Progress in Nutrition 2018; Vol. 20, Supplement 2: 145-152 DOI: 10.23751/pn.v20i2-S.6019

Original article

Adipokines and Visceral Adiposity Index in relation to clinical findings of NAFLD patients

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Summary. *Objective:* The present study aimed to investigate the concentrations of some adipokines and their relationship with clinical findings of patients with nonalcoholic fatty liver disease (NAFLD). Additionally we measured the visceral adiposity index in relation to clinical characteristic of patients. *Methods:* This study was a cross-sectional study in 83 NAFLD patients. Plasma levels of omentin-1e-1, vaspin were measured. Anthropometric indices metabolic status was assessed. Visceral adiposity index and atherogenic index of plasma were calculated according to suggested formula. *Results:* Plasma omentin-1 levels directly correlated with weight of patients ($p<0.05$). Similar association was found for hip circumference ($p<0.05$). Plasma levels of omentin-1 did not correlate with fasting blood sugar (FBS) or HOMA-IR (Homeostatic model assessment). We found that omentin-1 correlated positively with the NAFLD severity. In correlation analysis, the level of vaspin was found to be directly correlated with plasma insulin ($p < 0.05$). In addition, in male patients; vaspin value was in positive strong association with HOMA-IR (<0.001). In addition in both genders, VAI (visceral adiposity index) and AIP (atherogenic index of plasma) are in strong direct relationship with ultrasound findings of patients. *Conclusions:* In the present study, we demonstrated gender-dependent differences in adipokines concentration; women had higher levels of omentin-1 and vaspin. Additionally we observed that an increase in body fat, weight often leads to increased secretion of adipokines that in turn worsen metabolic NAFLD disease. In this regard, we found a direct correlation between vaspin levels and ALT (alanine aminotransferase) activity in female patients. Interestingly, omentin-1 was in positive association with severity of disease reflected by ultrasound observations. In addition, an abnormal level of circulating lipids, which is reflected by atherogenic index of plasma, is in significant direct correlation with ultrasound grading of liver disease. Another novel finding of this study is that AIP is associated with AST (aspartate aminotransferase) activity.

Key word. Nonalcoholic Fatty Liver Disease, Visceral Adiposity Index, Adipokines, Omentin-1, Vaspin, Liver Enzym

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the accumulation of liver fat exceeding 5% in the absence of significant alcohol intake(1). NAFLD is a crucial health problem and its prevalence has risen rapidly in parallel with obesity and DM2 epidemic. Prevalence of NAFLD, depending on the studied population and diagnosis method, has been reported about 6–45% (2, 3). Numerous factors have been proposed to contribute to multiple-hit pathogenesis of NAFLD including IR and adipokines(3). In fact NAFLD is regarded as the hepatic component of metabolic or insulin resistance (IR) syndrome (4). Impaired pattern of adipokines secretion plays an essential role in the pathogenesis of IR syndrome, including NAFLD by altering insulin sensitivity in insulin-targeted organs such as liver and skeletal muscles(5). Based on

abundant evidence Adipokines derived from visceral adipose tissue (VAT) may play a crucial role in the pathogenesis of NAFLD and may be responsible for fat accumulation and insulin resistance so may have potential usefulness as noninvasive diagnostic tests in patients with NASH (nonalcoholic steatohepatitis) (6, 7). Previous studies reported positive relationship between serum vaspin levels and hepatocyte ballooning degeneration in NAFLD patients. These study indicated vaspin as a positive correlate of liver fibrosis, independent of possible confounders such as sex, age, metabolic and histological parameters (8-11). Increased vaspin levels indicated in NAFLD patients compared with healthy controls(10). Omentin is an adipokine closely associated with obesity, insulin resistant, and glucose metabolism. Although patients with impaired glucose regulation have reduced levels of omentin, in NAFLD the elevated levels have been reported(12, 13). Reasons of this paradoxical increase have not been clearly identified(14). It is supposed that insulin resistance act as an independent risk factor affecting negatively serum omentin level. Due to this assumption omentin/ HOMA-IR index was proposed to define relationship between omentin concentration and HOMA-IR value(15).

The VAI, a novel gender-specific index, accurately reflects visceral fat function and insulin resistance(16). The VAI, initially developed as an indicator of visceral adipose function for the assessment of cardiometabolic risk, has been also proposed for the detection of NAFLD (17). Relation of VAI and some of adipokines have been described in previous studies (15, 18). However there is a lack of information regarding the relationship between VAI and adipokine profile.

In NAFLD, lipid disorders is characterized by atherogenic dyslipidemia, postprandial lipemia and HDL dysfunction which are key risk factors for CVD (cardiovascular disease) (19, 20). In 2016, A Meta-Analysis indicates NAFLD as a risk factor for cardiovascular disease(21). The importance of this association is underlined by demonstrating of the cardiovascular disease as a major cause of mortality in individuals with NAFLD in observational studies(22). It has been shown that AIP, the ratio of TGs (triglycerides) to HDL-C (High-density lipoprotein), was a strong predictor of cardiovascular disease(23). Considering the high cardiovascular event rate in NAFLD patients, it is worth recognizing the NAFLD patients with higher risk of cardiovascular disease.

Method

Study Setting and Design and Subjects

This study was designed as a cross-sectional study to investigate the association between the liver function and serum adipokines. In addition the relations of adipokines with anthropometric and biochemical parameters were measured. Serum adipokines including Omentin-1 and Vaspin were measured. Liver function was assessed by serum activity of liver enzymes and ultrasound findings. A total of 83 patients participated in this study from the university hospital in Jahrom, Iran. Inclusion criteria were age between 20 and 50 years with the confirmed documented diagnosis of NAFLD. Exclusion criteria included pregnancy and lactation, chronic diseases including kidney diseases, diabetes and malignancy, smoking, menopause. The aim of study was explained completely to subjects and the written consent was obtained from all patients. Furthermore, approval was obtained from the ethical committee of Jahrom University of Medical Sciences.

Anthropometric measurements

Anthropometric measurements including weight, height, waist circumference (WC) and hip circumference (HC) were measured in light clothing and without shoes position. Weight and height were measured by seca scale (Hamburg Germany) and a stadiometer attached to the scale respectively. Body mass index (BMI) was calculated from measurement height in meters and weight in kilograms. Waist circumference measurements made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference measurements have been taken around the widest portion of the buttocks. Then, waist -to-hip ratio (WHR) was determined.

The visceral adiposity index (VAI) was calculated as this following gender- specific equations (Figure 1)

Sample collection and laboratory assessment

In order to analyze serum concentration of adipokines and lipid profiles and liver enzymes, approximately 10 ml of venous blood samples were taken from

all patients after a 12-h overnight fasting. Centrifugation at 4 ˚C for 10 min at 2500 r.p.m was used to separate serum and plasma. Then, all the samples were frozen at – 80 ˚C.

An enzymatic procedure was used to analysis total cholesterol, HDL cholesterol (high-density lipoprotein-cholesterol) and triglyceride levels. If triglyceride concentration was <400 mg/dl, the Friedewald equation was used to calculate LDL cholesterol levels. The atherogenic index of plasma (AIP) was calculated as log (TG/HDL) with TG and HDL expressed in molar concentration. Commercial ELISA kit was used to analysis serum Vaspin and Omentin-1 as adipokines as well as serum ALT and AST.

A radiologist specialist performed all the abdominal ultrasonography by using an East Medical sonographic scanner equipped with a convex 3.5 MHz browser. Histopathological grading of NAFLD was scored according to the NAFLD activity score (NAS) based on Brunt method (24) .

Brunt et al (reference)

This scoring system is the unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores. Additionally, NAS has reasonable inter-rater reproducibility that is useful for studies of both adults and children with any degree of NAFLD.

Statistical analysis

All the values reported are expressed as mean ± SD and were analyzed using the statistical package SPSS/PC+ for Windows (v.15.0 Chicago, Illinois, USA). P values < 0.05 were considered to be statistically significant. Since data were not normally distributed, the strength of association between variables was calculated using Spearman Rho correlation test.

$$\text{Males: VAI} = \left(\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{1.03}\right) \times \left(\frac{1.31}{\text{HDL}}\right)$$

$$\text{Females: VAI} = \left(\frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{0.81}\right) \times \left(\frac{1.52}{\text{HDL}}\right)$$

Figure 1. VAI: visceral adiposity index; WC: waist circumference; BMI: body mass index; TG: triglyceride; HDL: high-density lipoprotein.

Results

The clinical and biochemical features of patients are presented in Table 1. Frothy one of 83 patients (49.4%) were classified as having grade 1 NAFLD, 28 (33.7%) grade 2, and 14 (16.9%) grade 3. The concentrations of omentine-1 and vaspin were relatively higher in females than males. As it was expected, the percent of body fat and BAI have shown higher values in women.

Plasma omentin-1

Mean ± SD plasma omentin was 254.78±114.85 ng/L in males and 315.16 ± 83.45 ng/L in females (Table 1). Plasma omentin levels directly correlated with weight of patients (r=0.375; p= 0.01 and r=0.319; p=0.04, for males and females respectively). Similar association was found for HC (r=0.392; p= 0.01 and r=0.347; p=0.03, for males and females respectively). Plasma levels of omentin-1 did not correlate with FBS or HOMA-IR (Table 2). When we investigated the relationship between omentin and circulating levels of liver enzymes as well as severity of liver fibrosis, we found that omentin correlated positively with the NAFLD (Table 3). Additionally we subclassified the subjects in two groups in accordance with their disease severity: we categorized patients with grade 3 in the same group with grade 2, and then we have observed a significant higher level of omentin-1 compared to grade 1 patient (data not shown).

We calculated the BAI and then investigated the relationship between circulating levels of vaspin and omentin-1 with this index. We found a positive correlation with omentin-1 in females but not for males.

Serum vaspin

Mean ± SD serum vaspin was 6.49± 2.22 ng/L in the men group and lower from the values of the women group (7.40 ± 2.30 ng/L) (Table 1). The simple correlations between measured variables are shown in

Table 1. Anthropometric Characteristics and biochemical parameters of the study participants

Variable	Mean ± SD
gender(M:F)	83 (42/41)
Age (year)	36.71 ± 7.21
Weight (kg)	83.07 ± 12.83
Height (cm)	168.07 ± 8.32
BMI (kg/m2)	29.41 ± 4.18
Waist circumference (cm)	99.07 ± 10.43
Hip circumference (cm)	104.85 ± 7.03
WHR	
Male	0.96 ± 0.07
Female	0.93 ± 0.08
Body fat (%)	
Male	29.44 ±5.83
Female	35.72 ± 8.27
BAI	
Male	42.91 ± 4.07
Female	46.01 ± 5.52
Triglyceride (mg/dL)	197.13 ± 54.22
Total cholesterol (mg/dL)	209.52 ± 36.19
HDL-C (mg/dL)	38.38 ± 8.10
LDL-C (mg/dL)	149.31 ± 27.86
AIP	
Male	0.716 ± 0.16
Female	0.696 ± 12
VAI	
Male	7.70 ± 3.09
Female	10.04 ± 2.84
FBS (mg/dL)	105.42 ± 11.44
Insulin (mlU/mL)	14.47 ± 3.14
HOMA-IR	
Male	3.81 ± 1.0
Female	3.72 ± 0.84
Vaspin (ng/mL)	
Male	6.49 ± 2.29
Female	7.40 ± 2.30
Omentin-1 (ng/mL)	
Male	254.78 ± 114.85
Female	315.16 ± 83.45
AST (U/l)	46.91 ± 11.19
ALT (U/l)	44.78 ± 10.36
NAFLD grade (N,%)	
Grade 1	41 (49.4%)
Grade 2	28 (33.7%)
Grade 3	14 (16.9%)

Data are the mean ± SD.

Table 2. The correlation of adipokines with anthropometric and biochemical parameters in NAFLD patients

Parameter	Omentin-1 r, p-value	Vaspin r, p-value
Weight (kg)		
Male	0.375, 0.01	0.169 , 0.29
Female	0.319 , 0.04	0.02 , 0.90
BMI (kg/m2)		
Male	0.15 , 0.34	0.069 , 0.67
Female	0.298 , 0.06	0.048 , 0.76
Waist circumference (cm)		
Male	0.176 , 0.26	0.119 , 0.45
Female	0.221 , 0.16	0.044 , 0.78
Hip circumference (cm)		
Male	0.392 , 0.01	0.268 , 0.09
Female	0.347 , 0.03	0.092 , 0.57
WHR1		
Male	0.015 , 0.92	0.017 , 0.9
Female	0.26 , 0.87	0.097 , 0.55
Body fat (%)		
Male	0.05 , 0.75	0.056 , 0.73
Female	0.282 , 0.07	0120 , 0.46
BAI		
Male	0.177 , 0.26	0.41 , 0.80
Female	0.327 , 0.04	0.120 , 0.46
FBS (mg/dL)		
Male	-0.032 , 0.84	0.024 , 0.88
Female	- 0.202 , 0.20	0.023 , 0.89
Insulin (mlU/mL)		
Male	0.349 , 0.02	0.617 , <0.001
Female	-0.086 , 0.59	0.354 , 0.02
HOMA-IR		
Male	0.255 , 0.10	0.548 , <0.001
Female	-0.203 , 0.20	0.242 , 0.13

P < 0.05 indicates significant correlation.

table 2. In correlation analysis, the level of vaspin was found to be directly correlated with plasma insulin ($p < 0.05$ for both genders). In addition, in male patients; vaspin value was in positive STRONG association with HOMA-IR (0.548, <0.001).

The relation of liver enzymes and ultrasound findings of participants with adipokines are presented in table 3. Dividing patients according to gender, we have observed a statistically significant correlation between vaspin concentrations and ALT activity in females. Additionally, vaspin and omentin-1 concentrations

Table 3. Correlation of liver function parameters with adipokines in NAFLD patients

Parameter	ALT r, p-value	AST r, p-value	Ultrasound findings r, p-value
Omentin-1			
Male	0.180 , 0.253	0.257 , 0.101	0.388 , 0.011
Female	0.175 , 0.273	0.257 , 0.105	0.462 , 0.002
Vaspin			
Male	0.278 , 0.075	0.210 , 0.182	0.337 , 0.029
Female	0.398 , 0.010	0.150 , 0.351	0.336 , 0.032
VAI		0.320 , 0.039	
Male	0.225 , 0.151	0.111, 0.49	0.562 , <0.001
Female	0.223 , 0.161		0.397 , 0.010
AIP		0.312 , 0.045	
Male	0.154 , 0.330	0.107 , 0.504	0.462 , 0.002
Female	0.201 , 0.207		0.385 , 0.013

P < 0.05 indicates significant correlation.

were directly associated with severity of fibrosis based on ultrasound findings in both genders. Further exploratory analysis revealed that in male subjects AST activity is in association with VAI and AIP. In addition in both genders, VAI and AIP are in strong direct relationship with ultrasound findings.

Discussion

In the present study, we demonstrated gender-dependent differences in adipokines concentration; women had higher levels of omentin-1 and vaspin. Our findings are comparable with previous study in type 2 diabetic patients (24) and children (25). There is a proposed hypothesis accounting for this gender difference: higher concentrations of adipokines in females could simply reflect the higher fat mass(24). Vaspin is member of the serine protease inhibitor family. Vaspin roles in human health and disease are only beginning to unravel and preliminary efforts have yielded conflicting results. One findings of the present study is the strong association of vaspin with insulin levels. Similarly, a possible positive link between vaspin and insulin resistance has been suggested (26). Esteghamati et al. (24) also, recorded a higher vaspin level in patients with diabetes in comparison with normoglycemic subjects. It is hypothesized that the increased vaspin levels seen are an adipocytes' compensatory response to antagonize a yet unknown protease escalated in dysregulated metabolism (27). Whether vaspin is actively involved in pathogenesis of NAFLD or is merely a disease surrogate of disease remains to be elucidated.

In both genders, omentin-1 levels were correlated positively with weight and hip circumference. This seems paradoxical given that obesity, a condition with elevated body weight is associated with decreased omentin-1 levels (28). However, fat mass appears to be a key factor for increased adipokines production. Additionally, adipose tissue, as an endocrine organ, has been reported to release multiple regulating proteins, adipokines. These adipokines exert local, peripheral and central effects. A recent review study indicated that altered production in adipokines secretion could play a pivotal role in development of metabolic syndrome and NAFLD (8).

Further exploratory analysis showed that BAI is associated with circulating omentin-1 in female patients. It is indicated that excessive adipose tissue accumulation and adipocyte hypertrophy can promote pathogenic adipocyte and adipose tissue effects which called adiposopathy. Adiposopathy, in turn, results in abnormal levels of circulating lipids, with dyslipidemia being a major atherosclerotic coronary heart disease risk factor(29). Additionally an increase in body fat often leads to increased secretion of proinflammatory adipokines that in turn worsen metabolic disease, including dyslipidemia and atherosclerosis(29).

In order to confirm our hypothesis, we further evaluated the role of AIP, which is calculated based on concentrations of TG and HDL, in severity of disease. AIP was in significant direct correlation with ultrasound grading of liver disease. Another novel finding of this study is that AIP is associated with AST activity. Generally, in the context of cardiovascular (CV) risk factors, the dyslipidemia is of great importance. NAFLD has been associated with CV risk factors including obesity, dyslipidemia, hyperglycemia and hypertension (19). In NAFLD, dyslipidemia is characterized by elevated TG and LDL-C levels and by decreased high-density lipoprotein cholesterol (HDL-C) concentrations(19, 20). Long-term dyslipidemia contributes to fat accumulation in the liver and development of steatosis. Liver fat deposition and oxidative stress result in the increased secretion of inflammatory markers, such as interleukin-6, tumor necrosis factor-α, C-reactive protein, and fibrinogen. In addition, circulating adipokines and cytokines as well as associated lipotoxicity, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress are involved in steatosis. Thereby, the AIP is suggested as a useful predictor of the risk of CV disease and is associated with the NAFLD severity(20).

Adipokines in relation to liver function

In this regard, we found a direct correlation between vaspin levels and ALT activity in female patients. Interestingly, omentin-1 was in positive association with severity of disease reflected by ultrasound observations. Given that Aktas et al. (10) reported a positive correlation between vaspin and liver fibrosis ,these findings are not surprising. Additionally in studies (10, 30) with histologically confirmed NAFLD, higher circulating vaspin levels were observed in NAFLD patients. These changes in the vaspin levels support the hypothesis of its compensatory effects on obesity and glucose homeostasis(31). One recent review study suggested that since vaspin suppressed leptin and TNF-α production (32), it could be beneficial in treating NASH-related fibrosis. Regarding the observed correlation between omentin-1 levels and ultrasound observations of patients; our findings are in line with a previous study. Yilmaz et al. (14) reported a positive association of elevated serum omentin levels with hepatocyte ballooning degeneration in patients with NAFLD. There is no additional studies that could confirm results, the possibility that higher omentin levels in these NAFLD patients merely result from a compensatory counter-regulatory mechanism to the increased IR could not be excluded(8). However, the exact mechanisms underlying the potential effects of these adipokines in NAFLD patients cannot be directly inferred from the present data. The role for vaspin and omentin-1 in metabolic regulation is remained to be evaluated.

VAI

Dividing patients according to gender, we have observed that VAI is in positive significant association with the severity of liver fibrosis as well as AST activity in male patents. These findings are in line with previously reported (33) association between VAI and fibrosis in NAFLD patients, independent of insulin resistance. There is evidence (34) of a direct association between visceral fat, evaluated by magnetic resonance, and severity of fibrosis .Similarly, a prospective study on Asian populations, suggested visceral obesity, reflected by WC, as a predictor of fibrosis progression in NAFLD patients(35). More recently, visceral obesity was reported to be a significant predictor of fibrosis in NAFLD(36). However, the conflicting findings regarding the complex relationship between visceral obesity and histological features in patients with NAFLD has been reported(37). Of note, one study with several superiorities over mentioned study, including relatively larger number of patients, and the direct measurements of visceral fat mass using CT scanning reported the similar results to our findings(36).

The precise mechanisms by which visceral fat exerts its harmful role in the pathophysiology of NAFLD remain to be identified; however, there are several potential mechanisms. It has been suggested (16) that VAI is indirectly indicator of both fat distribution and function in non-obese, healthy patients and in primary care patients. Therefore, this index reflects other nonclassic cardiometabolic risk factors, such as impaired pattern of adipocytokines(16). According to the portal/fatty acid flux theory, since visceral fat, possess distinctive location and increased lipolytic activity; releases toxic free fatty acids, then, these fatty acids

carried directly to the liver in high concentrations and lead to the development of hepatic insulin resistance through the accumulation and storage of hepatic fat (34, 38, 39). It has been indicated that insulin sensitivity, lipolytic activity, and adipocytokines production, which play a main role in the pathogenesis of chronic disease in the general population, may be indirectly represented by VAI(40). Taken together, VAI appears capable to predict fibrosis in NAFLD Patients.

Limitation

The major limitation of the present study is first the relatively small number of subjects in the sample. Secondly, regarding the cross-sectional design of the study, we could not confirm a causal link between the levels of measured adipokines as well as calculated indices in the pathogenesis of NAFLD. The precise roles of adipokines, AIP and VAI in the development of NAFLD need to be confirmed in future study.

Conclusion

To sum up, our data suggest that omentin-1 and vaspin are likely involved in the metabolic dysregulation and obesity-related disease. Also, VAI and AIP appear capable to predict disease severity in NAFLD Patients. The strategy for weight loss, body fat reduction, improved blood dyslipidemia as well as insulin resistance; in order to observe their potential effects on omentin and vaspin levels is suggested.

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