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Research Paper

Evaluation of 10 Years Atherosclerotic Cardiovascular Risk, Vitamin D and Metabolic Profiles in Smokers

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ABSTRACT

Background: Cardiovascular diseases (CVD) are the primary cause of death and a significant contributor to disability. Atherosclerosis cardiovascular diseases (ASCVD) are responsible for high mortality rates, causing millions of deaths each year. The most important avoidable cause of ASCVD and death is cigarette smoking. This study examined the relationship between 10-year ASCVD in smokers with 25(OH)D and metabolic profiles.

Methods: This cross-sectional study was conducted at the Beheshti Hospital in Kashan City, Iran. A total of 144 smokers between the ages of 40 and 75 participated in this study. Addiction and cardiovascular specialists evaluated the patient health questionnaire, and the appropriate tool was used to quantify the 10-year ASCVD risk. Nitric oxide (NO), γ-glutamyl-l-cysteinyl-glycine (GSH), high-sensitivity C-reactive protein (Hs-CRP), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total antioxidant capacity (TAC) and 25(OH)D were determined, too.

Results: About 93% of the 144 participants in this study were men and their mean age was 52.6±8.56 years. The average risk of ASCVD was 10.44±8.72%. Patients' lifetime and 10-year risk for ASCVD was significantly and negatively correlated with blood 25(OH) D, HDL, GSH, NO and TAC ($P<0.05$) and positively with TG, LDL, Hs-CRP, smoking duration, and number of cigarettes ($P<0.05$). Additionally, a negative correlation was seen between the amount of 25(OH)D and the amount of time spent smoking ($P<0.05$).

Conclusion: The results of this study showed that with increased levels of vitamin D, HDL cholesterol, NO, glutathione, and TAC, the risk of developing atherosclerotic CVD was reduced over 10 years. Also, the risk of developing ASCVD over the next 10 years increased with increased levels of TC, LDL-c, TG, Hs-CRP levels and duration and amount of smoking and hypertension.

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Introduction

It has been demonstrated that smoking cigarettes accelerates the development of atherosclerosis (AS), a key risk factor for cardiovascular disease (CVD) [1, 2]. There is compelling evidence that smoking hastens the development of fragile plaque with a large necrotic core [3]. According to previous research using 465 AS plaques, smokers have a much higher incidence of thin-cap fibroatheroma and lipid plaque than nonsmokers [4]. In addition, smoking increases the generation of pro-inflammatory markers and reactive oxygen species, which can damage blood vessels and allow inflammatory cells to infiltrate [5]. Smoking also interferes with the macrophage's ability to secrete cholesterol, promoting foam cell formation [6].

Cigarette smoke can cause cancer, mutagenicity, and cytotoxicity [7]. According to a meta-analysis, smoking low tar is associated with a 14% reduced risk of heart disease compared to smoking high tar [8]. Heavy metals, phenols, nitrogen oxides, free radicals, and aromatic hydrocarbons are abundant in cigarette tar. Its major constituents circulate through the bloodstream, damaging the vascular beds and affecting the systemic or local immune-inflammatory state [9]. Aniline and hydroquinone (free radicals) are potent inducers of cell death via the RIPK1/ROS and caspase 9/3-dependent pathways, respectively [10, 11].

One of the most important fat-soluble vitamins in the body is vitamin D, of which D2 and D3 are the most important. In addition to controlling serum phosphorus and calcium levels, 25(OH)D is the first circulating form of vitamin D and is critical for the immune response and cell proliferation [12, 13]. Vitamin D insufficiency increases the risk of ischemic stroke [14]. Nowadays, 25(OH)D insufficiency is a serious health problem in humanity [15]. There is increasing evidence that smoking has adverse effects on the metabolism of calcium and 25-hydroxyvitamin D [16-18]. According to a report that included 5714 participants between the ages of 30 and 79, nonsmokers had higher vitamin D levels than smokers [19]. Serum 25(OH)D concentrations were significantly higher in nonsmokers than smokers, according to Hermann et al. [20].

The lack of agreement about whether smoking lowers circulating vitamin D levels may be due to differences in research design, participant characteristics (e.g. sex, age, health status, and weight) and testing methods [21]. Research on whether smokers typically have low vitamin D levels has continued in recent years. This study, focusing on cigarette smokers, will examine the association between metabolic variables, vitamin D levels, and 10-year risk of atherosclerotic CVD.

Materials and Methods

Study subjects

We investigated the association between 25(OH) D levels, metabolic factors, and the 10-year risk of atherosclerotic cardiovascular diseases (ASCVD) in cigarette smokers. Convenience sampling was used in this study to identify 144 patients, from cigarette smokers who accompanied patients to the central laboratory of Kashan University of Medical Sciences, cardiovascular clinic and Shahid Beheshti Hospital of Kashan University of Medical Sciences (Kashan City, Iran). The following were the inclusion criteria: 40 to 75 years old, smoking for more than one year and at least one pack of cigarettes a day (scoring 4 on the Fagerström test), lacking any known CVD at the time of the study, and completing the informed consent form. The exclusion criteria included unwillingness to have blood drawn, obesity and diabetes mellitus, and unwillingness to participate in the research at any stage during the research. The sample size was calculated 144 by the Equation 1:

$$1.\ n=\frac{Z^2p\ (1-p)}{d^2}$$

n=with p=0.4, d=0.08, z=1.96 and CI=95% [22].

Measurements of common CVD comorbidities

For this study, blood pressure was measured three times at 3-minute intervals after a 10-minute rest period. Systolic blood pressure and diastolic blood pressure were averaged from multiple readings. Each participant had a fasting blood sample taken to measure cholesterol and blood glucose levels. Levels of high-sensitivity C-reactive protein (Hs-CRP), nitric oxide (NO), triglycerides (TG), glucose, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and total cholesterol (TC) were measured using commercial kits and an autoanalyzer [23].

Hs-CRP and NO analysis

For inflammatory indicators, serum samples were assayed for Hs-CRP levels using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The lowest levels detected were 10 ng/mL, and the intra- and inter-assay coefficients of varia-

tion for Hs-CRP were 12%. An ELISA reader (BioTek, Winooski, Vermont, USA) was used to measure the absorbance at 450 nm [24].

The Griess reaction was used to measure NOx, which was confirmed by the laboratory. The ELISA reader (BioTek, Winooski, Vermont, USA) was used to measure the absorbance at 540 nm after a 30-minute incubation at 37 °C. The NOx concentration of serum samples was determined using the linear standard curve generated by 0-100 µM sodium nitrate. The intra- and inter-assay coefficients of variance were 4.4% and 5.2, respectively [25].

Instruments and equipment

We used a biochemical analyzer from VitalScientific, a Biochemical reagent (Company Spankeren, Netherlands). Commercial kits were purchased from Pars Azmoon Inc., Iran. 25-Hydroxy vitamin D assay for vitamin D was acquired from Biosource Europe S.A., Belgium.

Blood chemical analysis

Enzymatic kits (Pars Azmun, Tehran, Iran) were used to quantify total, HDL, and LDL cholesterol and triglyceride levels. All inter- and intra-assay CVs for lipid parameters were less than 5%. 25-Hydroxyvitamin D levels were assessed using an ELISA kit (IDS, Boldon, UK).

Statistical analysis

Descriptive statistics (e.g. Mean±SD, median, etc.) and inferential statistics (e.g. the Pearson correlation coefficient and Spearman correlation coefficient, when appropriate) were used for data analysis. A $P<0.05$ was considered significant. The statistical program SPSS software, version 27 was used to analyze the data.

Results

Demographic and clinical characteristics of the participants are shown in Table 1. Their Mean±SD age at recruitment was 52.60±8.56 years and almost 93.1% of the participants were men. Their mean 10-year ASCVD of the male and female groups in these studies were 10.92±8.79 and 4.03±4.27, respectively ($P<0.001$). In addition, men were found to have a higher 10-year risk of ASCVD than women of various ages. According to the Bonferroni test and Kruskal-Wallis, the unemployed, illiterate, and divorced group has a higher mean 10-year ASCVD risk than other relative groups ($P<0.05$). Also, the 10-year ASCVD of one pack per day smoked varied significantly among the smoking groups. Based on the Mann-Whitney U test, the final model also showed that statin treatment was independent and most associated considerably with 10-year ASCVD (21.04±8.70, $P<0.05$) (Table 1).

The Spearman's rho showed a significant negative association between 25(OH)D blood levels and smoking duration and quantity (-0.486 and -0.139, respectively). In the participating groups, the mean 25(OH)D and non-deficiency were 24.3% (<20 ng/mL) and 75.7%, respectively. We speculate that patients with higher 10-ASCVD are associated with lower 25(OH)D levels ($P<0.001$). We also found that 25(OH)D levels were inversely correlated with 10-year ASCVD (Spearman's rho, correlation coefficient -0.619, $P<0.001$). The results of Spearman's rank correlation studies showed a direct association between ASCVD and smoking duration and quantity. The two categories examined both reached statistical significance (correlation coefficients of 0.786 and 0.222, respectively, $P<0.05$) (Table 2).

Multivariate analysis using the generalized linear model (GLM) was used to clarify the effects of 25(OH)D and the presence of TAC, HDL, Hs-CRP, hypertension and smoking duration. Thus, in smokers, the risk of ASCVD was positively associated with TAC, Hs-CRP, hypertension, and the duration of its strength. At the same time, 25(OH)D and HDL-c levels were inversely correlated. The ASCVD levels of all selected independent variables were statistically significant (Table 3).

The mean TAC values of the participant group were significantly higher than those of the other parameters. In addition, the participant group's mean Hs-CRP levels were significantly lower than those of the other variables. The mean LDL, TG, and TC levels were significantly higher than HDL (Table 4).

Discussion

The results of our study showed that the duration of smoking was inversely correlated with 25(OH)D levels. Research by Yuan and Ni found that exposure to tobacco smoke, including passive and active, was associated with suboptimal vitamin D status, including vitamin D deficiency and insufficiency [26]. Another study found that smokers had statistically significantly lower blood levels of 25(OH)D than nonsmokers [27]. According to Mousavi et al. smoking can negatively affect the vitamin D endocrine system and most commonly lead to vitamin D deficiency [28].

Table 1. Demographic and clinical characteristics of the participants

Variables		No.	Mean±SD	P
			ASCVD	
Average 10-year risk of ASCVD		144	10.44±8.72	-
Gender	Male	134	10.92±8.79	<0.001
	Female	10	4.03±4.27	
Job	Unemployed	30	20.67±9.7	<0.001
	Employed	20	6.02±3.79	
	Freelance	94	8.12±6.43	
Education	Illiterate	23	23.01±8.43	<0.001
	Educated (Primary)	27	11.79±7.66	
	Educated (Diploma)	61	6.98±5.51	
	Educated (University)	33	6.96±6.02	
Marital status	Married	112	9.95±7.71	~0.031
	Single	7	4.24±2.59	
	Divorced	25	14.34±12.19	
Number of frequency cigarette smoking	1 pack per day smoked	108	9.54±8.40	~0.021
	2 packs per day smoked	32	12.55±9.05	
	≥3 packs per day smoked	4	17.87±10.51	
With a history of underlying disease	Without a history of underlying disease	56	18.48±8.78	<0.001
		88	5.32±2.86	
With hypertension	Without hypertension	51	19.42±8.54	<0.001
		93	5.51±3.06	
Antihypertensive drug use	No antihypertensive drug use	50	19.63±8.50	<0.001
		94	5.55±3.07	
Statin treatment	No Statin treatment	38	21.04±8.70	<0.001
		106	6.64±4.66	
Taking aspirin	Not taking aspirin	74	16.09±8.79	<0.001
		70	4.47±2.37	

ASCVD: Atherosclerosis cardiovascular diseases.

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According to another study, children exposed to secondhand smoke may have oxidative damage in vascular endothelial cells and accelerated generation of inflammatory cytokines due to increased oxidants and decreased antioxidants, namely the greater oxidative stress index. In those exposed to passive smoking as children, this condition may accelerate the ASCVD process [29]. In another study, there was a 75% reduction between those with optimal 25(OH)D levels and those with severe deficiency after full adjustment. A similar decrease in mortality was seen for CVD. In addition, individuals with adequate 25(OH)D levels had an 85% lower risk of

Table 2. Correlation between 10-year risk of ASCVD and metabolic profiles

Variables	Spearman's Rho	P
25(OH)D	-0.619	<0.001
Triglyceride	0.505	<0.001
TC	0.737	
HDL-c	-0.501	
LDL-c	0.650	
Hs-CRP	0.709	<0.001
Nitric oxide	-0.517	
TAC	-0.537	<0.001
GSH	-0.515	
Duration of smoking	0.786	<0.001
Quantity of smoking	0.222	0.008

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Abbreviations: ASCVD: Atherosclerosis cardiovascular diseases; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; TAC: Total antioxidant capacity; GSH: γ-Glutamyl-l-cysteinyl-glycine.

Table 3. Relationship between risk factors and 10-year risk of ASCVD by GLM model

Risk Factor	B (95% CI)	Std. Error	P
25(OH)D	-0.011	0.003	0.002
TC	0.008	0.001	<0.001
HDL	-0.019	0.008	0.022
Hs-CRP	0.094	0.026	<0.001
Duration of smoking	0.025	0.003	<0.001
History of hypertension	0.391	0.076	<0.001

Abbreviations: ASCVD: Atherosclerosis cardiovascular diseases; HDL: High-density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; GLM: Generalized linear model.

sudden death than those with severe deficiency. Mortality from congestive heart failure also showed a significant trend. Fatal myocardial infarction was not significantly correlated with vitamin D levels. In addition, there was no significant correlation between 25(OH)D levels and the risk of fatal stroke [30]. Thompson et al. showed that vitamin D supplementation may reduce the risk of major cardiovascular events, particularly coronary revascularization and myocardial infarction. Those taking statins or other cardiovascular medications at baseline may experience this protective effect more strongly [31]. Robert Scragg et al. showed that monthly high-dose vitamin D supplementation did not prevent CVD. More research is needed to determine how daily or weekly doses affect the risk of CVD [32]. Although observational studies have shown robust inverse relationships between HDL-c and ASCVD incidence, several investigations of genetically mediated HDL levels and trials of HDL-c-raising drugs that have not yet demonstrated therapeutic benefit have cast doubt on the causal role of HDL in preventing ASCVD, also by accumulating in the arterial intima, atherogenic lipoproteins containing apolipoprotein B (mostly LDL) cause ASCVD. On the other hand, an important mechanistic link between clinical risk factors and ASCVD promotes systemic inflammation [33].

Our results showed that a higher risk of developing ASCVD is associated with elevated levels of TG, LDL, and TC. Clinical and epidemiological evidence suggests elevated triglyceride levels are a marker of CV risk. Ac-

Table 4. The level of metabolic profiles in smokers (n=144)

Variables	Min-max	Mean±SD
25(OH)D (ng/mL)	11.6–58.2	25.81±8.38
GSH (µmol/L)	482–931.8	672.94±93.11
NO (mg/dL)	31.7–66.8	44.73±7.62
Hs-CRP (ng/mL)	1.9–9.1	5.05±1.49
TC (mg/dL)	140–260.3	179.42±24.06
LDL (mg/dL)	71–181.8	110.60±16.64
HDL (mg/dL)	33–51.6	40.91±3.83
TG (mg/dL)	93-239	141.62±21.81
TAC (mg/mL)	534.7–1217.1	903.63±149.91

Abbreviations: HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; GSH: γ-Glutamyl-l-cysteinyl-glycine; NO: Nitric oxide; TC: Total cholesterol; TG: Triglyceride; TAC: Total antioxidant capacity.

cording to Budoff, compared with HDL, which has not been shown to play a causative role in CV disease, the genetic data for TG support a causative role for these lipids in ASCVD and compare favorably with those linking LDL to ASCVD [34].

Our current study demonstrates an inverse relationship between the 10-year ASCVD rate and NO levels and compares the higher category of Hs-CRP levels. According to the survey by Teimouri et al. inflammatory markers are involved in the immunological process that causes vascular remodeling and plaque deposition. These are also associated with a higher risk of CVD [35]. In another report, 786 people developed CVD during 7 years of follow-up. As the participants' Hs-CRP/HDL-C ratio increased, the incidence of new CVD gradually increased. In addition, the results showed that the TG, HDL, smoking, alcohol consumption, age, sex, marital status, and place of residence of the study participants were statistically significantly different [36].

According to another study, smoking-induced oxidative stress promotes endothelial dysfunction and slows coronary blood flow in individuals whose coronary arteries appear angiographically normal. In addition, smokers had increased oxidative stress as evidenced by decreased glutathione levels and increased malondialdehyde and superoxide dismutase levels compared to control subjects [37]. In addition, Steven et al. [38] have shown that ASCVD and CVD are closely related to inflammation. Classical anti-inflammatory therapies have demonstrated protective effects in several patterns of CVD; in particular, established drugs with pleiotropic immunomodulatory properties have demonstrated beneficial cardiovascular effects.

The current study had some limitations. The cross-sectional report did not specify vitamin D levels by sun exposure. This gap should be considered one of this study's limitations when interpreting our results. Also, we did not evaluate diet and physical activity in the subject's study. Thus, its effectiveness is suggested in other reports. In addition, the sample size in our study was small due to limited funding. Future investigations are needed to evaluate a larger population of smokers.

Conclusion

This study has highlighted the probable processes linking 25(OH)D insufficiency and alterations in metabolic variables to the initiation and progression of 10-year ASCVD event risk. Maintaining optimal vitamin D levels benefits inflammation, immune response, endothelial function, lipid metabolism, and vascular health, all of which play critical roles in AS and CVD. However, more research is needed to demonstrate causality, determine ideal vitamin D levels, and analyze the other variables.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Kashan University of Medical Sciences, Kashan, Iran (Code: IR.KAUMS.MEDNT.REC.1403.114) and was carried out following the ethical standards of the Declaration of Helsinki.

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Authors' contributions

Data collection: Elaheh Bagherian, Amir Ghaderi, Mehrdad Simani and Hasan Rajabi Moghaddam; Data analysis, writing, review, editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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