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Original Research Article

Screening of Biomarkers of Metabolic Syndrome in Cigarette Smokers in Adama, Ethiopia

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ABSTRACT

Introduction: Smoking is a major risk factor of cardiovascular disease. Evidence suggests that smoking may reduce insulin sensitivity, induce insulin resistance, and exacerbate other cardiovascular risk factors such as elevated plasma triglycerides, reduced high density lipoprotein–cholesterol, and hyperglycemia. Several studies have also shown that smoking may increase the risk of metabolic syndrome.
Materials and Methods: In the present community-based, cross-sectional study, 99 individuals were divided into two groups, cigarette smokers (50 members) and non-smokers(49 members).The survey included questions about age, education level, occupation, income, marital status, smoking habits, alcohol and khat consumption, exercise, previous and current diseases, and family disease history, among all individuals. Blood pressure, plasma lipid profiles and CRP were measured.
Results: There were no statistically significant differences in body mass index (p= 0.667), systolic blood pressure (p=0.107) and diastolic blood pressure (p= 0.256) between smokers and non-smokers. There were, however, statistically significant elevations in total cholesterol (p = 0.000), LDL-C (p = 0.002) and triglycerides (p=0.000), HDL-C (p= 0.025) and CRP (p=0.001) in smokers compared with non-smokers.
Conclusion: We found that cigarette smoking is associated with elevated plasma triglycerides, total cholesterol, HDL-C LDL-C and CRP levels. The HDL-C elevation in smokers was related to increased alcohol consumption: smokers who did not use alcohol had HDL-C levels similar to non-smokers. Among smokers, alcohol consumption was also significantly associated with an increase in both systolic and diastolic blood pressure. The sample size of this research was small, so further studies with larger sample size are recommended.

Key words:-Metabolic Syndrome, C-reactive protein, cigarette smokers

INTRODUCTION

Tobacco use is the most prevalent cause of preventable deaths worldwide. It is responsible for one in ten adult deaths or 6 million deaths each year. In the 20th century, tobacco-related diseases caused the deaths of 100 million people and it is predicted that one billion people will die in the 21st century from tobacco-related diseases. One in every two smokers will die from tobacco-related disease. In addition, 600,000 people, mostly women and children, die annually from second-hand (passive) smoking. A number of adverse effects are associated with tobacco use, including cardiovascular disease, chronic obstructive pulmonary

disease and numerous types of cancer, especially lung cancer. [1]

Cigarette smoke is a complex mixture of over 5000, and possibly as many as 7000, chemicals, including about 70 known carcinogens. [2,3] Nicotine is the major addictive component of tobacco and most adults who smoke became addicted to tobacco when they were teenagers. Smoking in youth leads to addiction and long-term smoking, and therefore targeting youth in smoking prevention programmes is a major means of reducing subsequent adult morbidity and mortality associated with tobacco use.

Smoking is a major risk factor for cardiovascular disease. Previous studies have shown that smoking reduces insulin sensitivity, induces insulin resistance, and enhances cardiovascular risk factors, such as elevated plasma triglycerides, reduced high density lipoprotein–cholesterol (HDL-C), and hyperglycaemia. Several studies have also shown that smoking is associated with an increased risk of the Metabolic Syndrome, and multiple components of cigarette smoke also have proinflammatory effects. [4-6]

The Metabolic Syndrome consists of dyslipidemia (elevated triglycerides and low levels of plasma high-density lipoprotein cholesterol (HDL-C)), elevation of blood pressure and glucose, increased waist circumference, prothrombotic and proinflammatory states. The risk of atherosclerotic cardiovascular disease accompanying the Metabolic Syndrome is approximately doubled compared with an absence of the syndrome. The Metabolic Syndrome appears to promote the development of atherosclerosis at multiple levels. Elevation of apoB-containing lipoproteins initiates atherogenesis and drives atherosclerotic plaque development. Atherosclerotic plaque development is accelerated by low levels of HDL-C, by oxidized LDL, by elevated glucose levels and by inflammatory cytokines, and Metabolic Syndrome is a complex of metabolic factors that are associated with a 2-fold risk of CVD and a 5-fold risk of diabetes. [7-9]

Nicotine, carbon monoxide, and other tobacco metabolites derived from smoking also play important roles in insulin resistance. Furthermore, several mechanisms by which cigarette smoking promotes dyslipidemia have been proposed, including reduced lipoprotein lipase activity, increased 3-hydroxy-3-methylglutaryl-CoA reductase activity, increased glucose-6-phosphatase dehydrogenase activity, increased central obesity and increased inflammation. [4-6] Recent work has indicated that epigenetic mechanisms may be involved in Metabolic Syndrome and type 2 diabetes. [10]

Cigarette smoking is a potent source of free radicals, which reduce levels of reactive oxygen species (ROS) scavengers and induce oxidative damage. Free radicals also oxidize low density lipoprotein (LDL) cholesterol. Oxidized LDL-cholesterol increases the risk of atherosclerosis.. Moderate and short term duration of cigarette smoking have been observed to change lipoprotein profiles in a manner that may induce dysfunction and metabolic disorders. [11] Slagter*et al* found that smoking was also associated with elevated triglycerides, low HDL_C levels, unfavourable changes in blood levels apolipoproteins ApoA-1, ApoB, unfavourable lipoprotein particle size and increased waist circumference. [12]

The World Health Organization (WHO) estimated in 2011 that 34% of Ethiopian population suffers from non-communicable diseases, with a national cardiovascular disease prevalence of 15%, cancer and chronic obstructive pulmonary disease prevalence of 4% each, and diabetes mellitus prevalence of 2%, [13] although Ethiopia is among the nations with a relatively low prevalence of cigarette

smokers, with less than 10% of males, and less than 1% of females, being smokers. [14] Nevertheless, studies on smoking prevalence in Ethiopia are sparse, so these estimates may be inaccurate. For example, in one rural town in eastern Ethiopia, 28% of those studied said that they smoked daily. [15] Other studies have indicated that the use or misuse of addictive substances, such as cigarettes, alcohol, and khat (*Catha edulis*Forsk) is increasingly prevalent in Ethiopia. [16] In addition, there is evidence that smokers have an increased risk of developing HIV infection and tuberculosis (TB), worse severity of disease symptoms, and increased mortality from HIV and TB. [17] Since HIV and TB are relatively common in developing countries, including Ethiopia, knowledge of smoking habits and counselling of HIV and TB patients about smoking are important public health imperatives. The aim of this study was, in particular, to search for associations between smoking and Metabolic Syndrome in a representative population-based sample in Adama (Nazret) Ethiopia.

MATERIALS AND METHODS

The study was conducted in Adama Hospital Medical College, Adama (Nazret), Ethiopia. A community-based, cross-sectional study was done, involving99 individuals who were randomly divided into two groups: smokers (50 people) and non-smokers (49 people).The survey included questions about age, education level, occupation, income, marital status, smoking habits, alcohol and khat consumption, exercise, previous and current diseases, and family disease history, among all individuals. The number of pack-years of cigarettes smoked was calculated from the total number of years spent smoking multiplied by the number of packs (one pack=20 cigarettes) smoked daily. Arterial blood pressure was measured after subjects rested in a sitting position for at least 5 minutes. Blood pressure was taken using standard mercury sphygmomanometer by a professional nurse. Weight and height were measured using a standard weighing scale with height scale attached. Body Mass Index (BMI)was calculated as the weight in kilogram divided by the square of the height in metres.

For biochemical analysis, 10 ml of blood was collected and the plasma prepared by standard methods. Plasma lipid profile was determined by an autoanalyzer machine (Humastar300).The methods are based on standard lipid profile determinations found in the Johns Hopkins Laboratory Procedure Manual (2003-2004).CRP was analysed by immunoprecipitation with latex-enhanced turbidimetric assay (Cobas Integra 800 Analyzer, Roche Diagnostics).The data was analyzed using SPSS version 20 and the values were analyzed using correlations and cross tabulation and confidence interval of 95% were taken, with p-values of less than 0.05 considered to be statistically significant. The research proposal was ethically approved by the Ethical Review Committee of the Department of Medical Biochemistry, College of Medicine and Health Sciences, Addis Ababa University, with Ref. No. SOM/BCHM/012/2006.

RESULTS

Education and cigarette smoking. From the sample population of smokers, 82% were literate and 18% were illiterate, while in non-smokers 87.8% were literate and 12.2% were illiterate but the difference was not statistically significant(p= 0.577)

Marital status of respondents. In the sample of smokers, 14% weremarried, 70% single, 14% divorced and 2% widowed; and of non-smokers 16.3% were married, 77.6% single and 6.1% divorced.

Income status of respondents. In non-smokers 24.5% of respondents earned<500 birr per month, 34.7% earned 500 to1000 birr/month, 14.3% earned 1001

to2000birr/month and 26.5% earned more than 2000 birr per month. 16% of smokers earned<500 birr per month, 40% of smokers earned 500 to 1000 birr/ month, 20% earned 1001-2000 birr/month and 24% earned more than 2000 birr/ month (20 Ethiopian birr = approximately one US dollar).

Smoking status and parental smoking. From those who responded that their parents smoke, 50% were smokers themselves and 50% were non-smokers; and from those who responded that their parents do not smoke. 51% were smokers and 49% were non-smokers.

Knowledge about risks of cigarette smoking.83.8 % of respondents knew about health risks of cigarette smoking while 16.2% responded that they do not know about such risks. From those who knew that smoking was a health risk, 27.7% considered smoking to be a risk for cancer, 55.4% for lung disease, 3.6% for heart disease, 1.2% for lung cancer specifically, and 12% thought that smoking causes other problems, including loss of appetite, gastritis, depression, immunosuppression, skin disease, neurological disorders, halitosis, oral disease and decreased life expectancy.

Smoking and use of other drugs. The distribution of smoking status with khat chewing and alcohol use showed that smokers tended to drink alcohol more frequently than non-smokers, and 80% of smokers also chewed *khat*. In the sample population there was a statistically significant increase in use of marijuana in cigarette smokers compared with non-smokers(p= 0.006)

Age and Metabolic Syndrome. In the sample population of smokers and non smokers there was statistically significant correlation between age and triglyceride (r= 0.257, p= 0.010), age and total cholesterol (r=0.365, p=0.000) and age and CRP (r=0.397, p=0.000). There was no statistically significant correlation between age and systolic blood pressure (r=0.090, p= 0.375), age and diastolic blood pressure (r=0.046, p= 0.655), age and HDL (r=0.165, p=0.103), or age and LDL (r=0.102, p=0.341).In smokers there was statistically significant correlation between age and total cholesterol (r= 0.361, p= 0.010), age and CRP (r=0.428, p= 0.002). But there was no statistically significant correlation between age and HDL (r=0.075, p=0.605), age and LDL (r=-0.021 p=0.895), age and systolic blood pressure (r=0.112, p=0.438), age and diastolic blood pressure (r=-0.046, p=0.753) and age and triglycerides (r=0.194, p=0.178).

Blood pressure differences between smokers and non smokers: The frequency distribution of systolic and diastolic blood pressure in all of the sample population is shown in Table-1 24.2% of the sample population have systolic blood pressure ≥135 and 24.3% have diastolic blood pressure ≥90. There appears to be a difference in systolic blood pressure in smokers whose mean blood pressure was 119.3 mm Hg when compared to 114.8 mm Hg of non smokers but the difference was not statistically significant(p= 0.107). Also there was higher mean of diastolic blood pressure in smokers (79.8 mm Hg) than non smokers (77.35 mm Hg) but the difference was not statistically significant(p= 0.256)

Table 1 Difference in levels of systolic and diastolic blood pressure in smokers and non smokers

Blood Pressure	Smokers	Non smokers	Significance (p- value)
Systolic	119.3 ± 16.22	114.8 ± 10.7	0.107
Diastolic	79.8 ± 12.2	77.35 ± 8.84	0.256

Cigarette smoking and BMI. There was no statistically significant correlation(p=0.667) between BMI in smokers (20.71±2.43)and non-smokers(20.94 ± 2.94)

Cigarette smoking and Biochemical parameters. Level of plasma total cholesterol, HDL, LDL and CRP in smokers and non-smokers are given in smokers and non-smokers in Table 2. Of the smokers

16.8% had LDL levels ≥ 130 mg/dl, 62% had triglycerides level ≥ 150 mg/dl, 24 % had total cholesterol ≥ 200 mg/dl, among these 5 individuals had triglycerides level > 600 mg/dl and one individual had 858 mg/dl of triglycerides. In all these laboratory tests levels were higher among cigarette smokers. There was significantly higher total cholesterol (p= 0.000), Triglycerides (p= 0.000), HDL (P=0.025), LDL (P=0.002) and CRP (p=0.001) among smokers than non smokers.

Pack-year smoking history and biomarkers of Metabolic Syndrome. There was statistically significant correlation between pack years and C-reactive protein (r=0.293, p-value=0.039), triglycerides (r=0.501, p-value=0.000) and total cholesterol (r=0.419, p-value=0.002). But there was no statistically significant correlation between pack years and HDL(r= 0.062, p-value=0.669), systolic(r=0.89,p-value=0.540) and diastolic blood pressure (r=0.043, p-value=0.764).

Table 2 Lipid profiles and CRP in smokers and non-smokers

Blood levels	Smokers	Non smokers	Significance(p-value)
Total Cholesterol(mg/dl)	179.56 ±48.8	134.05 ± 40.25	0.000
Triglycerides (mg/dl)	254.39 ± 192.21	118.3 ± 86.66	0.000
HDL-C(mg/dl)	47.76 ± 16.09	39.97 ± 17.91	0.025
LDL-C(mg/dl)	89.92 ± 34.70	70.31 ± 23.78	0.002
CRP(mg/l)	3.02 ± 1.04	1.07 ± 0.89	0.001

Combinatorial effects of cigarette smoking with other drugs. There was no statistically significant difference in smokers who chew khat and who do not in levels of lipids expect total cholesterol, no statistically significant difference in systolic and diastolic blood pressure and C - reactive protein between those who chew khat and those who do not in smokers (Table-3).

In smokers amounts of alcohol consumed per day was significantly correlated with levels of systolic and diastolic blood pressure, high density lipoprotein. But amount of alcohol consumed per day were not significantly correlated with levels of total cholesterol, LDL, triglycerides and CRP 9Table-4).

Table 3 Combinatorial effects of khat chewing and cigarette smoking

Khat chewing			
	Yes	No	Significance (p-value)
SBP	120.4± 16.67	113.13 ± 12.8	0.244
DBP	80.48 ± 12.48	76.25 ± 10.61	0.375
TG	250.37±191.41	275.53 ± 208.36	0.738
TC	173.53 ± 36.7	211.25 ± 86.1	0.044
HDL	48.32 ± 16.36	44.84 ± 15.33	0.58
LDL	86.39 ± 32.47	115.31 ± 43.6	0.081
CRP	2.58 ± 1.53	5.35 ± 4.32	0.076

Table 4 Combinatorial effects of alcohol consumption and cigarette smoking

	Alcohol per day			
	None	1-2 drinks	>2 drinks	Significance(p- value)
SBP	110 ± 8.16	117.5 ± 12.58	122.08 ± 17.46	0.035
DPB	71 ± 8.75	77.5 ± 9.57	82.5 ± 12.28	0.006
HDL	38.25 ± 11.88	49.4 ± 16.52	50.22 ± 16.45	0.044
TC	157.65 ± 37.02	157.07 ± 19.94	188.15 ± 51.74	0.057
LDL	82.17 ± 22.21	64.28 ± 28.64	94.55 ± 37. 13	0.263
TG	237.49 ± 237.86	265.6 ± 167.89	257.84 ± 186.49	0.792
CRP	1.87 ± 1.62	2.49 ± 1.44	3.4 ± 2.63	0.279

DISCUSSION

This study was undertaken to evaluate a possible association between metabolic syndrome and cigarette smoking in Adama (Nazret), Ethiopia. Our findings showed that the prevalence of smoking was the same in literate and illiterate individuals (p=0.577). This may be inaccurate, due to small sample size, so in the future the research should be done with a bigger sample size. Wagenknecht *et al*., and Gilman*et al.,* found that the prevalence of

smoking decreased with increasing education. [18,19]

We found that parental smoking status was not significantly associated with smoking in children. In contrast, Wilkinson *et al.* reported that children of smokers were more likely themselves to smoke and reported more favorable attitudes toward smoking compared to children of non-smokers. [20] Tilson*et al.*, also found that parental smoking was significantly associated with youth smoking. [21] Flay *et al*. reported that having a parent who smokes affects smoking initiation through imitation of parental behavior and it also influences smoking attitudes, norms, and beliefs. [22]

There was no statistically significant difference in body mass index between smokers and non-smokers (P=0.667). These may be due to living style, behavioural patterns between the two groups which were not considered during the study. Additionally, there are other factors associated with both BMI and smoking (e.g. poor dietary choices, poor sleeping habits, etc.) that may mediate or moderate this relationship. These finding does not match with the findings of O'Loughlin *et al*., who found smoking to significantly reduce body mass index in regular smokers. [23]

This study indicated that there is no statistically significant difference in blood pressure between the smokers and non smokers and also pack years. This finding is in line with Okubo *et al*., and contrast to Au *et al*., finding that longer duration of smoking or pack years of cigarettes had a higher risk of hypertension. [24,25] Dyer *et al*., found that blood pressure in smokers was lower than that of non-smokers and other researchers believed that smoking would raise blood pressure. [26] It has been shown that smoking would raise blood pressure and heart rate through its acute vasoconstriction effect. [27] The relation between long-term smoking and hypertension is still unclear and controversial. [28] It is established that smoking could cause acute increase in blood pressure on release of catecholamines induced by nicotine. [29]

It has long been established that nicotine has a considerable influence over increasing the lipid levels in blood. Lipid has important roles in virtually all aspect of life, serving as hormones or hormones precursors, aiding in digestion, providing energy storage metabolic fuel, acting as functional and structural component in cell membranes and forming insulation to allow nerve conduction or to prevent heat lost but their excessive concentrations are associated with various metabolic disorders. [30]

The result of this work showed a statistically significant different in the total cholesterol level of smokers ($p<0.05$) when compared with non-smokers, this indicated that the cigarette smokers have increased serum concentration of cholesterol than non-smokers. The result of this work is in line with work of Adedeji and Etukudo, where high concentration of cholesterol was recorded in smokers when compared with the nonsmokers. [31] In contrast Waheeb and Alharbi in their work, which was on the influence of cigarette smoking on lipid profile in male university students recorded non significant results in total cholesterol in smokers when compared with non-smokers. [32] The increase in total cholesterol level seen in the smokers was as a result of increase in the activity of hepatic HMG-CoA reductase [33] and Natio HK, [34] reported that hepatic HMGCoA reductase, the main rate limiting enzyme in cholesterol synthesis is subject to induction and repression by several hormones, dietary factors and drugs one of which is nicotine. Increased cholesterol is a causative factor of the etiology of atherosclerotic disease. [35] The rise in blood cholesterol levels in smokers may be through catecholamine and adenyl cyclase axis including tissue lipolysis. [36] Within the smoking group of people plasma total cholesterol was higher

among heavy drinkers than light drinkers and also those who do not drink daily. This finding is not in line with that reported by Wakabayashi, who found that total cholesterol in smokers to be lower in the drinker subgroups. [37]

The findings of smoking being associated with high TG were consistent with previous studies. [12,38] One possible explanation for this association is that nicotine may increase sympathetic nerve activity, which stimulates to release of catecholamines and thereby induces lipolysis, with a consequent increase in plasma concentration of TG. [39]

Significantly increased level of LDL was observed among smokers than non smokers in consonance with reported by Craig *et al*., and Khurana*et al*., where it was reported that increase to LDL level in cigarette smokers were due to the down regulation of LDL receptors and failure of receptor mediated endocytosis by metabolite of cigarette. [40,41] This finding is in line with the work of Brischetto *et al.*, specifically attributed the down regulation of LDL receptor to inhibiting action of smoke allylamine and nicotine. [42] Adedejiand Etukudo, also reported high level of LDL in smokers, suggesting that there is increased LDL-Cholesterol synthesis of smokers who are dangerous to their health but is in contrast to findings of Gupta *et al*., [31,43] Carl and Edward reported that clinically increase in LDL cholesterol is associated with increased risk of coronary heart disease. [44]

In our research level of HDL was significantly raised in cigarette smokers compared with non smokers and this finding was not consistent with findings of Min Yu *et al*., and Craig *et al*., who showed levels of HDL to be significantly lower among cigarette smokers and the investigation in the current report could not interpret the results obtained by Siekmeier *et al*., where in the HDL-C levels are same for smokers and non-smokers. [45-47] Moreover, the present results differ from another report where smokers had lowered but non-significant HDL cholesterol (HDL-C) contents. [48] Our finding may be due to alcohol use of the smokers as slight and moderate alcohol consumption may have beneficial effect on HDL levels. [49] Indeed, in our study smokers who drank alcohol who drank alcohol at all had higher HDL-C levels than smokers who drank no alcohol, and smokers who did not drink alcohol had HDL-C levels similar to non-smokers. Most of the smokers in our study were labourers, and physical activity may have contributed to their raised HDL-C levels. These findings agree with those of previous studies. [50,51] HDL-C has been shown to be higher in drinkers than in nondrinkers and tends to be higher as alcohol intake increases. [52]

In our study, plasma C-reactive protein was significantly higher among smokers when compared with never smokers (p=0.000). Hastie *et al* found that in adult smokers without CHD, CRP levels fell slowly after smoking cessation but remained elevated for up to 5 years after smoking cessation, and that there was a positive dose relationship between pack-years and CRP level. [53] Wannamethee *et al*., also found an elevated CRP in smokers. [54] Because tobacco constituents induce inflammatory pathways, CRP may be a marker for this effect, though some studies have conflicting evidence for this. [55] Smokers also have increased numbers of white blood cells, mainly because of a particular increase in polymorphonuclear neutrophils, which are released from the bone marrow and recruited to inflamed tissue. [56] IL-b and IL-6, which are increased to lung inflammation and are implicated in the induction into CRP gene expression, may mediate the stimulation of bone marrow cells. [57]

Patterson *et al.* analyzed factors influencing total cholesterol and HDL-cholesterol using multiple regression

analysis. They found that total cholesterol increased with age, while HDL-cholesterol showed little variation on age in both sexes. They also found lower HDL-cholesterol levels among men and women who abstained from alcohol, and indicated that cigarette smoking was associated with significant increases in total cholesterol values and decreases in HDL-cholesterol values. [(58)]

In our research total cholesterol increased with age while there was no statistically significant association with age and HDL. Also, the higher the number of pack-years, the higher was the plasma triglycerides and total cholesterol. These observations are in tune with the findings of other workers, [(59)] but pack years was not correlated with HDL, LDL, systolic and diastolic blood pressure in our study.

Our research found that cigarette smoking raises triglycerides, total cholesterol, and LDL and also raise systolic and diastolic blood pressure even if the difference in this two were not statistically significant. Among smokers alcohol consumption was significantly associated with an increase in both systolic and diastolic blood pressure as well as increased HDL-C. Except for HDL-C, these are all risk factors for the development of Metabolic Syndrome. However raised HDL-C may be more complex to interpret, because although high HDL-C appears to protect against cardiovascular disease, whether or not the elevated HDL-C seen here is not clear, since it may involve elevations in detrimental subpopulations of HDL-C particles.

Limitations

This cross-sectional study does not establish that these associations between Metabolic Syndrome parameters and smoking status are caused by the smoking itself, and further, prospective studies would be necessary to assess this. Therefore, the results are merely reflective of associations observed between smoking and clinical/biochemical parameters. In addition, amount of salt intake and other dietary practices that could influence the blood pressure and biochemical parameters were not considered in the questionnaire, and the data rely also the reliability of self-reported information from subjects.

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