Mediation Role of Body Fat Distribution (FD) on the Relationship Between CAV-1 rs3807992 Polymorphism and Metabolic Syndrome in Overweight and Obese Women

Faezeh Abaj
Tehran University of Medical Sciences School of Nutritional Sciences and Dietetics
Said Abdul Ghafour Saeedy
Herat University Faculty of Medicine
Khadijeh Mirzaei (mina_mirzaei101@yahoo.com)
Tehran University of Medical Sciences https://orcid.org/0000-0003-0231-0478

Research article

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Abstract

Background: Metabolic syndrome (MetS) carries increased risk of the mortality of almost all chronic diseases. The most frequently used methods for calculation of a continuous MetS (cMetS) score have used the MetS severity z- score. Caveolin-1 (CAV-1(is one of the gens that is suggested by some authors that has a great effect on the visceral fat. This study was designed to investigate the relationship between CAV-1 markers and cMetS, the associations between CAV-1 rs3807992 and FD; and to assess FD mediators of the predicted association between CAV-1 and cMetS.

Methods: The current cross-sectional study was conducted on 404 overweight and obese females. The CAV-1 rs3807992 and anthropometric data were measured by the PCR-RFLP method and bioelectrical impedance analysis (BIA), respectively. Serum profiles (HDL-C, TG, FPG, and Insulin) were measured by standard protocols.

Results: Individuals with GG allele had significantly lowered (Z-MAP (p=0.02), total cMetS (p=0.03)) and higher Z-HDL (p=0.001) compared with A allele carrier. There was a significant specific indirect effect (standardized coefficient = 0.19; 95% CI: 0.01–0.4) of VFL. Although, total body fat was significantly associated with CAV-1 rs3807992 and cMetS, the specific indirect effect was not significant (standardized coefficient = 0.21; 95% CI: (-0.006,0.44). Visceral fat level contributed to significant indirect effects of 35% on the relationship between CAV-1 and cMetS.

Conclusion: Higher visceral adipose tissue may affect the relationship between CAV-1 and MetS. Although CAV-1 rs3807992 is linked to visceral fat in our study, the influence of this polymorphism on MetS is not via total fat.

Introduction

Metabolic syndrome (MetS) refers to a set of metabolic disorders that are associated with a high risk of cardiovascular disease. Its components include abdominal obesity, high blood pressure (BP), hypertriglyceridemia, hyperglycemia and low level of high-density lipoprotein-cholesterol (HDL-C) [1, 2]. According to health consequences, MetS carries increased risk of the morbidity and mortality of almost all chronic diseases [3, 4]. There is a lack of consensus on the definition of MetS and lately, the number of definitions and guidelines for this syndrome has increased hugely [5]. During the last decade, symmetrical to the changes in definitions of the MetS, alternative approach for the monitoring of MetS was also improved. Alongside the lack of a universal definition for MetS, the fact that MetS was defined as a dichotomous variable, paved the way for the development of continuous score of the syndrome. Explanation of the development of the continuous score is clear, since information loss is expected to occur due to dichotomy (present/absent) of current MetS definitions [6].

So far, he most frequently used methods for calculation of a continuous MetS score has used the MetS severity z- score [7]. The MetS severity z-score, an inexpensive and clinically-available continuous measure of MetS, was derived from standardized loading coefficients of a confirmatory factor analysis

for fasting blood sugar (FBS), triglycerides, triglycerides, waist circumference, blood pressure and HDL-cholesterol; and is used to identify individuals at a high risk of diabetes [8].

There is strong evidence in studies that concomitant with obesity, genetic factors have a role in FD. It appears that genetic factors have a more prominent impact on visceral fat than on other adipose tissues. It is suggested by some authors that apart from total body fat mass, genetic factors have a great effect on the visceral fat [9].The availability of enormous genomic information, in this post-genome-wide association study (GWAS) period, have facilitated the field for fine-mapping and translation of genetic information into clinical practice. Caveolin-1 (CAV-1) is one of the gens that receives a lot of attentions in these studies [10, 11]. Caveolae are small invaginations in the cell membrane and CAV-1 is the principal element of caveolae that acts as an integral element [12], has an important role in signal transduction and trafficking and interacts with steroid receptors and ion channel activation. CAV-1 is widely studied in cardiovascular and kidney tissue [13].

In this research, we centered on the caveolin-1 (CAV-1) gene which is located on chromosome 7q31.2. CAV-1 [12]. High levels of CAV-1 expression is observed in adipocytes. Furthermore, CAV-1 is implicated in both lipogenic and adipogenic processes [14]. It is shown by various studies that CAV-1 mRNA expression is increased in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) of obese patients[15].

Numerous gene loci that have potentially regulator action on fat distribution (FD) are revealed by recent GWAS for a measure of FD. Moreover, genes with fat depot-specific expression design, particularly SAT vs VAT, furnish credible candidate genes that participate in FD regulation. The sexual dimorphic effect has been revealed by sex-stratified studies at 20 Waist-Hip Ratio (WHR)-associated loci. 19 out of these 20 loci exhibited more powerful effects in women [16, 17]. Lack of caveolae, as seen in lipoatrophic diabetic caveolin-deficient patients, severely compromises fat cell expansion. But caveolar protein expression is not all the time associated with obesity [18]. Risk of developing obesity related metabolic and cardiovascular complications such as metabolic syndrome is affected in large quantities by adipose tissue dysfunction and ectopic fat [19].

This study was designed for the purpose of investigation of the relationship between *CAV-1* markers and cMetS, investigate the associations between CAV-1 common variants and FD, and to assess FD mediators of the predicted association between CAV-1 and cMetS.

Methods

Samples

Totally 404 healthy overweight, or obese women aged > 18 years without a history of any surgery or chronic diseases, who read and signed the written informed consent entered this cross-sectional study.

Pregnant women, and who were taking medications were excluded. After a review of medical history, laboratory tests were obtained from participants. The protocol of this study has been explained in detail previously. Measured parameters were height, weight, BMI (weight [kg]/square of height [m2]), waist circumference, waist-to-hip ratio, and blood pressure. Obesity and overweight were defined as BMI 30 kg/m2 and BMI 25–29.9 kg/m2, respectively. Visceral fat level (VFL), total body fat (TBF), percent body fat (%BF), skeletal muscle mass (SMM), soft lean mass (SLM), were measured by tetrapolar bioelectrical impedance analysis (InBody 770 scanner, Inbody Co, Seoul, Korea). According to the manufacturer's instructions, first, participants removed their shoes, coats, and sweaters, then they stood barefoot on the balance scale and held the handles of the machines.

Clinical measures and DNA analysis

Blood samples were collected after 12–14 h fasting to evaluate serum TG, HDL-C and FBS, which were measured via enzymatic methods using standard protocols. DNA's extraction was accomplished by a high-salt method as described previously [20]. PCR-RFLP method was used to determine CAV-1 rs3807992 genotypes polymorphisms. For amplification, we utilized the following primers: 3'AGTATTGACCTGATTTGCCATG5' R:5'GTCTTCTGGAAAAAGCACATGA-3' .Finally, the PCR was conducted in a final volume of 20 µl, containing 1 µl extracted DNA, 1 µl Forward primers, 1 µl Reverse primers 7 µl distilled water and 10 µl Taq DNA Polymerase Master Mix (Ampliqon; Germany) under the following conditions: each reaction started with a cycle of DNA templates were denatured at 94 °C for 3 minute amplifications consisted 40 cycles of (94 °C 15 s, 53 °C 30 s, 72 °C 30 s.), with a final extension at 72 °C for 3 minutes. (10 µl) DNA was digested with 0.5 µl of the Hin1II(NlaIII) enzyme (Fermentase, Germany) at 37 °C overnight. Electrophoresis was conducted to visualize all PCR products.

Continuous risk score for MetS (cMetS)

To calculate a continuous risk score for MetS used Z score for standardized residuals [(WC, FBS, HDL-C, TG, Mean Arterial Pressure (MAP)] by regressing them on age. Since the standardized HDL-C is conversely associated with the MetS risk, it was multiplied by — 1. MAP calculated from measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) variables. The sum of the standardized residuals (z scores) for the subjects' variables was used to compute cMetS score.

Statistical methods

One-Way ANOVA and ANCOVA tests were used for determining the association between quantitative variables in three groups of genotypes. To investigate whether the relationship among CAV-1 rs3807992 polymorphism and cMetS was mediated by FD, we used tests of mediation which were the most common statistical methods for detecting indirect effect between independent and outcome variables. For the first time, Baron and Kenny developed this analysis [21]. $P < 0.05$ was considered statistically significant.

Results

We investigated 404 healthy women with a mean age of (36.67 ± 36) years. Based on CAV-1 rs3807992, we had three groups of participants. Their characteristics information is shown in Table1. The mean fat mass index (FMI), VFL and obesity degree (%) were significantly higher in AA compared to AG and GG ($p < 0.05$). In addition, we couldn't find any significance among CAV-1 rs groups. The mean values for each part of continues metabolic syndrome score which is divided in different groups by CAV-1 genotypes is presented in Table2. There was a significant correlation between Z-score (MAP, HDL-C) and finally cMetS with caveolin polymorphism in this study. GG group had significantly lowered (Z-MAP ($p = 0.02$), total cMetS ($p = 0.03$)) and higher Z-HDL ($p = 0.001$) compared with AA and AG groups. Mediation analysis shown in Fig. 1, in both of analysis, the direct effect of caveolin polymorphism on cMetS were not significant despite that only the VFL created a significant specific indirect (standardized coefficient = 0.19; 95% CI: 0.01–0.4) after controlling for age and energy intake. Although, Total body fat was significantly associated with caveolin-1 rs3807992 and cMetS, the specific indirect effect was not significant (standardized coefficient = 0.21; 95% CI: (-0.006,0.44). Therefore, VFL contributed to significant indirect effects of 35% on the relationship between CAV-1 rs3807992 and cMetS.

Table 1
Baseline characteristics of all participants according to genotype CAV-1 rs3807992

Variables	AA	AG	*GG*	*Pvalue* [a]	*Pvalue* [b]
Age(year)	35.67 ± 8.71	*35.85* ± 8.91	37.56 ± 9.49	0.15	
BMI (kg/m2)	31.64 ± 3.96	30.93 ± 3.89	30.57 ± 3.88	0.09	0.18
WC (Cm)	100.52 ± 9.38	99.13 ± 9.65	98.22 ± 9.3	0.14	0.33
WHR	0.94 ± 0.05	1.94 ± 9.59	0.93 ± 0.05	0.2	0.17
BFM (Kg)	36.51 ± 10.04	34.67 ± 7.97	33.49 ± 7.96	**0.01**	0.17
FFM (Kg)	46.80 ± 5.76	46.25 ± 5.90	46.26 ± 5.48	0.71	0.59
SMM (Kg)	25.68 ± 3.40	25.57 ± 3.73	25.34 ± 3.27	0.69	0.54
SLM (Kg)	43.66 ± 4.97	43.55 ± 5.64	43.44 ± 5.24	0.94	0.75
BF%	42.86 ± 6.25	42.49 ± 4.53	41.62 ± 5.47	0.15	0.3
WHR	0.94 ± 0.05	1.94 ± 9.59	0.93 ± 0.05	0.19	0.24
VFL	16.42 ± 3.22	16.12 ± 2.99	15.46 ± 3.4	**0.04**	0.09
VFA(Cm2)	175.05 ± 40.89	165.71 ± 36.91	170.42 ± 125.32	0.78	**0.03**
Obesity degree %	149.91 ± 22.57	142.1 ± 23.55	142.7 ± 18.96	**0.01**	0.17
FFMI (Kg)	18.1 ± 1.56	17.74 ± 1.66	18.42 ± 9.5	0.72	0.73
FMI (Kg)	14.19 ± 3.76	13.44 ± 3.06	12.93 ± 3.25	**0.01**	0.07
Total body mineral content (Kg)	2.62 ± 0.34	2.64 ± 0.34	2.65 ± 0.35	0.76	0.19
BFM: Body Fat Mass, FFM: Fat Free Mass, SMM: Skeletal Muscle Mass, BF: Body Fat SLM: soft lean mass; VFA: visceral fat area; WC: waist circumference; BF: body fat; WHR: waist height ratio					
Values are means (SD), P-value for curd model, P-value for adjusted model by age, energy intake, physical activity level					

Table 2
Mean values of components of continuous metabolic risk score by CAV-1 rs3807992

	AA	AG	GG	Pvalue
	Mean ± SD	Mean ± SD	Mean ± SD	
Z_Waist circumference	0.1496 ± 0.994	-0.0014 ± 1.02	-0.1065 ± 0.979	0.11
Z_MAP	0.1492 ± 0.891	0.1866 ± 1.19	-0.1704 ± 0.978	**0.02**
Z_FBS	-0.0472 ± 0.86	-0.0308 ± 1.19	0.0324 ± 0.992	0.84
Z_HDL-C	-0.1613 ± 0.842	-0.3417 ± 1.05	0.2358 ± 1.02	**0.001**
Z_Triglycerides	0.112 ± 1.19	0.1523 ± 1.05	-0.104 ± 0.864	0.19
Z_TOTAL	0.3897 ± 2.67	0.2624 ± 3.739	-0.6099 ± 2.42	**0.03**

Z: standardized components of a continuous metabolic syndrome risk score, FBS: Fasting Blood Glucose, MAP: Mean Arterial pressure

Discussion

Since the attribution mechanism of CAV-1 variants to MetS is unclear at the present, this association have been studied by a small number of existing researches. Furthermore, regardless of that relation among the caveolae function, adipose tissue and lipid profile, MetS which is linked to CAV-1 has not been studied regarding the body FD. We believe that this is the first work that has suggested a conceivable pathway to illustrate the association between CAV-1 rs3807992 and MetS. To a notable extent, we offered a hypothetical mechanism whereby CAV-1 is able to increase MetS risk via fat FD. As mentioned in the results section, although the rs3807992 polymorphism was statically related with visceral and total body fat, we found evidence in mediation analysis with visceral fat (VF) and total body fat (TF), that only visceral fat level (VF) explains the association between rs3807992 and MetS syndrome. On the best of our knowledge, the indirect effect of CAV-1 rs3807992 on MetS via VFL and total body fat is a new approach that has not been shown or even suggested before.

Noteworthy, the present mediation analysis is especially interesting in that the arguable link which is present between visceral and total body fat is known. A close relation is present among anthropometric values and FD; the risk of developing MetS increases in persons who have fat deposition in visceral adipose than total body fat deposition [20]. The importance of visceral adipose tissue in the pathophysiology of metabolic disorders can be hallmarked by comparing specifications of VAT with SAT. VAT is linked with the development of insulin resistance, is lipolitically more active and carry more risk factor for the development of obesity, dyslipidemia, cardiovascular and metabolic disease [21, 22]. Insulin resistance develops as a consequence of visceral adiposity and VAT are bioenergetically more active than subcutaneous fat [23]. Regarding these special characteristics, visceral fat led to many metabolic

disorders such as alteration in lipid profile (low HDL-C and high TG levels) and disturbances in glucose homeostasis [24–26].

This is remarkable that lipodystrophies with defective local fat deposition that is seen in mutations of CAV-1 gene, indicate new locus in the metabolic disease. It has been established by previous studies that CAV-1 has a significantly regulator role in FD and genetic lipodystrophies in humans [27]. In addition to the fact that visceral and total fat stores have big differences in their role in pathophysiology and progression of obesity, CAV-1 is now specified as gene involved in FD and potential mechanisms contribute to its variability. Regarding this, we have investigated the effect of these pathways and association with CAV-1 and MetS. In our study, CAV-1 rs3807992 was associated with VFL. Previous findings had not indicated a special direct or indirect role for VFL in the increase of the development of MetS in individuals carrying the risk allele. However, studies show the association of expression of CAV-1 mRNA in VAT in obese women compared with lean subjects [15].

At the present time, the functionality of the near-CAV-1 region (which includes rs3807992) is not well understood. Finally, to identify the biological mechanism and causal links between CAV-1 common variants, VFL and FD preclinical studies should be done.

Caveolin-1 null mutation-caused lipodystrophy has been revealed and different mechanisms have been described for this. According to the following mechanism, Caveolin 1 null mutation could have caused lipodystrophy by abnormality in lipid transport by caveolae, disturbances in adipocyte differentiation pathway and composition of lipid droplets [23, 28]. Basic studies have shown that lean body phenotype of CAV-1- null mice are smaller than their wild type counterparts. The lean body phenotype of Cav-1 null mice is accordant with the three functions that are attributed to CAV-1 and caveolae in adipocytes, including unity and function of the lipid droplet; binding, transport, and storage of cholesterol and fatty acids; and increase in insulin signaling. These possible functional roles for CAV-1 may be inherited [29].

Documented links are present between VF and total body fat with metabolic syndrome. At the other hand, other studies documented that these differences in FD in tissues could be genotype-related. Regarding the presence of mentioned documents, our results cast a new light and mechanism on the mediation role for VAT rather than total fat with consider to CAV-1-linked MetS. It is also noteworthy that concomitant with previous findings, we noticed a positive relationship between FD and CAV-1 in metabolic disorders. This finding suggests that CAV-1 variants may affect MetS through more known factors such as VAT. Specifically, our primary results suggest a possible pathway to MetS risk by VAT, and the presence of the CAV-1 rs3807992 risk allele.

However, our important found pathway does not relate to total body fat mechanism. Our results suggest that an allele of the rs3807992 polymorphism might have had a role in the sensitivity to high VFL. To date, association between VFL to CAV-1 variants in humans remains unknown. Overall, in spite of the fact that rs3807992 was not the only polymorphism associated with MetS, it was also the only single nucleated polymorphism (SNP) related to VFL. The present study also might have a clinical implication; association of CAV-1 with body composition in our study could suggest a CAV-1–lipogenic pathway

interaction. Especially considering that CAV-1 is highly expressed in the adipose tissue, and the interplay between CAV-1 gene with lipogenic genes has been reported [30].

This finding is accordant with what has been found in former studies. We proposed caveolin interaction with visceral fat can affect fatty acid function, and then cause metabolic disorders. Excess visceral fat could be related to changes in circulating fatty acid composition [31]. Altered activities of fatty acid desaturases and disturb plasma fatty acid metabolism, and causes adipose tissue dysfunction. However, it seems that a possible genetic interaction between CAV-1 and fatty acid composition with the lipogenic system genes, may also be accountable for our result in this study. Highlighting the potential of applying this finding in the prevention and treatment of CAV-1-linked obesity and cardiovascular disease that is result of high VFL.

Since the beginning of human studies on caveolin gene, limitations were present due to the lack of information on body composition in these studies. So, researchers have not been able to investigate the visceral fat factor which may have been the cause of some observed results. So, we have a tendency to research this gap.

Limitations

Notwithstanding our novel findings, it suffers from some limitations. All participants in our sample were women; and there have been studies reporting sex differences for the effect of CAV-1 on various body composition.

Conclusion

It appears that increased VAT fat accounts for the association between CAV-1 rs3807992 and MetS. Although rs3807992 is linked to visceral fat in our study, the influence of this polymorphism on MetS is not via total fat. If replicated, this suggested pathway has the potential to have important impact on our understanding of CAV-1-linked MetS.

Abbreviations

BIA: Bioelectrical impedance analysis

BMI: Body mass index

bp: Base pair

CVD: Cardiovascular disease

DBP: Diastolic blood pressure

FBS: Fasting blood sugar

FFQ: Food frequency questionnaire

GLM: General linear model

GWAS: Genome-wide association studies

LDL: Low-density lipoprotein

MA: Minor Allele

PCR: Polymerase chain reaction

RFLP: Restriction fragment length polymorphism

SNP: Single nucleotide polymorphism

TC: Total cholesterol

TG: Triglyceride

VAT: Visceral adipose tissue

WC: Waist circumference

WHO: World Health Organization

Declarations

Ethics approval and Consent to participate:

The protocol of the study was approved by the ethics committee of TUMS (Ethics number: 97-03-161-41017). All participants completed a written informed consent

Consent for publication:

'Not applicable'

Competing interests:

The authors declare no conflict of interest

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Authors' contributions: FA:

Conceptualization; Methodology; Investigation; Formal analysis; Software; Writing Original draft. SA S: Writing - review & editing. KM: Supervision; Validation; Project administration

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Figures

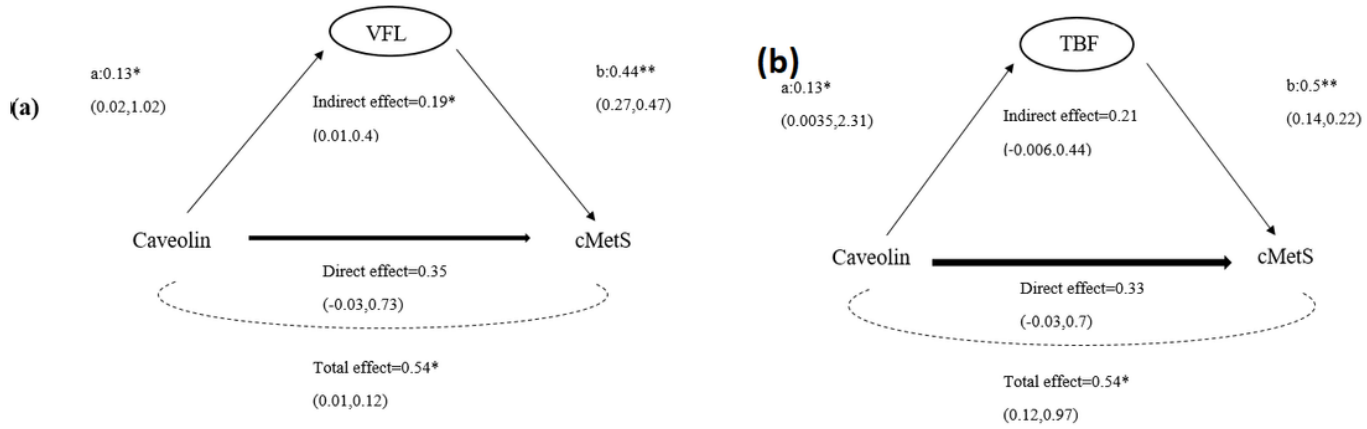

Figure 1

Mediation effects of VFL and TBF on the association between Caveolin-1 rs807992 polymorphism and cMetS (VFL; a), (TBF; b). Confounding factors were age, energy intake. standardized coefficients were shown along with their estimated p values: “a” is the linear regression coefficient of the CAV-1rs3807992–cMetS association; “b” is the linear regression coefficient of the VLF and TBF of cMetS. * $p < 0.05$; ** $p < 0.001$. The analysis was done using SPSS Process Andrew 3.3 with 5000 bootstrap samples Statistically significant paths do NOT contain zero between lower and upper level confidence intervals.