Endokrynologia Polska
DOI: 10.5603/EP.a2018.0026
Tom/Volume 69; Numer/Number 3/2018
ISSN 0423–104X

Adiponectin expression in visceral adiposity is an important determinant of insulin resistance in morbid obesity

Ekspresja adiponektyny w otyłości trzewnej jest istotnym wyznacznikiem insulinooporności w otyłości olbrzymiej

Anca Sirbu[1, 2], Laura Buburuzan[3], Steliana Kevorkian[3], Sorina Martin[1, 2], Carmen Barbu[1, 2], Catalin Copaescu[1, 4], Bogdan Smeu[4], Simona Fica[1, 2]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*Elias University Hospital, Bucharest, Romania*
[3]*University of Bucharest, Department of Biochemistry and Molecular Biology, Bucharest, Romania*
[4]*Ponderas Hospital, Bucharest, Romania*

Abstract

Introduction: Visceral adiposity is associated with decreased serum adiponectin levels, peripheral resistance to insulin, and an increased risk of cardio-metabolic complications. However, the link between adiponectin expression in visceral adipose tissue (VAT), its serum levels, and metabolic protection is controversial. The aim of this study was to investigate the relationship between the adiponectin gene expression in VAT and clinical and metabolic parameters in patients with severe obesity.

Material and methods: This is a cross-sectional study that included 51 severely obese patients (age 43.24 ± 11.29 years, BMI 45.13 ± 8.67 kg/m^2), extensively evaluated clinically and biologically (metabolic tests, serum adiponectin measurements, HOMA-IR) before bariatric surgery. Omental adipose tissue was sampled during the intervention and the relative quantification of adiponectin gene expression was performed by real-time PCR.

Results: Adiponectin mRNA in VAT was significantly higher in obese insulin-sensitive patients than in the rest of the obese patients ($p < 0.05$) and negatively correlated with HOMA-IR ($r = –0.354$, $p = 0.016$) and uric acid ($r = –0.304$, $p = 0.045$). After adjustment for gender, TG/HDL ratio and uric acid, adiponectin expression ($\beta = –0.439$, $p = 0.001$), waist circumference ($\beta = 0.467$, $p = 0.001$), and serum adiponectin ($\beta = –0.339$, $p = 0.011$) remained significantly associated with HOMA-IR, together explaining more than 50% of its variation.

Conclusions: In severely obese patients, adiponectin gene expression in VAT is negatively correlated with serum levels of uric acid and is an independent determinant, together with anthropometric parameters of visceral obesity and serum adiponectin levels, of insulin resistance. **(Endokrynol Pol 2018; 69 (3): 252–258)**

Key words: *adiponectin expression, visceral adipose tissue, HOMA-IR, insulin resistance, severe obesity*

Streszczenie

Wstęp: Otyłość trzewna związana jest ze zmniejszonym stężeniem adiponektyny w surowicy krwi, obwodową opornością na działanie insuliny oraz ze zwiększonym ryzykiem powikłań sercowo-metabolicznych. Jednak związek między ekspresją adiponektyny w trzewnej tkance tłuszczowej, jej stężeniem w surowicy krwi a ochroną metaboliczną jest kwestią sporną. Celem niniejszej pracy było zbadanie związku między ekspresją genu adiponektyny w trzewnej tkance tłuszczowej a klinicznymi i metabolicznymi parametrami pacjentów ze znaczną otyłością.

Materiał i metody: To przekrojowe badanie obejmowało 51 znacznie otyłych pacjentów (wiek 43,24 ± 11,29 roku, BMI 45,13 ± 8,67 kg/m^2), szczegółowo ocenionych pod względem klinicznym i biologicznym (testy metaboliczne, pomiary stężenia adiponektyny w surowicy krwi, wskaźnik HOMA-IR) przed operacją bariatryczną. Podczas operacji pobrano tkankę tłuszczową sieci. Względna ocena ilościowa ekspresji genu adiponektyny była przeprowadzona metodą PCR w czasie rzeczywistym.

Wyniki: Poziom mRNA adiponektyny w trzewnej tkance tłuszczowej był znacząco wyższy u otyłych pacjentów wrażliwych na insulinę niż u pozostałych otyłych pacjentów ($p < 0,05$) oraz ujemnie skorelowany ze wskaźnikiem HOMA-IR ($r = –0,354$, $p = 0,016$) i kwasem moczowym ($r = –0,304$, $p=0.045$). Po uwzględnieniu płci, wskaźnika TG/HDL i kwasu moczowego, ekspresja adiponektyny ($\beta = –0,439$, $p = 0,001$), obwód talii ($\beta = 0,467$, $p = 0,001$) i poziom adiponektyny w surowicy krwi ($\beta = –0,339$, $p = 0,011$) pozostały istotnie związane ze wskaźnikiem HOMA-IR, łącznie wyjaśniając ponad 50% jego wariancji.

Wnioski: W przypadku znacznie otyłych pacjentów ekspresja genu adiponektyny w trzewnej tkance tłuszczowej jest ujemnie skorelowana ze stężeniem kwasu moczowego w surowicy krwi i razem z antropometrycznymi parametrami otyłości trzewnej oraz stężeniem adiponektyny w surowicy krwi jest niezależnym wyznacznikiem insulinooporności. **(Endokrynol Pol 2018; 69 (3): 252–258)**

Słowa kluczowe: *ekspresja adiponektyny, trzewna tkanka tłuszczowa, HOMA-IR, insulinooporność, znaczna otyłość*

Anca Sirbu, Lecturer in Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Endocrinology Department, Elias University Hospital; bd Marasti, no 17, sector 1, Bucharest, Romania, tel.: 0040213161600/111, e-mail: ancaelenasirbu@yahoo.com

Introduction

Obesity has been associated with a substantial amplification in the risk of cardiovascular and metabolic diseases, with increased morbidity and mortality [1, 2]. However, these conditions do not occur invariably in obese patients, with some groups of individuals being more susceptible or, on the contrary, somehow protected against developing cardio-metabolic pathology.

Numerous studies have shown abdominal adiposity to be strongly correlated with insulin resistance, with differences in the amount of visceral fat explaining routinely the variability of insulin sensitivity in obese patients [3]. These clinical observations led to the so-called "portal paradigm" that hypertrophied visceral adipocytes, whose basal lipolysis is enhanced in obesity, release increased levels of free fatty acids into the portal system, which leads to hepatic insulin resistance and failure of pancreatic beta-cells [4]. This theory has been questioned in recent years by the discovery of the endocrine role of adipose tissue and of the pleiotropic adipocytokines, involved in the control of many metabolic processes.

Adiponectin, the adipocyte hormone with the highest plasma concentration, is considered a modulator of carbohydrate and lipid metabolism and a marker of insulin sensitivity [5]. Although mainly produced in adipose tissue, serum adiponectin concentrations are negatively correlated with the amount of visceral adiposity [6]. However, the link between adiponectin expression in adipose tissue, its serum levels, and metabolic protection is controversial.

The aim of our study was to investigate the relationship between the adiponectin gene expression in visceral adipose tissue and clinical and metabolic parameters in patients with severe obesity, undergoing bariatric surgery.

Material and methods

The study group included 51 patients (70.5% women, 29.5% men) with severe obesity, who underwent laparoscopic sleeve gastrectomy in a highly specialised Bariatric Surgery Clinic. All patients met the 1991 NIH Consensus Conference guidelines for bariatric surgery [7]. This study was conducted according to the standards of good clinical practice and the Declaration of Helsinki and was approved by the institutional Ethics Committee (Decision 1/10.02.2011). All patients signed an informed consent form.

Approximately one month before surgery, patients were extensively evaluated in our Endocrinology, Diabetes, and Nutrition Disorders Department, as described elsewhere [8]. Exclusion criteria were: diabetic patients requiring insulin due to difficulties in assessing insulin resistance, as well as patients with severe chronic kidney disease (estimated glomerular filtration rate < 30 mL/min), liver failure, cancer, and other severe systemic diseases.

Body weight was measured in light clothing and without shoes, to the nearest 0.5 kg; height was measured to the nearest 0.5 cm; waist circumference (WC) was measured at the midway between the lower border of the rib cage and the iliac crest, while hip circumference was measured around the widest portion of the buttocks. After overnight fasting, blood samples were obtained and immediately used for the determination of glucose, liver enzymes, uric acid, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG). For the other tests, plasma was separated by centrifugation at 4000 rpm/min for 6 minutes at 20° C and then frozen at –80°C. Insulin and high-sensitivity C-reactive protein (hs-CRP) were assayed using a two-site, solid-phase, enzyme-labelled chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Products Ltd.). Serum adiponectin and TNF-α levels were measured using an ELISA kit (DRG Instruments, Germany). For adiponectin the detection rate was 0.39 mg/l, the intra-assay CV was 0.9–7.4%, and the inter-assay CV was 2.4–8.4%. For TNF-α the detection rate was 0.7 pg/ml, the intra-assay CV was 6.3–6.6%, and the inter-assay CV was 3.3–4.5%.

In all patients not previously diagnosed with diabetes mellitus, we performed a 75-g oral glucose tolerance test (OGTT), with blood samples taken at 0 and 2 hours. In conformity with the American Diabetes Association criteria [9] all patients with fasting plasma glucose ≥ 126 mg/dL or 2-hour plasma glucose ≥ 200 mg/dL during OGTT were considered as having diabetes mellitus. Patients with fasting plasma glucose between 100 and 125 mg/dL or with two-hour plasma glucose between 140 and 200 mg/dL were considered as having prediabetes [9].

To assess IR, the homeostasis model assessment of IR (HOMA-IR) was used [10]. Non-diabetic patients in the inferior quartile of HOMA (that is HOMA < 2.85) were considered **insulin sensitive** (IS+), while the rest of the patients were considered **insulin resistant** (IS–). Visceral adiposity index (VAI), a novel sex-specific index highly correlated with visceral adiposity measured by magnetic resonance imaging (the gold standard method), was defined using the Amato formula [11]:

$$\text{VAI men} = \left(\frac{\text{waist circumference}}{39.68 + 1.88 \times \text{BMI}}\right) \times \frac{\text{TG}}{1.03} \times \frac{1.31}{\text{HDL}}$$

$$\text{VAI women} = \left(\frac{\text{waist circumference}}{36.58 + 1.89 \times \text{BMI}}\right) \times \frac{\text{TG}}{0.81} \times \frac{1.52}{\text{HDL}}$$

Patients were considered to have metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III definition [8].

Biological material

A piece of omental adipose tissue of about 0.5 g was sampled from all patients during surgery and was immediately submerged in RNA preserving solution (RNAlater — Qiagen GmbH Germany) and stored at –80° C, for further analysis of adiponectin gene expression (mRNA). The relative quantification of adiponectin gene expression was performed by real-time PCR, using beta-actin as a reference gene.

Isolation of total RNA

Total RNA was extracted from visceral fat sample with TRI Reagent (Sigma-Aldrich). The concentration and purity of extracted RNA was quantified using a spectrophotometer Biospec-Nano (Shimadzu Biotech, Kyoto, Japan), and the RNA integrity was checked by visual inspection of the bands corresponding to the 28S rRNA and 18S rRNA by electrophoresis in 2% agarose gel.

Adiponectin gene expression was assessed by real-time RT-PCR. For reverse transcription reaction total RNA was used together with the iScript synthesis kit (Bio-Rad, Hercules, CA, USA) and the protocol indicated by the manufacturer.

The set of primers used in the amplification reaction were selected using Primer 3 program, namely: Adiponectin: forward primer 5′-CATGACCAGGAAACCACGACT-3′ and reverse primer 5′-TGAATGCTGAGCGGTAT-3′; reference gene, β actin: forward primer 5′-GCCTCGCTGTCCACCTTCC-3′ and reverse primer 5′-GCTGTCACCTTCACCGTTCC -3′.

The reactions were performed on a thermocycler iCycler iQ (Bio-Rad) using an excitation filter set/ /transmitter specific for the SYBR Green (λex 490 nm/ /λem 530 nm). Quantitative PCR reaction was performed in a final volume of 25 μL containing 5 μL of diluted template cDNA, 12.5 μL 2 × BioRad iQ SYBR Green Supermix™, 200 nM of each sense and antisense primer. The amplification program consisted of: initial denaturation cycle — 95°C, 3 min 30 sec.; 45 cycles of amplification: denaturation — 30 sec. 95°C, hybridisation — 30 sec. 58°C, elongation and fluorescent signal acquisition — 30 sec. 72°C; the program for determining the melting curve: 85 cycles of 10 seconds each, with an increasing variation of temperature in 0.5°C increments, starting at 55°C.

Changes in the level of adiponectin to beta-actin mRNA were calculated based on the formula [12] $(1/2)^{CT\ adiponectin - CT\ \beta\text{-actin}}$. All determinations were made in triplicate and the arithmetic mean of the results was used for the analysis.

Statistical processing

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago IL), version 17.0. Continuous variables with normal distribution are presented as mean ± standard deviation (SD), and those with non-Gaussian distribution are presented as medians (interquartile range). The value of adiponectin expression (corrected to beta-actin) was used as a decimal logarithm. Comparisons between groups were made using parametric and non-parametric tests (Student t-test or Mann-Whitney test for continuous variables, the chi-square test for categorical ones). Correlations were performed using the Pearson/Spearman test, and linear regression analysis was used to identify the influence of various parameters on the level of HOMA-IR. $P < 0.05$ was considered as statistically significant for all tests.

Results

Our study included 51 severely obese patients (36 women), with mean BMI = 45.13 ± 8.67 kg/m^2 (men: 49.99 ± 10.64 kg/m^2, women: 43.11 ± 6.92 kg/m^2, p = 0.008) and mean age = 43.24 ± 11.29 years (no significant difference between genders). Eleven patients (21.5%) had type 2 diabetes and another 11 had prediabetes (two with impaired fasting glucose and 11 with impaired glucose tolerance).

Table I presents the general characteristics of the study patients, according to the presence of insulin sensitivity. Since no statistically significant differences were observed between adiponectin gene expression in omental fat in men and women, all patients were included in the analysis, without gender segregation. As expected, the insulin-sensitive obese group had a lower WHR (although there was no significant difference in BMI level or in gender-adjusted weight) and a significantly more beneficial metabolic profile (higher values of HDL-cholesterol, and lower levels of triglycerides, uric acid, and visceral adiposity index — VAI). The presence of insulin sensitivity was also associated with lower levels of inflammation markers (C-reactive protein, TNF-alpha) and higher values of serum adiponectin.

Adiponectin gene expression in visceral adipose tissue was significantly higher in obese insulin-sensitive patients than in the rest of the obese patients (Table I). This difference is maintained and becomes even more evident after adjustment for gender and BMI (Figure 1).

In univariate analysis, there was no significant correlation between adiponectin gene expression in the visceral adipose tissue and anthropometric indices (such as weight, BMI, waist circumference, or WHR) or with serum adiponectin level. Among metabolic parameters, adiponectin expression was negatively correlated with

Table I. *General characteristics of the patients included in the study according to insulin sensitivity*
Tabela II. *Ogólna charakterystyka pacjentów objętych badaniem w zależności od wrażliwości na insulinę*

	IS+ (n = 15)	IS– (n = 36)	p
Gender — female (%)	93.3%	61.1%	0.04
Age (years)	41.33 ± 12.99	44.03 ± 10.6	NS
Smokers (%)	40%	38.9%	NS
Weight [kg]	112.07 ± 13.24	130.42 ± 29,86	0.027
BMI [kg/m^2]	42.37 ± 7.02	46.28 ± 9.11	NS
WC [cm]	114.67 ± 18.15	129 ± 20.15	0.021
WHR	0.86 ± 0.08	0.95 ± 0.1	0.005
*HDL-cholesterol [mg/dl]	56 (27)	43 (13)	0.02
Triglycerides [mg/dl]	115.27 ± 45.52	172.61 ± 55.67	0.001
*LDL-cholesterol [mg/dl]	115 (50)	130 (43)	NS
Total cholesterol [mg/dl]	206.53 ± 40.56	205.86 ± 31.03	NS
*VAI	4.1 (2.66)	6.38 (5.23)	0.001
Hypertensive (%)	40%	52%	NS
MetS (%)	40%	77.8%	0.02
Uric acid [mg/dl]	5.02 ± 1.17	6.06 ± 1.35	0.019
*CRP [mg/dl]	0.39 (0.76)	0.73 (1.28)	0.028
*TNF-alpha [pg/ml]	5.2 (1.5)	6.6 (2.2)	0.016
*Plasma adiponectin [mg/l]	7.72 (1.26)	6.49 (2.65)	0.019
Adiponectin gene relative expression	–1.89 ± 0.6	–2.23 ± 0.57	0.038

*marks variables with non-Gaussian distribution
Continuous variables with normal distribution are presented as mean ± standard deviation (SD), while those with non-Gaussian distribution are presented as medians (interquartile range).
IS+ — insulin sensitive patients; IS- — patients without insulin sensitivity; BMI — body mass index; WC — waist circumference; WHR — waist/hip ratio; VAI — visceral adiposity index; MetS — metabolic syndrome; CRP — C reactive protein; TNF — tumoural necrosis factor

HOMA-IR (r = –0.354, p = 0.016) and uric acid, after gender adjustment (r = –0.304, p = 0.045).

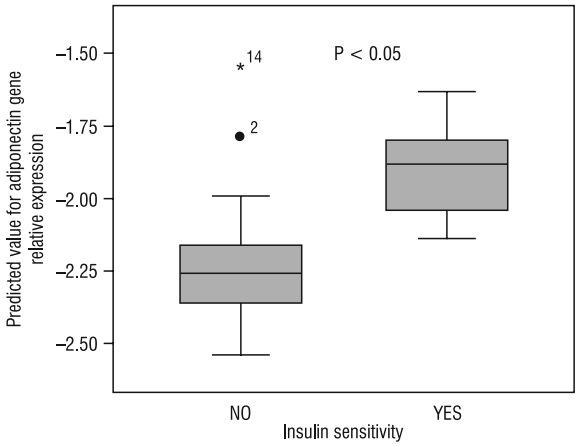
In the following stage of the analysis we tried to identify the role of adiponectin gene expression as a determinant of insulin resistance assessed by HOMA-IR. Other clinical and biological parameters significantly correlated with HOMA-IR in the univariate analysis were: waist circumference (r = 0.343, p = 0.017), HDL-cholesterol (r = –0.388, p = 0.009), triglycerides (r = 0.355, p = 0.013), TG/HDL ratio (r = 0.450, p = 0.002), uric acid (r = 0.431, p = 0.003), and serum adiponectin (r = –0.314, p = 0.036). Gender was another significant determinant of HOMA-IR levels (HOMA-IR — logarithmic value — for women: 0.516 ± 0.25, for men: 0.688 ± 0.27, p = 0.047)

A linear regression analysis, stepwise method was subsequently performed, with HOMA-IR as the dependent variable and factors previously shown to significantly correlate to its level as independent variables (gender, waist circumference, TG/HDL ratio, uric acid, serum adiponectin, adiponectin gene expression). In this model, serum adiponectin, waist circumference, and adiponectin gene expression in visceral adipose tissue were independent determinants of HOMA-IR levels, together explaining about 50% of its variability (Table II).

Discussion

This study analyses the link between adiponectin gene expression in visceral adipose tissue (VAT) and biological and clinical parameters in severely obese patients. Our data showed no relationship between adiponectin mRNA from VAT and anthropometric indices (BMI, waist circumference) or serum levels of adiponectin, but a negative correlation with two of the parameters of metabolic damage in obesity — uric acid levels and HOMA-IR. In regression analysis, adiponectin gene expression level was an independent determinant of HOMA-IR value, and, together with serum concentration of adiponectin and waist circumference, explained more than 50% of its variability.

It is well-known that obese patients have low levels of serum adiponectin [13], while low plasma adiponec-



Insulin sensitivity	Mean adiponectin mRNA	Standard error	95% confidence interval	
			Lower bound	Upper bound
NO	–2.270	.097	–2.465	–2.074
YES	–1.824	.152	–2.130	–1.517

Figure 1. *Adiponectin gene relative expression in visceral adipose tissue, according to insulin sensitivity status. Bars illustrate estimated marginal means ± SE of adiponectin expression, as determined by analysis of covariance after adjustment for gender and BMI*

Rycina 1. *Względna ekspresja genu adiponektyny w trzewnej tkance tłuszczowej, zgodnie ze stanem wrażliwości na insulinę. Słupki na wykresie ilustrują przybliżone wartości brzegowe ± SE (standard error; błąd standardowy) ekspresji adiponektyny, określone przez analizę kowariancji po uwzględnieniu płci i wskaźnika BMI*

Table II. ***Multiple regression analysis, stepwise method, the determinants of HOMA-IR***

Tabela II. ***Analiza regresji wielokrotnej, metoda krokowa, determinanty HOMA-IR***

Dependent variable	Independent variable	B	P
*HOMA-IR ($r^2 = 0.503$, $p < 0.001$)	*Serum adiponectin	–0.339	0.011
	Waist circumference	0.467	0.001
	*Adiponectin gene expression	–0.439	0.001

*marks logarithmically transformed variables
Excluded variables: gender, TG/HDL ratio, uric acid

tin concentrations predict increases in visceral adiposity and insulin resistance, but the mechanisms behind this association have not been fully elucidated [14]. One hypothesis stipulates a defect in adiponectin synthesis at adipocyte level, because circulating levels of adiponectin are directly related to production of adipocytes due to adiponectin being secreted almost exclusively by mature adipocytes [15]. There have been several studies investigating the relationship between adiponectin gene expression in various adipose tissue compartments and patients' anthropometric parameters, but the results are contradictory. While negative correlation between adiponectin gene expression in the subcutaneous adipose tissue and BMI was certified by several authors [16], the link between adiponectin mRNA in visceral adipocytes and overall adiposity is less obvious, with some studies that support a link [16] and other that do not identify a relationship with BMI [17, 18]. In the present study we could not establish a clear correlation between adiponectin gene expression in omental adiposity and BMI or other anthropometric parameters. A possible explanation is the profile of our group of patients: relatively young and with severe obesity but without an extremely deteriorated metabolic pattern. In these patients, the characteristically increased subcutaneous fat deposits may even have a protective role, leading to a prevalence of metabolic disorders significantly lower than expected compared to overweight or normal-weight patients [19].

Our study could not reveal a relationship between adiponectin mRNA in visceral adipose tissue and its serum levels. This might be due to the differences in morphology and cellularity among the adipose tissue depots or to the differential impact of various adiposity compartments on adiponectin serum concentration. In vitro studies have shown that adiponectin gene expression is more reduced in visceral fat than in subcutaneous compartment, which suggests that the latter may be more important for the circulating adiponectin. In addition, in a population-based study including nearly 800 young Danes, Frederiksen concluded that subcutaneous adiposity, rather than the visceral, is a major determinant of serum adiponectin levels [20]. Other possible explanations for the lack of a relationship between adiponectin mRNA and its serum level may be the existence of a posttranscriptional defect in protein translation or secretion, or its enhanced capture/degradation in obese patients. Studies in patients receiving PPAR-γ agonists showed a significant increase in total adiponectin levels, unaccompanied by change of adiponectin mRNA, suggesting that regulation is made at posttranscriptional level [21]. In another study evaluating the effect of pioglitazone on adiponectin translation, Banga et al. identified an adipocitary cytoplasm factor, most probably a protein, that constitutively inhibits adiponectin translation in obese patients, as an important component of insulin resistance syndrome [22].

Even in the absence of a clear relationship with BMI, adiponectin gene mRNA in VAT was negatively correlated with two of the biological parameters which characterise metabolic damage in obesity — uric acid serum

levels and insulin resistance, estimated by HOMA-IR. Regarding uric acid, there are several studies proving that hyperuricaemia is not only a secondary marker of obesity and its associated insulin resistance, but also a potential determinant of metabolic syndrome [23]. In a research project that investigated the effect of hyperuricaemia on the production of adiponectin, Baldwin showed that uric acid causes a dramatic reduction of adiponectin mRNA in murine and human adipocyte cell lines, and its effect seems to be mediated by inhibition of PPAR-γ [24]. In our study we also identified a negative correlation between serum levels of uric acid and adiponectin gene expression in visceral adipose tissue, and, furthermore, this relationship proved to be independent of BMI, which demonstrates the role of uric acid as a marker (or maybe determinant) of metabolic complications in patients with severe obesity.

One of the important results of this study was the demonstration of a negative correlation between omental expression of adiponectin gene and HOMA-IR. This relationship remained significant after adjustment for serum levels of adiponectin and waist circumference, and together these three parameters explained about 50% of HOMA-IR variability. It is well known that in obese patients, the amount of intra-abdominal adipose tissue is one of the most important determinants of the degree of insulin resistance [25]. Compared with subcutaneous adipocytes, the visceral ones are less sensitive to insulin and have a higher level of basal lipolysis, which leads to the release of free fatty acids and pro-inflammatory adipokines (TNF-alpha, IL-6) in the portal system and subsequent insulin-resistance [4]. Our study showed that obese patients with insulin sensitivity have a higher level of adiponectin mRNA than the insulin resistant ones. Furthermore, in linear regression analysis, both adiponectin gene visceral expression and serum adiponectin were independent predictors of HOMA-IR. Similar results were recently reported by Chen et al., who analysed adiponectin gene expression in the omental adipose tissue in 40 patients, of whom 25 were obese and showed an inverse correlation with HOMA-IR. In the same study, adiponectin gene expression was significantly increased (by about five times) after gastric bypass intervention, paralleling the improvement in insulin resistance [26].

We are aware that this study has some limitations that originate firstly from the relatively small number of analysed patients and, on the other hand, from the inability to properly quantify the distribution of adiposity, which would have brought additional information on the contribution of visceral fat in the determinism of insulin resistance. It would have been also useful to determine adiponectin complexes of high molecular weight (HMW) because it is well-know that many of the beneficial effects of adiponectin are due to this isoform, especially those related to insulin sensitivity and protection against cardiovascular diseases [27].

Conclusions

In conclusion, we showed that, in severely obese patients, adiponectin gene expression in visceral adipose tissue is negatively correlated with serum levels of uric acid and is an independent determinant, together with anthropometric parameters of visceral obesity and serum adiponectin levels, of insulin resistance.

Conflicts of interest

No conflict of interest, financial or other, exists.

References

1. Frühbeck G, Toplak H, Woodward E, et al. Executive Committee of the European Association for the Study of Obesity. Obesity: the gateway to ill health - an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts. 2013; 6(2): 117–120, doi: 10.1159/000350627, indexed in Pubmed: 23548858.
2. Kivimäki M, Kuosma E, Ferrie JE, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. Lancet Public Health. 2017; 2(6): e277–e285, doi: 10.1016/S2468-2667(17)30074-9, indexed in Pubmed: 28626830.
3. Marcadenti A, de Abreu-Silva EO. Different adipose tissue depots: Metabolic implications and effects of surgical removal. Endocrinol Nutr. 2015; 62(9): 458–464, doi: 10.1016/j.endonu.2015.05.010, indexed in Pubmed: 26300495.
4. Mithieux G. Metabolic effects of portal vein sensing. Diabetes Obes Metab. 2014; 16 Suppl 1: 56–60, doi: 10.1111/dom.12338, indexed in Pubmed: 25200297.
5. Gao He, Fall T, van Dam RM, et al. Evidence of a causal relationship between adiponectin levels and insulin sensitivity: a Mendelian randomization study. Diabetes. 2013; 62(4): 1338–1344, doi: 10.2337/db12-0935, indexed in Pubmed: 23274890.
6. Kishida K, Funahashi T, Shimomura I. Adiponectin as a routine clinical biomarker. Best Pract Res Clin Endocrinol Metab. 2014; 28(1): 119–130, doi: 10.1016/j.beem.2013.08.006, indexed in Pubmed: 24417951.
7. Gastrointestinal Surgery for Severe Obesity. Ann Intern Med. 1991; 115(12): 956, doi: 10.7326/0003-4819-115-12-956.
8. Sirbu A, Gologan S, Arbanas T, et al. Adiponectin, body mass index and hepatic steatosis are independently associated with IGF-I status in obese non-diabetic women. Growth Horm IGF Res. 2013; 23(1-2): 2–7, doi: 10.1016/j.ghir.2012.10.001, indexed in Pubmed: 23111188.
9. American Diabetes Association. Standards of medical care in diabetes — 2012. Diabetes Care. 2012; 35 Suppl 1: S11–S63, doi: 10.2337/dc12-s011, indexed in Pubmed: 22187469.
10. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and ?-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28(7): 412–419, doi: 10.1007/bf00280883.
11. Amato MC, Giordano C, Galia M, et al. AlkaMeSy Study Group. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010; 33(4): 920–922, doi: 10.2337/dc09-1825, indexed in Pubmed: 20067971.
12. Schmittgen TD, Zakrajsek BA, Mills AG, et al. Quantitative reverse transcription-polymerase chain reaction to study mRNA decay: comparison of endpoint and real-time methods. Anal Biochem. 2000; 285(2): 194–204, doi: 10.1006/abio.2000.4753, indexed in Pubmed: 11017702.
13. Turer AT, Khera A, Ayers CR, et al. Adipose tissue mass and location affect circulating adiponectin levels. Diabetologia. 2011; 54(10): 2515–2524, doi: 10.1007/s00125-011-2252-z, indexed in Pubmed: 21779869.
14. Han SJ, Boyko EJ, Fujimoto WY, et al. Low Plasma Adiponectin Concentrations Predict Increases in Visceral Adiposity and Insulin Resistance. J Clin Endocrinol Metab. 2017; 102(12): 4626–4633, doi: 10.1210/jc.2017-01703, indexed in Pubmed: 29029184.
15. Kadowaki T, Yamauchi T, Okada-Iwabu M, et al. Adiponectin and its receptors: implications for obesity-associated diseases and longevity. Lancet Diabetes Endocrinol. 2014; 2(1): 8–9, doi: 10.1016/S2213-8587(13)70120-7, indexed in Pubmed: 24622657.

16. Lihn AS, Bruun JM, He G, et al. Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. Mol Cell Endocrinol. 2004; 219(1-2): 9–15, doi: 10.1016/j.mce.2004.03.002, indexed in Pubmed: 15149722.
17. Degawa-Yamauchi M, Moss KA, Bovenkerk JE, et al. Regulation of adiponectin expression in human adipocytes: effects of adiposity, glucocorticoids, and tumor necrosis factor alpha. Obes Res. 2005; 13(4): 662–669, doi: 10.1038/oby.2005.74, indexed in Pubmed: 15897474.
18. Yang WS, Chen MH, Lee WJ, et al. Adiponectin mRNA levels in the abdominal adipose depots of nondiabetic women. Int J Obes Relat Metab Disord. 2003; 27(8): 896–900, doi: 10.1038/sj.ijo.0802367, indexed in Pubmed: 12861229.
19. Drapeau V, Lemieux I, Richard D, et al. Metabolic profile in severely obese women is less deteriorated than expected when compared to moderately obese women. Obes Surg. 2006; 16(4): 501–509, doi: 10.1381/096089206776327215, indexed in Pubmed: 16608618.
20. Frederiksen L, Nielsen TL, Wraae K, et al. Subcutaneous rather than visceral adipose tissue is associated with adiponectin levels and insulin resistance in young men. J Clin Endocrinol Metab. 2009; 94(10): 4010–4015, doi: 10.1210/jc.2009-0980, indexed in Pubmed: 19755479.
21. Tonelli J, Li W, Kishore P, et al. Mechanisms of Early Insulin-Sensitizing Effects of Thiazolidinediones in Type 2 Diabetes. Diabetes. 2004; 53(6): 1621–1629, doi: 10.2337/diabetes.53.6.1621.
22. Banga A, Unal R, Tripathi P, et al. Adiponectin translation is increased by the PPARgamma agonists pioglitazone and omega-3 fatty acids. Am J Physiol Endocrinol Metab. 2009; 296(3): E480–E489, doi: 10.1152/ajpendo.90892.2008, indexed in Pubmed: 19088251.
23. Zhu Y, Hu Y, Huang T, et al. High uric acid directly inhibits insulin signalling and induces insulin resistance. Biochem Biophys Res Commun. 2014; 447(4): 707–714, doi: 10.1016/j.bbrc.2014.04.080, indexed in Pubmed: 24769205.
24. Baldwin W, McRae S, Marek G, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. Diabetes. 2011; 60(4): 1258–1269, doi: 10.2337/db10-0916, indexed in Pubmed: 21346177.
25. Lopes HF, Corrêa-Giannella ML, Consolim-Colombo FM, et al. Visceral adiposity syndrome. Diabetol Metab Syndr. 2016; 8: 40, doi: 10.1186/s13098-016-0156-2, indexed in Pubmed: 27437032.
26. Chen J, Spagnoli A, Torquati A. Omental gene expression of adiponectin correlates with degree of insulin sensitivity before and after gastric bypass surgery. Obes Surg. 2012; 22(3): 472–477, doi: 10.1007/s11695-011-0568-x, indexed in Pubmed: 22161113.
27. Caselli C. Role of adiponectin system in insulin resistance. Mol Genet Metab. 2014; 113(3): 155–160, doi: 10.1016/j.ymgme.2014.09.003, indexed in Pubmed: 25242063.