

ADIPOKINE PROFILE AND METABOLIC SYNDROME IN PATIENTS WITH SIMILAR ADIPOSE TISSUE MASS AND DISTRIBUTION

Ivona Mitu¹, Cristina-Daniela Dimitriu¹, Cristina Preda², O. Mitu^{3*},
Irina-Iuliana Costache³, Manuela Ciocoiu¹

“Grigore T. Popa” University of Medicine and Pharmacy Iasi
Faculty of Medicine

1. Department of Morpho-Functional Sciences (II)
2. Department of Medical Specialties (II)
3. Department of Medical Specialties (I)

*Corresponding author. E-mail: mituovidiu@yahoo.co.uk

ADIPOKINE PROFILE AND METABOLIC SYNDROME IN PATIENTS WITH SIMILAR ADIPOSE TISSUE MASS AND DISTRIBUTION (Abstract): In order to establish more efficient ways to prevent metabolic syndrome (MetS) in clinical settings, we need to thoroughly understand the physiopathology behind this cluster of risk factors for cardiometabolic diseases. The main point of focus concerning MetS still embraces the metabolic and secretory products of the abdominal adipose tissue. Our study aims to clearly define an adipokine profile for patients with MetS and assess possible correlations between obesity parameters, biochemical markers and adipokines. **Material and methods:** This is a cross-sectional study, elaborated over a period of two years, which involved 104 patients divided into 2 groups: with MetS and without MetS. Patients were considered as having MetS if they presented WC > 88 cm (women) / 104 cm (men) and more than one criterion of the following: glucose \geq 100 mg/dL, HDL < 40 mg/dL (men) / < 50 mg/dL (women), TG \geq 150 mg/dL, SBP/DBP \geq 130/85 mmHg. Dual-Energy X-ray Absorptiometry (DEXA) was performed to assess adipose tissue distribution. All patients underwent clinical and paraclinical evaluation, including the measurements of insulin, adiponectin and leptin. **Results:** Leptin levels present a strong and positive correlation with almost all obesity parameters evaluated, with or without MetS. The strongest correlation is observed for trunk fat percentage (without MetS: $r=0.648$, $p<0.001$; with MetS: $r=0.723$, $p<0.001$). In the group of patients without MetS adiponectin level is not associated with fat percentages, whereas in the group of patients with MetS adiponectin reports a weak and positive correlation between total fat, arms fat and legs fat percentages. Adiponectin is negatively correlated with HOMA-IR and insulin in both groups, suggesting that insulin resistance is linked to the change in adiponectin levels. Patients that present MetS also report an association between HDL and adiponectin ($r=0.280$, $p=0.02$). **Conclusions:** Patients with MetS that did not follow prior treatment for any chronic disease and are characterized by similar adipose tissue percentage and distribution, report the following: lower adiponectin levels than patients without MetS, but still a positive association with HDL; no modification in leptin levels compared to patients without MetS; negative correlation between adiponectin and insulin resistance; strong association between leptin and adipose tissue mass. **Keywords:** ADIPOKINES, ADIPOSE TISSUE, OBESITY, METABOLIC SYNDROME.

Adipokine profile and metabolic syndrome in patients with similar adipose tissue mass and distribution

Adipose tissue is an active and complex endocrine organ, with important implications in glucose and lipid metabolism. The development of metabolic syndrome (MetS) focuses mainly on high abdominal fat, considered the most pathogenic depot that contributes to metabolic abnormalities (1, 2). The pathways that describe MetS are not yet clearly explained in the literature and debates still arise when the role, consequences and regulation of the secretory function of the adipose tissue is being discussed.

Adipokines are a class of cytokine mediators secreted by adipose cells. Adiponectin and leptin are two of the most studied adipokines, presenting opposite effects (3). Adiponectin has anti-atherogenic, anti-inflammatory and anti-diabetic properties (4, 5), while leptin promotes inflammation immune response and high cardiovascular risk (6). Thus far, the specific values of these adipokines vary among study populations with MetS. A possible bias might be the medication participants are taking for chronic diseases in studies or maybe the adiponectin or leptin paradox already present.

Therefore, a correct interpretation of the values for adiponectin, leptin and their ratio are very important in order to thoroughly stratify the pathologies the patient is at risk for (dyslipidemia, diabetes mellitus, hypertension). The first step of our study was to assess an adipokine profile in patients with MetS, but with no prior treatment, no known chronic disease and no antecedent acute atherosclerotic pathology. The next step was to identify and compare possible correlations between fat mass, MetS biochemical parameters and adipokine levels, alongside insulin and insulin-resistance, in patients with or without MetS.

MATERIAL AND METHODS

Our study was conducted over a period of 2 years and included participants that did not present any known chronic disease and had no antecedent acute atherosclerotic pathology. The study was approved by the University Ethics Committee, number 1/27.07.2020 and all participants signed an informed consent before entering the study. Exclusion criteria included pregnant women and patients that refused to sign the informed consent. All investigations were performed by trained personnel, in the same clinic and laboratory, using the same tools and analyzers, during the entire study.

The population included in the study was divided into two groups: one group of patients that presented MetS (35 participants) and one group without MetS (69 participants). The status of MetS was defined as present if patients had waist circumference (WC) > 88 cm (women) / 104 cm (men) and met at least 2 of the following criteria: glucose ≥ 100 mg/dL, HDL < 40 mg/dL (men) / < 50 mg/dL (women), TG ≥ 150 mg/dL, SBP/DBP $\geq 130/85$ mmHg (7).

Clinical and anthropometric measurements

Prior to clinical evaluation, patients did not engage in physical exercise at least 30 minutes before and did not consume caffeine or alcohol. Anthropometric parameters were measured: height (tape meter stadiometer), weight (Tanita BC730), waist and hip circumference (flexible tape) at the umbilical and greater trochanter level, respectively. Blood pressure was measured twice with a valid automated device and a mean value was considered.

Adiposity measurements

In order to accurately appreciate adiposity percentages and fat mass values, along-

side lean mass and bone mineral content, Dual-Energy X-ray Absorptiometry (DEXA) was used, as a gold standard for this measurement. We report values expressed as kg of adipose tissue per whole body/specific areas of the body or percentages of adipose tissue calculated from total body weight or a specific area weight (left and right arm, left and right leg, trunk).

Biochemical parameters

Patients included in the study were evaluated during morning time, blood samples being collected after 12 hours overnight fast. Serum samples were obtained after centrifugation at 4°C and 4,500 x g, for 10 minutes. To avoid preanalytical errors, samples were transported to the laboratory within a 2-hr. frame, with a special isothermal bag for biological samples. There was an exception for insulin, which required sample centrifugation in maximum 15 minutes after collection. Serum for insulin, adiponectin and leptin was stored in separate tubes at -20°C.

Insulin levels were measured using an enzyme-labeled chemiluminescent immunometric assay kit, Immulite 2000 Insulin, provided by Siemens (catalog number

L2KIN2). Quantitative determination of the adiponectin and leptin levels was performed using enzyme-linked immunosorbent assay (ELISA) kits supplied by Biovendor-Laboratorni medicina a.s., Brno, Czech Republic: Adiponectin Human ELISA Competitive kit, CE-IVD, limit of detection 26 ng/mL, catalog number RD195023100 and Leptin Human ELISA, CE-IVD, limit of detection 0.2 ng/mL, catalog number RD191001100.

To calculate the homeostasis model assessment for insulin resistance (HOMA-IR) we applied the formula reported in the literature (8):

$$\text{HOMA-IR} = [\text{insulin } (\mu\text{U/mL}) \times \text{glucose } (\text{mg/dL})] / 405.$$

Markers for the metabolic syndrome were determined using the spectrophotometric method applied to each specific kit. HDL-chol was measured using the direct method (elimination/peroxidase), TG using the glycerol phosphate oxidase method and glucose using the glucose-6-phosphate dehydrogenase method.

We estimated the visceral adiposity per total body with the previous validated equations (9):

Men: eVAI = $\left(\frac{AC}{39.68 + (1.88 \times \text{BMI})} \right) \times \left(\frac{TG}{1.03} \right) \times \left(\frac{1.31}{\text{HDL} - \text{chol}} \right)$
Women: eVAI = $\left(\frac{AC}{36.58 + (1.89 \times \text{BMI})} \right) \times \left(\frac{TG}{0.81} \right) \times \left(\frac{1.52}{\text{HDL} - \text{chol}} \right)$

Normal values are 1 for both men and women, if they are non-obese and present normal adipose tissue distribution.

Statistical analysis

The database of all 104 patients was elaborated in *Microsoft Excel 2003* (Microsoft Corporation, Redmond, WA, USA) and the statistics of the data was performed with *SPSS version 23.0* (IBM Corporation, Armonk, NY, USA). There were no miss-

ing data in our database. For each continuous variable we reported the mean ± standard deviation (SD), minimum value and maximum value. Categorical values were expressed as frequencies (percentages). One-way ANOVA and chi-square tests were applied for comparison of parameters between the group with MetS and the group without. Statistical power was calculated and presented as eta squared (η^2) for each

**Adipokine profile and metabolic syndrome
in patients with similar adipose tissue mass and distribution**

variable. In order to assess the presence/absence of correlations between variables and their strength, Pearson correlation was performed. A p value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population divided in the 2 groups (with MetS and without MetS) are presented in first table. Our groups did not differ concerning age, gender, BMI or fat mass parameters, sug-

gesting a good homogeneity and thus preserving possible bias at a minimum level. Regardless of no significant differences in percentages of adiposity, eVAI is significantly higher in patients with MetS, because of the variation of HDL, TG and WC.

Our study further investigated correlations between obesity parameters and adipokine levels, including their ratio and insulin values, alongside insulin resistance (tab. II).

**TABLE I
Baseline characteristics of the study population**

	Patients without MetS (n=35)			Patients with MetS (n=69)			p	η ²
	Mean±SD	Min value	Max value	Mean±SD	Min value	Max value		
Age (years)	58.29±7.54	45	75	60.13±8.48	39	75	0.28	0.01
Gender							0.16	-
Females	82.9% (29)	-	-	69.6% (48)	-	-		
Males	17.1% (6)	-	-	30.4% (21)	-	-		
WC (cm)	102.75±11.62	89	138	110.34±12.22	90	160	0.003	0.08
HC (cm)	111.86±9.33	95	132	115.43±10.87	100	155	0.10	0.03
WHR	0.92±0.06	0.79	1.08	0.96±0.06	0.81	1.08	0.003	0.08
BMI (kg/m ²)	30.61±5.08	22.75	44.40	32.38±5.42	21.91	53.31	0.11	0.02
FM Total (%)	40.17±6.50	18.9	49.40	40.07±6.32	26.10	53.20	0.94	<0.01
Trunk Fat (%)	39.29±6.93	17.10	50.40	40.82±6.13	28.30	60.20	0.25	0.01
Arms Fat (%)	43.91±8.26	18.89	54.98	42.80±8.97	23.99	59.20	0.54	<0.01
Legs Fat (%)	42.21±7.87	20.16	55.18	40.10±8.05	22.44	55.46	0.20	0.02
eVAI	3.36±1.47	1.38	8	7.88±5.42	1.42	33.66	<0.001	0.19
SBP (mmHg)	131.34±23.44	107	222	141.14±17.60	94	198	0.01	0.05
DBP (mmHg)	82.17±12.92	65	130	87.85±11.13	53	119	0.02	0.05
Adiponectin(μg/mL)	15.74±13.03	4.89	25.65	13.03±4.83	4.53	28.53	0.01	0.06
Leptin (ng/mL)	24.21±15.02	2.60	47.60	24.80±14.93	3.80	58.20	0.851	<0.01
LAR	0.53±0.41	0.06	1.81	0.61±0.40	0.08	2.27	0.317	<0.01
Insulin (μU/mL)	12.28±7.41	2.13	32.20	20.83±12.07	5.80	52	<0.001	0.13
HOMA-IR	2.98±1.94	0.49	8.53	6.48±5.08	1.48	27.25	<0.001	0.13
Glucose (mg/dL)	96.54±15.53	76	157	120.58±40.13	85	336	0.001	0.10
TG (mg/dL)	97.63±27.73	53	149	183.91±84.76	49	488	<0.001	0.25
HDL (mg/dL)	59.03±12.29	34	82	49.39±13.23	20	85	0.001	0.11

TABLE II
Correlations between adiposity parameters and hormones related to obesity

	Group		Adiponectin	Leptin	LAR	Insulin	HOMA-IR
BMI (kg/m ²)	without MetS	r	-0.22	0.510*	0.538*	0.338*	0.238
		p	0.195	0.002	0.001	0.047	0.168
	with MetS	r	-0.157	0.412*	0.436*	0.436*	0.387*
		p	0.199	<0.001	<0.001	<0.001	0.001
WC (cm)	without MetS	r	-0.208	0.404*	0.410*	0.322	0.253
		p	0.229	0.016	0.014	0.059	0.142
	with MetS	r	-0.181	0.167	0.271*	0.498*	0.501*
		p	0.137	0.171	0.024	<0.001	<0.001
HC (cm)	without MetS	r	0.012	0.470*	0.344*	0.152	0.120
		p	0.947	0.004	0.043	0.385	0.492
	with MetS	r	-0.108	0.465*	0.485*	0.378*	0.340*
		p	0.376	<0.001	<0.001	0.001	0.004
WHR	without MetS	r	-0.346*	0.101	0.248	0.326	0.247
		p	0.042	0.565	0.151	0.056	0.153
	with MetS	r	-0.158	-0.401*	-0.241*	0.300*	0.358*
		p	0.194	0.001	0.046	0.012	0.003
FM Total (%)	without MetS	r	0.063	0.673*	0.572*	0.218	0.200
		p	0.717	<0.001	<0.001	0.208	0.250
	with MetS	r	0.310*	0.760*	0.583*	-0.024	-0.115
		p	0.010	<0.001	<0.001	0.842	0.346
Trunk Fat (%)	without MetS	r	-0.056	0.648*	0.593*	0.284	0.216
		p	0.751	<0.001	<0.001	0.098	0.212
	with MetS	r	0.174	0.723*	0.605*	0.120	0.020
		p	0.153	<0.001	<0.001	0.328	0.873
Arms Fat (%)	without MetS	r	0.078	0.670*	0.539*	0.277	0.272
		p	0.655	<0.001	0.001	0.108	0.114
	with MetS	r	0.315*	0.736*	0.571*	-0.102	-0.164
		p	0.008	<0.001	<0.001	0.405	0.178
Legs Fat (%)	without MetS	r	0.211	0.535*	0.403*	0.044	0.093
		p	0.223	0.001	0.016	0.802	0.595
	with MetS	r	0.443*	0.659*	0.430*	-0.207	-0.279*
		p	<0.001	<0.001	<0.001	0.088	0.020
eVAI	without MetS	r	0.040	0.280	0.258	0.251	0.246
		p	0.818	0.103	0.135	0.146	0.155
	with MetS	r	-0.121	-0.067	0.018	0.095	0.180
		p	0.321	0.584	0.881	0.438	0.139

*WC=waist circumference, HC=hip circumference, WHR=waist-hip-ratio, FM total=fat mass total, eVAI=estimated visceral adipose index, LAR=leptin-adiponectin-ratio.

Leptin levels present a strong and positive correlation with almost all obesity parameters evaluated, with or without MetS. A stronger association is reported in

**Adipokine profile and metabolic syndrome
in patients with similar adipose tissue mass and distribution**

the MetS group concerning leptin and fat mass (total, trunk, arms, legs), suggesting that in patients with MetS adipose tissue is associated with a higher stimulation of

leptin secretion. Moderate to strong correlations are observed between LAR levels and all obesity parameters. These values do not vary significantly between groups.

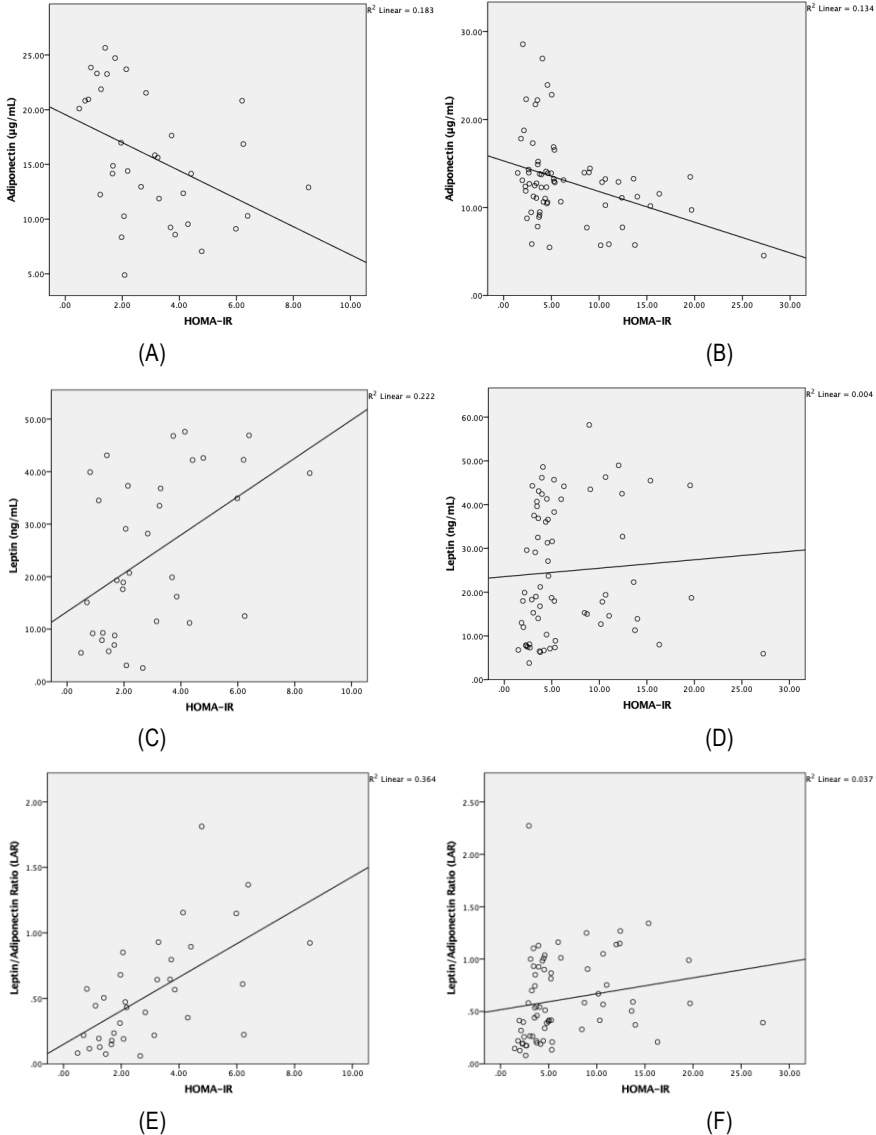


Fig. 1. Correlations between Adiponectin and HOMA-IR in (A) group without MetS ($r=-0.428$, $p=0.01$) and (B) group with MetS ($r=-0.366$, $p=0.002$); Correlations between Leptin and HOMA-IR in (C) group without MetS ($r=0.471$, $p=0.004$) and (D) group with MetS ($r=0.066$, $p=0.592$); Correlations between LAR and HOMA-IR in (E) group without MetS ($r=0.604$, $p<0.001$) and (F) group with MetS ($r=0.191$, $p=0.116$).

In patients with MetS, insulin has higher values once the BMI is higher, but this does not seem to be associated with fat mass percentages of the whole body or of different areas of the body. At the same time, our results report moderate and positive correlations with fat mass expressed in kg and not percentages: trunk fat (kg) ($r=0.369$, $p=0.029$), left arm fat (kg) ($r=0.504$, $p=0.002$), right arm fat (kg) ($r=0.496$, $p=0.002$). In the other group, insulin is also associated only with fat mass expressed in kg: total fat (kg) ($r=0.332$, $p=0.005$), right arm fat (kg) ($r=0.300$, $p=0.012$), trunk fat (kg) ($r=0.419$, $p<0.001$).

In the group of patients without MetS adiponectin level is not associated with fat percentages in different areas of the body or total fat percentage, whereas in the group of patients with MetS adiponectin reports a weak and positive correlation between fat mass total, arms fat and legs fat percentages. Trunk fat percentage is not associated with adiponectin levels ($p>0.05$). Therefore, our study further analyzed the relationship between adipokines, and HOMA-IR. Adiponectin is negatively correlated with HOMA-IR and insulin in both groups, suggesting that insulin resistance is linked to the change in adiponectin levels (fig. 1).

Regarding biochemical parameters, glucose presents moderate correlations with HOMA-IR in the MetS group ($r=0.563$, $p<0.001$) and in the group without MetS ($r=0.521$, $p=0.001$). Patients that present MetS also report an association between glucose and insulin ($r=0.238$, $p=0.049$) and between HDL and adiponectin ($r=0.280$, $p=0.02$).

DISCUSSION

Adiponectin levels differ statistically be-

tween the 2 groups, suggesting that the value decreases when MetS is present, even if patients present the same percentage of adipose tissue per total body and per different areas of the body. This result is supported by other studies from the literature that report a lower secretion rate of adiponectin in obesity-related diseases, including diabetes mellitus, dyslipidemia, hypertension or atherosclerotic cardiovascular disease (10-12). Recent reviews treat adiponectin as a potential therapeutic target for MetS, discussing drugs that increase plasma adiponectin (PPAR γ agonists thiazolidinediones, phytochemicals, L-cys-teine), alongside their safety concerns and limitations (12-14). However, several clinical studies and a more recent meta-analysis report associations between high adiponectin and mortality (15-17). This adiponectin paradox seems to be characterized by adiponectin resistance, due to altered signal transduction and insulin sensitivity, as a consequence of T-cadherin hydrolysis (18-19).

In our cohort, adiponectin level correlates well with insulin resistance in both groups, while with body fat parameters the correlation is not present in the group without MetS. Having a very similar mean concerning the percentages of adipose tissue reported for specific areas of the body and even for the whole-body surface, these results suggest that insulin and insulin resistance are more relevant for adiponectin levels than obesity. Studies support our findings even though the entire mechanism of action of adiponectin is not yet known. When binding to its receptors AdipoR1 and AdipoR2, adiponectin activates adenosine monophosphate dependent kinase (AMPK), PPAR γ and probably other signaling pathways that still need to be discovered (12, 20).

Adipokine profile and metabolic syndrome in patients with similar adipose tissue mass and distribution

Leptin presents strong correlations with adipose tissue in both groups, reflecting an even stronger relationship in patients with MetS. Of all the areas analyzed, trunk area reports the strongest correlation, implying that abdominal adipose tissue plays a key role in leptin secretion.

Our study included the index calculated for visceral adipose tissue (eVAI), which did not correlate with adipokines or insulin. A paper on 5113 participants reports that ethnicity plays a role in establishing the cardiometabolic risk of patients and that in Europeans visceral adipose tissue (measured by ultrasonography) showed stronger positive associations with most of the cardiometabolic risk factors than subcutaneous fat (21). However, another recent study on samples of abdominal adipose tissue obtained from both subcutaneous and visceral fat depots show that adipokine dysregulation is first seen in subcutaneous adipose tissue, rather than in visceral adipose tissue. This conclusion suggests that endocrine dysfunction in the subcutaneous adipose tissue may represent an early risk sign of MetS (22).

Results from our analysis present LAR as a parameter with a direct proportional relationship with fat mass, regardless of the body surface area studied. The correlations are always stronger in patients with MetS, but not as strong as leptin alone. Although LAR levels are higher in patients with MetS, the difference between the 2 groups is not statistically significant, possibly because of the similar leptin values between the 2 groups. Even though adiponectin values differ significantly, leptin presents a stronger correlation and therefore weights more in the ratio between the 2. In the literature, high LARs report a higher risk of developing type 2 diabetes mellitus (23). Also, in a study with a 2.8-year fol-

low-up timeframe, LAR had a better predictive value than adiponectin alone for the regression of MetS, suggesting that LAR may be used as a clinical marker for the management of MetS (24).

HOMA-IR is shown to correlate best with adiponectin in patients with MetS and with LAR in patients without MetS. Leptin and LAR do not correlate with insulin resistance in patients with MetS, but it is important to highlight those only patients with no known metabolic or cardiovascular disease were included in this study. There are some patients with high glucose values, but they are not confirmed with diabetes. Therefore, this can explain the lack of association between LAR and HOMA-IR in patients with MetS.

Several studies reported a positive correlation between adiponectin and HDL (25-28), similar to our findings in the study. Adiponectin is an antiatherogenic adipokine, with an important role in prevention. It has been demonstrated that hypoadiponectinemia is an effective predictor for decreased cholesterol efflux capacity (a measure of HDL quality and quantity) in adults, regardless of the obesity status or degree (29).

CONCLUSIONS

Patients with MetS that did not follow prior treatment for any chronic disease and are characterized by similar adipose tissue percentage and distribution, report the following: lower adiponectin levels than patients without MetS, but still a positive association with HDL; no modification in leptin levels compared to patients without MetS; negative correlation between adiponectin and insulin resistance; strong association between leptin and adipose tissue mass.

**CONFLICT OF INTEREST
AND FUNDING**

The authors declare that there is no con-

flict of interest, and they received no specific funding regarding this scientific research.

REFERENCES

1. Fox CS, Massaro JM, Hoffmann U, *et al.* Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham heart study. *Circulation* 2007; 116: 39-48.
2. Mongraw-Chaffin M, Allison MA, Burke GL, *et al.* CT-derived body fat distribution and incident cardiovascular disease: the multi-ethnic study of atherosclerosis. *J Clin Endocrinol Metab* 2017; 102: 4173-4183.
3. Yamauchi T, Kamon J, Waki H *et al.* Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem* 2003; 278: 2461-2468.
4. Esteve E, Ricart W, Fernández-Real JM. Adipocytokines and insulin resistance: the possible role of lipocalin-2, retinol binding protein-4, and adiponectin. *Diabetes Care*. 2009; 32(Suppl 2): S362-367.
5. Juergen Eckel. *The Cellular Secretome and Organ Crosstalk*. Chapter 2 - Adipose Tissue: A Major Secretory Organ. Academic Press; 2018.
6. Patel SB, Reams GP, Spear RM, Freeman RH, Villarreal D. Leptin: linking obesity, the metabolic syndrome, and cardiovascular disease. *Curr Hypertens Rep* 2008; 10: 131-137.
7. Grundy SM, Cleeman JI, Daniels SR, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112: 2735-2752.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412-419.
9. Amato MC, Giordano C, Galia M *et al.* Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes care* 2010; 33: 920-922.
10. Ntzouvani A, Fragopoulou E, Panagiotakos D, *et al.* Reduced circulating adiponectin levels are associated with the metabolic syndrome independently of obesity, lipid indices and serum insulin levels: a cross-sectional study. *Lipids Health Dis* 2016; 15: 140 / doi: 10.1186/s12944-016-0311-7.
11. Nigro E, Scudiero O, Monaco ML, *et al.* New insight into adiponectin role in obesity and obesity-related diseases. *Biomed Res Int* 2014; 2014: 658913 / doi: 10.1155/2014/658913.
12. Roy B, Palaniyandi SS. Tissue-specific role and associated downstream signaling pathways of adiponectin. *Cell Biosci* 2021; 11: 77 / doi: 10.1186/s13578-021-00587-4.
13. Abhijit AG, Amrita AK, Aniket AK. A potential therapeutic target for metabolic syndrome. *Cytokine & Growth Factor Reviews*. 2018; 39: 151-158.
14. Achari AE, Jain SK. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. *Int J Mol Sci* 2017; 18(6): 1321 / doi: 10.3390/ijms18061321.
15. Menzaghi C, Trischitta V. The adiponectin paradox for all-cause and cardiovascular mortality. *Diabetes*. 2018; 67(1): 12-22 / doi: 10.2337/dbi17-0016.

**Adipokine profile and metabolic syndrome
in patients with similar adipose tissue mass and distribution**

16. Ortega Moreno L, Lamacchia O, Salvemini L, *et al.* The paradoxical association of adiponectin with mortality rate in patients with type 2 diabetes: evidence of synergism with kidney function. *Atherosclerosis*. 2016; 245: 222-227.
17. Scarale MG, Fontana A, Trischitta V, Copetti M, Menzaghi C. Circulating adiponectin levels are paradoxically associated with mortality rate. A systematic review and meta-analysis. *J. Clin. Endocrinol. Metab* 2019; 104: 1357-1368.
18. Kalkman HO. An Explanation for the Adiponectin Paradox. *Pharmaceuticals (Basel)* 2021; 14(12): 1266 / doi: 10.3390/ph14121266.
19. Maeda N, Funahashi T, Matsuzawa Y, Shimomura I. Adiponectin, a unique adipocyte-derived factor beyond hormones. *Atherosclerosis* 2020; 292: 1-9 / doi: 10.1016/j.atherosclerosis.2019.10.021.
20. Yadav A, Kataria M, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clinica Chimica Acta* 2013; 417: 80-84.
21. Rønn PF, Andersen GS, Lauritzen T, *et al.* Abdominal visceral and subcutaneous adipose tissue and associations with cardiometabolic risk in Inuit, Africans and Europeans: a cross-sectional study. *BMJ Open* 2020; 10: e038071.
22. Korac A, Srdic-Galic B, Stancic A, Otasevic V, Korac B, Jankovic A. Adipokine signatures of subcutaneous and visceral abdominal fat in normal-weight and obese women with different metabolic profiles. *Archives of Medical Science* 2021; 17(2): 323-336.
23. Liao PJ, Ting MK, Wu IW, Chen SW, Yang NI, Hsu KH. Higher Leptin-to-Adiponectin Ratio Strengthens the Association Between Body Measurements and Occurrence of Type 2 Diabetes Mellitus. *Frontiers in Public Health*. 2021; 9: 678-681 / doi: 10.3389/fpubh.2021.678681.
24. Kang DR, Yadav D, Koh SB, Kim JY, Ahn SV. Impact of Serum Leptin to Adiponectin Ratio on Regression of Metabolic Syndrome in High-Risk Individuals: The ARIRANG Study. *Yonsei Med J* 2017; 58(2): 339-346.
25. Vergès B, Petit JM, Duvillard L, Dautin G, Florentin E, Galland F, Gamber P. Adiponectin is an important determinant of apoA-I catabolism. *Arterioscler Thromb Vasc Biol* 2006; 26: 1364-1369.
26. Uslu S, Kebapçı N, Kara M, Bal C. Relationship between adipocytokines and cardiovascular risk factors in patients with type 2 diabetes mellitus. *Exp Ther Med* 2012; 4: 113-120.
27. Yamamoto Y, Hirose H, Saito I *et al.* Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clin Sci (Lond)* 2002; 103(2): 137-142.
28. Martin LJ, Woo JG, Daniels SR, Goodman E, Dolan LM. The relationships of adiponectin with insulin and lipids are strengthened with increasing adiposity. *J Clin Endocrinol Metab* 2005; 90(7): 4255-4259.
29. Marsche G, Zelzer S, Meinitzer A, *et al.* Adiponectin Predicts High-Density Lipoprotein Cholesterol Efflux Capacity in Adults Irrespective of Body Mass Index and Fat Distribution. *The Journal of Clinical Endocrinology & Metabolism* 2017; 102(11): 4117-4123.