Interaction Between Caveolin-1 Polymorphism with Dietary Fat Quality Indices and the Relationship with Visceral Adiposity Index (VAI) and Body Adiposity Index (BAI) Among Overweight and Obese Women: A Cross-Sectional Study

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Abstract

Background & Aims:

Caveolin-1 (CAV-1) in adipocyte tissue, and other parts of body, possess numerous biological functions. In the present study, we sought to investigate the interaction between CAV-1 polymorphism with dietary fat quality indices and the relationship with visceral adiposity index (VAI) and body adiposity index (BAI) among overweight and obese women.

Methods

This study was conducted on 386 women, aged 18-48 years old. Biochemical measurements were measured by standard protocols. We used a food frequency questionnaire (FFQ) to calculate the dietary intake and the indices of dietary fat quality intake. Anthropometric values and body composition were measured by standard methods. Finally, the CAV-1 genotype was measured using PCR-RFLP method.

Results

We found a marginally significant difference in waist-to-hip ratio (WHR) ($P=0.06$) and BAI ($P=0.06$) of participants, after adjusting with potential cofounders. For dietary intakes, after adjusting with the energy intake, mean differences in biotin ($P=0.04$) and total fiber ($P=0.06$) were significant and marginally significant, respectively. The interaction between two risk allele genotype group (AA) with omega-6 to omega-3 ratio (W6/W3) on BAI, after adjustment with potential cofounders (age, physical activity, energy intake, education), was marginally positive ($\beta = 14.08$, 95%CI= -18.65,46.81, $P= 0.07$). In comparison to the reference group (GG), there was a positive interaction between the two risk allele (AA) with W6/W3 ratio on VAI ($\beta = 2.81$, 95%CI= 1.20,8.84, $P= 0.06$) in the adjusted model.

Conclusions

We found that there may be an interaction between CAV-1 genotypes with dietary quality fat indices on VAI and BAI among overweight and obese women.

1. Introduction

Overweight and obesity represent notable risk factors for many non-communicable diseases, and contributes significantly to global mortality rates (1–3). Indeed, it has been estimated that by 2030, the prevalence of obese and overweight will increase significantly (4). Obesity and overweight are associated with many diseases and clinical conditions, such as diabetes, cardiovascular disease (CVD), disability, and depression, and early mortality (5).

Various anthropometric indexes can be used to get an overview of the body composition and health status of the body (6). For example, body mass index (BMI), hip circumference (HC), waist circumference (WC), and WHR can be used to measure and monitor obesity (7). In recent years, novel anthropometric indices have been introduced in an effort to accurately measure body fat distribution, such as VAI and BAI (8). BAI appears to represent a good assessment of fat percentage using HC, height, and gender (9). Whilst VAI is used to evaluate adipose tissue and its function, and, in addition to gender, it uses anthropometric parameters, such as waist circumference and body mass index and also biochemical parameters such as blood triglyceride concentration and blood cholesterol (10).

Throughout the body, including adipose tissue, the plasma membrane contains small (50-100 nm) complex, invaginations, flask-shaped specialized structures, called caveolae, that contains cholesterol and sphingolipids in its structure (11). Caveolae are involved in lipid metabolism, signal transduction, and endocytosis (12–15), in addition to the metabolism of lipids (16). Caveolae contain proteins called caveolin (17), which are integral membrane proteins that have scaffolding functions, and are regulators of many signaling pathways (18, 19). There are three forms of caveolin: caveolin 1, caveolin 2, and caveolin 3, which are expressed differently and can all affect obesity (20). Caveolin-1 is predominantly expressed in adipose tissue, caveolin-2 is expressed with caveolin-1 to form hetero-oligomers and, finally, caveolin-3 is the muscle-specific isoform of caveolin (12, 15). Caveolin, as an interactive gene, interacts with cholesterol and plays an important role in its metabolism and regulation (21). Due to the notable interaction of caveolin with cholesterol, animal studies have shown the significant effect of a high-cholesterol diet on the expression of the caveolin gene (22).

The quality of dietary fat has been reported to be closely related to obesity and body fat percentage, and to examine this relationship, the positive and negative effects of different fats and fatty acids in the diet should be examined (23). Indeed, most studies have been performed on the role of diet in the expression of the caveolin gene in animals. According to such studies, caveolin can be influenced and regulated by obesity and diet (24). Fat consumption is known to impact adipose tissue (25). Moreover, in order to evaluate the quality of dietary fat, several indicators can be used, including cholesterol-saturated fat index (CSI) (26) and W6/W3 ratio (27).

This study sought to investigate the interaction between the quality of dietary fat intake and the CAV-1 gene and their relationship with visceral adiposity index and body adiposity index.

2. Methods And Materials

2.1. Participants

A total of 386 women, aged 18-48 years old, were randomly selected from among participants in a cross-sectional study performed in 2016-2017. The inclusion criteria were: obese or overweight (BMI > 25 kg/m²), no alcohol consumption, and no smoking. Women with CVD, kidney failure, stroke, thyroid disease, liver disease, cancer, inflammatory illnesses, and those taking any therapeutic medications and

weight loss supplements, or any supplements that affect weight, were excluded from the study. Pregnant and menopausal women and those who reported a total daily energy intake outside of 800- 4200 kcal (3344- 17556 kJ) were also excluded from the study. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences (TUMS) with the following identification: IR.TUMS.VCR.REC.1397.920. All methods were carried out in accordance with relevant guidelines. All participants of study completed a written informed consent.

2.2. Measurement of biochemical parameters

All blood samples were collected at the Nutrition and Biochemistry laboratory of the School of Nutritional Sciences and Dietetics, TUMS. Serum triglycerides (TG) concentrations were assayed with triacylglycerol kits (Pars Azmoon Inc, Tehran, Iran) by using enzymatic colorimetric tests with Glycerol-3-phosphate oxidase Phenol 4-Aminoantipyrine Peroxidase (GPO-PAP). Total cholesterol (total-chol) levels were measured by the cholesterol oxidase Phenol 4-Aminoantipyrine Peroxidase (CHOD-PAP), and low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured by the direct method and immune inhibition.

2.3. Assessment of anthropometric measures

Weight was measured with digital scales and recorded to the nearest 100 g while the subjects were minimally clothed and unshod. Height was measured using a tape measure while the subjects were standing, unshod, and had shoulders in a normal position. BMI was calculated by dividing the weight by the square of the height, waist circumference (WC) was measured at the narrowest part of the abdomen, HC was measured as the maximum circumference over the buttocks, and the minimal circumference was recorded to the nearest 0.1 cm. To reduce error, all measurements were taken by the same technician. For measuring the fat distribution, we used BAI and VAI (for women) with the following formulas:

- BAI was calculated using the following formula (9):

$$BAI = \frac{\text{Hip Circumference (cm)}}{\text{height (m)}^{1.5}} - 18$$

- VAI was calculated using the formula (10):

$$\text{Women: VAI} = \left(\frac{\text{Waist Circumference (cm)}}{36.58 + (1.89 \times BMI)} \right) \times \left(\frac{TG}{0.81} \right) \times \left(\frac{1.52}{HDL} \right)$$

2.4. Assessment of dietary intake

To evaluate the dietary intake of participants, we used a 147-item semi-quantitative FFQ, with high validity and reliability (28), during face-to-face interviewing. The extracted FFQ values were then changed to grams/day. For the evaluation of macro-and micronutrient content, N4 software was used.

2.5. Measurement of Fat quality indices

Fat quality indices include CSI and W6/W3 ratio which are calculated through their respective formulas.

- CSI: Indicates the state of cholesterol and saturated fats, which helps a person in self-care against the state of cholesterol (26).

$$CSI = \frac{\text{Cholesterol}}{\text{Saturated fat}}$$

- w-6/w-3 ratio: Omega 6/Omega 3 are two essential fats that are categorized as PUFAs. The total amount of omega-6s and omega-3s are divided by each other to get a ratio (27).

$$W - 6 / W - 3 \text{ Ratio} = \frac{\sum \omega - 6}{\sum \omega - 3}$$

2.6. Genotyping

For genotyping the Cav-1 polymorphisms, DNA was extracted from whole blood via a Mini Columns kit (Type G; Genall; Exgene). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was employed to investigate Cav-1 polymorphisms (rs3807992) in gene fragments (major allele G and minor allele A). PCR was carried out using the following primers:

F:3'AGTATTGACCTGATTTGCCATG5'R:5'GTCTTCTGGAAAAAGCACATGA-3', according to previous study (29). We gave risk allele genotypes GG, AG, and AA the values 2, 1, and 0.

2.7. Assessment of other variables

We assessed the physical activity of the participants with a validated International Physical Activity Questionnaire (IPAQ) (30). According to IPAQ scoring protocol, the participants were divided into 3 categories of physical activity: (1) low active (<600 MET- min/week); (2) moderate active ($\geq$ 600 MET- min/week); and (3) high active ($\geq$ 3000 MET- min/week) (31). We also designed and used a standard

socio-economic demographic questionnaire to collect general background information, including education, and marital status.

2.8. Statistical Analysis

Statistical analysis was performed using SPSS v.25 software (SPSS Inc., IL, USA) and the significance level was, *a priori*, considered $P \leq 0.05$, while $P=0.06$ was considered as marginally significant. There were no missing values in the analysis. Our data followed a normal distribution, which was confirmed using the Kolmogorov-Smirnov test. All data were expressed as means and standard deviation (SD), and categorical variables were expressed as numbers and percentages. The Pearson's chi-square test was used for categorical variables and to determine the Hardy-Weinberg Equilibrium. One-way analysis of variance (ANOVA) was used to evaluate the association between dietary intake indices, anthropometric parameters, and biochemical parameters, and analysis of covariance (ANCOVA) was used to evaluate and control for confounders. BMI consider as collinear variable for anthropometrics and body composition variables, these variables control with energy intake, age and, physical activity. To investigate the mean differences between groups, post-hoc multiple comparison analysis (Bonferroni corrected), was used. To estimate interactions between CAV-1 genotypes and VAI and BAI, we used a generalized linear model, conducting a crude and adjusted model, where we controlled several potential cofounders (age, energy intake, physical activity, education). The reference group was genotype without risk allele (GG).

3. Result

3.1. Study population characteristics

A total of 386 overweight and obese women were evaluated in this study. The participant characteristics were: age 36.67 (9.10) years, BMI 31.26 (4.29) kg/m², VAI 2.48 (2.13), BAI 29.58 (7.62), CSI 9.74 (3.43), and W6/W3 ratio 12.65 (0.10). Among the participants, 286 (70.8%) women were married and 110 (27.2%) had a good economic status. The overall prevalence of CAV-1 genotypes in the study was 50% (193), 23.3% (90), and 25.5% (103) for AA, AG, and AA respectively.

3.2. Baseline characteristics of study participants among the CAV-1 genotypes

The baseline characteristics of study participants, categorized according to the CAV-1 genotypes, are presented in **Table 1**. As shown in this table, P-values for all variables were reported before the adjustment in the crude model, and after adjustment with potential confounders including age, physical activity, energy intake, and BMI. BMI was considered as collinear for anthropometrics and body composition variables. In the crude model, there was a significant mean difference among the study participants in terms of BMI ($P=0.01$), diastolic blood pressure (DBP) ($P=0.02$), HDL ($P=0.001$), LDL ($P=0.03$), and VAI ($P=0.006$). After adjustment with potential cofounders, the mean difference became marginally significant in the WHR and BAI of participants. The mean difference of HDL and VAI remained

significant in the adjusted model. According to Bonferroni post-hoc testing, the mean difference in WHR, VAI, and HDL was between AA and GG genotype groups, such that the mean was higher in AG genotype for WHR and VAI, and for HDL was higher in GG genotype; while, in BAI, there was a difference between AA and AG genotypes, such that in the AG genotype was higher. In categorical variables, a significant mean difference among the participants was seen in terms of their education status after controlling for cofounders. There was no significant difference in terms of other variables in **Table 1**.

Table1. Baseline characteristics of study participants categorized according to the Cav-1 genotypes in obese and overweight women (n=386)					
Variables	CAV-1 genotypes				
	GG (N=193)	AG (N=90)	AA (N=101)	P-value	P-value*
	Mean ± SD				
Demographic characteristics					
Age(Y)	37.56 ± 9.49	35.85 ± 8.91	35.67 ± 8.71	0.15	0.33
Onset of obesity(Y)	23.04 ± 10.02	23.76 ± 9.04	22.59 ± 8.41	0.72	0.19
Physical activity(MET/h)	1215.46 ± 2033.81	1379.12 ± 2823.33	1073.74 ± 1761.48	0.74	0.77
Anthropometric Measurements					
Weight(kg)	79.71 ± 10.91	81.10 ± 12.24	83.01 ± 14.05	0.08	0.38
Height(cm)	161.30 ± 6.08	161.27 ± 5.34	160.68 ± 5.80	0.66	0.80
WC(cm)	96.61 ± 15.20	95.57 ± 18.23	100.26 ± 12.01	0.16	0.25
HC(cm)	113.59 ± 9.49	111.44 ± 6.76	116.10 ± 11.07	0.09	0.07
BMI(kg/m ²)	30.68 ± 4.02	31.06 ± 4.06	32.19 ± 4.75	0.01	0.07
WHR	0.93 ± 0.05 ^b	1.94 ± 9.59 ^b	0.94 ± 0.05	0.19	0.06
BAI	29.35 ± 7.94	28.57 ± 8.72 ^a	30.96 ± 5.80 ^a	0.18	0.06
VAI	2.13 ± 1.24 ^b	3.27 ± 3.47 ^b	2.62 ± 2.05	0.006	0.006
Blood pressure					
SBP (mm Hg)	109.60 ± 15.05	113.05 ± 17.98	112.79 ± 12.04	0.19	0.78
DBP (mm Hg)	75.87 ± 10.77	79.45 ± 11.63	79.22 ± 8.85	0.02	0.47
Biochemical variables					
FBS (mg/dL)	87.98 ± 9.62	87 ± 11.39	86.91 ± 8.46	0.70	0.74
TC (mg/dL)	186.76 ± 33.74	187.58 ± 44.95	179.21 ± 30.67	0.29	0.27
TG (mg/dL)	113.11 ± 51.20	126.77 ± 61.42	123.90 ± 70.50	0.28	0.21
HDL (mg/dL)	49.07 ± 11.16 ^b	42.84 ± 11.39 ^b	44.90 ± 9.17	0.001	0.03
LDL (mg/dL)	98.88 ± 22.66	89.49 ± 26.45	92.54 ± 24.13	0.03	0.08
GOT (U/L)	18.27 ± 7.44	17.96 ± 7.03	17.95 ± 9.13	0.95	0.53

Table1. Baseline characteristics of study participants categorized according to the Cav-1 genotypes in obese and overweight women (n=386)					
GPT (U/L)	19.04 ± 13.95	19.35 ± 11.66	20.71 ± 15.81	0.71	0.61
Supplements intake				0.18	0.83
Yes	87 (57.6%)	27 (17.9%)	37 (24.5%)		
No	83 (47.7%)	42(24.1%)	49(28.2%)		
Marital status				0.98	0.20
Single	55(51.4)	24(22.4)	28(26.2)		
Married	137(50.6)	63(23.2)	71(26.2)		
Education status				0.17	0.009
Illiterate	1(25)	2(50)	1(25)		
Under diploma	20(41.7)	12(25)	16(33.3)		
Diploma	68(46.6)	33(22.6)	45(30.8)		
Bachelor and higher than	103(57.2)	40(22.2)	37(20.6)		
Economic status				0.20	0.23
Poor	39(45.3)	19(22.1)	28(32.6)		
Moderate	83(47.4)	46(26.3)	46(26.3)		
Good	62(59)	19(18.1)	24(22.9)		
Family history of obesity				0.55	0.15
Yes	129(51.2)	56(22.2)	67(26.6)		
No	48(45.3)	28(26.4)	30(28.3)		

Table1. Baseline characteristics of study participants categorized according to the Cav-1 genotypes in obese and overweight women (n=386)

SD: Standard Deviation, IPAQ: International Physical Activity Questionnaire, WC: Waist Circumference, BAI: Body Adiposity Index, VAI: Visceral Adiposity Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, GOT: Glutamic Oxaloacetic Transaminase, GPT: Glutamate Pyruvate Transaminase, BMI: Body Mass Index, HC: Hip Circumference, WHR: Waist-to-Hip Ratio, TC: Total cholesterol

Values are represented as means $\pm$ SD. BMI is collinear.

Categorical variables: N(%)

Independent T test (P value) was performed to identify significant differences between Cav-1 genotypes in crude model

ANCOVA (P value*) was performed to adjusted potential confounding factors (age, energy intake, Physical activity, BMI)

BMI consider as collinear variable for anthropometrics and body composition variables, these variables control with energy intake, age and, physical activity

p-values <0.05 were considered as significant.

^a The significant difference was seen between AA and AG

^b The significant difference was seen between GG and AG

3.3 Dietary intakes of all subjects according to CAV-1 genotypes in obese and overweight women

Dietary intakes of all subjects according to CAV-1 genotypes in obese and overweight women are presented in **Table 2**. Regarding fat components of foods, no significant difference was found .in crude and adjusted models. The result was the same for macronutrients and energy, with no significant difference in the crude and adjusted models. According to micronutrients, there was no significant difference among participants in the crude model. But after adjustment for energy intake, mean differences in Biotin (P=0.04) and total fiber (P=0.06) were significant and marginally significant, respectively. There was no significant difference in terms of other variables in **Table 2**.

Table2. Dietary food intakes of all subjects according to Cav-1 genotypes in obese and overweight women (n=386)					
Variables	GG (n=193)	AG (n=90)	AA (n=101)	P-value	P-value ^a
	Mean±SD				
Fat Components of foods					
Cholesterol (g/d)	259.32 ± 8.95	256.24 ± 13.73	242.17 ± 12.18	0.51	0.26
Saturated Fats (mg/d)	28.55 ± 0.94	28.19 ± 1.45	27.12 ± 1.28	0.66	0.23
MUFA (mg/d)	31.50 ± 0.95	31.35 ± 1.46	31.01 ± 1.30	0.95	0.73
PUFA (mg/d)	19.99 ± 0.72	20.14 ± 1.10	20.29 ± 0.98	0.96	0.99
Linoleic acid (mg/d)	17.28 ± 0.68	17.38 ± 1.05	17.53 ± 0.93	0.97	0.99
Linolenic acid (mg/d)	1.20 ± 0.05	1.30 ± 0.08	1.23 ± 0.07	0.60	0.62
EPA (mg/d)	0.03 ± 0.003	0.03 ± 0.005	0.03 ± 0.00	0.61	0.63
DHA (mg/d)	0.10 ± 0.01	0.10 ± 0.01	0.12 ± 0.01	0.56	0.59
Trans fats (mg/d)	0.001	0	0.001	0.08	0.07
CSI	9.49 ± 0.26	9.50 ± 0.40	9.36 ± 0.35	0.95	0.96
W6/W3	12.65 ± 0.009	12.64 ± 0.01	12.64 ± 0.01	0.95	0.17
Macronutrients and Energy					
Energy(Kcal)	2621.64 ± 721.37	2597.22 ± 723.78	2677.85 ± 858.75	0.84	-
Carbohydrate (gr/day)	370.78 ± 10.29	374.19 ± 15.79	379.33 ± 14.01	0.88	0.84
Protein (g/d)	88.49 ± 2.43	90.42 ± 3.73	88.32 ± 3.31	0.89	0.73
Total fat (gr/day)	94.10 ± 2.71	95.89 ± 4.16	93.89 ± 3.69	0.92	0.77
Micronutrients					
Sodium (mg/d)	4200.47 ± 121.13	4406.56 ± 185.93	4237.80 ± 164.91	0.64	0.59
Potassium (mg/d)	4360.21 ± 131.69	4449.45 ± 202.13	4143.65 ± 179.28	0.44	0.07
Vitamin A(RAE) (mg/d)	801.97 ± 34.99	753.84 ± 53.71	764.69 ± 47.64	0.69	0.51

Table2. Dietary food intakes of all subjects according to Cav-1 genotypes in obese and overweight women (n=386)					
Beta carotene (mg/d)	5490.89 ± 303.02	5219.52 ± 465.11	4940.81 ± 412.53	0.55	0.45
Vitamin C (mg/d)	197.04 ± 10.81	194.27 ± 16.59	197.43 ± 14.71	0.98	0.94
Calcium (mg/d)	1161.14 ± 35.38	1184.05 ± 54.31	1156.44 ± 48.17	0.92	0.83
Iron (mcg/d)	18.65 ± 0.50	18.46 ± 0.77	19.02 ± 0.68	0.85	0.51
Vitamin D (ug/d)	2.01 ± 0.13	2.05 ± 0.21	1.92 ± 0.19	0.88	0.83
Vitamin E (mg/d)	17.61 ± 0.77	16.84 ± 1.19	17.63 ± 1.05	0.84	0.78
Thiamin (mg/d)	2.04 ± 0.05	2.08 ± 0.08	2.17 ± 0.07	0.37	0.12
Riboflavin (mg/d)	2.20 ± 0.06	2.21 ± 0.10	2.21 ± 0.09	0.99	0.95
Niacin (mg/d)	25.21 ± 0.78	25.24 ± 1.20	25.77 ± 1.06	0.90	0.89
Vitamin B6 (mg/d)	2.18 ± 1.06	2.22 ± 0.09	2.10 ± 0.08	0.60	0.16
Total Folate (µg/d)	603.19 ± 15.003	608.42 ± 23.02	621.79 ± 20.42	0.76	0.73
Vitamin B12 (mcg/d)	4.26 ± 0.20	4.37 ± 0.31	4.54 ± 0.28	0.72	0.78
Biotin (mcg/d)	39.70 ± 1.43	39.03 ± 2.20	35.26 ± 1.95	0.17	0.04
Pantothenic acid (mg/d)	6.56 ± 0.20	6.63 ± 0.31	6.28 ± 0.27	0.63	0.27
Vitamin K (mcg/d)	228.18 ± 16.61	201.62 ± 25.49	196.37 ± 22.61	0.45	0.41
Phosphor (mg/d)	1644.12 ± 43.89	1667.96 ± 67.37	1606.34 ± 59.76	0.78	0.30
Magnesium (mg/d)	464.57 ± 12.53	463.81 ± 19.23	445.40 ± 17.05	0.64	0.10
Zinc (mg/d)	12.94 ± 0.35	13.13 ± 0.54	12.75 ± 0.48	0.87	0.45
Copper (mcg/d)	2.01 ± 0.06	1.95 ± 0.09	2.03 ± 0.08	0.83	0.48
Manganese (mg/d)	7.02 ± 0.24	7.40 ± 0.36	6.92 ± 0.32	0.58	0.46
Selenium (mcg/d)	119.26 ± 3.61	121.68 ± 5.55	120.58 ± 4.92	0.93	0.96
Chromium (mg/d)	0.11 ± 0.007	0.11 ± 0.01	0.10 ± 0.01	0.77	0.69
Total fiber (g/d)	44.55 ± 1.59	43.17 ± 2.44	48.95 ± 2.17	0.15	0.06
Caffeine (mg/d)	145.83 ± 13.10	177.69 ± 20.12	141.93 ± 17.84	0.33	0.34

Table2. Dietary food intakes of all subjects according to Cav-1 genotypes in obese and overweight women (n=386)

SD: Standard Deviation, MUFA: Monounsaturated Fatty Acid, PUFA: Polyunsaturated Fatty acid, EPA: Eicosapentaenoic Acid, DHA: Docosahexaenoic Acid, CSI: Cholesterol-Saturated Fat Index.

Values are represented as means $\pm$ SD.

Independent T test (P value) was performed to identify significant differences between Cav-1 genotypes in crude model

ANCOVA (P value*) was performed to adjusted potential confounding factors (energy intake)

p-values <0.05 were considered as significant

3.4. The association of genotype variant of CAV-1 with BAI and VAI in crude and adjusted Linear Regression Models in overweight and obese women

The association of genotype variant of CAV-1 with BAI and VAI in the crude and adjusted linear regression model are presented in **Table 3**. After controlling for the potential cofounders (age, energy intake, physical activity), in comparison to reference group (GG), there was a marginally significant positive association between the AA genotype and BAI ($\beta = 0.94$, 95%CI= 0.006,4.33, $P=0.06$). A positive association between AG genotype and VAI, in comparison to reference group (GG), was observed in the crude model ($\beta = 67.77$, 95%CI= 26.06, 109.48, $P=0.001$). On the other hand, after adjusting for cofounders (age, energy intake, physical activity), a positive association was found in comparison to reference group (GG) for the AA and AG genotypes with VAI ($\beta = 42.12$, 95%CI= -2.74,86.98, $P= 0.06$), ($\beta = 84.12$, 95%CI= 32.16,136.07, $P= 0.002$), respectively.

Table3. association of genotype variant of Cav-1 with BAI and VAI in crude and adjusted Linear Regression Models in overweight and obese women (n=386)					
Variables	Model	Genotypes	B	95% CI	P-value
BAI	Crude	AA	1.60	-0.61, 3.81	0.15
		AG	-0.78	-3.04, 1.47	0.49
	Adjusted	AA	0.94	0.006, 4.33	0.06
		AG	-2.06	-5.89, 1.76	0.29
VAI	Crude	AA	32.19	-5.77, 70.16	0.09
		AG	67.77	26.06, 109.48	0.001
	Adjusted	AA	42.12	-2.74, 86.98	0.06
		AG	84.12	32.16, 136.07	0.002
CI: Confidence Interval, BAI: Body Adiposity Index, VAI: Visceral Adiposity Index					
Comparisons between groups were determined based on logistic regression analysis					
Generalized linear model Adjusted (age, energy intake, Physical activity, education)					
GG consider as reference group					

3.5. Interactions between CAV-1 genotypes and CSI on BAI and VAI in overweight and obese women

The interaction of CAV-1 genotypes with CSI on BAI and VAI in the crude and adjusted model are presented in **Table 4**. In the crude model, in terms of BAI, there was a negative interaction between two risk allele risk (AG) with CSI ($\beta = -0.30$, 95%CI= -0.99,0.37, $P = 0.38$) in comparison to the reference group (GG), and after controlling for potential cofounders (age, physical activity, energy intake, education), this interaction remained negative between AG and CSI ($\beta = -0.58$, 95%CI= -1.67,0.50, $P = 0.29$). For VAI, a positive interaction was observed between two risk allele (AA) with CSI in the crude and adjusted model, in comparison to reference group (GG) ($\beta = 0.11$, 95%CI= -0.09,0.31, $P = 0.28$), ($\beta = 0.11$, 95%CI= 0.11,0.34, $P = 0.04$), respectively (Figure 1).

Table 4. Interactions between Cav-1 genotypes and dietary fat quality indices in overweight and obese women (n=386)			
Interaction type	B	(95%) CI	P-value
BAI			
Crude			
AA*CSI	-0.16	-0.64, 0.61	0.96
AG*CSI	-0.30	-0.99, 0.37	0.38
Adjusted			
AA*CSI	-0.36	-1.41, 0.68	0.49
AG*CSI	-0.58	-1.67, 0.50	0.29
BAI			
Crude			
AA*W6/W3	4.03	-22.02, 30.09	0.76
AG*W6/W3	-6.45	-37.63, 24.73	0.68
Adjusted			
AA*W6/W3	14.08	18.65, 46.81	0.07
AG*W6/W3	-12.91	-52.43, 26.61	0.52
VAI			
Crude			
AA*CSI	0.11	-0.09, 0.31	0.28
AG*CSI	-0.09	-0.31, 0.12	0.37
Adjusted			
AA*CSI	0.11	0.11, 0.34	0.04
AG*CSI	-0.06	-0.32, 0.19	0.62
VAI			
Crude			
AA*W6/W3	2.04	-4.01, 8.11	0.50
AG*W6/W3	-3.76	-10.81, 3.29	0.29
Adjusted			

Table 4. Interactions between Cav-1 genotypes and dietary fat quality indices in overweight and obese women (n=386)			
AA*W6/W3	2.81	1.20, 8.84	0.06
AG*W6/W3	-5.66	-14.79, 3.46	0.22
CI: Confidence Interval, BAI: Body Adiposity Index, VAI: Visceral Adiposity Index, CSI: Cholesterol-Saturated fat Index			
P value with unadjusted (crude)			
P value with adjustments for potential confounding factors including (Age, Physical activity, energy intake, education)			

3.5.1. Interactions between CAV-1 genotypes and W6/W3 ratio on BAI and VAI in overweight and obese women

In the crude model, the interaction between one risk allele group (AG) with W6/W3 ratio on BAI, in comparison to reference group (GG), was negative, but not significant ($\beta = -6.45$, 95%CI= -37.63,24.73, $P = 0.68$), and the interaction between two risk allele genotype group (AA) with W6/W3 ratio on BAI after adjustment with potential cofounders (age, physical activity, energy intake, education) was marginally positive ($\beta = 14.08$, 95%CI= -18.65,46.81, $P = 0.07$) (Figure 2). In terms of VAI, in comparison to reference group (GG), there was a positive interaction between two risk allele (AA) with W6/W3 ratio ($\beta = 2.81$, 95%CI= 1.20,8.84, $P = 0.06$) in the adjusted model (Figure 3).

4. Discussion

To our knowledge, this cross-sectional study is the first study to have investigated the interaction between CAV-1 genotypes and dietary fat quality indices on VAI and BAI among overweight and obese women. Accordingly, our results showed that there may be an interaction between CAV-1 genotypes and dietary fat quality indices (CSI, W6/W3 ratio) on BAI and VAI in overweight and obese women.

We found that the interaction of increased adherence to W6/W3 ratio consumption with AA carriers of CAV-1 was positive on VAI and BAI, additionally, we noted a positive interaction between CSI with AA risk allele on VAI. To our knowledge, no study has been conducted directly on this subject, but according to some related studies, CAV-1 may have a direct impact on the regulation of HDL, TG, and cholesterol, and in general, CAV-1 impacts on fatty acid metabolism (21, 32, 33). In another study, the CAV-1 expression was decreased in adipocytes of obese subjects (34). An animal study showed that consumption of a high-cholesterol diet can affect the expression of CAV-1 (22). We found that the AA risk allele group of CAV-1 has higher BAI than other groups, whilst in terms of VAI, the AG genotype group was higher than others. BAI and VAI represent novel indicators of obesity that have been scarcely studied (35, 36). Female AA allele risk had a significantly higher BMI compared to the reference group (GG), which is consistent

with previous studies (29). According to Catalan et al, CAV-1 expression in visceral adipose tissue and subcutaneous adipose tissue is associated positively BMI and body fat (32).

According to our results, females with the AG risk allele have higher WHR and DBP values in comparison to the GG group, whilst the value of HDL and LDL was higher in the reference group (GG). As previously mentioned, CAV-1 has a critical role in lipid homeostasis, which can affect adipose tissue, blood vessels, and liver, to alter the regulation of TG, cholesterol, VLDL, and HDL (33). However, our results did not show any significant difference in macronutrients, energy, and fat components of foods of subjects, with the only difference found in biotin and total fiber.

Caveolae are formed from lipid rafts and contain cholesterol, glycosphingolipids, and CAV-1 (37), and can elicit an uptake of lipid metabolites, including several fatty acid species, triacylglycerol, and cholesterol, (38–40). The roles of CAV-1 are variegated, with its' most important functions in cholesterol homeostasis, signal transduction, cellular and systemic lipid metabolism, and regulation of lipid and lipoprotein metabolism (32, 33, 41). CAV-1 expressed in different parts of the body, such as fibroblasts, epithelial, and endothelial cells, and also in adipocytes (42). It is interesting that the CAV-1 works as an element in lipid droplets and can effect lipid droplet accumulation and breakdown (43). According to Chang et al, a high-fat diet causes CAV-1 to be secreted more in adipose tissue in comparison to a normal diet in mice, therefore, adipose tissue may be considered the main source of CAV-1 secretion (44). Razani et al found that CAV-1 in adipocyte and endothelial cells has an effect on obesity, mediated by diet (45). Moreover, some studies have shown that CAV-1 acts as a tumor suppressing protein by inhibiting the functional signaling activity of several mutated genes, and thus disrupts the cell transformation process (46–54). The mechanism by which CAV-1 acts as a tumor suppressor remains under investigation, however, may putatively be because CAV-1 is a scaffolding protein and interacts with and regulates signaling pathways, in addition to a possibility that this protein may regulate proto-oncogenes (12). Moreover, cytokines like TNF-A and IL-1B can effect CAV-1 mRNA expression (55).

CAV-1 is involved in lipogenesis and adipogenic processes as CAV-1 mRNA (56)., and CAV-1 can functionally suppress transforming growth factor-beta (TGF- β) by modifying the phosphorylation state of SMAD. Another potential mechanism is that the interaction between CAV-1 with transforming growth factor-beta type 1 receptor (T α R-1) may influence TGF- β inhibition (55). Further, CAV-1 can impact cytokine signaling by interactions with the janus kinase (JAK) family, cytokine receptors, and the proteasome pathway (15, 57).

There are several limitations in the present study that must considered when interpreting out findings. This study was a cross-sectional study, thereby precluding causal inferences being drawn. Next, the sample size used to conduct this study was small, and we used a FFQ to investigate the intakes of subjects, which, given its' self-reported nature, may be influenced by recall bias. Furthermore, this study was conducted only on women, so that results may not generalized to all sexes. Nevertheless, despite the noted limitations, our study has numerous strengths, including; this is, to our knowledge, the first study to have investigated the interaction between CAV-1 genotypes with dietary fat quality indices on VAI and BAI

among overweight and obese women, moreover, we used detailed genetic factors in the study. Further, since we conducted this study on women only, greater specificity and insight maybe gleaned.

5. Conclusion

Based on the findings of the present study, it appears that there may be an interaction between CAV-1 genotypes with dietary quality fat indices and an association with VAI and BAI among overweight and obese women. Two risk allele (AA) significantly interacted with CSI and W6/W3 ratio consumption, and impacted on BAI and VAI. Nevertheless, we recommend that more studies be done in this area to confirm the veracity of our findings.

Abbreviations

BAI: body adiposity index; **BMI**: body mass index; **CAV-1**: caveolin-1; **CI**: confidence interval; **CSI**: Cholesterol-saturated fat index; **CVDs**: cardiovascular diseases; **DBP**: diastolic blood pressure; **DNA**: deoxyribonucleic acid; **FFQ**: food frequency questionnaire; **HC**: hip circumference; **HDL**: high-density lipoprotein; **IL-1 β** : Interleukin 1 beta; **IPAQ**: international physical activity questionnaire; **JAK**: janus kinase; **LDL**: low-density lipoprotein; **MET**: metabolic equivalent of task; **mRNA**: messenger ribonucleic; **PUFA**: polyunsaturated fatty acid; **SD**: standard deviation; **TG**: triglyceride; **TGF- β** : transforming growth factor beta; **TNF- α** : tumor necrosis factor alpha; **T β R-1**: transforming growth factor-beta type 1 receptor; **VAI**: visceral adiposity index; **WC**: waist circumference; **WHR**: waist-to-hip ratio; **W6/W3**: omega-6 to omega-3 ratio.

Declarations

Authors' Contributions

The project was designed and wrote by RGE and KhM. Data were analyzed by FS. Data were collected by AM, and CC proofread the manuscript for native English writing. All authors read and approved the final manuscript.

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Competing interests

The authors express that they have no competing interests.

Availability of data and materials

The data that confirm the findings of this study are available from Khadijeh Mirzaei Data are available from the authors upon reasonable request and with permission of Khadijeh Mirzaei.

Consent for publication

Informed written consent for the publication of information or other personal information was obtained from all study participants.

Ethics approval and consent to participate

Ethics approval for the study protocol was confirmed by The Human Ethics Committee of Tehran University of Medical Sciences (TUMS) with the following identification:

IR.TUMS.VCR.REC.1397.920. All participants signed a written informed consent that was approved by the Ethics committee.

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Figures

Figure 1

Interaction between CAV-1 genotypes (GG as the reference group) and CSI intake on VAI. VAI (The P-value for AA genotype: 0.61; P-value for CSI intake: 0.99; P-value for interaction between AA genotype and CSI intake: 0.28)

Figure 2

Interaction between CAV-1 genotypes (GG as the reference group) and W6/W3 intake on BAI. VAI (The P-value for AA genotype: 0.76; P-value for W6/W3 intake: 0.52; P-value for interaction between AA genotype and W6/W3 intake: 0.76)

Figure 3

Interaction between CAV-1 genotypes (GG as the reference group) and W6/W3 intake on VAI. VAI (The P-value for AA genotype: 0.51; P-value for W6/W3 intake: 0.80; P-value for interaction between AA genotype and W6/W3 intake: 0.50)