International Journal of General Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Aldehyde dehydrogenase 2 rs671 a/A Genotype is Associated with an Increased Risk of Early Onset Coronary Artery Stenosis

Hui Rao[1], Xianfang Wang[2], Yu Luo[3], Liu Liang[1], Wei Ye[1], Xuemin Guo[1]

[1]Department of Laboratory Medicine, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, People's Republic of China; [2]Center for Cardiovascular Diseases, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, People's Republic of China; [3]Department of Gynaecology, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, People's Republic of China

Correspondence: Xuemin Guo, Department of Laboratory Medicine, Meizhou People's Hospital, No. 63 Huangtang Road, Meijiang District, Meizhou, People's Republic of China, Email Guoxm12@126.com

Background: The role of aldehyde dehydrogenase 2 (ALDH2) in cardiovascular diseases has been gradually studied. However, it is unclear whether *ALDH2* polymorphism is associated with the risk of early onset (onset age ≤55 years old in men and ≤65 years old in women) coronary artery stenosis (CAS). The association between *ALDH2* single nucleotide polymorphism (SNP) rs671 and risk in patients with early onset CAS was investigated in this study.

Methods: The study included 213 early onset CAS patients and 352 individuals without CAS were set as controls. The *ALDH2* rs671 polymorphism was genotyped by polymerase chain reaction (PCR) - microarray. Differences in *ALDH2* rs671 genotypes and alleles between patients and controls were compared. Multiple logistic regression analysis was performed after adjusting for gender, body mass index (BMI), smoking history, drinking history, and diabetes mellitus to assess the relationship between *ALDH2* rs671 genotypes and early onset CAS risk.

Results: The frequency of the *ALDH2* rs671 G/G genotype was lower in the early onset CAS patients (43.7% vs 55.3%, p=0.007) than that in the controls. The frequency of the *ALDH2* rs671 A allele was higher (32.9% vs 25.0%) than that in the controls (p=0.005). After adjusting for other confounding factors, multivariate logistic regression showed that *ALDH2* rs671 A/A genotype (A/A vs G/G: odds ratio (OR) 2.508, 95% confidence interval (CI): 1.130–5.569, p=0.024), overweight (BMI≥24.0 vs 18.5–23.9: OR 5.047, 95% CI: 3.275–7.777, p<0.001), history of smoking (yes vs no: OR 2.813, 95% CI: 1.595–4.961, p<0.001), and diabetes mellitus (yes vs no: OR 2.191, 95% CI: 1.397–3.437, p=0.001) were the independent risk factors of early onset CAS.

Conclusion: In men ≤55 years old and women ≤65 years old, individuals with *ALDH2* rs671 A/A genotype, overweight (BMI ≥24.0 kg/m^2), smoking history, and diabetes mellitus increased risk of developing CAS.

Keywords: aldehyde dehydrogenase 2, gene polymorphism, coronary artery stenosis, early onset

Introduction

Cardiovascular disease (CVD) is one of the major causes of disease burden and even death.[1] Atherosclerosis refers to the deposition of lipid and complex carbohydrate substances in the intima of the arteries, accompanied by the proliferation of fiber tissue and the deposition of calcium salts, which can lead to a large class of cardiovascular diseases.[2,3] Atherosclerotic cardiovascular diseases (ASCVD) include acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina pectoris, ischemic stroke, transient ischemic attack (TIA), and peripheral artery disease (PAD), which increase the risk for cardiovascular events.[4] Atherosclerosis can lead to artery stenosis.[5,6] Coronary artery stenosis (CAS) is the formation of atherosclerotic plaque in the coronary arteries, resulting in the narrowing of the coronary arteries. There is a complex hemodynamic relationship between coronary stenosis and functional myocardial blood supply. In general, CAS often causes myocardial ischemia.[5] The Third Report of the Adult Treatment Panel National Cholesterol Education Program (NCEP-ATP III) guideline defines early onset (premature) coronary heart

Received: 23 January 2024
Accepted: 18 May 2024
Published: 24 May 2024

disease as patients with coronary heart disease whose onset age is ≤55 years in men and ≤65 years in women.[7] Predicting the risk of CAS is important for the prevention and treatment of CAS, especially the early onset CAS.

Aldehyde dehydrogenases can metabolize toxic aldehydes into low-toxic carboxylates, thereby reducing cell and tissue damage caused by oxidative stress.[8,9] Among all kinds of aldehyde dehydrogenases, aldehyde dehydrogenase 2 (ALDH2) is particularly important.[10,11] More and more studies have shown that ALDH2 is closely related to cardiovascular diseases such as atherosclerosis, hypertension, and cardiac insufficiency.[12,13] However, the relationship between ALDH2 and CAS risk is poorly understood. ALDH2 is encoded by the *ALDH2* gene, which is located on chr12q24 and contains 13 exons.[14] ALDH2 activity in vivo is influenced by *ALDH2* gene polymorphisms.[15] *ALDH2* single nucleotide polymorphism (SNP) rs671 (G>A) is one of the most studied and important polymorphisms in *ALDH2* gene. The change of A leads to the change of 504 amino acids from glutamic acid to lysine (Glu504Lys), and the activity of ALDH2 enzyme is reduced, or even completely lost. The Glu504Lys polymorphism can lead to a 30–50% enzyme activity of ALDH2.[16,17]

There are not many studies on the relationship between *ALDH2* polymorphisms and vascular stenosis. Qu et al found that *ALDH2* rs671 A allele is a protective factor severe intracranial vascular stenosis in Han Chinese.[18] Sung et al found that *ALDH2* polymorphism was not associated with cerebrovascular stenosis and stroke functional outcomes.[19] To date, there have been no reports on the relationship between *ALDH2* polymorphisms and the risk of early onset CAS. In the present study, *ALDH2* rs671 G>A allele/genotype frequencies and the association between *ALDH2* rs671 and the risk of early onset CAS patients were analyzed.

Materials and Methods

Study Participants

This study was a case-control study. 213 patients with early-onset CAS were enrolled as the study group, and 352 non-CAS patients of the same age group were enrolled as the control group from November 2019 to April 2023 in Meizhou People's Hospital, Guangdong Province, China. CAS is diagnosed by coronary computed tomography angiography.[5] Inclusion criteria of patients: (1) patients were diagnosed with CAS; (2) men with ≤55 years old and women with ≤65 years old; (3) the clinical data of the cases were complete. The inclusion criteria of the control group were: (1) non-CAS individuals who had been tested for *ALDH2* rs671 polymorphism; (2) complete demographic information. Exclusion criteria: (1) congenital heart disease, cardiomyopathy, or congestive heart failure; (2) with severe organ dysfunction; (3) with malignant tumor; (4) with serious infectious diseases. Basic information collected and included in the analysis included age, sex, body mass index, smoking history, and alcohol abuse history. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Human Ethics Committees of Meizhou People's Hospital. The flowchart of present study is shown in Figure 1.

Data Collection

Basic information was collected from our hospital's medical record system, including age, gender, body mass index (BMI), history of smoking, and history of drinking. BMI was divided into three subgroups based on the Chinese criteria:[20,21] <18.5 kg/m^2, 18.5–23.9 kg/m^2, and ≥24.0 kg/m^2. Early morning fasting blood collection, serum separation. Lipid levels in serum samples were assessed using an automated biochemical analysis system (Olympus AU5400 system, Tokyo, Japan). The serum lipid-lipoprotein level measures include total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), Apolipoprotein A1 (Apo-A1), and Apolipoprotein B (ApoB).

DNA Isolation and ALDH2 Genotyping

Genomic DNA was extracted from venous blood collected from EDTA anticoagulant collection vessels using a blood DNA isolation kit (Qiagen GmbH, Germany). The quality and concentration of the DNA were assessed using a Nano-Drop 2000™ spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA). Polymerase chain reaction (PCR)-gene chip method was used for *ALDH2* genotyping (BaiO Technology Co, Ltd., Shanghai, China). The PCR procedure was: 5 minutes at 94°C for initial denaturation, and 35 thermal cycles (94°C for 25s, 56°C for 25s, and 72°C for 25s). The

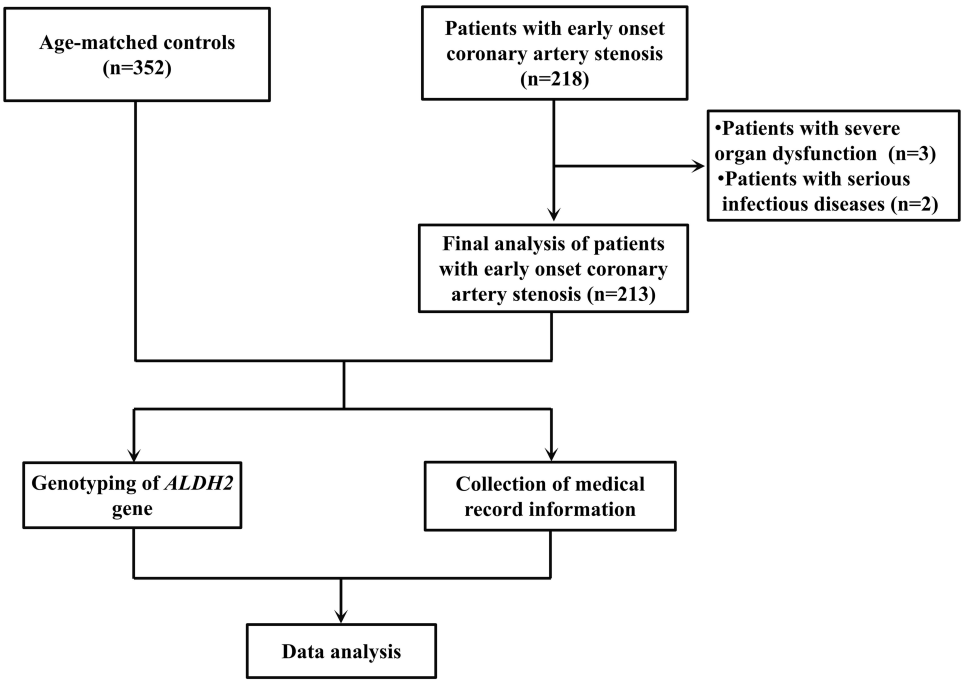

Figure 1 The flowchart of this study.

products amplified by PCR were added into the gene chip, the amplification products of the wild-type template were hybridized with the wild-type probes, and the amplification products of the mutant template were hybridized with the mutant probes, and the genotype of the sample was determined by the hybridization reaction signal.

Statistical Analysis

Continuous variables were expressed as means ± standard deviations and were compared using either Student's *t*-test or the Mann–Whitney *U*-test. Genotype composition ratios and allele frequencies between groups were analyzed with the *Chi*-square test. Hardy-Weinberg equilibrium in the patients and controls was evaluated by *Chi*-square test. Univariate analysis and multivariate regression logistic analysis were applied to examine the relationship between *ALDH2* gene polymorphisms and early onset CAS. Multiple logistic regression analysis was performed after adjusting for gender, body mass index (BMI), history of smoking, history of drinking, and diabetes mellitus to assess the relationship between *ALDH2* rs671 genotypes and early onset CAS risk. $p<0.05$ was considered to represent statistical significance. All statistical analysis were performed using SPSS statistical software version 26.0 (IBM Inc., USA).

Results

Characteristics of Subjects

There were 213 early onset CAS patients, and 352 controls in this study. The proportions of male and female in disease group and control group were 63.8% and 36.2%, 63.6% and 36.4%, respectively. There were 107 (30.4%) cases with BMI <18.5 kg/m^2 and 53 (15.1%) cases with BMI ≥24.0 kg/m^2 in controls, while 10 (4.7%) cases with BMI <18.5 kg/m^2 and 117 (54.9%) cases with BMI ≥24.0 kg/m^2 in patients. The proportion of overweight subjects in the patient group was much higher than that in the control group, the difference in BMI distribution among the groups was statistically significant ($p<0.001$). The proportion of smoking history, drinking history, and diabetes mellitus in patient group and control group were 27.7%, 5.6%, 37.1%, and 17.3%, 9.9%, 16.5%, respectively. The differences of TC ($p<0.001$), TG ($p<0.001$), HDL-C ($p=0.006$), LDL-C ($p<0.001$), Apo-A1 ($p<0.001$) and Apo-B ($p<0.001$) levels among the groups were statistically significant (Table 1).

Table 1 Clinical Characteristics of the Subjects of This Study

Variables	Total (n=565)	Controls (n=352)	CAS Patients (n=213)	*p* values
Gender				
Male, n(%)	360(63.7%)	224(63.6%)	136(63.8%)	1.000
Female, n(%)	205(36.3%)	128(36.4%)	77(36.2%)	
BMI (kg/m^2)				
<18.5	117(20.7%)	107(30.4%)	10(4.7%)	<0.001
18.5–23.9	278(49.2%)	192(54.5%)	86(40.4%)	
≥24.0	170(30.1%)	53(15.1%)	117(54.9%)	
History of smoking, n(%)	120(21.2%)	61(17.3%)	59(27.7%)	0.004
History of alcoholism, n(%)	47(8.3%)	35(9.9%)	12(5.6%)	0.084
Diabetes mellitus, n(%)	137(24.2%)	58(16.5%)	79(37.1%)	<0.001
Serum lipid-lipoprotein levels				
TC, mmol/L	4.38±1.21	4.08±1.04	4.87±1.31	<0.001
TG, mmol/L	1.68±1.41	1.38±1.13	2.16±1.66	<0.001
HDL-C, mmol/L	1.10±0.38	1.07±0.40	1.16±0.33	0.006
LDL-C, mmol/L	2.47±0.86	2.33±0.76	2.70±0.95	<0.001
Apo-A1, g/L	0.98±0.30	0.93±0.29	1.08±0.28	<0.001
Apo-B, g/L	0.81±0.26	0.76±0.24	0.89±0.28	<0.001

Abbreviations: CAS, coronary artery stenosis; BMI, body mass index; Values for age expressed as mean ±SD. TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B.

Distribution of the ALDH2 Genotypes and Alleles Between the Patients and Controls

The results of Hardy-Weinberg equilibrium test showed that the *ALDH2* rs671 genotypes in the early onset CAS patients (χ^2=0.871, p=0.351), and controls (χ^2=0.727, p=0.394) confirmed to the Hardy-Weinberg equilibrium, respectively. Compared to the controls, the frequency of the *ALDH2* rs671 G/G genotype was lower in the early onset CAS patients (43.7% vs 55.4%, p=0.007). The frequency of the *ALDH2* rs671 G allele was lower (67.1% vs 75.0%) and A allele was higher (32.9% vs 25.0%) than that in the controls respectively, the difference in *ALDH2* rs671 alleles distribution between the two groups was statistically significant (p=0.005) (Table 2).

Clinical Characteristics and Serum Lipid-Lipoprotein Levels of Subjects Stratified by ALDH2 rs671 Genotypes

The subjects were grouped according to *ALDH2* rs671 genotypes, and the differences in clinical features and lipid levels were compared between the groups. *ALDH2* rs671 G/G, G/A, and A/A genotype groups had statistically significant differences in

Table 2 Distribution Frequencies of *ALDH2 rs671* Genotype and Allele in Patients and Controls

Variable	Genotype/Allele	Total (n=565)	Controls (n=352)	CAS Patients (n=213)	χ^2	*p* values
ALDH2 rs671 genotypes						
	G/G	288(51.0%)	195(55.4%)	93(43.7%)	7.313	0.007
	G/A	238(42.1%)	138(39.2%)	100(46.9%)	3.264	0.079
	A/A	39(6.9%)	19(5.4%)	20(9.4%)	3.291	0.086
ALDH2 rs671 alleles						
	G	814(72.0%)	528(75.0%)	286(67.1%)	8.147	0.005
	A	316(28.0%)	176(25.0%)	140(32.9%)		
	HWE (χ^2, *P*)	χ^2=1.172, p=0.279	χ^2=0.727, p=0.394	χ^2=0.871, p=0.351		

Abbreviations: ALDH2, aldehyde dehydrogenase 2; CAS, Coronary artery stenosis; HWE, Hardy Weinberg Equilibrium.

the proportion of patients with a history of alcohol consumption (p=0.001). There were no statistically significant differences in the BMI distribution, history of smoking, diabetes mellitus, and serum lipid-lipoprotein levels among *ALDH2* rs671 G/G, G/A, and A/A genotype groups (all p>0.05) (Table 3).

Logistic Regression Analysis of Risk Factors Associated with Early Onset CAS Patients

Logistic regression analysis was used to evaluate independent factors of early onset CAS. Univariate regression analysis was performed to obtain the unadjusted odds ratio (OR), and multiple logistic regression analysis was performed to obtain the adjusted OR. Univariate logistic regression showed that *ALDH2* rs671 G/A genotype (G/A vs G/G: OR 1.519, 95% confidence interval (CI): 1.064–2.171, p=0.022), A/A genotype (A/A vs G/G: OR 2.207, 95% CI: 1.124–4.334, p=0.021), overweight (BMI≥24.0 vs 18.5–23.9: OR 4.928, 95% CI: 3.262–7.443, p<0.001), history of smoking (yes vs no: OR 1.828, 95% CI: 1.216–2.748, p=0.004), and diabetes mellitus (yes vs no: OR 2.988, 95% CI: 2.012–4.439, p<0.001) were the risk factors of early onset CAS. After adjusting for other confounding factors, multivariate logistic regression showed that *ALDH2* rs671 A/A genotype (A/A vs G/G: OR 2.508, 95% CI: 1.130–5.569, p=0.024), overweight (BMI≥24.0 vs 18.5–23.9: OR 5.047, 95% CI: 3.275–7.777, p<0.001), history of smoking (yes vs no: OR 2.813, 95% CI: 1.595–4.961, p<0.001), and diabetes mellitus (yes vs no: OR 2.191, 95% CI: 1.397–3.437, p=0.001) were the independent risk factors of early onset CAS (Table 4).

Table 3 Clinical Characteristics and Serum Lipid-Lipoprotein Levels of Subjects Stratified by *ALDH2 rs671* Genotypes

Variables	G/G (n=288)	G/A (n=238)	A/A (n=39)	*p* values
Gender				
Male, n(%)	183(63.5%)	152(63.9%)	25(64.1%)	1.000
Female, n(%)	105(36.5%)	86(36.1%)	14(35.9%)	
BMI (kg/m^2)				
<18.5	65(22.6%)	44(18.5%)	8(20.5%)	0.810
18.5–23.9	141(49.0%)	118(49.6%)	19(48.7%)	
≥24.0	82(28.5%)	76(31.9%)	12(30.8%)	
History of smoking, n(%)	61(21.2%)	50(21.0%)	9(23.1%)	0.973
History of alcoholism, n(%)	36(12.5%)	11(4.6%)	0(0)	0.001
Diabetes mellitus, n(%)	70(24.3%)	59(24.8%)	8(20.5%)	0.883
Serum lipid-lipoprotein levels				
TC, mmol/L	4.37±1.25	4.39±1.14	4.31±1.36	0.932
TG, mmol/L	1.72±1.38	1.65±1.52	1.48±0.67	0.550
HDL-C, mmol/L	1.10±0.38	1.12±0.38	1.06±0.33	0.616
LDL-C, mmol/L	2.46±0.90	2.49±0.79	2.47±0.93	0.932
Apo-A1, g/L	0.99±0.31	0.97±0.28	0.96±0.28	0.706
Apo-B, g/L	0.81±0.26	0.81±0.26	0.79±0.29	0.832

Abbreviations: BMI, body mass index; Values for age expressed as mean±SD. TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B.

Table 4 Logistic Regression Analysis of Risk Factors for CAS

Variables	Univariate OR (95% CI)	*p* values	Multivariate OR (95% CI)	*p* values
Gender (Male/Female)	1.009(0.708–1.438)	0.959	0.701(0.448–1.096)	0.119
BMI (kg/m^2)				
18.5–23.9	1.000(reference)	–	1.000(reference)	–
<18.5	0.209(0.104–0.419)	<0.001	0.241(0.118–0.491)	<0.001
≥24.0	4.928(3.263–7.443)	<0.001	5.047(3.275–7.777)	<0.001
History of smoking (Yes/No)	1.828(1.216–2.748)	0.004	2.813(1.595–4.961)	<0.001
History of alcoholism (Yes/No)	0.541(0.274–1.066)	0.076	0.472(0.195–1.145)	0.097
Diabetes mellitus (Yes/No)	2.988(2.012–4.439)	<0.001	2.191(1.397–3.437)	0.001

(*Continued*)

Table 4 (Continued).

Variables	Univariate OR (95% CI)	*p* values	Multivariate OR (95% CI)	*p* values
ALDH2 rs671 genotypes				
G/G	1.000(reference)	–	1.000(reference)	–
G/A	1.519(1.064–2.171)	0.022	1.468(0.968–2.226)	0.071
A/A	2.207(1.124–4.334)	0.021	2.508(1.130–5.569)	0.024

Abbreviations: BMI, body mass index; ALDH2, aldehyde dehydrogenase 2; OR, odds ratio; CI, confidence interval.

Discussion

CAS is a direct pathogenic factor of coronary artery disease (CAD), and the more severe the degree of CAS, the more likely it is to cause myocardial ischemia. Therefore, it is necessary to understand the risk factors leading to CAS. Previous studies mainly focused on the discussion of the risk factors of CAS in the general population and the elderly population.[22,23] This study investigated risk factors for early onset CAS and found that *ALDH2* rs671 A/A genotype, overweight, smoking history, and diabetes mellitus were independent risk factors for early onset CAS.

SNP rs671 is the main polymorphic site of *ALDH2* gene, which is related to the enzyme activity of ALDH2. Genotype G/G is a wild homozygote, and the enzyme activity encoded by this gene is normal. When the mutation occurs at this site, the spatial structure of the enzyme changes and the activity decreases, resulting in the deposition of aldehydes and easy damage to mitochondria.[24,25] The *ALDH2* rs671 inactivation polymorphism is widely present in East Asian populations and is associated with an increased risk of cardiovascular disease.[12] Several studies have reported the relationship between *ALDH2* gene polymorphism and CAD and coronary spastic angina (CSA). Xu et al found that people with *ALDH2* gene mutation are more likely to develop coronary artery lesions than those with wild type.[26] Studies have shown that *ALDH2* rs671 polymorphism may be a risk factor for CAD.[27,28] The study by Mizuno et al found that the *ALDH2* re671A allele was a significant risk factor for CSA.[29] In addition, *ALDH2* rs671A allele may be a protective factor for severe intracranial vascular stenosis in Han patients with ischemic stroke.[18] However, the relationship between *ALDH2* rs671 and CAS has not been reported before this study. The present study showed that individuals with *ALDH2* rs671 A/A genotype increased risk of early onset CAS. This study enriched the data on the association between *ALDH2* gene polymorphism and cardiovascular and cerebrovascular disease risk.

The mechanism of action of ALDH2 in the development of CAD is also being explored. The formation of foam cells plays an important role in the occurrence and development of atherosclerosis, Wei et al found that ALDH2 plays an important role in the formation of foam cells through the 4-HNE/PPARγ/CD36 pathway.[30] Another animal experiment showed that ALDH2 is also involved in the migration of coronary endothelial cells, which is involved in the process of coronary atherosclerosis.[31] Yang et al found that ALDH2 may slow the progression of atherosclerosis by reducing endoplasmic reticulum stress and smooth muscle cell apoptosis.[32]

Obesity can lead to the development of cardiovascular disease and can also directly contribute to the development of cardiovascular risk factors, including dyslipidemia, type 2 diabetes, and hypertension.[33,34] There is evidence that a higher body mass index is associated with an increased risk of most cardiovascular diseases.[35,36] The severity of CAS is higher in obese patients than in normal-weight patients.[37] Compared with normal patients, patients with obesity had lower coronary artery volume and myocardial mass ratio.[38] Of course, there are studies with different conclusions: BMI has no association with coronary atherosclerosis.[39,40] The mechanism by which obesity increases the risk of CAS include changes in body composition that affect hemodynamics and alter the microscopic structure of the coronary arteries.[41] In addition, diabetes mellitus is also a risk factor for CAD.[42,43] Carlos Iribarren et al found that diabetes mellitus is an independent risk factor for early-onset CAD.[44] However, there have been no reports on the relationship between diabetes mellitus and the risk of early onset CAS.

Smoking is strongly associated with higher rates of CAD, heart failure, abdominal aortic aneurysm, ischemic stroke, transient ischemic attack, peripheral artery disease, and arterial hypertension.[45] Smokers have a higher risk of CAD severity.[46] A higher percentage of smokers was observed in patients with higher immature platelet fraction (IPF) values, smoking was an independent predictor of higher IPF values, and IPF was associated with cardiovascular disease.[47] And smoking is one of the

predictors of CAS in Japanese men.[48] Majumder et al revealed that smoking is an independent risk factor for significant stenosis in coronary artery.[49] The mechanism of the role of smoking in the progression of atherosclerosis may be related to the effect of tobacco components on endothelial dysfunction, inflammation and lipid changes.[50]

The present study showed that individuals with *ALDH2* rs671 A/A genotype, overweight, smoking history, and diabetes mellitus increased risk of developing CAS among men ≤55 years old or women ≤65 years old. This study had some limitations. First, this case-control study is based on hospitalized patients and physical examination subjects, and selection bias of population is inevitable Second, in addition to analyzing the basic demographic information, smoking and drinking status and *ALDH2* gene polymorphism of the subjects, this study did not collect and analyze other possible influencing factors, such as eating habits, sleep quality, and physical exercise status. Third, because the number of cases included in the current study is not enough, this study did not grade and compare the CAS patients according to the degree of CAS, but that's one of the things we are working on.

Conclusion

In men ≤55 years old and women ≤65 years old, individuals with *ALDH2* rs671 A/A genotype, overweight, smoking history, and diabetes mellitus increased risk of developing CAS. Revealing the characteristics and risk of early onset CAS is of great significance for the prevention and treatment of CAS.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

As this study was a retrospective study, it was not possible for all participants to return to the hospital to sign informed consent. All participants were informed on the study procedures and goals and the informed consent from all the participants was obtained in verbal form through the telephone communication, which approved by the Ethics Committee of the Meizhou People's Hospital. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

Acknowledgments

The authors thank their colleagues, who were not listed in the authorship of the Department of Laboratory Medicine, Meizhou People's Hospital, for their helpful comments on the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Science and Technology Program of Meizhou (Grant No.: 2019B0202001).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982–3021. doi:10.1016/j.jacc.2020.11.010
2. Libby P. The changing landscape of atherosclerosis. *Nature*. 2021;592(7855):524–533. doi:10.1038/s41586-021-03392-8

3. Rizzoni D, Agabiti-Rosei C, De Ciuceis C, Boari GEM. Subclinical hypertension-mediated organ damage (HMOD) in hypertension: atherosclerotic cardiovascular disease (ASCVD) and calcium score. *High Blood Press Cardiovasc Prev*. 2023;30(1):17–27. doi:10.1007/s40292-022-00551-4
4. Sheikh Beig Goharrizi MA, Ghodsi S, Memarjafari MR. Implications of CRISPR-Cas9 genome editing methods in atherosclerotic cardiovascular diseases. *Curr Probl Cardiol*. 2023;48(5):101603. doi:10.1016/j.cpcardiol.2023.101603
5. Mézquita AJV, Biavati F, Falk V. Clinical quantitative coronary artery stenosis and coronary atherosclerosis imaging: a consensus statement from the quantitative cardiovascular imaging study group. *Nat Rev Cardiol*. 2023;20(10):696–714. doi:10.1038/s41569-023-00880-4
6. Min JK, Chandrashekhar Y. Atherosclerosis, stenosis, and ischemia: one primary, one secondary, and one tertiary. *JACC Cardiovasc Imaging*. 2018;11(4):531–533. doi:10.1016/j.jcmg.2017.12.006
7. Third Report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143–3421. PMID: 12485966. doi:10.1161/circ.106.25.3143
8. Duan Y, Gao Y, Zhang J, et al. Mitochondrial aldehyde dehydrogenase 2 protects gastric mucosa cells against DNA damage caused by oxidative stress. *Free Radic Biol Med*. 2016;93:165–176. doi:10.1016/j.freeradbiomed.2016.02.001
9. Gao Y, Xu Y, Hua S, Zhou S, Wang K. ALDH2 attenuates Dox-induced cardiotoxicity by inhibiting cardiac apoptosis and oxidative stress. *Int J Clin Exp Med*. 2015;8(5):6794–6803. PMID: 26221217.
10. Lin CL, Chien RN, Chen LW. The aldehyde dehydrogenase ALDH2*2 allele, associated with alcohol drinking behavior, dates back to prehistoric times. *Biomolecules*. 2021;11(9):1376. doi:10.3390/biom11091376
11. Wang W, Wang C, Xu H, Aldehyde Dehydrogenase GY. Liver Disease and Cancer. *Int J Biol Sci*. 2020;16(6):921–934. doi:10.7150/ijbs.42300
12. Zhang J, Guo Y, Zhao X. The role of aldehyde dehydrogenase 2 in cardiovascular disease. *Nat Rev Cardiol*. 2023;20(7):495–509. doi:10.1038/s41569-023-00839-5
13. Maiuolo J, Oppedisano F, Carresi C. The generation of nitric oxide from aldehyde dehydrogenase-2: the role of dietary nitrates and their implication in cardiovascular disease management. *Int J Mol Sci*. 2022;23(24):15454. doi:10.3390/ijms232415454
14. Yoshida A, Rzhetsky A, Hsu LC, Chang C. Human aldehyde dehydrogenase gene family. *Eur J Biochem*. 1998;251(3):549–557. doi:10.1046/j.1432-1327.1998.2510549.x
15. Mizoi Y, Yamamoto K, Ueno Y, Fukunaga T, Harada S. Involvement of genetic polymorphism of alcohol and aldehyde dehydrogenases in individual variation of alcohol metabolism. *Alcohol Alcohol*. 1994;29(6):707–710. PMID: 7695788.
16. Perez-Miller S, Younus H, Vanam R, Chen CH, Mochly-Rosen D, Hurley TD. Alda-1 is an agonist and chemical chaperone for the common human aldehyde dehydrogenase 2 variant. *Nat Struct Mol Biol*. 2010;17(2):159–164. doi:10.1038/nsmb.1737
17. Chen YC, Peng GS, Tsao TP, Wang MF, Lu RB, Yin SJ. Pharmacokinetic and pharmacodynamic basis for overcoming acetaldehyde-induced adverse reaction in Asian alcoholics, heterozygous for the variant ALDH2*2 gene allele. *Pharmacogenet Genomics*. 2009;19(8):588–599. doi:10.1097/FPC.0b013e32832ecf2e
18. Qu Y, Zhang HL, Yu LM, Sun Y, Wu HL, Chen YG. Aldehyde dehydrogenase 2 polymorphism as a protective factor for intracranial vascular stenosis in ischemic stroke in Han Chinese. *Int J Neurosci*. 2016;126(4):342–347. doi:10.3109/00207454.2015.1017760
19. Sung YF, Lu CC, Lee JT, et al. Homozygous ALDH2*2 is an independent risk factor for ischemic stroke in Taiwanese men. *Stroke*. 2016;47(9):2174–2179. doi:10.1161/STROKEAHA.116.013204
20. He W, Li Q, Yang M, et al. Lower BMI cutoffs to define overweight and obesity in China. *Obesity*. 2015;23(3):684–691. doi:10.1002/oby.20995
21. Tang J, Zhu X, Chen Y, et al. Association of maternal pre-pregnancy low or increased body mass index with adverse pregnancy outcomes. *Sci Rep*. 2021;11(1):3831. doi:10.1038/s41598-021-82064-z
22. Kishi S, Magalhães TA, Cerci RJ, et al. Comparative effectiveness of coronary artery stenosis and atherosclerotic plaque burden assessment for predicting 30-day revascularization and 2-year major adverse cardiac events. *Int J Cardiovasc Imaging*. 2020;36(12):2365–2375. doi:10.1007/s10554-020-01851-3
23. Kim S, Kang W, Cho S, et al. Associations between blood lead levels and coronary artery stenosis measured using coronary computed tomography angiography. *Environ Health Perspect*. 2021;129(2):27006. doi:10.1289/EHP7351
24. Zhong S, Li L, Liang N, et al. Acetaldehyde Dehydrogenase 2 regulates HMG-CoA reductase stability and cholesterol synthesis in the liver. *Redox Biol*. 2021;41:101919. doi:10.1016/j.redox.2021.101919
25. Luo J, Lu Z, Zhong Z, et al. ALDH2 deficiency exacerbates MCD-diet induced MASLD by modulating bile acid metabolism. *Free Radic Biol Med*. 2023;212:34–48. doi:10.1016/j.freeradbiomed.2023.12.017
26. Xu L, Zhao G, Wang J, et al. Impact of genetic variation in aldehyde dehydrogenase 2 and alcohol consumption on coronary artery lesions in Chinese patients with stable coronary artery disease. *Int Heart J*. 2018;59(4):689–694. doi:10.1536/ihj.17-165
27. Zhang LL, Wang YQ, Fu B, Zhao SL, Kui Y. Aldehyde dehydrogenase 2 (ALDH2) polymorphism gene and coronary artery disease risk: a meta-analysis. *Genet Mol Res*. 2015;14(4):18503–18514. doi:10.4238/2015.December.23.38
28. Ye CY, Xin JR, Li Z, et al. ALDH2, ADCY3 and BCMO1 polymorphisms and lifestyle-induced traits are jointly associated with CAD risk in Chinese Han people. *Gene*. 2022;807:145948. doi:10.1016/j.gene.2021.145948
29. Mizuno Y, Hokimoto S, Harada E, Kinoshita K, Yoshimura M, Yasue H. Variant aldehyde dehydrogenase 2 (ALDH2*2) in east asians interactively exacerbates tobacco smoking risk for coronary spasm- possible role of reactive aldehydes. *Circ J*. 2016;81(1):96–102. doi:10.1253/circj.CJ-16-0969
30. Wei S, Zhang L, Bailu W, et al. ALDH2 deficiency inhibits Ox-LDL induced foam cell formation via suppressing CD36 expression. *Biochem Biophys Res Commun*. 2019;512(1):41–48. doi:10.1016/j.bbrc.2019.02.012
31. Roy B, Sundar K, Palaniyandi SS. 4-hydroxy-2-nonenal decreases coronary endothelial cell migration: potentiation by aldehyde dehydrogenase 2 inhibition. *Vascul Pharmacol*. 2020;131:106762. doi:10.1016/j.vph.2020.106762
32. Yang MY, Wang YB, Han B, et al. Activation of aldehyde dehydrogenase 2 slows down the progression of atherosclerosis via attenuation of ER stress and apoptosis in smooth muscle cells. *Acta Pharmacol Sin*. 2018;39(1):48–58. doi:10.1038/aps.2017.81
33. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American heart association. *Circulation*. 2021;143(21):e984–e1010. doi:10.1161/CIR.0000000000000973
34. Dikaiou P, Björck L, Adiels M, et al. Obesity, overweight and risk for cardiovascular disease and mortality in young women. *Eur J Prev Cardiol*. 2021;28(12):1351–1359. doi:10.1177/2047487320908983

35. Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. *Eur Heart J*. 2020;41(2):221–226. doi:10.1093/eurheartj/ehz388
36. Abdul-Rahman T, Lizano-Jubert I, Garg N, et al. The common pathobiology between coronary artery disease and calcific aortic stenosis: evidence and clinical implications. *Prog Cardiovasc Dis*. 2023;79:89–99. doi:10.1016/j.pcad.2023.06.002
37. Lind L, Markstad H, Ahlström H, et al. Obesity is associated with coronary artery stenosis independently of metabolic risk factors: the population-based SCAPIS study. *Atherosclerosis*. 2022;362:1–10. doi:10.1016/j.atherosclerosis.2022.10.007
38. Lowenstern A, Ng N, Takagi H. Influence of obesity on coronary artery disease and clinical outcomes in the ADVANCE registry. *Circ Cardiovasc Imaging*. 2023;16(5):e014850. doi:10.1161/CIRCIMAGING.122.014850
39. Nafakhi H, Al-Mosawi AA, Al-Buthabhak K. Sex-related differences in the association of BMI and pericardial fat volume with coronary atherosclerotic markers in young. *Angiology*. 2021;72(3):285–289. doi:10.1177/0003319720974237
40. Auer J, Weber T, Berent R, et al. Obesity, body fat and coronary atherosclerosis. *Int J Cardiol*. 2005;98(2):227–235. doi:10.1016/j.ijcard.2003.11.007
41. Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? *Vasc Health Risk Manag*. 2019;15:89–100. doi:10.2147/VHRM.S168946
42. Jang JJ, Bhapkar M, Coles A, et al. Predictive model for high-risk coronary artery disease. *Circ Cardiovasc Imaging*. 2019;12(2):e007940. doi:10.1161/CIRCIMAGING.118.007940
43. Kuneman JH, El Mahdiui M, van Rosendael AR, et al. Coronary volume to left ventricular mass ratio in patients with diabetes mellitus. *J Cardiovasc Comput Tomogr*. 2022;16(4):319–326. doi:10.1016/j.jcct.2022.01.004
44. Iribarren C, Go AS, Husson G, et al. Metabolic syndrome and early-onset coronary artery disease: is the whole greater than its parts? *J Am Coll Cardiol*. 2006;48(9):1800–1807. doi:10.1016/j.jacc.2006.03.070
45. Larsson SC, Mason AM, Bäck M, et al. Genetic predisposition to smoking in relation to 14 cardiovascular diseases. *Eur Heart J*. 2020;41(35):3304–3310. doi:10.1093/eurheartj/ehaa193
46. Sun J, Han W, Wu S, et al. Combined effect of hyperhomocysteinemia and smoking on the severity of coronary artery disease in young adults ≤ 35 years of age: a hospital-based observational study. *BMC Cardiovasc Disord*. 2021;21(1):484. doi:10.1186/s12872-021-02302-0
47. Nardin M, Verdoia M, Negro F, Rolla R, Tonon F, De Luca G. Impact of active smoking on the immature platelet fraction and its relationship with the extent of coronary artery disease. *Eur J Clin Invest*. 2020;50(2):e13181. doi:10.1111/eci.13181
48. Imatoh T, Miyazaki M, Kadowaki K, Babazono A, Sato M, Une H. Interaction of low serum adiponectin levels and smoking on coronary stenosis in Japanese men. *Int J Cardiol*. 2006;110(2):251–255. doi:10.1016/j.ijcard.2005.11.039
49. Majumder AR, Rahman MA, Momen A, et al. Association of Echocardiographic Epicardial Fat Thickness with the Angiographic Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome. *Mymensingh Med J*. 2022;31(1):142–148. PMID: 34999694.
50. Bolorunduro O, Cushman C, Kapoor D, et al. Comparison of coronary atherosclerotic plaque burden and composition of culprit lesions between cigarette smokers and non-smokers by in vivo virtual histology intravascular ultrasound. *J Invasive Cardiol*. 2015;27(8):354–358. PMID: 25999135.