Original Paper

Relationship between Adipocytokines, Nontraditional Anthropometric Indices and Coronary Heart Disease Risk in Diabetic Patients

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ABSTRACT: Introduction: Diabetes mellitus type 2 (T2DM) significantly increase the risk of cardiovascular (CV) disease morbidity and mortality. This study aimed to evaluate the potential of some novel anthropometric indices and adipocytokines to evaluate CV risk among T2DM patients. Methods: A total of 112 patients (men, 57; women, 55) with T2DM visiting Family Medicine and Endocrine counseling in the area of Health centers of Sarajevo Canton were included in this study. The sera samples were analyzed for fasting blood glucose (FBG), HbA1c, lipid profile parameters, adiponectin, and resistin levels. The Adiponectin/Resistin Index (A/R Index) was estimated using the formula. The novel anthropometric measurements, including the Conicity index (CI), Lipid Accumulation Product (LAP), visceral adiposity index (VAI), abdominal volume index (AVI), and Body adiposity index (BAI) were estimated. The 10-year risk for coronary heart disease (CHD) and fatal coronary heart disease (fCHD) is calculated by using UKPDS Risk software. Results: The adiponectin was shown as a statistically significant negative association with CHD in female subjects, and the A/R index as a statistically significant association with CHD and fCHD in male subjects. The AVI is superior to the CI, LAP, VAI, and BAI in assessing cardiometabolic risk in T2DM patients. Conclusions: Our study indicated that measuring adiponectin and A/R index, together with measuring AVI as a measure of general volume, can be used as surrogates in the evaluation of high cardiovascular risk among T2DM patients.

KEYWORDS: *Type 2 diabetes mellitus, Anthropometric indices, Adipocytokines, Coronary Heart Disease, Fatal Coronary Heart Disease.*

Introduction

Cardiovascular (CV) diseases are common in patients with diabetes mellitus (DM), regardless of the type of diabetes, and the morbidity and mortality of this group of diseases are estimated to be two to five times higher than in non-diabetics of similar age [1].

Risk factors (smoking, hypertension, and hyperlipoproteinemia) still play an essential role in developing CVD; however, they are present in only about half of patients with type 2 diabetes mellitus (T2DM).

Therefore, in the last ten years, in addition to endothelial dysfunction, insulin resistance, elevated insulin levels, and hyperglycemia, special attention has been focused on non-traditional risk factors, among which indicators of adipose tissue dysfunction are becoming increasingly important.

In accordance with previous, fat distribution may be a useful and important tool for evaluating the risk and prognosis of coronary artery disease [2].

Today, it is known that adipose tissue is not just an accumulation of fat cells, but it is an active immune and endocrine organ with a significant role in the development of CV complications of T2DM [3].

For this reason, the assessment of adipose tissue activity and quantity is a very important diagnostic procedure in the prevention and prediction of the development of CV consequences of diabetes.

In this sense, anthropometric indices and adipose tissue products-adipocytokines play a central role today.

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There have been numerous publications associating increased circumferences of some human body areas with insulin resistance or increased risk of CVD during recent years.

The most commonly used anthropometric measurements, waist circumference (WC), hip circumference (HC), and body mass index (BMI), are good indicators of increased body weight but have certain limitations in the quantification of visceral adipose tissue (different measurement techniques, ethnic differences, inability to distinguish adipose and muscle tissue, children and young people, pregnancy) [4-6].

Beside that, studies have demonstrated that in patients with acute coronary syndromes and CV disease with diabetes there may be an "overweight paradox" phenomenon, with better CV prognosis among patients with higher BMI [7].

Therefore, the combination of existing indices and biochemical parameters, primarily lipid profile, seeks to obtain new, better, and more accurate indicators of visceral adipose tissue, and thus better tools in assessing CV risk which considered to be more practical, non-invasive, simple and fast to measure.

Adipose tissue has been revealed as an endocrine organ, secreting a variety of hormones, which elicit a variety of local and systemic responses.

Adipocytokines-adiponectin and resistin, in addition to leptin, are of great importance for metabolic homeostasis.

Their plasma concentration is inversely (adiponectin) or directly (resistin) associated with obesity, T2DM, and their effect on insulin resistance is also opposed.

In addition, hypoadiponectinemia has been reported as a risk factor for developing CVD, whereas in humans, resistin is involved in the pathways that lead to atherosclerosis, the main factor related to coronary heart disease (CHD) [8,9].

This study aims to identify the utility of the novel anthropometric indices and adipocytokines in estimating CHD risk associated with T2DM.

It could be crucial in preventing the cardiometabolic risk that is identified as an important condition associated with premature mortality and impairments in patients' physical, psychological, and social aspects of life.

Materials and Methods

This cross-sectional design study included a sample of 112 adult subjects with a confirmed diagnosis of T2DM.

Patients were chosen randomly in Family Medicine and Endocrine counseling in the area of Health centers of Sarajevo Canton.

Subjects with one of the following disorders or conditions were excluded from the study: patients with DMT1, poorly controlled DM; acute hepatic and urinary tract disorders and infections; heart diseases (valvular disorders, arrhythmias, impulse delivery blocks, myocardial infarction) or stroke in the period of 6 months before the begining of the study; immune disorders and autoimmune reactions; pregnancy; febrile episodes; or excessive consumption of alcohol and/or psychotropic drugs.

The research was conducted in accordance with principles of the Declaration of Helsinki on the rights of patients involved in biomedical research (Revison 2013).

An ethical approval was obtained from the Ethical Committee of Faculty of Medicine of the University of Sarajevo (protocol number: 02-3-4-4493).

The samples of blood were obtained from an antecubital vein between 8:0 AM and 10: 0 AM after a 12-hour overnight fast.

The standard venipuncture procedure was used to obtain venous blood samples in gel tubes.

The blood is centrifugated to separate the serum 30 minutes after blood is collected.

The samples were kept at-20°C until they were analyzed.

All participants' lipid profiles (high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) were measured using a spectrophotometric assay on the same analyser.

HbA1c was evaluated using an immunoturbidimetric technique (Roche Cobas 400, Mannheim, Germany).

A commercial enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biotechnology Inc., USA) was used in accordance with the manufacturer's instructions to evaluate the levels of serum adiponectin and resistin.

The Adiponectin/Resistin Index (A/R Index) was estimated using the following formula:

A/R Index=(1+log10 Resistin-log10 adiponectin) [10].

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Weight, height, WC, HC, systolic and diastolic blood pressure (SBP, DBP) of all individuals were recorded for the purpose of calculating anthropometric indices and CV risk.

Waist and hip circumference lengths were measured and waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were found.

Body mass index (BMI) is determined by the division between person's body weight (kg) and square of height (m^2).

The Conicity index (CI), Lipid Accumulation Product (LAP), visceral adiposity index (VAI), abdominal volume index (AVI) and Body adiposity index (BAI) were estimated according to the following formulas where WC, HC nad H are in cm, triglycerides and HDL in mmol/L, BMI in kg/m^2 [11,12]:

$$CI=WC/0.109\ \sqrt{(BW/H)}$$

$$LAP\ (males)=(WC-65)\times triglycerides$$

$$LAP\ (females)=(WC-58)\times triglycerides$$

$$VAI\ (males)=(WC/39.68+(1.88\times BMI))x(triglycerides/1.03)x(1.31/HDL)$$

$$VAI\ (females)=(WC/36.58+(1.89\times BMI))x(triglycerides\ /0.81)x(1.52/HDL)$$

$$BAI=HC\ /H^{1.5}-18.$$

$$AVI=[2\ cm\times(WC)^2+0.7\ cm\times(WC-HC)^2\ ]/1000.$$

The United Kingdom Prospective Diabetes Study (UKPDS) Risk software was used for prediction of the 10-year risk of developing CHD, and fatal coronary heart disease (fCHD) among T2DM patients.

Age, sex, ethnicity, smoking status, atrial fibrillation status, diabetes duration, HbA1c, SBP, TC, and HDL-c were all factors included in the UKPDS risk engine equation [13].

SPSS 21.0 was used for statistical analysis. Each value was presented as the mean±SD, median, and interquartile range.

The Kolmogorov-Smirnov test was used to determine the distribution of variables.

The Mann-Whitney U Test or Student's t Test was used to compare the groups, depending on how the variables were distributed.

Correlations between continuous variables were assessed using Pearson’s or Spearman’s correlation.

Multiple linear regression was used to assess predictors of the CHD and fCHD.

A p value of less than 0,05 indicated the statistically significant difference.

Results

The total sample comprised 112 participants (57 (50.89 %) subjects of male gender and 55 (49.11%) subjects of female gender).

The baseline characteristics of all subjects enrolled in the study are presented in Table 1.

There were no statistically significant significant difference was found in age, duration of diabetes.

The male patients had significantly higher values of BMI, WC, HC, WHR, WHtR compared to female patients. (Table 1).

Table 1. Baseline characteristics and traditional anthropometric indices in T2DM patients grouped by gender.

Parameter	Male (n=57)	Female (n=55)	p
Age (years)	48,76±4,56	48,51±4,42	NS (0,786)
Diabetes mellitus (years)	6 (5-8)	6 (4,5-8)	NS (0,392)
BMI (kg/m^2)	26,40±1,58	25,12±1,69	<0,001
Waist circumference (cm)	102,27±6,3	92,97±6,96	<0,001
Hip circumference (cm)	100,29±4,45	92,75±5,75	<0,001
WHR	1,03 (0,98-1,05)	1,01 (0,97-1,02)	0,008
WHtR	0,58 (0,55-0,6)	0,54 (0,51-0,55)	<0,001

Note: Data expressed as mean (±SD) and median (IQR); Body mass index, BMI; waist-to-hip ratio, WHR; Waist-to-height ratio, WHtR; probability, p.

Among 112 participants included in the study, 57 (50.89%) were male and 55 (49.11%) female gender.

Table 1 presents the basic characteristics of all participant.

Age and diabetes duration were not significantly different in a way that was statistically significant.

In comparison to female patients, the BMI, WC, HC, WHR, and WHtR values of the male patients were significantly higher. (Table 1).

We found that the male patients had significantly higher values of CI, LAP, VAI, AVI, resistin, A/R index, CHD and fCHD, and significantly lower values of adiponectin compared to female patients.

No significant difference was found in BAI values between male and female patients (Table 2).

Table 2. The nontraditional anthropometric indices, adipokines and coronary heart disease risk in T2DM patients grouped by gender.

Parameter	Male (n=57)	Female (n=55)	p
CI	1,37±0,05	1,31±0,06	<0,001
LAP	76,94±19,58	44,67±18,46	<0,001
VAI	158,22±57,85	105,36±28,87	<0,001
AVI	21,01±2,64	17,39±2,61	<0,001
BAI	25,33±1,86	25,55±2,37	NS (0,627)
Adiponectin (ng/ml)	39,44±1,14	40,75±1,49	<0,001
Resistin (g/ml)	283,27±15,40	269,21±22,42	0,006
A/R index	2,85±0,04	2,80±0,05	<0,001
CHD	17,5 (13,2-22,5)	9 (4,75-17,05)	<0,001
fCHD	8,8 (5,5-12,4)	4,5 (2,2-10,4)	0,005

Note: Data expressed as mean (±SD) and median (IQR); Conicity index, CI; Lipid Accumulation Product, LAP; Visceral Adiposity Index, VAI; Abdominal Volume Index, AVI; Body Adiposity Index, BAI; Adiponectin/Resistin Index, A/R Index; Coronary Heart Disease, CHD; fatal Coronary Heart Disease, fCHD; probability, p.

The correlations of 10-year risk for CHD, fCHD, adipokines, and anthropometric indices are shown in Table 3.

Adiponectin was significantly negatively correlated with CHD and fCHD in both male and female subjects.

Resistin, A/R index, CI, LAP, AVI, and BAI were significantly positively correlated with CHD and fCHD in both male and female subjects.

VAI was significantly positively correlated with CHD and fCHR in female subjects and with CHD in male subjects.

No statistically significant correlation was found between VAI and fCHR in male subjects.

Table 3. Pearson rank correlation between 10-years risk for CHD, fCHD, adiponectin, resistin, A/R index and anthropometric indices.

Parameter	CHD		fCHD	
	Male (n=57)	Female (n=55)	Male (n=57)	Female (n=55)
Adiponectin (ng/ml)	- 0,528**	- 0,737**	- 0,544**	- 0,794**
Resistin (g/ml)	0,543**	0,665**	0,535**	0,683**
A/R index	0,523**	0,571**	0,517**	0,566**
CI	0,369*	0,417**	0,416**	0,452**
LAP	0,455**	0,513**	0,439**	0,535**
VAI	0,297*	0,538**	0,190	0,546**
AVI	0,605**	0,589**	0,650**	0,649**
BAI	0,469**	0,332*	0,539**	0,356*

Note: Adiponectin/Resistin Index, A/R Index; Conicity index, CI; Lipid Accumulation Product, LAP; Visceral Adiposity Index, VAI; Abdominal Volume Index, AVI; Body Adiposity Index, BAI; Coronary Heart Disease, CHD; fatal Coronory Heart Disease, fCHD; *p<0,05; **p<0,01.

The multivariate regression analysis using CHD and fCHD as dependent variables and adiponectin, resistin, A/R index and anthropometric indices as independent variables are shown in Table 4.

In female subjects, adiponectin was a statistically significant negative associated with CHD 0,49 (-5,08 to-0,01).

In male subjects, the A/R index and AVI were a statistically significant positive associated with CHD [0,57 (13,97 to 171,77); 0,74 (0,25 to 3,69)], as well as with fCHD [0,55 (8,37 to 119,34); 0,83 (0,37 to 2,79)] (Table 4).

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Table 4. Multivariate regression analysis using CHD, and fCHD as dependent variables and adiponectin, resistin, A/R index and anthropometric indices as independent variables

Parameter	Male (n=57)	Female (n=55)	Male (n=57)	Female (n=55)
	Regression coefficient (95% CI)		Regression coefficient (95% CI)	
Adiponectin (ng/ml)	0,09 (-2,06 to 3,22)	-0,49 (-5,08 to -0,01)*	0,124 (-1,31 to 2,40)	-0,41 (-3,22 to 0,2)
Resistin (g/ml)	0,001 (-0,18 to 0,18)	0,06 (-0,10 to 0,14)	-0,07 (-0,15 to 0,10)	0,08 (-0,06 to 0,1)
A/R Index	0,57 (13,97 to 171,77)*	-0,06 (-57,54 to 39,30)	0,55 (8,37 to 119,34)*	-0,08 (-40,7 to 24,84)
CI	-0,38 (-109,79 to 14,31)	-0,15 (-86,16 to 50,63)	-0,35 (-74,76 to 12,52)	-0,28 (-69,84 to 22,74)
LAP	0,02 (-0,02 to 0,12)	-0,01 (-0,27 to 0,26)	-0,008 (-0,08 to 0,08)	-0,07 (-0,20 to 0,16)
VAI	0,09 (-0,02 to 0,04)	0,38 (-0,04 to 0,18)	0,02 (-0,02 to 0,02)	0,38 (-0,02 to 0,12)
AVI	0,74 (0,25 to 3,69)*	0,18 (-1,99 to 3,08)	0,83 (0,37 to 2,79)*	0,46 (-0,75 to 2,67)
BAI	-0,04 (-1,40 to 1,08)	0,004 (-0,80 to 0,83)	0,02 (-0,81 to 0,93)	-0,04 (-0,64 to 0,46)
	Dependent variable: CHD		Dependent variable: fCHD	

Note: Adiponectin/Resistin Index, A/R Index; Conicity index, CI; Lipid Accumulation Product, LAP; Visceral Adiposity Index, VAI; Abdominal Volume Index, AVI; Body Adiposity Index, BAI; Coronary Heart Disease, CHD; fatal Coronory Heart Disease, fCHD; *p<0,05.

Discussion

The possible contribution of adipose tissue to the development of diabetic vascular problems has received a lot of focus in recent years.

To our knowledge, this is the first research that evaluated the possible role of nontraditional anthropometric indices and adipokines as predictors of CHD in Bosnian T2DM patients.

In the present study, male T2DM patients demonstrated significantly higher BMI, WC, HC, WHR, WHtR, CI, LAP, VAI, AVI; resistin, A/R index, CHD, and fCHD values compared with female patients; however, the adiponectin values were significantly lower in male T2DM patients compared with female patients.

In addition, a large cross-sectional study among the adult Asian population in Singapore highlighted that males tended to have higher mean height, weight, WC, HC, BMI, WHR, and WHtR but lower mean BAI [14].

Gender differences in the regional fat distribution and CV risk are probably determined by a complex interplay of genetic and epigenetic factors and by the direct effect of sex hormones on adipocyte function.

The main findings of the present study were that among all the adipocytokines, adiponectin was shown as a statistically significant negative predictor of CHD in female subjects, and the A/R index as a statistically significant positive predictor of CHD and fCHD in male subjects.

These results were consistent with the study conducted by Schulze et al. [15] where increased adiponectin levels were associated with a reduced risk of CHD among men with T2DM.

High adiponectin level remained independently associated with decreased risk of CHD after adjusting for age, BMI, and alcohol consumption, but did not significantly differ after adjustment for HDL-C.

This finding concluded that this observed association is probably determined by HDL-C and not by adiponectin's anti-inflammatory role.

In addition, several studies have confirmed findings that elevated adiponectin levels are associated with a lower risk of CHD in patients with T2DM [16,17].

On the contrary, some studies and meta-analyses have reported that the association between serum adiponectin level and CHD is weaker than suspected [18,19].

For this reason, the A/R index is used to point out the potential effects of other adipokines, primarily resistin, on adiponectin concentration and explain these conflicting results of mentioned studies.

In the available literature, since this is a recently established relationship, we have not found a large amount of data on the use of the

A/R index in assessing and predicting CV risk in diabetics.

Rubio-Guerra A.F. et al. [20] examined the correlation of carotid wall thickness, directly related to the increased risk of developing myocardial infarction, with A/R index values in hypertensive subjects with T2DM.

Their results showed that the A/R index value is more strongly associated with atherosclerosis than individual adiponectin and resistin levels and can be used as a reliable indicator of CV risk in diabetes type 2 patients with hypertension.

From the above, it can be concluded that this ratio can provide a more integrated and more precise explanation of the pathogenesis of the disease and the increased CV risk of individual adiponectin values.

Another important finding of the present study is a significant negative relationship between adiponectin and CHD risk and fCHD, and a positive significant correlation between resistin, A/R index, and most of the standard and novel anthropometric indices of obesity (CI, LAP, AVI, BAI) with CHD and fCHD in both male and female subjects.

The VAI score was also significantly positively correlated with CHD and fCHR in female subjects and with CHD in male subjects.

However, we found no significant relationship between VAI and fCHR only in males.

Different mechanisms have been suggested to explain the linkage between abdominal obesity and cardiometabolic complications, including the interplay between inflammatory response and cytokines and other regulatory molecules released by abdominal adipose tissue.

[AD1] Adipose tissue-induced systemic inflammation tends to increase over time and may worsen the CV risk.

Numerous studies indicated that visceral adipose tissue (VAT) compared with subcutaneous adipose tissue (SAT) is a more pathogenic adipose depot [21,22].

Excess visceral adiposity correlates with increased secretion of inflammatory cytokines and reduced secretion of adiponectin which is protective adipokine and has anti-inflammatory and anti-atherogenic properties [23].

After the multiple linear regression analysis, another important finding of this study is that the AVI is superior to the CI, LAP, VAI, and BAI in predicting cardiometabolic risk in T2DM patients.

As reported by other authors [24], AVI is superior to the other anthropometric indices for predicting MetS in both men and women.

The AVI has been identified as a sensitive indicator of metabolic abnormalities linked to abdominal obesity and as a significant risk predictor of DM in the population, according to a recent study that examined the link between different AVI pathways and risk of DM according to gender and across early, middle, and late adulthood among participants in the China Health and Nutrition Survey (CHNS).

According to the aforementioned studies, the immediate rise trajectory group-which had the greatest baseline AVI-had a considerably higher chance of later developing DM than the other groups [25].

Similar data were published by Wu et al. [26], who carried out a 20-year follow-up study to analyze the impact of other anthropometric indices, besides BMI, on adults glycemia.

Their findings revealed AVI as a good predictor of the development of insulin resistance, b-cell impairment, increased fasting insulin, and diminished glucose tolerance.

A cross-sectional, population-based study on Mexican subjects from a middle-income neighborhood showed that AVI was strongly associated with impaired glucose tolerance (IGT) and T2DM [27].

However, the exact mechanism by which AVI contributes to T2DM development is not fully understood. It is possible that the increased AVI, which is surrogates of WC and abdominal fat, will cause deleterious metabolic effects, such as decreased insulin sensitivity, glucose intolerance, increased production of proinflammatory cytokines, dyslipidemia, and atherosclerosis [28].

Our results regarding the potential role of VAI as a surrogate for estimating the risk of developing coronary bean disease in diabetic patients are consistent with the results of previous studies.

Han et al. [29] discovered that VAI, as a as an accessible marker of visceral fat mass, was substantially linked with the severity of CHD in type 2 diabetics.

The few limitations of the present study must be noted. Firstly, the current study was performed in a single center, with a comparatively small cohort size.

Another limitation is the cross-sectional design of the study.

We do not follow up the patient, which may affect the association of anthropometric indices

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and adipocytokines with CHD risk associated with T2DM.

Therefore, further large-sample studies with longer follow-ups are needed to support our findings.

Conclusions

To summarize, this first Bosnian study highlights the usefulness of the novel anthropometric indices and adipocytokines in predicting CHD risk in T2DM patients.

It reveals that the A/R index shows better performance in predicting CHD and fCHD in males, while adiponectin shows association with the CDH only in females.

Furthermore, the results confirm that among the novel anthropometric indexes, AVI best predicts CHD and fCHD in male but not in female patients with DMT2.

Conflict of interests

The authors declare that there are not conflicts of interest.

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