (HDL-C) levels, and heightened triglycerides (TG) and blood pressure (BP)[1-3]. With an estimated one-fourth of the global adult population grappling with MetS[4], its emergence in developed nations is frequently linked to imbalances in energy intake and sedentary lifestyles[3,4]. Of notable interest is the parallel between MetS and conditions marked by glucocorticoid excess, such as Cushing's syndrome (CS), which manifests in central obesity, hypertension, dyslipidemia, and insulin resistance[5-7]. Visceral obesity, a key MetS component, often coexists with metabolic risk factors like hypertension, atherogenic dyslipidemia, and impaired glucose tolerance, collectively referred to as MetS[8,9]. Assessment of visceral obesity commonly employs metrics, such as waist circumference or waist-to-hip ratio, with advanced imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) providing precise depictions of internal adipose tissue[10].

Cortisol's involvement in MetS adiposity is evident in CS, characterized by chronic exposure to excess glucocorticoids leading to the redistribution of adipose tissue towards central regions of the body, particularly in truncal and visceral depots[11]. Central obesity is also prevalent in sub-

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clinical CS (SCS) patients[12]. Laparoscopic adrenalectomies, accounting for over 75% of cases, frequently address endocrine abnormalities causing hypertension, including aldosteronoma, CS, Cushing's disease, and pheochromocytoma[13,14]. While the role of intra-abdominal visceral fat in MetS has been extensively studied, the significance of retroperitoneal fat area (RFA), comprising approximately one-fourth of visceral fat, remains unexplored. This clinical study aims to investigate the potential association between RFA measurements and MetS components in patients undergoing laparoscopic lateral transabdominal adrenalectomy. Through this exploration, we seek to enhance our understanding of the intricate links between specific fat depots and the pathogenesis of MetS, contributing valuable insights to the broader field of metabolic health.

Recent studies[9] have emphasized the complex interactions between different fat depots and metabolic syndrome. For instance, a study[8] highlighted the role of visceral fat in predicting metabolic risks and its association with cardiovascular diseases. Another study[15] explored the impact of fat distribution on insulin resistance, providing crucial insights into the mechanisms underlying MetS. These findings underscore the importance of considering various fat depots, including RFA, in metabolic health research. This study aims to build on this foundation by focusing on RFA's role in MetS.

Patients and Methods

Study Population

The research involved a cohort of 88 consecutive patients (55 women, 33 men; median age 45 years, range 28-67 years) who underwent laparoscopic adrenalectomy at the Istanbul Faculty of Medicine between January 2007 and June 2023. The patients were categorized into three groups: 29 with adrenal-dependent Cushing's syndrome (CS) (group 1), 19 with subclinical CS (SCS) (group 2), and 40 with nonfunctional adrenal incidentaloma (NFA) (group 3). Written informed consent was obtained from all participants, and the study received approval from the Ethics Committee of the Istanbul Medipol University Faculty of Medicine (E-10840098-202.3.02-2057).

Preoperative Evaluation

Nonfunctional adrenal incidentalomas (NFA) were identified through CT or MRI scans conducted for unrelated medical conditions. All masses displayed radiologic characteristics consistent with cortical adenomas. Additionally, physical examinations were performed, including waist circumference measurements, and body mass index (BMI) calculations were based on weight and height. A BMI exceeding 30 kg/m² was indicative of obesity. Systolic and diastolic blood pressure measurements were obtained, and a thorough endocrine workup was conducted to detect hormonal hypersecretion.

Hormonal Hypersecretion Assessment

Serum cortisol and plasma corticotropin (ACTH) levels were determined in the basal condition. An overnight 1-mg dexamethasone (DXM) test was administered, with adequate suppression defined as morning cortisol levels falling below 50 mmol/L. Patients with inadequate suppression underwent a 2-day low-dose DXM suppression test. Urinary metanephrine and normetanephrine levels were within normal limits, excluding pheochromocytoma and primary aldosteronism. Serum dihydroepiandosterone (DHEA) and 17a-hydroxyprogesterone concentrations were measured to rule out androgen-secreting activity and nonclassic 21-hydroxylase deficiency.

Criteria for SCS Diagnosis

The criteria for diagnosing SCS included the absence of overt signs or symptoms of hypercortisolism, incidental detection of the adrenal mass, and failure of both low-dose and high-dose DXM administration to suppress serum cortisol levels below 50 mmol/L.

Biochemical Analysis

Venous blood samples obtained after a 12- to 14-h overnight fast were subjected to biochemical analysis. Parameters including fasting glucose, triglycerides, total low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) cholesterol were analyzed using an autoanalyzer. Hypertriglyceridemia, low HDL-C, hypertension, impaired fasting glucose, and diabetes were defined based on established criteria.

Endocrine Assessment

All hormone assays were conducted using a commercial DPP Modular System. The laboratory adhered to standard ranges for cortisol, ACTH, 17-hydroxyprogesterone, DHEA-S, metanephrine, normetanephrine, plasma aldosterone, and plasma renin activity. Ratios of plasma aldosterone to plas-

ma renin activity were calculated for further evaluation of autonomous mineralocorticoid secretion in patients with ratios exceeding 20.

Metabolic Syndrome Criteria

MetS components were determined at baseline considering the following criteria[16]: high glucose levels (> 100 mg/dL), hypertension (> 130/85 mmHg), raised triglyceride levels (> 150 mg/dL), low high-density lipoprotein cholesterol levels (< 40 mg/dL in men; < 50 mg/dL in women), and abdominal obesity (waist circumference of > 102 cm in men; > 88 cm in women). The criteria are described as follows:

- High blood glucose levels, or hyperglycemia, occur when the body is not able to produce enough insulin to transport glucose from blood to cells, and it remains excessively in the bloodstream[17]. To assess glycemia levels, overnight fasting (at least 8 h) blood collections were analyzed in a local laboratory using standard enzymatic methods.
- Hypertension is the high blood pressure exerted on the blood vessels[18]. Blood pressure was measured in a seated position with a validated semi-automatic oscillometer (Omron HEM-705CP, Lake Forest, IL, USA). Three measures were taken after 5 min sitting at rest, waiting one minute between each take.
- Dyslipidemia is the altered blood lipid concentration. There are two MetS components related to dyslipidemia: high blood level of triglycerides, or hypertriglyceridemia, and low concentration of high-density lipoproteins (HDL) or low HDL-cholesterol[19]. Overnight fasting blood collections were analyzed in the local laboratory using standard enzymatic methods.
- Abdominal obesity or excessive accumulation of fat in the abdomen was assessed by measuring waist circumference two times using an anthropometric tape, halfway between the last rib and the iliac crest[20].

Measurement of Retroperitoneal Fat Area

The quantification of RFA involved utilizing Photoshop CS3 Extended Edition imaging software on an IBM PC-compatible computer. CT slices were scanned using a digital scanner, and the slice with the largest lesion diameter was chosen for calculations. Measurement scale calibration was conducted, and two regions of interest (ROIs) were created using the "Polygonal Laso Tool": one for RFA, which encompassed the lesion, and the other for the lesion itself. The area of each ROI was determined, and the results were recorded.

Statistical Analysis

Data, presented as mean ± SD, underwent statistical analysis using SPSS 11.1 (SPSS Inc., Chicago, IL, USA). Differences between variables were assessed with analysis of variance (ANOVA), Kruskal-Wallis, and Chi-squared tests. Relationships among parameters were explored using the Spearman correlation coefficient. Receiver operating characteristic (ROC) curves were generated to identify cutoff values for RFA in predicting MetS. Results were deemed statistically significant at $p < 0.05$.

Results

Patient Characteristics

Among the patients, the mean BMI, RFA, waist circumference, systolic/diastolic blood pressure (SBP/DBP), total cholesterol (TC), triglycerides (TG), and fasting glucose levels were 36.2 ± 4.5 kg/m², 33.3 ± 16 cm², 95.9 ± 18 cm, 129.3 ± 11.6/90.0 ± 7.8 mmHg, 4.5 ± 0.9 mmol/L, 0.5 ± 0.4 mmol/L, and 6.3 ± 1.7 mmol/L, respectively. The prevalence rates of hypertension, diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, impaired fasting glucose, central obesity, and Metabolic Syndrome (MetS) were 37.0%, 32.9%, 53.4%, 39.6%, 44.1%, 45.8%, and 46.5%, respectively (Tables I and II).

Group Comparisons

Comparisons among groups revealed no significant differences in age, sex, menopausal status, current smoking, or family history of premature ischemic heart disease (IHD). Group 1 (adrenal-dependent CS) exhibited significantly higher mean BMI and waist circumference compared to groups 2 (SCS) and 3 (NFA). Furthermore, group 1 demonstrated a significantly larger RFA compared to group 3. Rates of cardiometabolic risk factors were notably higher in group 1, particularly when compared to group 2. These differences highlight the pronounced metabolic disturbances in patients with adrenal-dependent CS, suggesting a stronger association between excess cortisol production and increased adiposity, particularly in the retroperitoneal region (Table III).

Table I. Patients' characteristics.

Parameters	Group 1 (CS) (n = 29)	Group 2 (SCS) (n = 19)	Group 3 (NFA) (n = 40)
Age (years)	43.4 ± 9.2	45.3 ± 8.2	49.1 ± 11.2
Sex (F:M)	19:10	13:6	31:9
BMI (kg/m^2)	41.1 ± 2.9	32.5 ± 2.5	31.26 ± 3.2
RFA (m^2)	49.1 ± 7.8	41.2 ± 13.0	23.3 ± 15.2
Waist circumference (cm)	113.5 ± 13.2	91.5 ± 12.2	87.7 ± 14.2
SBP (mmHg) / DBP (mmHg)	138.3 ± 11.2 / 95.3 ± 7.5	126.7 ± 10.1 / 87.0 ± 7.2	124.9 ± 8.0 / 88.2 ± 6.5
Peripheral obesity (%)	5.3	41.8	50
Triglyceride (mmol/L)	2.7 ± 0.5	2.2 ± 0.4	2.2 ± 0.3
Total cholesterol (mmol/L)	5.8 ± 0.9	5.1 ± 0.8	4.5 ± 0.7
Fasting glucose (mmol/L)	7.4 ± 2.3	6.3 ± 1.8	5.6 ± 0.9

CS: Cushing's syndrome, SCS: subclinical Cushing syndrome, NFA: nonfunctional adrenal incidentaloma, BMI: body mass index, RFA: retro-peritoneal fat area, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Evaluation of Patients with and without MetS

Patients with MetS had significantly higher BMI, waist circumference, and RFA compared to those without MetS. The rates of hypertension, diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, low HDL-C, impaired fasting glucose, and central obesity were also significantly higher in patients with MetS. This indicates that patients with MetS not only exhibit increased adiposity but also a higher burden of metabolic risk factors, emphasizing the need for comprehensive risk assessments in this population (Table IV).

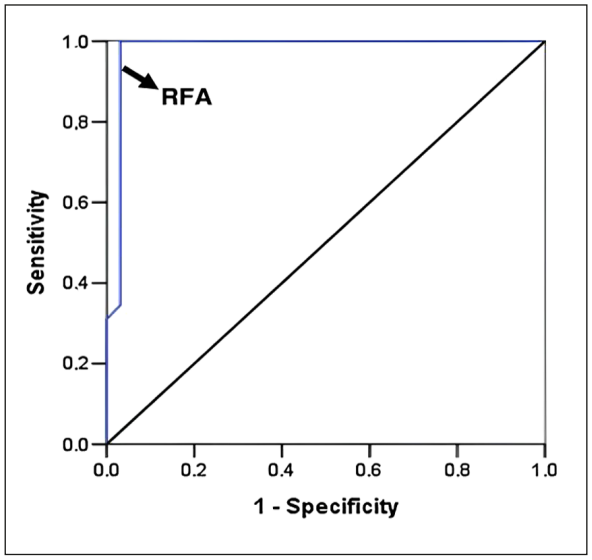

Figure 1. ROC curve analysis for RFA and MetS.

Correlations

Positive correlations were observed between BMI and RFA, central obesity, and MetS. Additionally, RFA exhibited positive correlations with central obesity and MetS. Waist circumference correlated positively with RFA, central obesity, and MetS. These correlations suggest a strong interrelationship between increased body fat, particularly in the retroperitoneal area, and the development of MetS. The findings imply that RFA could serve as a reliable marker for central obesity and MetS, providing a tangible link between specific fat depots and overall metabolic health (Table V).

ROC Curve Analysis

ROC curve analysis demonstrated a significant relationship between RFA and MetS, with an area under the curve of 0.969 (Figure 1).

The cutoff value for RFA predicting MetS was determined to be 36.6 cm², achieving high sensitivity and specificity. Notably, MetS was accurately predicted in 95% of patients based on RFA measurement. This analysis reinforces the potential of RFA as a predictive tool for MetS, offering a precise method for identifying at-risk individuals. The high predictive accuracy underscores the importance of including RFA measurements in routine evaluations for MetS.

These findings underscore the intricate associations between anthropometric parameters, retroperitoneal fat area, and the presence of metabolic syndrome, providing valuable insights for risk assessment and management strategies. The clear connections between increased RFA, higher BMI, central obesity, and MetS highlight the

Table II. Frequency of cardiometabolic risk parameters in the three groups.

Parameter	Group 1 (CS)	Group 2 (SCS)	Group 3 (NFA)
Family history of heart disease (%)	10.5	8.3	6.6
Current smoker (%)	25.7	26.6	30.0
Hypertension (%)	84.0	16.6	13.3
Diabetes mellitus (%)	63.7	33.5	13.5
Hypertriglyceridemia (%)	84.0	50.0	33.0
Impaired fasting glucose (%)	74.0	51.0	24.5
Hypercholesterolemia (%)	78.0	33.3	13.3
Central obesity (%)	97.5	41.6	16.5
Metabolic syndrome (%)	94.1	41.8	20.1

CS: Cushing's syndrome, SCS: subclinical Cushing syndrome, NFA: nonfunctional adrenal incidentaloma.

importance of targeted interventions to address specific fat depots in managing and mitigating metabolic risks.

Discussion

In this study, we explored the association between RFA and MetS, revealing a significant correlation between RFA and MetS components. The findings suggest that patients with higher RFAs face an elevated risk of MetS, independent of their BMI. Notably, MetS was prevalent in 95% of individuals with RFA levels exceeding 36.6 cm², indicating a proportional decrease in MetS risk as RFA levels decreased. The findings suggest that RFA could serve as a reliable marker for central obesity and MetS, indicating a tangible link between specific fat depots and overall metabolic health. However, it is important to interpret these results with caution due to several limitations. The study design precludes any conclusions about causality between RFA and MetS. A positive correlation does not imply a causal relationship. Furthermore, the routine use of advanced imaging technology for RFA measurement may not always be feasible in clinical practice. These factors must be considered when applying the study's findings to broader clinical contexts.

Metabolic syndrome, first recognized by Reaven[21] in 1988 as syndrome X or insulin resistance syndrome, has been extensively studied since its identification. A diagnosis is made when a patient exhibits three or more of the following criteria:

Table III. Anthropometric, clinical, and biochemical features in patients with and without metabolic syndrome.

Parameters	Patients with MetS	Patients without MetS	*p*
Age (years)	45.1 ± 9.2	41.9 ± 9.0	not significant
Sex (F:M)	42:17	31:21	not significant
BMI (kg/m^2)	37.3 ± 4.3	31.4 ± 2.7	0.05
RFA (m^2)	50.9 ± 5.2	19.4 ± 9.1	0.001
Waist circumference (cm)	111.0 ± 12.0	84.1 ± 9.0	0.02
SBP (mmHg) / DBP (mmHg)	133.7 ± 12.0 / 93.3 ± 7.0	126.4 ± 9.0 / 87.1 ± 7.2	0.01 / 0.03
Peripheral obesity (%)	6.9	41.6	0.001
Triglyceride (mmol/L)	2.5 ± 0.5	1.8 ± 0.2	0.01
Total cholesterol (mmol/L)	5.7 ± 0.8	4.3 ± 0.8	0.001
Fasting glucose (mmol/L)	6.8 ± 2.1	5.6 ± 1.5	not significant

MetS: metabolic syndrome, BMI: body mass index, RFA: retro-peritoneal fat area, SBP: systolic blood pressure.

Table IV. Frequency of cardiometric risk parameter.

Parameters	Patients with MetS	Patients without MetS	p
Family history of heart disease (%)	6.9	9.3	not significant
Current smoker (%)	17.2	18.7	not significant
Hypertension (%)	55.0	18.7	0.001
Diabetes mellitus (%)	41.0	25.0	0.02
Hypertriglyceridemia (%)	79.0	29.0	0.01
Impaired fasting glucose (%)	52.0	37.5	0.04
Hypercholesterolemia (%)	65.0	15.6	0.001
Central obesity (%)	82.7	12.5	0.001

MetS: metabolic syndrome.

Table V. Correlations between retroperitoneal fat area and metabolic syndrome, BMI, and central obesity.

Parameter		r	p
BMI	RFA	0.598	0.0001
	Central obesity	0.867	0.0001
	Metabolic syndrome	0.654	0.0001
RFA	Central obesity	0.635	0.0001
	Metabolic syndrome	0.895	0.0001
Waist circumference	RFA	0.625	0.0001
	Central obesity	0.799	0.0001
	Metabolic syndrome	0.762	0.0001

BMI: body mass index, RFA: retro-peritoneal fat area.

increased waist circumference, elevated triglycerides, high blood pressure, raised fasting glucose levels, and low HDL-C levels[22]. Chronic glucocorticoid excess is well-established to be linked with MetS, with features such as visceral obesity, insulin resistance, and hyperlipidemia.

Cushing's syndrome (CS), characterized by chronic exposure to excess glucocorticoids, leads to the redistribution of adipose tissue, primarily in the truncal and visceral regions. Patients with CS exhibit increased mortality, mainly attributed to cardiometabolic events[23]. In this study, patients with CS demonstrated high rates of hypertension, obesity, and hyperglycemia, underscoring the cardiometabolic risks associated with glucocorticoid excess.

Subclinical hypercortisolism, termed subclinical CS (SCS), is associated with a prevalence of insulin resistance, hypertension, obesity, impaired glucose tolerance, and dyslipidemia. SCS presents challenges in diagnosis due to the absence of specific signs and symptoms[24,25]. This study utilized a cutoff value of < 3 μg/dl for dexamethasone suppression tests to identify SCS.

Adrenal incidentalomas, discovered unintentionally during unrelated tests or treatments, have been proposed as a cause of MetS. Patients with nonfunctional adrenal incidentalomas have shown an increased prevalence of MetS. The study also acknowledges the limitations of using urine metanephrine assays for screening pheochromocytoma[26].

The correlations observed in this study reinforce the interplay between anthropometric parameters, hormonal conditions, and MetS. Waist circumference and BMI have traditionally been used as indices of obesity, but the study suggests that RFA may be a more reliable predictor of

MetS risk. RFA exhibited the strongest correlation with MetS among the parameters studied, indicating its potential as a valuable metric for risk assessment.

Recent evidence[27] highlights the role of adipose tissue as an endocrine organ capable of secreting cytokines that contribute to inflammation and insulin resistance. Central obesity, particularly visceral obesity, is strongly associated with MetS components[27,28]. While waist circumference has been a commonly used parameter, RFA measurement proved to be more accurate in predicting MetS risk in this study.

Conclusions

The measurement of RFA emerges as a potentially valuable and straightforward tool for assessing metabolic risk in patients. The study suggests that RFA could be considered a criterion for determining the need for adrenalectomy in individuals with adrenal incidentalomas. However, the authors emphasize the necessity for well-controlled intervention studies to further validate these findings.

Conflict of Interest
The authors declare that they have no conflict of interest.

Funding
None.

Authors' Contributions
Conceptualization: OAS. Methodology: OAS. Software: OAS. Validation: OAS. Formal analysis: YE. Investigation: YE. Resources: OAS. Data curation: OAS. Writing original draft: OAS. Writing, review, and editing: YE. Visualization: OAS, YE. Supervision: YE. Project administration: OAS, YE.

Data Availability
All data associated with this paper are available from the corresponding author upon request.

Ethics Approval
The study received approval from the Ethics Committee of the Istanbul Medipol University Faculty of Medicine (E-10840098-202.3.02-2057) and was conducted following the Helsinki Declaration and its latest amendments.

Informed Consent
Each patient provided consent for the use of their data in research.

Acknowledgments
We want to express our sincere gratitude to all parties who generously contributed to this study.

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AI Disclosure
This manuscript was created without the assistance of artificial intelligence or assisted technologies.

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