Are Caveolin-1 minor alleles more likely to be risk alleles in IR mechanisms in metabolic diseases?

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Research note

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Abstract

Objectives

Associations are present between insulin resistance (IR) and dyslipidemia and cardiometabolic factors. Caveolin-1 (CAV1) is involved in glucose/lipid homeostasis and may modulate IR signaling. We investigated the relationship between CAV1 and IR signaling in modulating dyslipidemia and fat composition in overweight and obese women with a prevalent variant in the CAV1 gene.

Results

There were no statistical differences in FPG, plasma insulin, and HOMA-IR (p > 0.05) between CAV1 variants. Individuals with AA and AG alleles were slightly older and had higher BMI, FMI, and VLF values; and tended to have lower total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) (p < 0.05). HOMA-IR levels predicted fat mass index (FMI) 0.47 (0.08,0.87), visceral fat level (VFL) 0.65 (0.23,1.07), TC 6.82 (1.76,11.88) and HDL-C -1.663 (-3.11, -0.214) only between minor allele carriers in unadjusted and adjusted models. (, CI (P < 0.01). Our r

Introduction

Preceding studies have established the principal role of Insulin resistance (IR) and resultant hyperinsulinemia in cardiometabolic risk factors [1, 2]. Inappropriate signaling of insulin has been associated with impaired fat distribution, adipocyte metabolism, and dyslipidemia [3]. According to studies, insulin resistance is associated with obesity, especially visceral obesity, hypercholesterolemia, hypertriglyceridemia, and low HDL-C concentration [4-7]. The exact mechanisms for the insulin-induced defects including adipocyte dysfunction are unclear. However, a number of genomic and nongenomic pathways are present that mediate these IR effects. Furthermore, these effects could be secondary to alternative plasma membrane proteins, and other receptors [8].

Caveolin-1 (CAV1), a 21-24 kDa integral membrane protein, is the main structural protein of caveolae. CAV1 acts as scaffolding and has been involved in transmembrane signaling [9]. CAV1 is an important constituent of the lipid raft that control their activity and cooperates with several signaling pathways, involving steroid receptors [10]. As has been explored in preceding studies, CAV1 gene variants were correlated with IR, dyslipidemia, diabetes mellitus, and metabolic syndrome [11]. Moreover, it is suggested by some authors that CAV1 knockout (KO) mice display numerous metabolic defects, including hyperglycemia, IR, and dyslipidemia [12, 13].

The main location of the insulin receptor of the adipocyte is suggested to be in caveolae and bound to immobilized caveolin to excites their signaling [14]. The clinical significance of the relationship between CAV1 and IR-mediated mechanisms in adipose tissue in the pathogenesis of insulin resistance in humans has been discussed. Here, we talk about the hypothesis that the CAV1-IR mechanism is a mediator of
cardiometabolic disorder in caveolin genotypes. We investigated the potential interplay between IR levels and a selected human CAV1 gene variant in modulating dyslipidemia and body fat composition.

In spite of the developing knowledge in understanding the role of insulin pathways in dyslipidemia, to date no study has considered whether this mechanism works the same in all participant; and whether minor alleles are more likely to be risk alleles in IR mechanisms in metabolic diseases or not.

**Methods**

**Subjects**

For this cross-sectional study, we analyzed the data which was collected from samples of Tehranian overweight/obese females, aged over 18 and were before menopause. Women with a history of chronic and inflammatory disease and who were pregnant or lactating, taking any therapeutic medications or follow a special diet or supplements were excluded. After the final exclusion, 404 women remained in the present analysis. The study participants were fully informed with respect to the research protocol and they signed a consent form before taking part in the research. Tehran university of medical sciences (TUMS) ethics committee agreed with these protocols.

**Procedures:**

Anthropometric variables were measured by standard protocols. We used digital scales for measuring weight, and measuring tape for measurement of height and waist circumference while the subjects were standing with bare feet. Body mass index (BMI) was calculated as a ratio of weight (kg) to height in meters squared. Bioelectrical impedance analysis (BIA 770 (South Korea)) is an electrical method of assessing human body composition and was used to assess the VFL, body fat mass (BFM) and FMI. International Physical Activity Questionnaires (IPAQ) was used to assess physical activity [15]. A Food Frequency Questionnaire (FFQ) used to calculate energy intake.

**Genotyping**

The Mini Columns kit (Type G; Genall; Exgene) was used for DNA extraction. The CAV1 SNP (rs3807992) was genotyped by PCR-RFLP method, using primers, Forward: 3’AGTATTGACCTGATTTGCCATG5’ Reverse :5’GTCTTCTGGAAAAAGCACATGA-3’. according to our pervious study [16].

**Measurements of Biochemical parameters**

We collected blood samples after 10 - 12 hours of overnight fasting. For measurement of FPG, Glucose Oxidase Phenol 4-Aminoantipyrine Peroxidase (GOD/PAP) method was used [17]. Furthermore, triacylglycerol kits (Pars Azmoon Inc, Tehran, Iran) was applied for the determination of serum TG level. The total TC level was evaluated by the cholesterol oxidase Phenol 4-Aminoantipyrine Peroxidase (CHOD-PAP) method [18]. Besides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were measured by the direct method and immunoinhibition [19].
**HOMA-IR calculation**

Homeostatic model assessment (HOMA) calculated by using this formula: HOMA-IR = [FPG (mmol/l) x fasting plasma insulin (mIU/l)]/22.5 [20].

**Statistical analysis**

IBM SPSS statistics (version 25) was used for all phases of the analysis (SPSS Inc, Chicago, IL, USA). The evaluation of the normality of quantitative variables was conducted by K-S (Kolmogorov– Smirnov) test. Independent Student's t-test was used to baseline analysis comparing by genotype status. The adjusted linear regression model was used to assess the relationship between HOMA-IR levels and cardiometabolic variables, first, in all participants without grouping; and subsequently in whom that were grouped by rs387992 genotype status adjusted for age, energy intake, and IPAC index. Data are presented as means±SD, and $P < 0.05$ is considered statistically significant.

**Results**

**Study population**

A total of 404 adults were analyzed. Our study had the following characteristics: age 36.67±9.1 years, body mass index (kg/m2) of 31.26±4.2. Using a dominant model for genetic analysis, a homozygous major allele (GG) of the rs3807992 CAV1 variant was observed in 50% of participants, and the other 50% were minor allele carriers (23.31% had an AG genotype and 26.6% had an AA genotype).

**Clinical and biochemical characteristics categorized by CAV1 genotype:**

Compared with those with the homozygous major allele of rs3807992 CAV1 variant, minor allele carriers had no statistical differences ($p>0.05$) in FPG, plasma insulin, and HOMA-IR, as are described in Table 1. Minor allele carriers were slightly older ($p=0.05$) and had higher BMI ($p=0.02$), FMI ($p=0.006$), VLF ($p=0.01$) values, and tended to have lower TC ($p=0.04$), LDL-C ($p=0.001$), and HDL-C levels ($p=0.003$) (Figure 1).

**The CAV1 variant modulates the effect of HOMA-IR on lipid hemostasis and lipid profile**

A statistically significant relationship was found between CAV1 variants and anthropometric data and lipid profile values. Since rs387992 genotype and HOMA-IR levels were associated with anthropometric data and lipid profile values, we considered whether they were independent predictors in a linear regression model or not. We found an association and both rs926198 status and HOMA-IR levels were significant predictors of lipid profiles and anthropometric status with a statistically significant interaction. To further analyze the relationship between these predictors, we stratified the effect of HOMA-IR on TC by genotype. Interestingly, HOMA-IR levels predicted TC only in minor allele carriers in unadjusted and, adjusted models ($p=0.003$), as noted in Table 2. Also, lower HDL-C levels were associated with HOMA-IR levels in all participants. Moreover, these results were driven by the effect on minor allele carriers of the
CAV1 gene variant (Table 2). There was a consistent significant interaction when analyzing HOMA-IR levels with rs926198 genotypes predicting HDL-C levels \((p=0.006)\). We assessed whether changes in HOMA-IR levels predicted changes in VLF and FMI levels. Indeed, HOMA-IR predicted higher VLF and FMI levels in the adjusted model in CAV1 minor allele carriers but not in major allele homozygotes \((p=0.002)\) (Table 2). In contrast, HOMA-IR levels were not associated with TG and LDL-C, because they were similar in both CAV1 genotype groups. The different effect of HOMA-IR on VLF, FMI, HDL-C, and TC levels in minor allele carriers may be attributed to an insulin signaling defect predicted by CAV1 genotype status.

**Discussion**

The unfolding story of caveolae and caveolin signaling in human health have started in the past. Our study has shown that the insulin pathway mediates some of the metabolic characteristics associated with defective caveolin genotype. Although HOMA-IR levels were similar in both carriers and non-carriers of the CAV1 minor allele, this study showed that HOMA-IR significantly estimates changes in TC, HDL-C, VLF, and FMI levels only in minor allele carriers of CAV1 gene variant. The relationship between TG and HOMA-IR seems to indicate that the effects of CAV1 on TG are IR independent.

The relationship of HOMA-IR levels activation with higher TC, lower HDL-C, and alteration in lipid composition in participants is supported by different studies [21]. IR is related to CVD & T2DM risk factors, such as dyslipidemia and Obesity (mainly visceral obesity). The involvement of HOMA-IR to CVD risks such as excess body fat and low HDL was well demonstrated [22]. The HOMA-IR is the utmost method used between IR indices in population-based studies [23].

Strong evidence is provided by early familial genetic studies to prove a genetic basis for both insulin resistance and the different constituents of the metabolic syndrome[24–30]. The major part of caveolae is CAV1, which has been revealed to lead to insulin resistant and cardiometabolic disease[31]. The G32124A (rs3807992) polymorphism is located at intronic region of Cav-1 gene. The variation of G32124A intronic polymorphism from Cav-1 may alter the normal expression or protein function of Cav-1 gene by regulating mRNA [32]. In CAV1 genotype, body fat distribution and dyslipidemia is suggested to be caused via probable mechanism of disruption in insulin signaling [33]. The expression of CAV1 gene, in the adipose tissue of obese women who have more fat storage, is greater compared to lean people who have less fat storage [34]. For this reason, we hypothesized that the observed phenotype in minor allele carriers, individuals may be manipulated by disruption of insulin receptor function, at least in theory.

A probable role for CAV1 in metabolic diseases is shown by animal studies and has indicated that CAV1-deficient mice exhibit variations in lipid parameters including TC and HDL-C [35]. Moreover, human studies on nonsense mutations show that severe CAV1 mutations exhibit insulin resistance and dyslipidemia [31]. The key mediator of cholesterol homeostasis is CAV1, and the function of CAV1 in HDL-C metabolism was confirmed by higher levels of plasma HDL-C in CAV1 deficiency [36]. The relationship of CAV1 variant and dyslipidemia are established by genome-wide association studies.
(GWAS) that exhibit a link of CAV1 gene proximal regions to low HDL-C level [37–39]. Regulation of insulin signaling in adipose tissue could be considered a potential mechanism by which CAV1 possibly alter lipid metabolism. Insulin promotes lipogenesis and inhibits lipolysis, which finally could alter adipose tissue metabolism. Insulin resistance is the consequence of obesity which is seen in CAV1 KO mice [40] and is consistent with the medical descriptions of overweight and obese subjects by showing decreased insulin sensitivity in adipose tissues.

HOMA-IR levels are associated with HDL-C, TC, VLF, FMI levels only in minor allele carriers that possibly could be accompanying with altered CAV1 expression. Our results support the theory that the mechanistic findings indication in the animal study likely also be valid to humans [41]. Because in our study the CAV1 variant was assessed only in Iranian women, these findings may not be applicable for people of other races. In future studies, investigating samples from a greater geographic area might prove more important findings. However, to our knowledge, this report is the first study showing that CAV1 minor allele predicted association between insulin resistance and dyslipidemia and body fat composition. Novel mechanisms such as insulin resistance that could be related to specific cardiometabolic disorder pathways associated with CAV1 deficiency in the human study are explored by this work. Whereas the history of human genetic researches on Caveolin is limited, this amount of research confirms a potential association between IR and CAV1. Our data have significant clinical consequences. First, we determined a genetic marker that could be used to screen for metabolic disease risk. Second, our results support the hypothesis that CAV1 is an emerging pathway that IR in humans leads to cardiometabolic disease.

**Conclusion**

Based on the present findings, it could be hypothesized that CAV1 (rs3807992) may be associated with increased metabolic disease risk factors in overweight and obese women. It appears that insulin pathways account for the association between CAV1 rs3807992 and metabolic factors among minor allele carriers; and this could be critical for clinical diagnosis and gene therapy. Due to limited studies on the CAV1 polymorphism, more researches are warranted to evaluate the impacts of insulin pathways on Caveolin- related metabolic disease.

**Limitations**

To the best of our knowledge, this was the first study to investigate the Chav-1 and IR-pathway with cardiometabolic factors, however, our study had several limitations such as having only overweight and obese women and because of financial limitation we couldn’t perform western blot analysis.

**Abbreviations**

BMI; Body mass index; FPG: Fasting Plasma Glucose; HDL-C; High-density lipoprotein cholesterol LDL-C; Low-density lipoprotein cholesterol; RFLP; Restriction fragment length polymorphism; TC; Total
cholesterol; TG: Triglyceride; FMI; Fat mass index; VFL; Visceral fat level; HOMA; Homeostatic model assessment.

Declarations

Ethics approval (IR.TUMS.VCR.REC 97-03-161-41017)

The protocol of the study was approved by the ethics committee of TUMS

All participants completed a written informed consent

Consent for publication: Not Applicable

Availability of data and materials: The data are not publicly available due to containing private information of participants.

Competing interests: The authors declare that they have no competing interests

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Author Contributions

FA: conceptualization, methodology, investigation, formal analysis, and software; writing original draft. SS; writing - review and editing. KM: supervision, validation, and project administration. All authors have read and approved the manuscript.

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**Tables**

**Table 1.** Clinical and biochemical characteristics categorized by Cav-1 variant rs3807992

| Variable | Minor Allele Carrier AA/AG | Major Allele Carrier GG | P-value |
|----------|-----------------------------|--------------------------|---------|
| Age      | 35.75±8.78                  | 37.56±9.49               | 0.05    |
| BMI      | 31.66±4.46                  | 30.68±4.01               | 0.02    |
| FMI      | 3.46±13.83                  | 3.25±12.93               | 0.006   |
| VFL      | 3.11±16.28                  | 3.40±15.46               | 0.01    |
| FBS      | 86.95±9.75                  | 87.98±9.62               | 0.31    |
| Insulin  | 1.22±0.25                   | 1.21±0.22                | 0.61    |
| HOMA-IR  | 3.53±1.82                   | 3.27±1.21                | 0.54    |
| TG       | 133.31±84.14                | 113.11±51.20             | 0.14    |
| HDL      | 44.04±10.16                 | 49.07±11.16              | 0.003   |
| LDL      | 91.27±25.07                 | 98.80±22.66              | 0.001   |
| TC       | 182.71±37.36                | 186.76±33.74             | 0.04    |

Values are mean (SD)

* P-value for curd model

** P-value for the adjusted model by age, physical activity level, energy intake, BMI

**Table 2.** Adjusted Linear Regression Models Assessing the Relationship Between **HOMA-IR** Levels and **Cardiometabolic Variables** in All Participants by rs387992 Genotype Status
| Cardiometabolic Variable | Category*       | HOMA-IR Adjusted b† (95% CI), P Value |
|-------------------------|----------------|-----------------------------------|
| FMI                     | All participants | 0.449 (0.17, 0.72) P = 0.002       |
|                         | Minor allele carriers | 0.47 (0.08, 0.87) P = 0.01       |
|                         | Major allele homozygous | 0.37 (-0.037, 0.77) P = 0.07     |
| VFL                     | All participants | 0.51 (0.19, 0.83) P = 0.002       |
|                         | Minor allele carriers | 0.65 (0.23, 1.07) P = 0.003       |
|                         | Major allele homozygous | 0.32 (-0.18, 0.83) P = 0.21     |
| TG                      | All participants | 15.25 (10.88, 21.63) P = <0.0001 |
|                         | Minor allele carriers | 17.21 (8.55, 25.88) P = <0.0001 |
|                         | Major allele homozygous | 17.6 (10.40, 24.81) P = <0.0001 |
| HDL                     | All participants | -1.473 (-2.52, -0.42) P = 0.006  |
|                         | Minor allele carriers | -1.663 (-3.11, -0.214) P = 0.02 |
|                         | Major allele homozygous | -0.87 (-2.5, 0.75) P = 0.29     |
| LDL                     | All participants | 1.64 (-0.72, 4.01) P = 0.17      |
|                        | Minor allele carriers | Major allele homozygous |
|------------------------|-----------------------|-------------------------|
|                        | 2.47 (-0.95, 5.9)    | 1.13 (-2.27, 4.54)      |
|                        | \( P = 0.15 \)       | \( P = 0.51 \)          |

|                       | TC                    | All participants        |
|-----------------------|-----------------------|-------------------------|
|                       | 6.82 (1.76, 11.88)    | 5.32 (153.65, 178.56)   |
|                       | \( P = 0.009 \)       | \( P = 0.003 \)         |

|                       |                       | Major allele homozygous |
|-----------------------|-----------------------|-------------------------|
|                       | 3.88 (-1.18, 8.95)    |                         |
|                       | \( P = 0.13 \)        |                         |

HOMA-IR indicates homeostasis model assessment of insulin resistance.

*Categorized by Caveolin 1 genotype rs926198  †Linear regression adjusted by age, energy intake, IPAC.  ‡\( P < 0.05 \)