RESEARCH ARTICLE

EFFECT OF ACTIVE SMOKING ON GLUCOSE TOLERANCE AND LIPID PROFILE

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ABSTRACT

Background: The acute effects of cigarette smoking in smokers include dyslipidemia and impaired insulin action that leads to abnormal glucose metabolism. Both dyslipidemia and insulin resistance are well-established major risk factor for cardiovascular disease.

Aims & Objective: To ascertain the prevalence of several degrees of glucose abnormalities in smokers and to assess the impact of active tobacco smoking on lipids profile in adult male population.

Material and Methods: A cross-sectional study was conducted with one hundred and fifty two active adult male smokers defined by persons smoking cigarettes over 2 pack years and fifty age and Body Mass Index (BMI) matched healthy control. Smokers were classified into mild to moderate (Group I) and severe (Group II) based on the number of pack years as 2 – 10 and more than 10 respectively. Glucose tolerance was assessed according to American Diabetes Association (ADA) guidelines and standard methods were adopted to check the lipid levels. Data analyses were performed with the SPSS 15.0 statistical software.

Results: An abnormal glucose metabolism was diagnosed in 66% (95% confidence interval [CI], 61.4%-71.6%) of the smokers. The mean HOMA-IR (Homeostasis model assessment-insulin resistance) in smokers was 6.8 + 3.1. Decreasing glucose tolerance was associated with insulin resistance i.e. from normal glucose tolerance condition through IGT, IFG to diabetic, the HOMA IR progressively increased (4.9 + 2.1, 6.7 + 4.2, 7.4 + 3.1 and 8.9 + 3.7 respectively). Atherogenic index as indicated by total cholesterol/HDL cholesterol and LDL cholesterol/HDL cholesterol ratio was significantly elevated in both the smoker groups as compared to non-smokers. According to the Adult Treatment Program III criteria, the metabolic syndrome was diagnosed in 44.07% (95% CI, 35.9%-47.3%) of the smokers. In fact only 10 participants (6%, 95% CI, 5.4% - 7.1%) showed good control of cardiovascular risk factors.

Conclusion: Abnormalities in lipid profile and glucose tolerance are directly correlated with smoking pack years in this study. Intense education program about adverse health events of smoking should be under taken through all means.

KEY-WORDS: Smoking; Glucose Tolerance; Lipid Profile; Cardiovascular Risk Factors

Introduction

Smoking, a global escalating public health problem, is estimated to kill 6 million people, causes hundreds of billions of dollars of economic damage worldwide each year and is practiced by approximately one-third of the male adult population accounting for approximately 120 million smokers in India.[1] Smoking related-diseases causes more deaths each year than by all deaths from human immunodeficiency virus (HIV), illegal drug use, alcohol use, motor vehicle injuries, suicides, and murders combined.[1]

In fact, a smoker's life expectancy is, on average, 13 years shorter than a nonsmoker's life expectancy.[2] Thus, cigarette smoking is now acknowledged to be one of the leading causes of preventable morbidity and mortality and is one of the largest single preventable causes of ill health particularly associated with/of coronary artery diseases. Over 30% of the population attributable risk for myocardial infarction is directly attributable to smoking.[3] The adverse effects of smoking on cardiovascular disease (CVD) risk are mediated through multiple interrelated mechanisms, including increased oxidative stress, endothelial injury and dysfunction, altered blood coagulation and derangements of lipid composition and metabolism.[4,5] In addition, an acute effect of cigarette smoking is, to increase the activity of the sympathetic nervous system and

the levels of circulating catecholamines.[6] Since catecholamines are powerful antagonists to insulin action[7], smoking may be linked to insulin resistance, that leads to impaired glucose and lipid metabolism[8] and a wealth of evidence indicates that insulin resistance, abnormal glucose and lipid metabolism are independent risk factors for CVD. Thus, in smokers, early diagnosis and treatment of an abnormal glucose metabolism may be particularly important to reduce cardiovascular disease.

Keeping in view the paucity of data on smoking related issues in India and the expected adverse effects of smoking on coronary function profile, this study was carried out to assess the impact of active tobacco smoking on glucose tolerance and lipids profile in male population.

Materials and Methods

This was an analytical observational cross-sectional study comprising of 152 healthy regular habitual adult male smokers defined by persons smoking cigarettes over 2 pack years and 50 age-matched healthy non-smokers selected through convenient non probability sampling. Participants with any severe illness (such as malignancy, severe infection, respiratory disease, renal disease, liver disease), using continuous or periodic steroid drugs, ex-smokers, family history of lipid disorders, alcoholic, females, lack of approval by physician and persons showing disinterest were excluded from the study. The primary end point was a combination of the prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM). Secondary end points were the prevalence of metabolic syndrome according the National Cholesterol Education Program III (ATP III guidelines).[9] In addition, we assessed the proportion of participants in whom cardiovascular risk factors (CVRFs) were not under control as established by the ATP III[9] guidelines.

All participants were studied as outpatient. Participants were interviewed for medical and nutritional history. Present and past history of each case was recorded in detail regarding their general information i.e. name, age, sex, address, religion, occupation, economic status, nutritional and personal habits, education, medication and history suggestive of any systemic illness. Each participant was then examined for various anthropometric parameters: Weight (Kg) and height (meters) were measured (using Omron digital body weight scale HN-286 and SECA 206 wall mounted metal tapes respectively). Body Mass Index (BMI) was calculated by Weight (Kg)/ height squared (m^2).[10] Waist circumference was assessed in the standing position, midway between the highest point of the iliac crest and the lowest point of the costal margin in the midaxillary line. Hip circumference was measured at the level of the femoral greater trochanter. All anthropometric measures reflect the average of 3 measurements (measured by same person on same instrument to avoid inter-instrument and inter personal variation). Blood pressure (BP) was measured three times in the seated position after 10 minutes of rest with a standard manual mercury sphygmomanometer (Diamond Deluxe Industrial Electronics and Products). The recorded pressure of the three measurements was averaged. Participants were assigned to a category of hypertensive status according to the Seventh Report of the Joint National Committee, JNC 7.[11] Hypertension(HTN) was defined with a systolic blood pressure equal to or exceeding 140 mmHg or diastolic BP equal to or exceeding 90 mmHg, and those who had used BP lowering medications. Age was defined as the age at the time of interview (though no documentary proof had been entertained) and smoking history was obtained from the patient which was then used to calculate smoking pack per year by using formula, {(Number of cigarettes smoked per day × Number of years smoked)/20}. In our study, smokers were classified into mild to moderate (Group I) and severe (Group II) based on the number of pack years as 2 – 10 and more than 10 respectively.

After an overnight fast of 12 hours, a standardized oral glucose tolerance test (OGTT) was performed following ADA guidelines[12], venous sampling was done at baseline and after 120 minutes of glucose taking. Participants with a previous diagnosis of diabetes mellitus were not submitted to the OGTT. Glucose tolerance was assessed according to American Diabetes Association (ADA)[12] i.e. subjects with a fasting plasma

glucose > 126 mg/dl and/or a 2 hour plasma glucose level > 200 mg/dl were considered to have diabetes; subjects with a fasting plasma glucose 110-125 mg/dl and with 2 hour plasma glucose level 140-199 mg/dl were considered to have impaired fasting glucose(IFG) and impaired glucose tolerance(IGT) respectively; and subjects with fasting plasma glucose < 110 mg/dl and 2 hour plasma glucose < 140 mg/dl were regarded as having normal glucose tolerance (NGT).

Serum and plasma was separated by centrifugation of blood sample and were subjected for analytical procedures. Glucose (Glucose oxidase method, CV % : 3.4)[13], cholesterol (Cholesterol oxidase method, CV % : 3.9)[14], triglycerides (Enzymatic method, CV % : 3.6)[15], HDL-C (Phosphpotungstic method, CV % : 4.7)[16], and HbA1C (Ion exchange resin method, CV % : 3.9)[17], were measured in fully automated analyzer (Bayer express plus). LDL and VLDL cholesterol[18] were calculated. Adult Treatment Panel III (ATP III) criteria[9] were used to classify plasma lipid levels.

Plasma insulin was measured by a highly specific immunoradiometric assay (CV % : 4.1)[19] with a two-site monoclonal antibody. Quality was controlled using standard solutions. HOMA IR (Homeostasis model assessment-insulin resistance) was used as a surrogate for the direct measurement of insulin resistance and was calculated as follows[20]:

HOMA IR= *fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5.

The prevalence of the metabolic syndrome was also assessed according to the ATP III criteria[9]; when three or more of the following five conditions were present: abdominal obesity (waist circumference ≥ 102 cm in men, ≥ 88 cm in women); serum triglycerides equal to or greater than 150 mg/dl; HDL cholesterol less than 39 mg/dl in men; systolic blood pressure equal to or greater than 130 mm Hg and/or diastolic blood pressure equal to or greater than 85 mm Hg; and fasting plasma glucose 110 mg/dl or greater. This study was carried out from February 2011 to April 2012 and was approved by Institutional Human Research Ethical Committee. Written informed consent was obtained from all participants. Data analyses were performed with the SPSS 15.0 statistical software. The results for continuous variables are mean ± SD and are well within the normal curve (i.e. normality is maintained). The two tailed (unpaired) student's test for independent samples, analysis of variance (ANOVA) was used, in assessment of the significance of difference between group means. For all analyses, the nominal level of statistical significance was <0.05.

Results

A total of 152 smokers and 50 controls were included in this study. Smokers were grouped, based on pack years, to group I and group II. Both the groups and control population were comparable in age and BMI. There was no difference noticed among smokers and non-smokers with reference to diet, physical activity and any other lifestyle.

Table-1: Characteristics of Study Population

Characteristics	Control Group (n = 50)	Group I (n = 102)	Group II (n = 50)
Age	41.3 ± 10.3	44.5 ± 9.6	43.1 ± 10.2
BMI (kg/m^2)	22.6 ± 3.9	23.1 ± 4.7	22.9 ± 4.4
Waist/hip ratio	0.91 ± 0.04	0.92 ± 0.06	0.91 ± 0.05
Systolic BP (mmHg)	124 ± 10	134 ± 14*	142 ± 12*
Diastolic BP (mmHg)	78 ± 4	86 ± 8*	88 ± 8*
Fasting plasma glucose (mg/dl)	84.7 ± 11.3	102.4 ± 13.8*	108.4 ± 15.9*
HbA1c (%)	5.7 ± 0.9	6.6 ± 1.3*	7.0 ± 1.6*
Fasting insulin (μU/ml)	14.1 ± 3.2	22.4 ± 4.6†	23.7 ± 4.3†
HOMA IR	2.9 ± 1.6	7.6 ± 2.1†	7.8 ± 2.9†
Triglycerides (mg/dl)	100.6 ± 22.8	113.7 ± 29.2	145.7 ± 29.2*
Total cholesterol (mg/dl)	162.5 ± 29.6	209.5 ± 26.3*	232.2 ± 22.6*
HDL- cholesterol (mg/dl)	44.5 ± 5.4	43.5 ± 4.4	39.5 ± 3.7*
LDL- cholesterol (mg/dl)	87.9 ± 18.4	123.2 ± 31.2*	143.7 ± 21.2*
VLDL- cholesterol (mg/dl)	22.6 ± 5.6	25.6 ± 6.2*	29.5 ± 5.2*
Metabolic syndrome (%)	4	40.8	56

*P<0.05 (Vs Control), †P<0.01 (Vs Control)

Table 1 shows the clinical characteristics of the participants. Hypertension was a concomitant health disorder for most participants. 72% [(CI),

64.7% - 79.2%] showed a systolic and or diastolic B.P. greater than or equal to 140/90 mmHg. The observed values for fasting serum lipid profile clearly indicates abnormalities of lipid profile worsen with increasing smoking pack year. Triglycerides and HDL-C were statistically significant between control and severe smokers only (Table 1).

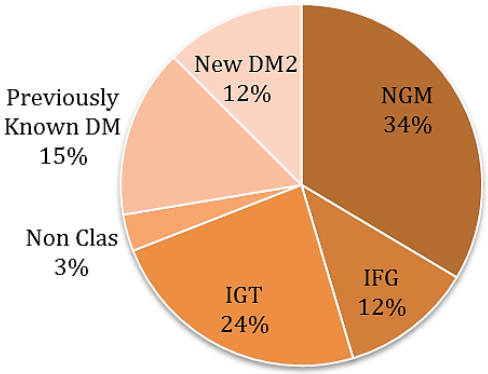

Figure-1: Classification of Smokers According to the Glucose Tolerance. Values are number of subjects (%). NGM: Normal glucose metabolism; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; Previously known DM: Previously known type 1 and type 2 diabetes mellitus; New DM2: Previously undiagnosed type 2 diabetes mellitus; Non Clas: Non-classifiable.

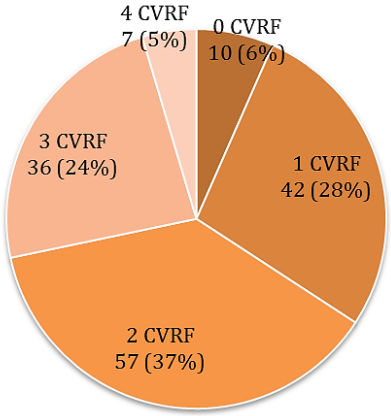

Figure-2: Number of Uncontrolled Cardiovascular Risk Factors (CVRFs). Values are number of subjects (%).

Of the 152 smokers participants, there were 51 (34%, 95% CI, 29.6% - 38.3%) with a normal glucose metabolism (Figure 1). An abnormal glucose metabolism was diagnosed in 66% (95% confidence interval [CI], 61.4%-71.6%) of the smokers. Impaired fasting glucose and impaired glucose tolerance was diagnosed in 12% (95% CI, 8.8%-13.2%) and 24% (95% CI, 17.1%-28.9%) respectively. Twenty three of the 152 smokers (15%) reported a previous diagnosis of diabetes mellitus (8 with type 1 diabetes and 15 with type 2 diabetes). Silent undiagnosed type 2 diabetes was shown in 12% (95% CI, 9.3%-16.6%) of the smokers. The mean HOMA-IR in smokers was 6.8 ± 3.1. Decreasing glucose tolerance was associated with insulin resistance i.e. from normal glucose tolerance condition through IGT, IFG to diabetic, the HOMA IR progressively increased (4.9 ± 2.1, 6.7 ± 4.2, 7.4 ± 3.1 and 8.9 ± 3.7 respectively). According to the ATP III criteria, the metabolic syndrome was diagnosed in 44.07% (95% CI, 35.9%-47.3%) of the smokers. In fact only 10 participants (6%, 95% CI, 5.4% - 7.1%) showed good control of cardiovascular risk factors. Most participants (100, 65.78%; 95% CI, 60.3%-69.4%) showed two or more uncontrolled CVRFs (Figure 2). Of the CVRFs, blood pressure was the most affected one and was not optimally controlled in 72% of participants, lipids were not optimally controlled in 59% of the participants and weight was not optimally controlled in 29% of participants.

Table-2: Atherogenic Index as Indicated by Various Risk Factors

Characteristics	Control Group (n = 50)	Group I (n = 102)	Group II (n = 50)
TC/HDL-C	3.80 ± 0.49	4.42 ± 0.67*	5.42 ± 0.83†
TC/HDL-C	2.34 ± 0.34	2.87 ± 0.55*	3.63 ± 0.71†

*P<0.05, †P<0.01; TC: Total Cholesterol, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol

Atherogenic index as indicated by various risk ratios are shown in table 2. The risk ratio calculated as total cholesterol/HDL cholesterol and LDL cholesterol/HDL cholesterol was significantly elevated in both the groups.

Discussion

This study shows that cigarette smoking acutely deteriorates glucose tolerance and the level of smoking produces progressive unfavorable changes in serum lipid profile. 152 smokers and 50 non-smokers of comparable age, BMI and WHR were evaluated to examine the effects of smoking on glucose tolerance and lipid profile. Abnormal glucose metabolism was observed in 66% (95% confidence interval [CI], 61.4%-71.6%) of the smokers. The high prevalence of glucose abnormalities was evident despite the exclusion of patients with previously diagnosed diabetes

mellitus (15%). This effect is probably due to diminished sensitivity to insulin as indicated by significantly elevated HOMA IR index in smokers as compared to control group. Several mechanisms have been suggested to explain this, which includes, decrease in cellular glucose uptake and utilization i.e. impairment of mechanism involving early steps in insulin action (e.g. signal transduction, glucose transport, and/or glucose phosphorylation)[21] or by mechanisms operating simultaneously on different biochemical pathways. Nicotine may have direct or indirect effect via interaction with insulin receptors and for post receptive events. Smoking causes increased release of catecholamines[22], which might reduce the number of insulin binding sites as well as decreasing the synthesis of glucose transporters. There may also be other indirect effect of smoking on insulin action; such as, elevated levels of FFA, which impair insulin-mediated glucose uptake.[23]

The elevated mean HOMA-IR in these patients suggests that IR and hyperinsulinemia may contribute to the expression of CVRFs.[24] In addition, the present study diagnosed IFG, IGT, and silent undiagnosed diabetes in 45.3% of the study group and all these conditions substantially increases cardiovascular risk.[25]

Markers of smoking burden, i.e. cigarettes pack/years were associated with higher total cholesterol, LDL-C, and TG, along with lower HDL-C levels. Participants in the lower quintile (group I) of smoking burden had more favorable total cholesterol, LDL-C, and HDL-C particles than those with a greater smoking burden (group II), thereby revealing a direct dose response relationship. A plethora of evidence suggests that oxidation of low density lipoprotein generates potent proatherogenic mediators and may thus mediate an important role in the development of atherosclerotic vascular disease. The mechanisms by which smoking causes dyslipidemia includes increased catecholamine release, causing a surge in circulating free fatty acids, which may increase VLDL and LDL concentrations and reduce HDL-C concentrations.[26] Smoking reduces lecithin-cholesterol acyl-transferase, the enzyme responsible for etherifying free cholesterol and increasing HDL size[27], and may reduce levels of cholesterol ester transfer protein

The atherogenic ratios that indicate the risk for the development of atherosclerosis were found to be significantly elevated in smokers when compared to controls. The degree of IR and the extent of the related metabolic abnormalities are also strongly associated with smoking habits (Table 1). The constellation of these altered lipoproteins along with IR and abnormal glucose metabolism suggests that smokers are at a high risk for the development of cardiovascular disease.

Thus, the results of our study are particularly relevant. They contribute to disclose a substantial metabolic disturbance in smokers. Whether glucose tolerance should be routinely investigated in smokers is a challenging question because the magnitude of the added benefit from earlier detection of abnormal glucose metabolism is uncertain, however if one considers that undetected diabetes mellitus increases coronary heart disease by a factor of 2 or more and that specific therapies are clearly effective in reducing coronary heart disease, the magnitude of the cardiac benefit from an earlier detection of diabetes may be potentially substantial.

Conclusion

Metabolic abnormalities (glucose intolerance, altered lipid profile) are directly correlated with and smoking and duration of smoking pack years in this study. From the results, it may be concluded that, cigarette smoking induces IR and dyslipidemic state in the direction of increased risk for coronary artery disease. So it is strongly recommended to avoid smoking for the benefit of cardiac health and we underscore the need for the implementation of smoking prevention and health promotion programmes. Thus, findings from the present study have both clinical as well as public health implications.

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