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Total and high-molecular-weight adiponectin levels and prediction of insulin resistance

Rola stężeń adiponektyny całkowitej oraz frakcji wysokocząsteczkowej w przewidywaniu insulinooporności

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Abstract

Introduction: Adiponectin is a peptide secreted by adipocytes; its reduction is associated with obesity-related disorders, including insulin resistance (IR). The study analysed levels of total adiponectin and its high-molecular-weight (HMW) oligomer in a group of metabolically healthy adults and in patients with type 2 diabetes mellitus (T2DM) to evaluate these levels as potential predictors of the presence of IR.
Materials and methods: The study comprised 269 metabolically healthy adults and 300 patients with T2DM. Anthropometric and biochemical indices were measured, including total and HMW adiponectin levels; the Homeostatic Model Assessment of IR (HOMA-IR) index was calculated, and logistic regression analysis was used to predict the presence of IR.
Results: In healthy individuals, both total and HMW adiponectin levels were significantly higher than in diabetic patients. Total and HMW adiponectin levels were moderately correlated with the HOMA-IR index. Logistic regression analysis showed that increased levels of both total adiponectin (odds ratio [OR] 0.598, 95% confidence interval [CI] 0.483–0.723) and the HMW form (OR 0.360, 95% CI 0.242–0.511) are protective factors for the development of IR. The cut-off levels were 4.22 mg/L for total adiponectin and 2.75 mg/L for HMW adiponectin. The results are valid for middle-aged European adults.
Conclusions: Adiponectin levels below the indicated cut-offs may predict a potential risk for the development of IR. **(Endokrynol Pol 2018; 69 (4): 375–380)**

Key words: *total adiponectin, high molecular weight adiponectin, insulin resistance, odds ratio, predictions, cut-off points*

Streszczenie

Wstęp: Adiponektyna jest peptydem wydzielanym przez adipocyty, na zmniejszenie jej wydzielania mają wpływ choroby związane z otyłością, w tym insulinooporność (*insulin resistance*; IR). W badaniu poddano analizie stężenia adiponektyny całkowitej i jej wysokocząsteczkowego (*high-molecular-weight*; HMW) oligomeru w grupie metabolicznie zdrowych dorosłych oraz pacjentów z cukrzycą typu 2 (*type 2 diabetes mellitus*; T2DM). Stężenia te oceniano jako potencjalne czynniki predykcyjne obecności insulinooporności.
Materiał i metody: W badaniu wzięło udział 269 zdrowych pod względem metabolicznym dorosłych i 300 pacjentów z cukrzycą typu 2. Aby przewidzieć obecność insulinooporności, zmierzono wskaźniki antropometryczne i biochemiczne, w tym stężenia adiponektyny całkowitej i jej wysokocząsteczkowej frakcji, skalkulowano homeostatyczny model oceny insulinooporności (HOMA-IR) oraz zastosowano analizę regresji logistycznej.
Wyniki: Stężenia adiponektyny całkowitej i jej wysokocząsteczkowej frakcji były znacząco wyższe u osób zdrowych niż u pacjentów cukrzycowych. Były one również umiarkowanie skorelowane ze wskaźnikiem HOMA-IR. Analiza regresji logistycznej wykazała, że podwyższone stężenia zarówno całkowitej adiponektyny (iloraz szans [*odds ratio*; OR] 0,598, 95% przedział ufności [*confidence interval*; CI] 0,483–0,723), jak i wysokocząsteczkowej frakcji (OR 0,360, 95% CI 0,242–0,511) są czynnikami ochronnymi przed rozwojem insulinooporności. Stężenie graniczne dla całkowitej adiponektyny wynosiłi 4,22 mg/l, natomiast dla frakcji wysokocząsteczkowej 2,75 mg/l. Wyniki są zasadne dla dorosłych Europejczyków w średnim wieku.
Wnioski: Stężenia adiponektyny poniżej wskazanych poziomów granicznych mogą przewidywać potencjalne ryzyko rozwoju insulinooporności. **(Endokrynol Pol 2018; 69 (4): 375–380)**

Słowa kluczowe: *adiponektyna całkowita, adiponektyna wysokocząsteczkowa, insulinooporność, iloraz szans, przewidywania, punkty graniczne*

Introduction

Adiponectin, a protein produced by adipocytes, plays an important role in the metabolism of glucose and lipids. It is a key component in the interrelationship between adiposity, insulin resistance (IR), and inflammation [1]. Concentrations of total adiponectin decrease in association with the development of metabolic dysfunction such as obesity, IR, or type 2 diabetes mellitus (T2DM) [2]. However, it has been suggested that obesity

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may not be an independent factor affecting plasma adiponectin level, and that an obesity-related decrease in plasma adipokine levels may be a consequence of obesity-related metabolic disorders [3].

The discovery of adiponectin seems to be an important landmark in the study of obesity and the related metabolic dysfunction accompanied by IR. In metabolically healthy individuals, adiponectin circulates at relatively high concentrations and is readily quantified by available laboratory methods [4]. Adiponectin circulates in human serum as high-molecular-weight (HMW) and low-molecular-weight (LMW) oligomers. The ratio of the HMW form to the total adiponectin level is referred to as the adiponectin sensitivity index [5].

Adiponectin is involved in regulation of lipid and glucose metabolism. Increased fatty acid oxidation in skeletal muscles may be the basis of the insulin-sensitising effect of adiponectin. Studies have revealed that adiponectin enhances triglyceride catabolism, fatty acid uptake, and mitochondrial biogenesis, demonstrating the importance of adiponectin in regulating lipid metabolism in skeletal muscles. Decreased adiponectin concentrations have been linked to higher low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, probably due to a direct effect of adiponectin on lipoprotein lipase activity [2].

Concentrations of adiponectin and its HMW form have been extensively evaluated as epidemiological markers of the risk for developing IR, T2DM, or metabolic syndrome [6]. Adiponectin levels are very well correlated with the Homeostatic Model Assessment of IR (HOMA-IR) index in adults [7]. The adiponectin sensitivity index may be a useful parameter, in combination with others such as the oral glucose tolerance test, for a comprehensive assessment of IR [8]. Adiponectin has been proposed as a potential prognostic biomarker and a therapeutic target in patients with cardiometabolic diseases [9]. The present study aimed at assessing the potential use of decreased total and HMW adiponectin levels for predicting the presence of IR in middle-aged adults. Another aim was to specify the cut-off points signalling the development of IR.

Material and methods

Patients and samples

Data for the study were collected from January 2011 to April 2013. The study was approved by the institutional Ethics Committee, and informed consent was obtained from all participants. Two groups of subjects were enrolled. Group A (controls) comprised healthy individuals with no clinical or biochemical markers of metabolic disease. Group B (cases) consisted of patients with T2DM treated with oral antidiabetic drugs, most frequently metformin. Healthy controls were recruited at the Department of Exercise Medicine and Cardiovascular Rehabilitation, University Hospital Olomouc, and Blood Transfusion Department, University Hospital Olomouc. Diabetic patients were recruited at a diabetes outpatient centre of the Department of Internal Medicine, University Hospital Ostrava. Laboratory analyses were carried out at the Department of Clinical Biochemistry, University Hospital Olomouc. In all participants, waist circumference, body height and weight for body mass index (BMI) calculations, and blood pressure were measured. After 12-hour fasting, venous blood was collected.

Laboratory analysis

Venous blood samples were drawn in the morning after a 12-hour fast. After centrifugation, the serum was used for other analyses. Routine serum biochemical parameters were analysed on a Modular SWA (Roche, Basel, Switzerland) on the day of blood collection. Concentrations of adipokines and other special analytes were measured in sample aliquots stored at –80 (–20)°C for no longer than six months (see below). Total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were determined enzymatically on the above analyser. Concentrations of apolipoprotein B (ApoB) and ApoA1 were determined immunoturbidimetrically using Tina-quant ApoB and ApoA1 kits (Roche). C-reactive protein (CRP) was assessed by an ultrasensitive immunoturbidimetric method using the Tina-quant kit. Glucose was determined using the GOD-PAP method (Roche). All tests were performed using fresh sera on the day of blood collection. Insulin was determined by the IRMA method using a commercially available kit (Immunotech, Marseille, France) and specific antibodies. Total adiponectin (one separate aliquot stored at –80°C until the day of analysis) was determined with the Human Adiponectin ELISA immunochemical kits (Biovendor Laboratory Medicine, Brno, Czech Republic) according to the manufacturer's instructions and after verification of methods. HMW adiponectin was determined from the same aliquot by ELISA using the HMW Adiponectin ELISA Kit (Otsuka Pharmaceutical, Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using the computing environment R (R Foundation for Statistical Computing, Austria; http://www.r-project.org/). Data were presented as basic robust (median) and non-robust (mean, standard deviation) summary characteristics (Table I). The Shapiro-Wilk test was used to test normality. Because the metabolic parameters showed deviations from the normal distribution, Spearman's rank correlation

Table I. *Basic metabolic and clinical characteristics of subjects*

Tabela I. *Podstawowe cechy metaboliczne i kliniczne pacjentów*

Characteristics	Healthy (Group A) mean ± SD (median)	T2DM (Group B) mean ± SD (median)
N	269 (F143, M126)	300 (F175, M125)
Age (years)	57.5 ± 10.6	59.8 ± 11.2
BMI [kg/m²]	24.9 ± 1.8 (25.3)	33.6 ± 5.6 (30.8)*
Waist [cm]	76.2 ± 10.3 (80)	112.7 ± 9.3 (108)
BP systolic [mmHg]	123.1 ± 10.5 (120)	145.2 ± 8.6 (143)*
BP diastolic [mmHg]	76.8 ± 7.1 (80)	84.7 ± 10.9 (85)*
Total cholesterol [mmol/L]	4.96 ± 0.8 (4.94)	5.60 ± 1.02 (4.9)*
Triglycerides [mmol/L]	1.34 ± 0.6 (1.06)	2.08 ± 1.03 (1.8)*
HDL cholesterol [mmol/L]	1.51 ± 0.41 (1.45)	1.26 ± 0.32 (1.23)*
LDL cholesterol [mmol/L]	2.84 ± 0.78 (2.79)	3.09 ± 0.88 (3.03)*
Glucose [mmol/L]	5.20 ± 0.6 (5.0)	8.40 ± 1.8 (8.31)*
Insulin [mIU/L]	10.18 ± 2.3 (6.5)	14.78 ± 10.6 (11.4)*
ApoA1 [g/L]	1.61 ± 0.2 (1.56)	1.23 ± 0.25 (1.18)*
ApoB [g/L]	0.80 ± 0.2 (0.85)	0.94 ± 0.23 (0.91)*
CRP [mg/L]	0.77 ± 0.34 (0.68)	2.85 ± 0.4 (2.67)*
Total adiponectin [mg/L]	10.6 ± 3.6 (8.6)	5.1 ± 1.5 (4.1)*
HMW adiponectin [mg/L]	5.2 ± 1.3 (4.8)	2.9 ± 0.9 (2.8)*
HMW/total adiponectin ratio	0.49 ± 0.07	0.56 ± 0.05*
HOMA-IR	2.49 ± 3.57	5.43 ± 3.2*

*P < 0.001 (comparison with healthy subjects)
SD, standard deviation; M, male; F, female; BP, blood pressure
HOMA-IR = fasting insulin [μIU/mL] x fasting glucose [mmol/L] / 22.5

Table II. *Spearman's rank correlation coefficient (r) between total adiponectin or HMW adiponectin and the variables (HOMA-IR, insulin, glucose)*

Tabela II. *Współczynnik korelacji rang Spearmana (r) między adiponektyną całkowitą lub wysokocząsteczkową a zmiennymi (wskaźnik HOMA-IR, insulina, glukoza)*

Total adiponectin	HMW adiponectin	
HOMA-IR	–0.44	–0.41
Insulin	–0.39	–0.33
Glucose	–0.31	–0.29

P < 0.001

coefficient was used. Monotonic dependence of total adiponectin or HMW adiponectin on the HOMA-IR index, insulin and glucose was quantified using Spearman's rank correlation coefficient (*r*); at the same time, its significant difference from zero was tested (Table II). We verbally describe the strength of the correlation using the guide that Evans (1996) suggests for the absolute value of *r*: 0.00–0.19 very weak, 0.20–0.39 weak, 0.40–0.59 moderate, 0.60–0.79 strong, and 0.80–1.00 very strong [10]. The correlations were depicted as scatter diagrams. Logistic regression analysis with continuous predictors for IR prediction was used (Table III).

Table III. *Binary logistic regression of IR risk factors, gender adjusted*

Tabela III. *Binarna regresja logistyczna czynników ryzyka insulinooporności z uwzględnieniem płci*

	β estimate	SE	Wald	P-value	OR	95% CI
Total adiponectin	–0.515	0.103	–4.985	< 0.001	0.598	0.483–0.723
HMW adiponectin	–1.022	0.190	–5.368	< 0.001	0.360	0.242–0.511

SE, standard error; OR, odds ratio; CI, confidence interval

Gender-adjusted logistic regression had the diagnosis of T2DM as a binary variable. The level of statistical significance was set at 5%.

Results

Characteristics of the study population

Age, BMI, waist circumference, blood pressure, and metabolic parameters in both groups are shown in Table I. Group A (healthy individuals) consisted of 269 participants (143 females and 126 males) with a mean age of 57.5 years. In this group, the metabolic parameters showed normal values. The mean total adiponectin level was high at 10.6 mg/L. The mean HMW adiponectin level was 5.2 mg/L. The adiponectin sensitivity index was 0.49. The HOMA-IR index was low at 2.49, suggesting normal insulin sensitivity. The optimum HOMA-IR index values for identification of individuals with IR, as reported by epidemiological studies in the European population, range between 2.0 and 3.8 [11]. Group B (diabetic patients) comprised 300 individuals (175 females and 125 males) with a mean age of 59.8 years. These participants were treated with oral antidiabetic drugs for T2DM. In all the studied parameters, Group B was different from healthy subjects. Group B members had obesity (BMI 33.6), hypertension (145/85 mmHg), hypercholesterolaemia (5.6 mmol/L), hypertriglyceridaemia (2.08 mmol/L), and hyperglycaemia (8.4 mmol/L) at the time of measurement; sensitive CRP level was mildly increased (2.85 mg/L). Their total adiponectin level was significantly lower (5.1 mg/L) as compared with the healthy subjects. Similarly, the mean HMW adiponectin level was significantly lower (2.9 mg/L) than that in healthy individuals. The adiponectin sensitivity index was 0.56 in Group B. Their HOMA-IR index was 5.43, a value typical for patients with IR. However, the cut-off values of HOMA-IR differ for different races, ages, genders, diseases, complications, etc. due to the complexity of IR [11].

Correlations between adiponectin levels and other indices

Table II shows Spearman's rank correlation coefficients between total or HMW adiponectin levels and the HOMA-IR index, insulin levels, and glucose concentrations in all participants. A correlation coefficient of –0.44 between total adiponectin levels and the HOMA-IR index values suggested a moderate monotonic correlation between the parameters (Figure 1), while a correlation coefficient of –0.39 between total adiponectin and insulin levels suggested a borderline weak correlation between the parameters. Similarly, a moderate correlation (–0.41) was noted between HMW adiponectin levels and the HOMA-IR index values (Figure 2) and a weak correlation (–0.33) between HMW adiponectin and insulin levels.

Predicting the risk of IR

Results for prediction of IR risk for total adiponectin levels (odds ratio [OR] 0.598, 95% confidence interval [CI] 0.483–0.723) and HMW adiponectin levels

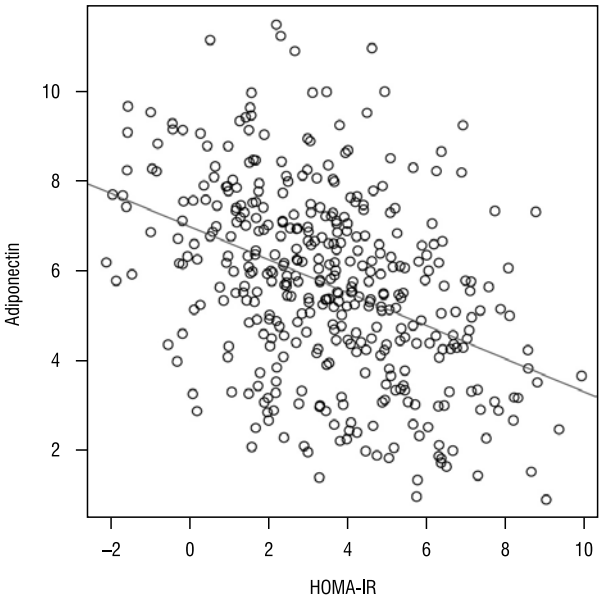

Figure 1. *Correlation between total adiponectin levels [mg/L] and the HOMA-IR index values (r = –0.44)*

Rycina 1. *Współzależność między stężeniami adiponektyny całkowitej [mg/l] i wartościami wskaźnika HOMA-IR (r = –0,44)*

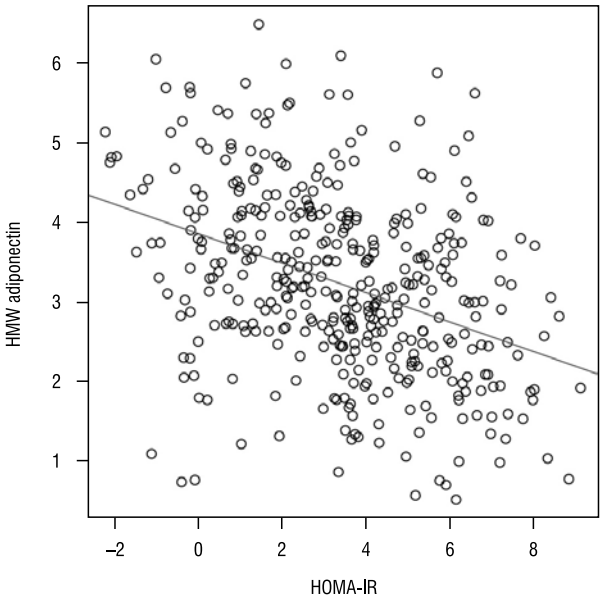

Figure 2. *Correlation between HMW adiponectin levels [mg/L] and the HOMA-IR index values (r = –0.41)*

Rycina 2. *Współzależność między stężeniami adiponektyny wysokocząsteczkowej [mg/l] i wartościami wskaźnika HOMA-IR (r = –0,41)*

(OR 0.360, 95% CI 0.242–0.511) are presented in Table III. Cross-validation was used to confirm cut-offs of 4.22 mg/L (sensitivity 0.698, specificity 0.785) and 2.75 mg/L (sensitivity 0.830, specificity 0.660) for total and HMW adiponectin levels, respectively. The OR results showed that increased total and HMW adiponectin levels were a protective factor against the development of IR. Adiponectin levels below the indicated cut-offs may predict a potential risk for the development of IR.

Discussion

IR is one of the main pathogenic mechanisms of T2DM and atherosclerosis that significantly contribute to morbidity and mortality of the population in developed countries. Correlations between adiponectin levels and the HOMA-IR index have been consistently found in adults [7, 12] although age- and gender-related differences have been admitted [13]. The present study also showed similar correlations with the HOMA-IR index. The essential measure is early diagnosis of IR allowing interventions including both lifestyle adjustments and early pharmacological therapy aimed at increasing insulin sensitivity [6].

Earlier studies showed that adiponectin was strongly interrelated with T2DM, obesity, and inflammation. Significant reduction of adiponectin concentrations in comparison with healthy controls has been reported even in prediabetes, which confirms the suggestion that decreased adiponectin levels play a role in the early stages of impaired glucose metabolism [14]. Impaired fasting glucose, impaired glucose tolerance, the HOMA-IR index, and serum adiponectin can be used for early detection of T2DM risk [15].

Adiponectin concentrations are indirectly associated with the development of inflammation. Adiponectin synthesis is decreased in all conditions related to inflammation such as IR, T2DM, or obesity [16]. Increased levels of CRP together with the development of obesity are accompanied by a decrease in adiponectin concentrations [17]. These observations indicate that the proinflammatory state and adiponectin levels are linked by biological mechanisms, partly independent of obesity [4]. In the present group of diabetic patients, a mild increase in CRP levels and a decrease in adiponectin levels were observed. According to a Japanese study, CRP and HMW adiponectin levels significantly correlated with metabolic syndrome accompanied by IR, but logistic regression analysis revealed that only HMW adiponectin and not CRP levels were associated with metabolic syndrome independently of obesity [18].

Much attention has been paid to the role of biologically active substances, such as adiponectin, in the pathogenesis of obesity-related disorders. With the development of obesity, the developing specific inflammatory state negatively influences adiponectin synthesis and may be a determining factor for the onset of IR. Low adiponectin concentrations are strongly correlated with IR present in T2DM independent of obesity [19–21]. Conversely, adequate adiponectin levels may reduce the risk for T2DM through many mechanisms, in particular fatty acid oxidation in the liver, increased peripheral glucose uptake, and stimulation of insulin secretion. Therefore, similar biomarkers such as adiponectin may provide an important view of potential metabolic dysfunction in the organism and may be potentially used for their prognostic abilities [22]. Significantly reduced levels of both total and HMW adiponectin were apparent in diabetic patients in the present study as well.

Some authors have claimed that differences in insulin sensitivity and degrees of IR are indicated by the HMW form rather than total adiponectin levels [23]. A decrease in HMW adiponectin levels accompanied by an increase in the HOMA-IR index in association with the development of IR was also reported in Asian ethnic groups in whom the relationship was even closer and the HOMA-IR index was even higher than in Europeans [24]. The present study does not suggest that HMW adiponectin levels are better at reflecting IR than total adiponectin levels.

Obesity is associated with an imbalance of adipocytokines including adiponectin. Massive weight loss is associated with increases in adiponectin levels [25]. The present study indicates that T2DM is accompanied by obesity. According to a study by Eglit et al., individuals who are obese and metabolically healthy have higher HMW adiponectin levels than obese persons with metabolic dysfunction including IR. The association is more pronounced in metabolically healthy women than in their male counterparts. The HMW form of adiponectin may aid in distinguishing between metabolically healthy and metabolically unhealthy obese individuals [26].

Limitations

There are some limitations of the present study, which might affect the results. Total adiponectin levels in diabetic patients were not significantly low. Even the median level was not below 4 mg/L, a typical concentration for fully developed IR. This could be due to the fact that a majority of diabetic patients were treated with antidiabetic drugs, mostly metformin, in various doses and for various periods of time. Antidiabetic drugs have been shown to increase adiponectin levels [27]. Thus, it may be assumed that, with respect to the identified adiponectin cut-off points, diabetic patients in the present study treated with oral antidiabetic drugs might have had even lower adiponectin levels without

their therapy. The results might also be affected by the presence of various comorbidities and their treatments in diabetic patients because, for example, some very frequently used hypolipidaemic drugs have also been reported to increase adiponectin levels [28]. Yet another limitation may be the case-control study design, particularly because it is difficult to accurately identify the temporal relationship between the development of IR and diagnosis of diabetes. Further research on the association between adiponectin levels and IR taking these potential confounding factors into consideration is needed.

Conclusions

The study results show that apart from traditional biomarkers such as homeostatic indices or the oral glucose tolerance test, adiponectin levels may also be used as biomarkers of the presence of IR. Increased levels of both total adiponectin (OR 0.598) and the HMW form (OR 0.360) are protective factors for the development of IR. Cross-validation was used to confirm the cut-offs (total adiponectin 4.22 mg/L, HMW form 2.75 mg/L) signalling the development of IR. The results are valid for middle-aged European adults.

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