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RESEARCH ARTICLE

The Effect of Smoking on Angiotensin Converting Enzyme and its Relationship with Severity of Cardiovascular Disease in Young Smokers

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Abstract

Smoking is considered a major risk aspect of cardiovascular disease (CVD). However, the mechanisms by which it causes CVDs are not clear. Angiotensin-converting enzyme (ACE) is a key enzyme in the renin-angiotensin-aldosterone system, which converts angiotensin-I to angiotensin-II regulates blood pressure and act as a vaso-constrictor may play a vital role in cardiovascular disease. Hence, this study aimed to investigate the potential relationship between ACE and smoking and its relationship with the severity of cardiovascular disease in young smokers. The study comprised 60 young smokers with coronary heart disease (CHD) aged between 20 to 45 years and 60 healthy non-smokers attending cardiology outpatient (OP), medicine OP, and master health check-up units in a control group. Serum ACE, *apolipoprotein-E* (APO-E) and high-sensitivity C-reactive protein (hsCRP) levels were measured using enzyme-linked immune sorbent assay and lipid profile was calculated by an enzymatic method. The mean serum ACE, APO-E and hsCRP levels were significantly ($P < 0.0001$) higher in smokers with CHD versus non-smokers. A significant positive correlation was found between ACE and APO-E ($r = 0.3776$), hsCRP ($r = 0.4614$), 5. waist/hip ratio ($r = 0.4673$), total cholesterol ($r = 0.4858$), triglyceride ($r = 0.3917$), low-density lipoprotein (LDL; $r = 0.4689$), TC/HDL (HDL; $r = 0.3225$) and HDL/LDL ($r = 0.3638$). Our study also shows a significant positive correlation between serum ACE, APO-E and hsCRP levels with different age group, duration of smoking and number of cigarettes per day in young smokers. The study outcomes showed that smoking produced a major effect on serum ACE, APO-E and hsCRP levels and is notably linked with the severity of CHD in young smokers.

Keywords: young smoker; smoking; angiotensin converting enzyme; cardiovascular disease; rennin angiotensin system.

Introduction

Smoking is the most effective and addictive habit, influencing human behaviour. It is now rising quickly throughout the globe and is the primary-threat to current and future world health. Smoking causes premature deaths of around 6 million people worldwide from cardiovascular disease (CVD), lung cancer and chronic obstructive pulmonary disease (COPD at an early age.[1] The average loss of life, compared with non-smokers, is 10–15 years and smokers suffer from tobacco-related problems such as CVD, stroke and dementia approximately 10 years earlier than non-smokers.[2,3] Epidemiologic study strongly supports the statement that unisex cigarette smoking increases the incidence of fatal coronary disease.[4,5] Even low tar cigarettes and smokeless tobacco also have shown to increase the risk of CVD vs. non-smokers.[6,7] Smoking leads to the production of angiotensin-converting enzyme (ACE) in the

pulmonary endothelial cells. Changes in the cardiovascular events associated with smoking may also increase enzyme activity.[8]

ACE is one of the vital constituents of the rennin angiotensin system (RAS). Angiotensin is hydrolysed by renin to produce angiotensin-I (Ang-I), which is later converted into a biologically active Ang-II by ACE. More recently, renin- and ACE-independent formation of Ang-II has also been reported.[9,10] The type 1 receptor of Ang-II mediates water and salt reabsorption, improve systemic drive and vasoconstriction.[11,12]

Cigarette smoking is also seen to affect the lipid parameter by accelerating the bad cholesterol and degrading the concentration of (high-density cholesterol [HDL-C]) good cholesterol.[13,14] The stable chemical component in cigarette promote an increase in the low-density lipoprotein cholesterol (LDL-C) concentration and oxidatively modify the lipids and proteins including, the *apolipoprotein-E* (APO-E).[15]

Smoking also induces inflammation and plays a pivotal role in the development of CVD. Studies have shown that smoking causes an increased level of multiple inflammatory markers, including C-reactive protein (CRP). These biomarkers are the predictor for the coronary syndrome.[16] So, this study investigated the relationship between ACE, APO-E and high sensitivity CRP (hsCRP) levels and its association with the severity of CVD in young smokers.

Materials and Methods

This cross-sectional study was carried out at the SRM Medical College Hospital and Research Centre, Chennai, India. The study included 60 young smokers with coronary heart disease (CHD) aged between 20 to 45 years and 60 healthy normal individuals (non-smokers) attending the cardiology outpatient (OP), medicine OP and master health check-up units. The included smokers with typical chest pain, abnormal creatine phosphokinase, *creatine kinase*-myocardial band troponin I, echocardiographic changes and coronary angiography. The smoking criteria were defined as individuals who have smoked 5–25 cigarettes per day for at least the past 12 months.[17] The patients with acute coronary syndrome, cardiomyopathy, chronic disease like liver failure, cancer patient, heart failure, pregnancy, cardiovascular accidents, serious systemic illness, and systemic inflammatory disease were excluded from the study. A standard questionnaire was used to obtain information regarding patient history and lifestyle characteristics during the routine cardiovascular health examination. Anthropometric measurements were taken during the physical examination, and 5 ml of overnight fasting blood samples were taken from each subject for further biochemical analysis. The study was approved by the institutional Ethics Committee of the SRM Medical college Hospital (IEC-1779, September 2019).

Assays

The concentration of serum ACE, APO-E and hsCRP were measured using a sandwich enzyme-linked immunosorbent assay. Plasma glucose level, serum triglyceride level and serum total cholesterol, HDL-C and LDL-C were measured enzymatically in the AU480 automatic analyser (Beckman coulter, Brea, CA).

Statistical Analysis

The quantitative variables were expressed as mean standard deviation using a statistical package, SPSS version 22 (SPSS, Chicago, IL). The results were analysed using the Student's t-test and analysis of variance (ANOVA) that analyses the difference between the mean levels of various parameters. Correlation between various variables was assessed using Pearson's correlation equation. $P < 0.05$ was considered statistically significant.

Result

Baseline and biochemical characteristics of the study groups

A total of 120 participants, 60 young smokers with CHD and 60 healthy participants classified as non-smokers, were included in this study. The baseline characteristics and biochemical parameters of the analysed groups are shown in Tables 1 and 2. The study showed a significant difference between the subject weight, body mass index (BMI), waist (W)/hip (H) ratio, blood pressure (BP), number of cigarettesper day and duration of smoking. Fasting

Table 1 Anthropometric measurements of smokers with CHD and non-smokers.

Parameter	Smoker (n = 60)	Non-smoker (n = 60)	t-value	P value[a]
Age (years)	37.64 ± 8.17	30.52 ± 10.96	5.6926	<0.0001
Height (cm)	170.87 ± 3.34	170.51 ± 2.49	0.3993	<0.6906
Weight (kg)	72.55 ± 5.44	64.39 ± 3.56	5.2876	<0.0001
BMI (kg/m^2)	24.26 ± 1.95	23.33 ± 1.41	5.5870	<0.0001
WC (cm)	90.51 ± 4.45	84.77 ± 3.26	5.6953	<0.0001
HC (cm)	98.8 ± 5.23	99.54 ± 3.11	0.6409	<0.5232
W/H ratio	0.91 ± 0.24	0.85 ± 0.12	6.8977	<0.0001
BP(S) mmHg	125.6 ± 4.2	117.5 ± 3.3	8.4234	<0.0001
BP(D) mmHg	74.3 ± 6.2	81 ± 1.2	4.3929	<0.0001
Number of cigarettes/day	9.1 ± 3.65	0	23.8912	<0.0001
Duration of smoking (years)	11.1 ± 7.03	0	12.2474	<0.0001

[a]P < 0.05 is statistically significant.
CHD: coronary heart disease; BMI, body mass index; W/H: waist/hip; WC: waist circumference; HC: hip circumference; BP(S): Systolic blood pressure; BP(D): Diastolic blood pressure.

Table 2 Biochemical parameters of smokers with CHD and non- smokers.

Parameter	Smoker (n = 60)	Non-Smoker (n = 60)	t-value	P value [a]
FBG (mg/dl)	100.3 ± 10.54	93.86 ± 6.46	3.1862	<0.0018
TC (mg/dl)	226.93 ± 29.72	161.72 ± 25.74	9.4182	<0.0001
TGL (mg/dl)	175.04 ± 49.71	91.72 ± 33.37	7.4889	<0.0001
HDL (mg/dl)	36.63 ± 6.70	42.5 ± 7.13	4.6473	<0.0001
LDL (mg/dl)	152.12 ± 21.02	105.63 ± 18.06	9.5082	<0.0001
VLDL (mg/dl)	33.73 ± 12.01	18.18 ± 6.59	5.9095	<0.0001
TC/HDL-C	5.41 ± 0.92	3.82 ± 0.61	8.7066	<0.0001
LDL/HDL-C	3.78 ± 0.70	2.49 ± 0.46	8.2556	<0.0001
ACE (U/L)	81.9206 ± 11.6100	44.36733 ± 8.17860	9.4828	<0.0001
APO-E (ng/ml)	53.36 ± 11.76	35.81 ± 6.92	9.1469	<0.0001
hsCRP (mg/L)	2.980 ± 0.983	0.788 ± 0.332	8.7218	<0.0001

[a] P <0.05 is statistically significant.
CHD: coronary heart disease; FBG: fasting blood glucose; TC: total cholesterol; TGL: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; ACE: angiotensin-converting enzyme; APO-E: *apolipoprotein-E*; hsCRP: high-sensitivity C-reactive protein.

blood glucose and lipid profile were significantly higher (P < 0.0001) in smokers with CHD subjects vs. non-smokers. The study group did not receive any lipid-lowering treatment. The mean serum levels of ACE, APO-E and hsCRP levels were significantly higher in smokers when compared to non-smokers.

Comparison of serum ACE, APO-E and hsCRP levels in different age groups

Table 3 shows that the levels of Serum ACE, APO-E and hsCRP were significantly higher in smokers with CHD with an increase in age (P < 0.0001) compared to non-smokers.

Correlation analysis

Table 4 shows a significant positive correlation between ACE and APO-E (r = 0.3776),hsCRP (r = 0.4614), W/H ratio (r = 0.4673), total cholesterol (TC ; r = 0.4858), triglyceride (TGL; r = 0.3917), low-density lipoprotein (LDL; r = 0.4689), TC/high-density lipoprotein (HDL; r = 0.3225) and HDL/LDL (r = 0.3638). Along with this, a linear regression analysis was performed to assess the

Table 3 Comparison of serum ACE, APO-E and hs-CRP levels in patients of different age groups.

Parameters	Smokers		Non-smokers (n = 60)	P value[a]
	≤ 35 years (n = 25)	>35 years (n = 35)		
ACE (U/L)	74.5128 ± 7.0390	85.1937 ± 7.3985	44.36733 ± 8.17860	<0.0001
APO-E (ng/ml)	44.08302 ± 12.42303	49.0923 ± 13.3418	36.94 ± 7.42	<0.0001
hsCRP (mg/l)	2.1211 ± 0.8469	3.4852 ± 1.0132	0.7789 ± 0.4179	<0.0001

[a]One-way analysis of variance calculation, P < 0.05 is statistically significant.
ACE: angiotensin-converting enzyme; APO-E: *apolipoprotein-E*; hsCRP: high-sensitivity C-reactive protein.

Table 4 Co-relation analysis ofdifferent parameters with ACE, APO-E and hsCRP in smokers with CHD.

Parameter	Smokers with CHD subjects					
	ACE		APO-E		hsCRP	
	r value	P value[a]	r value	P value[a]	r value	P value[a]
BMI (kg/m^2)	0.2288	0.078	0.3098	0.016	0.1716	0.189
W/H ratio	0.2979	0.020	0.2038	0.114	0.2273	0.08
FBG (mg/dl)	0.2432	0.061	0.2629	0.042	0.2771	0.032
TC (mg/dl)	0.4829	0.0001	0.4651	0.0001	0.318	0.013
TGL (mg/dl)	0.3924	0.0019	0.3805	0.0027	0.3278	0.0105
HDL (mg/dl)	0.2267	0.081	–0.1843	0.158	–0.1701	0.193
LDL (mg/dl)	0.6676	0.0001	0.5058	0.0001	0.5065	0.0001
VLDL (mg/dl)	0.2394	0.065	0.2033	0.119	0.1455	0.267
TC/HDL-C	0.3898	0.002	0.1300	0.322	0.2855	0.027
LDL/HDL-C	0.4967	0.0001	0.2869	0.0286	0.3301	0.0100
ACE (U/L)	—	—	0.5924	0.0001	0.4216	0.0007
APO-E (ng/ml)	0.5924	0.0001	—	—	0.4039	0.0013
hsCRP (mg/L)	0.4216	0.0007	0.4039	0.0013	—	—

[a]Pearson's correlation r value, P <0.05 is statistically significant.
CHD: coronary heart disease; BMI: body mass index; W/H: waist/hip; FBG: fasting blood glucose; TC: total cholesterol; TGL: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; ACE: angiotensin-converting enzyme; APO-E: *apolipoprotein-E*; hsCRP: high-sensitivity C-reactive protein.

correlation of ACE vs. APO-E, hsCRP, TC and LDL-C that varied with smoking status (Figure 1).

Our study also showed a significant positive correlation between serum ACE, APO-E and hsCRP levels with different age groups, duration of smoking and number of cigarettes per day in young smokers with CHD (Table 5).

Discussion

CVD is a chronic progressive disorder determined by the multifaceted relations flanked by environmental and genetic risk factors. Smoking is one of the primary independent environmental threat aspects which is causally associated with CVD.[18,19] Previous studies have shown that smoking or nicotine inhalation led to increased diastolic and systolic blood pressure,[20,21] which increased ACE concentration[21] and disrupted the renin-angiotensin-aldosterone system for the progression of CVD and its clinical implications.Some epidemiologic studies showed that serum ACE levels abnormally elevated in CVD and the patients with hypertension associated with coronary artery stenosis.[22]

In this study serum, ACE levels were significantly elevated in smokers with CHD than the non-smokers (control; P < 0.0001) which may reflect the effect of ACE on angiotensinogen-2 levels leading to adverse events such as CHD, which was consistent with the result of He et al.[23]

Serum APO-E levels were also significantly elevated in smokers vs. non-smokers (P <0.0001). A component of tobacco smoke, acrolein, was found to cause the oxidative modification of APO-E, which impaired the capability of APO-E interaction

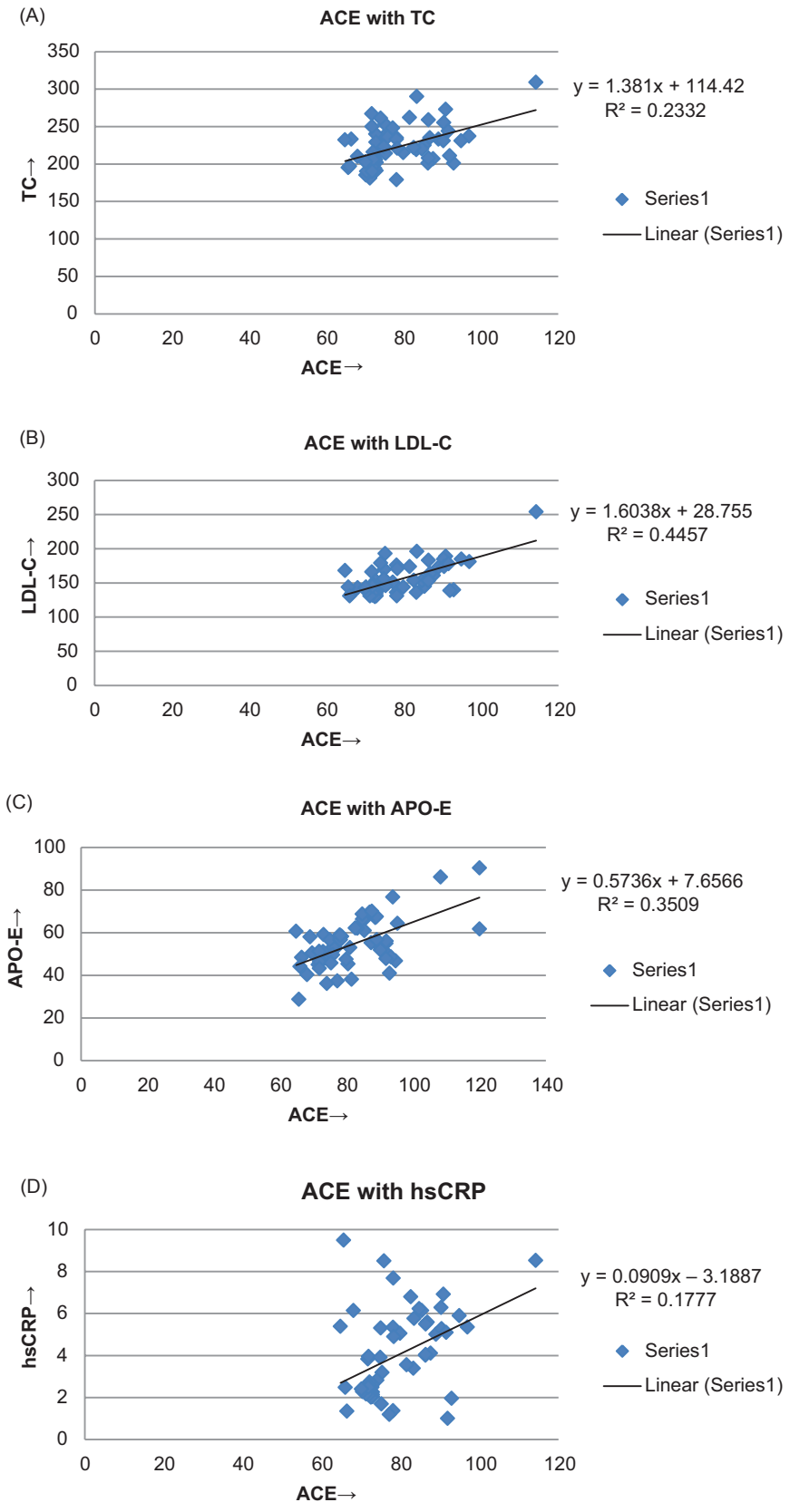

Figure 1 Linear regression analysis of ACE with TC, LDL-C, APO-E and hsCRP in smokers with CHD subjects.

Table 5 Co-relation of ACE, APO-E and hsCRP with age, duration and number of cigarettes per day in smokers with CHD.[a]

Parameter	Age (years)				Duration of smoking (years)				Number ofcigarettes/day			
	<35 (n = 25)		>35 (n = 35)		<10 (n = 23)		>10 (n = 37)		<10 (n = 39)		>10 (n = 21)	
	r value	P value	r value	P value	r value	P value	r value	P value	r value	P value	r value	P value
ACE	0.2584	0.046	0.5504	<0.0001	0.5741	<0.0001	0.5481	<0.0001	0.4106	0.0011	0.4851	<0.0001
APO-E	0.2895	0.024	0.3353	0.008	0.6313	<0.0001	0.2890	0.025	0.3270	0.010	0.6702	<0.0001
hsCRP	0.1334	0.309	0.3048	0.017	0.3686	0.003	0.2661	0.039	0.2512	0.052	0.4856	<0.0001

[a]Pearson's correlation r-value, P<0.05 is statistically significant.
CHD: coronary heart disease; ACE: angiotensin-converting enzyme; APO-E: apolipoprotein-E; hsCRP: high-sensitivity C-reactive protein.

with LDL receptor and heparin. Besides, the acrolein-modified APO-E interact with lipid surfaces decreased. Thus, it interfered with the regulation of plasma cholesterol homeostasis by disrupting the functional activity of APO-E.[24]

Many studies already revealed the relationship between chronic inflammatory responses and CVDs, hsCRP being one of the independent risk markers of inflammatory response. This study recorded a significant increase in the level of hsCRP in smokers with CHD (P <0.0001), which may be the cause for the formation of coronary atherosclerotic plaque.[25,26] A significant correlation between ACE with FBG, W/H ratio, TC, LDL-C and lipid levels in young smokers was also recorded in this study (P < 0.05). This outcome agreed with the previous studies.[27,28]

This study showed evidence of a significant correlation between the ACE and a total load of cardiovascular risk factors, particularly smoking, inflammatory marker (hsCRP) and APO-E in young smokers versus non-smokers (P < 0.05). In line with other studies where ACE levels were associated with smoking, inflammatory markers (like CRP and IL-6) and APO-E.[29,30]

This study also showed a significant positive relationship between serum ACE, APO-E and hsCRP levels with increasing age and number of cigarettes per day. No significant increase in the levels of ACE, APO-E and hsCRP levels with an increase in the smoking duration was consistent with a previous studies.[29,31] Our study showed a significant corelation between serum ACE, APO-E and hsCRP levels in young smokers with CHD.These levels could be a sensitive indicator for determining the extent of CHD.

Conclusion

The study showed a significant relationship between ACE, APO-E and hsCRP levels, which is notably linked with the severity of CHD with increasing age, duration of smoking and number of cigarettes per day in young smokers.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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