Interactions between Caveolin 1 polymorphism and the Mediterranean and Mediterranean-DASH Intervention for Neurodegenerative Delay diet (MIND) diet on Metabolic dyslipidemia in overweight and obese adult women: a cross-sectional study

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Research note

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Abstract

Objective: A higher incidence of metabolic dyslipidemia (MD) and its association with many diseases attracted considerable attention to its control. Caveolin 1 (CAV1) is a known gene associated with obesity. Today, a novel diet recognized as the Mediterranean and Mediterranean-DASH Intervention for Neurodegenerative Delay diet (MIND(is reported to have a positive effect on overall health. Hence, we aimed to investigate the interactions between CAV1 polymorphism and MIND diet on the MD in overweight and obese patients.

Results: Remarkably, there was a significant interaction between the MIND diet and CAV1 rs3807992 for dyslipidemia (β=-0.25±132, P=0.05) in the crude model. Whereby, subjects with dominant alleles had a lower risk of dyslipidemia and risk allele carriers with higher adherence to MIND diet may exhibit the lower dyslipidemia.This study presented the CAV1 gene as a possible genetic marker in recognizing people at higher risks for metabolic diseases. It also indicated that using the MIND diet may help in improving dyslipidemia through providing a probable interaction with CAV1 rs3807992 polymorphism.

Introduction

The changing prevalence of dyslipidemia in developed societies is a complex problem that has a contribution to the incidence of various diseases [1]. Some concerns exist regarding “Metabolic dyslipidemia” (MD), with high triglyceride and low levels of high-density lipoprotein (HDL) cholesterol, which is associated with an elevated risk of Coronary heart disease (CHD) [2, 3]. Dyslipidemia is a significant primary risk factor for atherosclerosis, which is considerably prevalent in Iran. Moreover, People with central obesity and diabetes have a greater susceptibility to dyslipidemia [4].

The gene, lifestyle, and dietary patterns are important factors that contribute to the risk of MD in people [5]. In this manner, genetically related investigations have examined cases linked to complex diseases related to dyslipidemia from various populations [6, 7]. Caveolin (CAV1) is capable of regulating different signal differences as well as controlling the homeostasis of cholesterol [8].It is associated with cholesterol release and risk factors of dyslipidemia [9].

The content of dietary patterns important as controlling factors linked to the risk of dyslipidemia. Hence, several investigations examined diets related to the concentrations of blood lipids [10]. In this case, some studies have investigated the interplays between Dietary Approaches to Stop Hypertension (DASH) diet and Mediterranean diet with Dyslipidemia separately. It should be noted that high intakes of saturated fatty acids and unhealthful styles positively influence MD, and the DASH diet is reported to have inverse associations with blood lipid concentrations [11]. A review on the correlation between dietary patterns and dyslipidemia also found that the DASH diet containing higher intakes of whole grains, fruits, vegetables, low-fat dairy products, fish, poultry, and nuts, as well as low intakes of, red meat, sodium, candy, and sugar-containing drinks reduce the risk of MD [12]. The Mediterranean and Mediterranean-

DASH Intervention for Neurodegenerative Delay diet (MIND(diet ingredients are replete with antioxidants that improve heart health and mitigate Hypertension (HTN) risk [13].

Furthermore, another study examined the main role of the CAV gene in developing cardiovascular disease with an effect on lipid factors and reported significant associations [14].

Hence, the present study intended to investigate the interaction between Mind diet with the CAV1 gene in association with MD. This study is the first to investigate the combination of DASH and Mediterranean diet with CAV1 genotypes. However, no published work is available about the interaction between CAV1 polymorphism and MIND diet MD.

Material And Methods

Study population

In the present cross-sectional research, a random selection of referral patients was performed from health centers in Tehran, Iran. This study was approved by the Ethics Commission of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1398.142).Subjects included healthful overweight and non-menopause women aged over 18 years on average, with a BMI ranging from 25 to 40 kg/m^2.

Participates in having an acute or chronic inflammatory disease or using medication such as birth control tablets regularly, with records of hypertension, cardiovascular disease, diabetes mellitus, disordered kidney, and hepatic functions, consuming alcohol or substance misuse, smokers, thyroid disease, malignant states, gestation, lactating, and menopause and participation whose reported daily energy intakes were 800–4200 kcal/day lactating women were excluded.

Biochemical assessment

All blood samples were collected at 8:00 to 10:00 A.M. after having an 8–12 h fasting state at the EMRC laboratory of Shariati hospital of TUMS .

On the same day of blood collection, fasting blood sugar (FBS), triglycerides (TG), total cholesterol level, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) was measured according to standard protocols .All of which were measured at the bio nanotechnology laboratory, Tehran University of Medical Science.

Anthropometric measurement

The anthropometric indices were measured for all participants. Weight (kg), Height(m) and waist circumference (WC,cm) and the waist-to-hip ratio (WHR) was measured. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Respectively the researchers assessed the body composition of all cases with the use of Body Composition Analyzer BC-418MA- In Body (United Kingdom).

The device calculates body fat percentage, fat mass, and fat-free mass (FFM) and predicts muscle mass based on data obtained by dual-energy X-ray absorptiometry (DXA) using bioelectrical impedance analysis

Dietary assessment

The diet scores were estimated using a semi-quantitative FFQ including a list of 147 food items this questionnaire has well-established reliability and validity specifically for Iranian adults.[15, 16], Domestic measurements and servings underwent conversion into weight (g day $^{-1}$), followed by converting food items to 18 food groups to extract dietetic models[17].

The software program, Nutritionist IV, was used for nutrient analysis and was modified for Iranian foods. A MIND diet score using the methodology described by Morris et al, focusing on 15 components. There was a maximum of 15 points, higher intake of brain-healthy food groups, was scored 0, 0.5, or 1 point depending on the level of consumption, while for unhealthy food groups the scoring was reversed [18].

Assessment of other variables

Assessment of physical activity was based on the International Physical Activity Questionnaire (IPAQ).

Low HDL ≤ 50mg/dl and TG > 150 mg /dl indices were considered for metabolic dyslipidemia in participants[19].

DNA Extraction and Sequencing of the Gene

For DNA extraction from whole blood by the Gene All Mini Columns Type kit, 1 ml of RBC lysis solution was initially decanted into a 2 ml microtube that contained 300 µl of the blood and subjected to gentle shaking 5 times, followed by overtaxing for 10 seconds and then centrifugation at 13000 rpm for 3 min. amplification of gene region containing CAV1 polymorphism (rs3807992) with G as the major allele and A as the minor allele was conducted via the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique using the following primers:

F: 3'AGTATTGACCTGATTTGCCATG5',R: 5'GTCTTCTGGAAAAAGCACATGA-3'

The process of PCR reactions was conducted with an initial denaturation step at 94°C for 3 min followed by 40 cycles of amplification including denaturation at 94°C for 1 min, annealing at 42–50°C for 1 min, and elongation at 72°C for 2 min. Homozygous AA genotype (1 band: 213bp), heterozygous AG genotype (3 bands: 118, 95, 213 bp), and homozygous GG genotype (2 bands: 118, and 95 bp).

Statistical analysis

Normality distribution was surveyed by applying Kolmogorov–Smirnov's test. Data were analyzed by IBM SPSS version 22.0 (SPSS, Chicago, IL, USA). Quantitative variables were reported by Mean SD and qualitative variables were expressed using percentages and number. Comparison of quantitative

variables between genotypes and MIND diet was performed using one-way analysis of variance (ANOVA) and Chi-square test and the analysis of covariance ANCOVA model was performed after adjustment for age, total energy intake, BMI, and physical activity. Binary logistic regression was used for calculating the odds ratio and 95% confidence intervals (95% CI) for assessing the interaction between the MIND diet and genotypes on metabolic dyslipidemia.

Results

Study Population Characteristics

This cross-sectional study was performed on 263 Iranian women with age between 18–48 years. The means (± SD) of age and BMI of individuals were 36.67 ± 9.10 and 161.2 ± 5.87 (kg / m^2).

The frequencies of the G allele were 38%. The overall prevalence of CAV-1 rs3807992 genotypes was 25.5%, 22.3%and 47.8%for AA, AG and GG respectively (**table S1**).

The demographic, anthropomorphic, and biochemical characteristics of participants across quartiles of MIND are shown in Table 2. After adjustment for BMI, age, total energy intake, and physical activity in, there was a significant difference in fat-free mass (FFM) (P = 0.03). The individuals in the fourth quartile had higher FFM rather than the first quartile. Moreover, there is a significant association between dyslipidemia (P = 0.01) and TG (P = 0.00) across the quartiles. It is shown that individuals with dominant alleles had higher dyslipidemia and a higher level of TG. Also, there was a marginally significant difference between groups for IPAQ and skeletal muscle mass (SSM) (P = 0.06).

Table 2
Participant Characteristics consist of anthropometric measurements, and body composition, blood parameters across the quartiles of the MIND diet

variables	Q1(n = 97)	Q2 (n = 98)	Q3 (n = 98)	Q4(n = 98)	P-value	P-value*
	Mean ± SD					
Age(year)	35.52 ± 8.69	37.49 ± 9.72	36.88 ± 9.71	36.88 ± 8.67	0.49	0.48
Weight (kg)	80.82 ± 12.21	80.43 ± 13.49	81.01 ± 12.01	82.40 ± 11.31	0.69	0.27
Height(cm)	161.04 ± 5.46	161.26 ± 5.96	161.20 ± 6.00	161.08 ± 6.17	0.99	0.63
IPAC(**MET-minutes/week**)	1007.75 ± 1754.61	785.62 ± 588.73	1339.00 ± 2699.21	1541.56 ± 2468.50	0.16	0.06
Body composition						
BMI(kg/m^2)	31.29 ± 4.49	30.87 ± 4.64	31.22 ± 4.28	31.68 ± 3.77	0.62	0.35
SMM(Kg)	25.19 ± 2.99	25.44 ± 3.54	25.51 ± 3.60	26.02 ± 3.49	0.38	0.06
FFM (Kg)	45.99 ± 5.01	46.19 ± 5.74	46.57 ± 6.03	47.23 ± 5.83	0.44	**0.03**
BFM (%)	35.13 ± 9.15	34.15 ± 9.82	34.54 ± 8.55	35.09 ± 7.37	0.83	0.87
WHR (%)	1.87 ± 9.24	0.93 ± 0.04	0.94 ± 0.05	0.93 ± 0.05	0.39	0.55
WC (cm)	99.43 ± 9.87	98.63 ± 10.54	99.80 ± 10.55	100.48 ± 9.33	0.63	0.27
PBF (%)	42.66 ± 5.65	42.04 ± 5.54	42.16 ± 5.51	42.03 ± 5.36	0.83	0.30
Blood pressure						
SBP(mmHg)	108.97 ± 17.22	112.77 ± 13.26	112.62 ± 14.61	111.07 ± 14.39	0.41	0.96
DBP(mmHg)	76.37 ± 12.63	79.75 ± 9.37	77.75 ± 9.74	76.39 ± 9.62	0.17	0.35
Biochemical assessment						
FBS(**mg/dl**)	86.30 ± 9.75	87.23 ± 9.08	88.20 ± 11.09	87.97 ± 8.76	0.72	0.77
TG(mg/dl)	124.33 ± 57.90	118.65 ± 65.13	121.53 ± 58.80	93.19 ± 50.9	0.13	0.45

variables	Q1(n = 97)	Q2 (n = 98)	Q3 (n = 98)	Q4(n = 98)	P-value	P-value*
	Mean ± SD					
HDL(mg/dl)	45.03 ± 9.16	48.43 ± 10.65	45.45 ± 9.77	47.83 ± 12.66	0.22	0.38
LDL(mg/dl)	90.67 ± 22.52	97.45 ± 24.92	94.53 ± 24.12	96.54 ± 24.82	0.46	0.49
HOMA-IR	3.33 ± 1.30	3.44 ± 1.35	3.38 ± 1.28	2.91 ± 0.89	0.34	0.92
insulin (mIU/ ml)	1.24 ± 0.22	1.18 ± 0.24	1.20 ± 0.24	1.22 ± 0.20	0.50	0.76
hs.CRP(mg/l)	4.59 ± 5.10	4.16 ± 4.51	3.92 ± 4.06	4.56 ± 4.93	0.84	0.61
ALT(mg/dl)	17.67 ± 7.10	17.30 ± 7.52	17.51 ± 7.47	18.60 ± 7.39	0.73	0.36
AST(mg/dl)	19.63 ± 13.36	17.43 ± 11.80	19.65 ± 14.16	19.81 ± 12.76	0.70	0.81
Cholesterol(mg/dl)	178.55 ± 38.37	190.16 ± 33.45	181.55 ± 37.48	188.63 ± 35.59	0.24	0.57
MIND-Score quartile						
AA%	28.7%	23.8%	28.7%	18.8%	0.67	0.45
AG%	15.9%	28.0%	25.6%	30.5%		
GG%	26.8%	24.7%	22.6%	25.8%		
Dyslipidemia						
Without	85(87.6%)	73(74.5%)	71(72.4%)	60(61.2%)	**0.00**	0.01
With	12(12.4%)	25(25.5%)	27(27.6%)	38(38.8%)		
HDL(mg/dl)						
< 50	63(64.9%)	61(62.2%)	58(59.2%)	51(52.0%)	0.06	0.74
≥ 50	34(21.5%)	37(23.4%)	40(25.3%)	47(29.7%)		
TG(mg/dl)						
< 150	66(68.0%)	50(51.0%)	47(48.0%)	24(24.5%)	**0.00**	**0.00**
≥ 150	31(32.0%	48(49.0%)	51(52.0%)	74(75.5%)		
Marital status						
Single	28(25.9%)	26(24.1%)	28(25.9%)	26(25.9%)	0.59	0.90
Married	68(24.2%)	71(25.3%)	70(24.9%)	72(25.6%)		

variables	Q1(n = 97)	Q2 (n = 98)	Q3 (n = 98)	Q4(n = 98)	P-value	P-value*
	Mean ± SD					
Educational level						
Illiterate	0.0%))0	0(0.0%)	2(50.0%)	2(50.0%)	0.61	0.27
underdiploma	9(18.4%)	14(28.6%)	14(28.6%)	12(24.5%)		
College education	87(25.9%)	83(24.7%)	82(24.4%)	84(25.0%)		
Economic status						
Low	9(22.5%)	9(22.5%)	10(25.0%)	12(30.0%)	0.47	0.91
Moderate	42(25.3%)	51(30.7%)	36(21.7%)	37(22.3%)		
Good	40(26.3%)	31(20.4%)	41(27.0%)	40(26.3%)		
Excellent	4(21.1%)	4(21.1%)	7(36.8%))7	4(21.1%)		
MD:metabolic dyslipidemia: TG > 150 and HDL < 40						
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; FFM, fat-free mass; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; BMR, basal metabolic rate; TG, triacylglycerol; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressureALT: alanine transaminase,AST: aspartate transaminase, IPAC:international physical activity questionnaire ,PBF: percent body fat, BFM:body fat mass, SMM: skeletal muscle mass.						
Quantitative variables were reported with mean and SD and qualitative variables with number and percentage.						
values were calculated by ANOVA as Mean ± SD.						
Variables are presented by mean±SD for continuous variables and frequency for categorical variables						
P values resulted from the analysis of one-way ANOVA for continuous variables and chi-square test for categorical variables. Tukey test was performed to compare each genotype with other types for continuous variables.						
*P-value is found by ANCOVA and adjusted for age, BMI, physical activity, and total energy intake						

Investigation of body composition, biochemical variables, and RMRs among the CAV-1 rs3807992 genotypes

Table S3 shows the association between anthropometric body composition, biochemical parameters, and CAV-1 rs3807992 genotypes. We observed that the individuals who had GG alleles had a higher level of DBP (p = 0.02). There is also a meaningful association between genotype and two categories of TG (P = 0.01). It was seen that 52.3% of GG carriers had TG < 150. It was seen that individuals with the higher carrier of AA had higher weight and lower levels of and DBP rather than other groups.

Investigation of dietary intake among the CAV-1 rs3807992 genotypes

The food group and nutrient intakes according to CAV-1 rs3807992 genotypes are shown in **Table S4**. Significant differences were seen in other vegetable and fast food group ($P < 0.05$).

Interaction of MIND diet and CAV-1 rs3807992 with dyslipidemia

Interaction between the MIND diet and CAV-1 rs3807992 gene variants on dyslipidemia is shown in **table 5**. There was a significant interaction between MIND diet and genotype for metabolic dyslipidemia (β=-0.25 ± 132,OR = 0.77,95% CI = 0.60-1.00 ,P = 0.05) in the crude model. Whereby, subjects with dominant alleles had a lower risk of dyslipidemia. Besides, in model one age, IPAC, BMI, and energy intake had been controlled for participants had (β=-0.34 ± 152,OR = 0.70, 95% CI = 0.52–0.95,P = 0.02), and after controlling for age, IPAC, BMI, energy intake, and job was observed subjects to have 0.64 fold in model two (β=-0.44± -=165,OR = 0.64, 95% CI = 0.46–0.88 ,P = 0.007), this inverse association becomes more significant.

Figure 1. Percentage of Metabolic dyslipidemia across CAV-1 rs3807992 genotypes based on a low and high intake of the MIND diet.the percentage of Metabolic dyslipidemia in low intake across GG, AG, and AA genotypes were respiratory –%, 27.8%, and 25%. The percentage of Metabolic dyslipidemia in high intake across GG, AG, and AA genotypes were respiratory –%, 19%, and 22.2%.

Discussion

In this study, we reported the novel finding that AA carriers of rs3807992 CAV1 gene variant had higher weight rather than other groups. In this manner, we should note that CAV1 is a main fatty acid-binding protein in adipocytes [20, 21]. CAV1 also directly binds to cholesterol. A high amount of cholesterol is one of the hallmarks of the biogenesis of specialized membrane lipid rafts, called caveolae. [22]. Because of this, a defect in the CAV1 function would cause defects in lipid homeostasis and weight gain differences.

Currently, there are limited data considering the CAV1 gene and metabolic diseases, including obesity, metabolic syndrome, and diabetes. [23, 24].

Recent studies exhibited that CAV1 can be transmitted to lipid droplets. Therefore, it seems that the activity of CAV1is essential to preserve the perilipin function and the following lipid droplet integrity, and thus its absence can result in the alterations of lipid droplet size [25, 26]. In this context, the association between CAV1 variant and weight may also be due to the proposed functions of CAV1 in adipocytes, including, maintaining the integrity of the lipid droplet and transporting cholesterol and fatty acids. This study also showed that their animal model exhibited a larger white adipose tissue after a high-fat diet [27].

The abnormal function of CAV1 is highly connected to dyslipidemia since CAV1 has different metabolic functions, including regulating cholesterol transfer mechanisms and oxidized LDL receptors [28]. However, the mechanisms that underlie the linkage between CAV1 gene polymorphisms and dyslipidemia have yet to be investigated. Previously, variants in the CAV1 gene have been connected to lip dystrophy, a disorder of unusual lipid distribution [29]. Today, various genome-wide studies have supported the correlation between the CAV1 variants and dyslipidemia, for instance, the low HDL and high triglycerides [30, 31].

Previous studies also showed the role of CAV1 in cardio metabolic disorders. They investigated CAV1-deficient mice and observed dyslipidemia, insulin resistance, and hypertension. These results were also reported in human studies with CAV1 mutations who exhibit dyslipidemia, insulin resistance, and diabetes [23, 32, 33]. It is demonstrated that another variant of the CAV1 gene means rs926198 is linked to dyslipidemia, particularly low HDL cholesterol and also other metabolic disorders, including diabetes, insulin resistance, metabolic syndrome, and cardiovascular risk in Caucasians and Hispanics. Therefore, it may be considered as a marker for cardio metabolic risk factors in non-obese people [34].

Remarkably, both knockout and autosomal recessive mutations in the CAV1 gene correlate with alterations in lipid and glucose metabolism despite a lean phenotype with reduced adiposity [35, 36].

Here we also elucidated that there was no significant association between all of the nutrients intakes across the three alleles of CAV-1rs3807992 genotypes. More importantly, there was a significant interaction between MIND diet and genotype for dyslipidemia and the AA carriers with higher adherence to the MIND diet may exhibit lower dyslipidemia. Nevertheless, there was no remarkable interaction between MIND diet and genotype on dyslipidemia after adjustments.

Diets that particularly restrict calorie intake improve lipid profiles [37]. Interestingly, it is declared that CAV1 variants correlate with lower expression of CAV1 and that CAV1 deficiency can affect different lipid and glucose mechanisms [38]. We should note that there is no study considering certain diets in lean humans with CAV1 risk alleles. But, a recent study showed that a caloric restriction regimen greatly decreased bodyweight, triglyceride, cholesterol, and insulin resistance in CAV1 knockout mice [39]. Another study showed that a high-fat diet-induced metabolic changes and CAV1 expression in subcutaneous adipocytes of rats [40].

Hypertension is regarded to follow a heritable pattern in family studies [41, 42]. Particularly, there is a certain region in chromosome 7 close to the CAV1 gene which is the most related region to both glucose and lipid metabolism but not augmented adiposity in Asian people [34]. Moreover, it is reported that this particular region close to the location of the CAV1 gene was associated with metabolic syndrome [43].

Previous studies on CAV1 deficient rodents showed higher blood pressure and vascular dysfunction [44, 45]. Herein, we also find a significant association between CAV1 genotypes with DBP, which remained significant after adjustment for age, BMI, physical activity, and total energy intake. Interestingly, AA carrier was associated with higher weight and lower DBP. However, another study on a Caucasian cohort with

subsequent replication in a Hispanic cohort did not observe any relationship between the CAV1 variant and hypertension [34].

Conclusion

Our results propose that the underlying mechanism may be a lower expression of CAV1 leading to changes in lipid and glucose metabolism. These data have significant clinical repercussions. First, the CAV1 gene seems to be a genetic marker that might help in recognizing people at higher risks for metabolic diseases. Second, the present study indicates that using a novel diet as a MIND diet may help in improving dyslipidemia by providing a possible interaction with CAV-1 rs3807992 gene variants. Finally, more large-scale clinical studies with longitudinal data are necessary to confirm our data and to investigate other available diets in this field of research.

Limitation

A food-frequency questionnaire (FFQ) was used to assess dietary intake that is self-reported and, accordingly, reliant on patient's memory. Financial restrictions rendered it impossible to carry out western blotting analysis to determine if rs-3807992 SNP alters CAV-1 expression. This research focused primarily on the composition of MIND diet. However, other dietary patterns can also contribute to the progression of MD. Finally, since this is an observational study, one cannot claim that the associations found in women (rather than men) are causal.

Abbreviations

MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay diet..MD :metabolic dyslipidemia. FFQ: Food Frequency Questionnaires. BMI: Body mass index. WC: waist circumference .WHTR: waist-to-height ratio .LDL: low-density lipoprotein .HDL: high-density lipoprotein. HTN: Hypertension. MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay diet. CAV1: Caveolin 1.CHD: Coronary heart disease .FFM: fat-free mass. MD: Metabolic dyslipidemia .IPAQ: International Physical Activity Questionnaire.TG: Triglycerides. DXA: dual-energy X-ray absorptiometry. ANCOVA: Analysis of Covariance. CHD: Coronary heart disease. LDL: low-density lipoprotein .DASH: Dietary Approaches to Stop Hypertension. HTN: Hypertension. TG: Triglycerides. FBS: fasting blood sugar. WC: waist circumference. WHR: waist-to-hip ratio. BMI: Body mass index. FFM: fat-free mass. DXA: dual-energy X-ray absorptiometry. DBP: diastolic blood pressure. IPAQ: International Physical Activity Questionnaire. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. ANOVA: one-way analysis of variance. SMM: skeletal muscle mass

Declarations

Acknowledgments

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Ethics approval and consent to participate

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 (Ethics Number IR.TUMS.VCR.REC.1398.142). All participants signed a written informed consent that was approved by the Ethics committee.

Consent for publication

Not applicable

Availability of data and materials

Participants of this study did not agree for their data to be shared publicly, so supporting data is not available

Competing interests

All authors declared that they have no competing interests.

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Authors' contributions

NKh andFSh Contributed to conception and design. FA and FK, Contributed to all experimental work. AM, Contributed to data and statistical analysis. KhM supervised the whole project. All authors meet the criteria listed above and have read and approve the submission, also participated in the finalization of the manuscript and approved the final draft.

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References

1. Kronenberg, F., *Scholarly articles for Prevalence of dyslipidemic risk factors in hemodialysis and CAPD patients.* 2003.
2. Jamal S.RanaMD, P.Y.L.H.M.J.S.J.K., *Risk of Cardiovascular Events in Patients With Type 2 Diabetes and Metabolic Dyslipidemia Without Prevalent Atherosclerotic Cardiovascular Disease.* The American Journal of Cardiology, 2020. **133**(2): p. 200-206.
3. Baker, J., *Vitamin D, Metabolic Dyslipidemia, and Metabolic Syndrome in Rheumatoid Arthritis.* 2012.
4. by Boudewijn Klop, J.W.F.E.a.C.C., *Dyslipidemia in Obesity: Mechanisms and Potential Targets.* Nutrients, 2013. **5**(4): p. 1218-1240.
5. Opoku, S., *Prevalence and risk factors for dyslipidemia among adults in rural and urban China: findings from the China National Stroke Screening and prevention project (CNSSPP).* 2019.
6. Berberich, A., *The role of genetic testing in dyslipidaemia.* 2019.
7. Kreutzer C, P.S., Schulte DM, Fangmann D, Türk K, Wolff S, van Eimeren T, Ahrens M, Beckmann J, Schafmayer C., *Influence of 6 genetic variants on the efficacy of statins in patients with dyslipidemia.* 2018.
8. Jean-Philippe Gratton, P.B., and William C. Sessa, *Caveolae and Caveolins in the Cardiovascular System.* Circulation Research., 2004. **94**: p. 1408-1417.
9. Xiao lin Peng, W.Q., Lin zhi Wang,Bin qing Huang,Chen jiang Ying,Xiu fa Sun,Li ping Hao, *Resveratrol Ameliorates High Glucose and high-fat/sucrose Diet-Induced Vascular Hyperpermeability Involving Cav-1/eNOS Regulation.* 2014. **10**.
10. by Li-Yin Lin , C.-Y.H., Hsiu-An Lee 4OrcID,Wan-Hsiang Wang ,Adi Lukas Kurniawan and Jane C.-J. Chao *Dietary Patterns in Relation to Components of Dyslipidemia and Fasting Plasma Glucose in Adults with Dyslipidemia and Elevated Fasting Plasma Glucose in Taiwan.* Nutrients, 2019. **11**(4).
11. Heno F. Lopes, K.L.M., Khaled Nashar, Jason D. Morrow, Theodore L. Goodfriend, and Brent M. Egan, *DASH Diet Lowers Blood Pressure and Lipid-Induced Oxidative Stress in Obesity.* Hypertension., 2003. **41**: p. 422-430.
12. Omar, S.H., *Mediterranean-Dash Intervention for Neurodegenerative Delay (MIND) Diet Slows Cognitive Decline After Stroke.* International journal ofmolecular science, 2019. **20**(11).
13. Brink, A.v.d., *The Mediterranean, Dietary Approaches to Stop Hypertension ...* 2019.
14. Sower, G.J.a.J.R., *Caveolin-1 in Cardiovascular Disease: A Double-Edged Sword.* Diabetes 2015. **64**(11): p. 3645-3647.
15. Parvin Mirmiran, c.a., 2 Firoozeh Hosseini-Esfahani,1 Mahsa Jessri,1 L. Kathleen Mahan,3 Niloofar Shiva,4 and Fereidoun Azizi, *Does Dietary Intake by Tehranian Adults Align with the 2005 Dietary*

Guidelines for Americans? Observations from the Tehran Lipid and Glucose Study. J Health Popul Nutr, 2005. **29**: p. 39-52.

16. Rezazadeh A, R.B.T.a.o.g.a.c.o.w.m.d.p.o.a.w.l.i.T., Iran., *The association of general and central obesity with major dietary patterns of adult women living in Tehran, Iran.* Journal of nutritional science and vitaminology, 2010. **56**: p. 132-8.
17. Mehdi Mollahosseini · Mohammad Hossein Rahim · Mir Saeed Yekaninejad, Z.M., Khadijeh Mirzaei, *Dietary patterns interact with chromosome 9p21 rs1333048polymorphism on the risk of obesity and cardiovascular risk factorsin apparently healthy Tehrani adults* European Journal of Nutrition 2018.
18. Martha Clare Morris, C.C.T., Yamin Wang, Frank M. Sacks, David A Bennett, Neelum T. Aggarwal, . *MIND Diet Associated with Reduced Incidence of Alzheimer's Disease.* HHS public access, 2015: p. 1007-1014.
19. MatthijsBoekholdtbcKay-TeeKhawf, p.S.R.E.V.J.A.-P.S.G.S.J.P.K.J.W., *Metabolic dyslipidemia and risk of future coronary heart disease in apparently healthy men and women: the EPIC-Norfolk prospective population study.* International Journal of Cardiology, 2010. **143**(3): p. 399-404.
20. Gerber, G.E., D. Mangroo, and B.L. Trigatti, *Identification of high affinity membrane-bound fatty acid-binding proteins using a photoreactive fatty acid.* Mol Cell Biochem, 1993. **123**(1-2): p. 39-44.
21. Trigatti, B.L., R.G. Anderson, and G.E. Gerber, *Identification of caveolin-1 as a fatty acid binding protein.* Biochem Biophys Res Commun, 1999. **255**(1): p. 34-9.
22. Londos, C., et al., *On the control of lipolysis in adipocytes.* Ann N Y Acad Sci, 1999. **892**: p. 155-68.
23. Chuengsamarn, S., et al., *Direct renin inhibition modulates insulin resistance in caveolin-1-deficient mice.* Metabolism, 2013. **62**(2): p. 275-281.
24. Zhang, W.-z., *An association of metabolic syndrome constellation with cellular membrane caveolae.* Pathobiology of Aging & Age-Related Diseases, 2014. **4**(1): p. 23866.
25. Pol, A., et al., *A Caveolin Dominant Negative Mutant Associates with Lipid Bodies and Induces Intracellular Cholesterol Imbalance.* Journal of Cell Biology, 2001. **152**(5): p. 1057-1070.
26. Ostermeyer, A.G., et al., *Accumulation of Caveolin in the Endoplasmic Reticulum Redirects the Protein to Lipid Storage Droplets.* Journal of Cell Biology, 2001. **152**(5): p. 1071-1078.
27. Razani, B., et al., *Caveolin-1-deficient mice are lean, resistant to diet-induced obesity, and show hypertriglyceridemia with adipocyte abnormalities.* J Biol Chem, 2002. **277**(10): p. 8635-47.
28. Patel, H.N.F.H.H., *Caveolin and caveolae in age associated cardiovascular disease.* J Geriatr Cardiol., 2013. **10**(1): p. 66-74.
29. Cao, H., et al., *Heterozygous CAV1 frameshift mutations (MIM 601047) in patients with atypical partial lipodystrophy and hypertriglyceridemia.* Lipids Health Dis, 2008. **7**: p. 3.
30. Tam, C.H., et al., *Genome-wide linkage scan for factors of metabolic syndrome in a Chinese population.* BMC genetics, 2010. **11**(1): p. 14.
31. Loos, R.J., et al., *Genome-wide linkage scan for the metabolic syndrome in the HERITAGE Family Study.* J Clin Endocrinol Metab, 2003. **88**(12): p. 5935-43.

32. Pojoga, L.H., et al., *Dissociation of hyperglycemia from altered vascular contraction and relaxation mechanisms in caveolin-1 null mice.* Journal of Pharmacology and Experimental Therapeutics, 2014. **348**(2): p. 260-270.
33. Kim, C.A., et al., *Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy.* The Journal of Clinical Endocrinology & Metabolism, 2008. **93**(4): p. 1129-1134.
34. Baudrand, R., et al., *A prevalent caveolin-1 gene variant is associated with the metabolic syndrome in Caucasians and Hispanics.* Metabolism: clinical and experimental, 2015. **64**(12): p. 1674-1681.
35. Chuengsamarn, S., et al., *Direct renin inhibition modulates insulin resistance in caveolin-1-deficient mice.* Metabolism, 2013. **62**(2): p. 275-81.
36. Kim, C.A., et al., *Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy.* J Clin Endocrinol Metab, 2008. **93**(4): p. 1129-34.
37. Emamgholipour, S., et al., *Acetylation and insulin resistance: a focus on metabolic and mitogenic cascades of insulin signaling.* Crit Rev Clin Lab Sci, 2020: p. 1-19.
38. Baudrand, R., et al., *Caveolin 1 modulates aldosterone-mediated pathways of glucose and lipid homeostasis.* Journal of the American Heart Association, 2016. **5**(10): p. e003845.
39. Mayurasakorn, K., et al., *Caloric restriction improves glucose homeostasis, yet increases cardiometabolic risk in caveolin-1-deficient mice.* Metabolism, 2018. **83**: p. 92-101.
40. Yang, N., et al., *High-fat diet up-regulates caveolin-1 expression in aorta of diet-induced obese but not in diet-resistant rats.* Cardiovascular Research, 2007. **76**(1): p. 167-174.
41. Raji, A., et al., *Insulin resistance in hypertensives: effect of salt sensitivity, renin status and sodium intake.* J Hypertens, 2001. **19**(1): p. 99-105.
42. Xiang, A.H., et al., *Evidence for joint genetic control of insulin sensitivity and systolic blood pressure in hispanic families with a hypertensive proband.* Circulation, 2001. **103**(1): p. 78-83.
43. Tang, W., et al., *Linkage analysis of a composite factor for the multiple metabolic syndrome: the National Heart, Lung, and Blood Institute Family Heart Study.* Diabetes, 2003. **52**(11): p. 2840-2847.
44. Pojoga, L.H., et al., *Effect of dietary sodium on vasoconstriction and eNOS-mediated vascular relaxation in caveolin-1-deficient mice.* Am J Physiol Heart Circ Physiol, 2008. **294**(3): p. H1258-65.
45. Gildea, J.J., et al., *Inhibition of renal caveolin-1 reduces natriuresis and produces hypertension in sodium-loaded rats.* Am J Physiol Renal Physiol, 2011. **300**(4): p. F914-20.

Figures

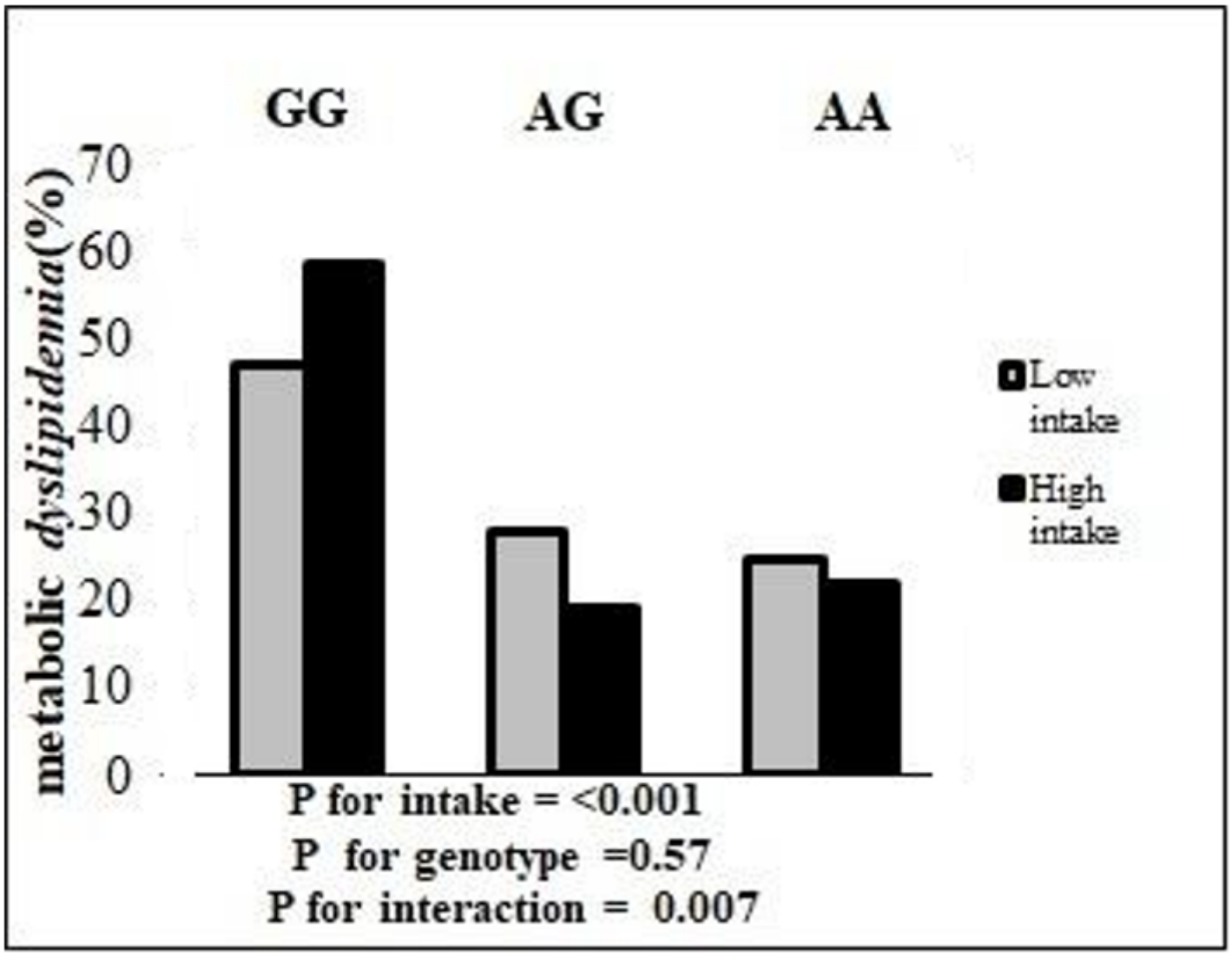

Figure 1

Percentage of Metabolic dyslipidemia across CAV-1 rs3807992 genotypes based on a low and high intake of the MIND diet.the percentage of Metabolic dyslipidemia in low intake across GG, AG, and AA genotypes were respiratory –%, 27.8%, and 25%. The percentage of Metabolic dyslipidemia in high intake across GG, AG, and AA genotypes were respiratory –%, 19%, and 22.2%.

Supplementary Files

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