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ASSESSMENT AND COMPARISON OF CARDIOVASCULAR RISK FACTORS AMONG SMOKERS AND TOBACCO CHEWERS

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ABSTRACT

Many adverse health effects have been reported with the use of tobacco (smokeless) in populations, including CVDs, buccal cavity cancers, soft tissue lesions of mouth and gum recession. The purpose of Present study is to evaluate and compare specific cardiovascular risk factors in individuals using smoked and smokeless tobacco products. Total of 220 age matched , male subjects were selected to participate in the study, who had a history of smoking or tobacco chewing or both. Base line history was collected through a questionnaire and anticoagulated venous blood samples were collected and analyzed for plasma glucose, lipid profile and blood glutathione levels. Results showed that in Pakistan middle class socioeconomic group has high prevalence of both forms of tobacco use. Mean BMI and prevalence of obesity were low in three tobacco groups. Systolic and diastolic BP were high in tobacco users but prevalence of hypertension was more in subjects using both forms of tobacco. Marked lipid profile and glutathione variations were present in all tobacco users. Plasma glucose concentrations also showed a non significant increase in three experimental groups as compared to controls.

Key words: Smokeless tobacco, Cardiac risk factors, Oxidative stress, Cigarette smoking, Tobacco chewing, Hyperlipidemia, Blood glutathione.

INTRODUCTION

Tobacco use is currently increasing in most population groups and in industrialized countries (Thun *et al*., 2000; US department of Health and Human services, 2004) and use of both smokeless and smoked tobacco products are gaining popularity in youth - among males and females both (Ray *et al*., 2003). Cigarette smoking is evidenced as a major risk factor for the prevalence of lung cancers, stroke, chronic obstructive lung diseases and coronary heart diseases (Bartecchi *et al*., 1994). Nicotine, an important substance of tobacco can produce toxic effects on cardiovascular system (Behera *et al*., 2003). Cigarette smoking is a widely prevalent habit however use of smokeless tobacco is present only in certain geographic areas (Warren *et al*., 2000). Smokeless tobacco is the type of tobacco that consumed orally but not smoked (Rogozinski, 2002). Its use is common in Asia (Khawaja *et al*., 2006) and is now being practiced in countries of the Middle East, Far East and Europe (Bates *et al*., 2003), and in USA (Changrani and Gany, 2005). According to Tobacco Control Fact Sheet users of smokeless tobacco were estimated as 100 million in both India and Pakistan (Tobacco control fact sheet, 1996) and about 35–40% (Gupta and Ray, 2003) of tobacco consumption is in smokeless form. Tobacco with lime, betel quid and tobacco tooth powder are common forms of smokeless tobacco in South Asia but the use of new products is also increasing (Gupta and Ray, 2003). Peoples like to use smokeless tobacco products because of their affordability and because of a widely held misconception that use of these products could be beneficial in stomach ach, toothache and headache (Gupta and Ray, 2003). According to some recent studies all forms of tobacco use is associated with oral and pharyngeal cancers (Mack, 2001; Gupta and Ray, 2003; Avon, 2004) and with other malignancies of the upper respiratory and digestive tract (Gupta and Ray, 2003; Bhurgri *et al*., 2004; Warnakulasuriya *et al*., 2005). Tobacco-related cancers contribute one-third of all population cancers in South Asia (Gupta and Ray, 2003) whereas increase of chewing of areca nut and its mixtures is associated with increase incidence of oral submucosal fibrosis in these countries (Gupta and Ray, 2003; Avon, 2004). Present study is designed to evaluate and compare specific cardiovascular risk factors in healthy adult individuals, associated with the use of smoked and smokeless tobacco products.

MATERIAL AND METHODS

Three collection camps were organized in urban areas of Karachi city from March 2007-November 2007. Aims, objectives and methodology of the study were explained in advance to local authorities and the work was done with their permission. All subjects were explained the criteria of study and a written consent was obtained from them. Subjects who consumed tobacco (smoked, smokeless) for more than eight years were included in the study. All 220 subjects were divided into four experimental groups. Group I: Normal control subjects (not using any form of tobacco. N = 55). Group II: Include smokers (not using any smokeless product. n = 55). Group III: Users of

smokeless tobacco (chewable form: *gutka, paan, tumbako*. n=55). Group IV: Subjects who are using both smoked and smokeless tobacco products (n=55).

Subjects selected for the study were normal healthy adult males of age 18-57 years, however subjects with diabetes mellitus, renal diseases, hepatic diseases, endocrine disorders or who are using drugs with cardiovascular effects were excluded. Base line history from all subjects were collected through a questionnaire then general and cardiovascular physical examination (BMI (body mass index), waist-hip ratio, systolic and diastolic blood pressure) was performed by the interviewer. Venous blood specimens were collected after an overnight fast for the measurement of glucose, glutathione (GSH), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Biochemical analysis: Plasma cholesterol and triglyceride levels were measured using enzymatic kit (Randox, UK), serum HDL-C levels were measured by dextran sulphate Mg (II) methods, using enzymatic kit (QCA, France). Serum LDL-C concentration was determined by polyvinyl sulphate method using enzymatic kit (QCA, France). Plasma glucose concentration was determined by O-Toluidine method (Winckers and Jacobs, 1971). Blood glutathione levels were measured by the method of Beutler *et al*., (1963).

Statistical Analysis: The data expressed as mean ± SEM and were analyzed by unpaired t-test. Value of $P < 0.05$ was chosen as the criteria of statistical significance.

Table I. Demographic Profile of subjects in different experimental groups.

	Experimental Groups			
	Control Group	**Smokers**	**Tobacco Chewers**	**Smokers + Tobacco chewers**
	N = 55	**N = 55**	**N = 55**	**N = 55**
Age (yr)	33.85 ± 1.43	37.16 ± 1.18	39.94 ± 1.30	37.36 ± 0.83
	Range (18-57)	Range (18-54)	Range (18-52)	Range (19-52)
Married	31 (56.3)	34 (61.8)	30 (54.4)	38 (69.0)
Socioeconomic Status				
High	6 (10.9)	5 (9)	4 (7.2)	4 (7.2)
Middle	31 (56.3)	36 (65.4)	27 (49.9)	37 (67.2)
Lower	18 (32.7)	14 (25.4)	24 (43.6)	14 (25.4)
Educational Status				
Illiterate	9 (16.5)	19 (34.5)	10 (18.1)	12 (21.8)
Primary	10 (18.1)	12 (21.8)	15 (27.2)	15 (27.2)
Secondary	20 (36.3)	9 (16.3)	18 (32.7)	11 (20)
Above secondary	16 (29)	15 (27.2)	12 (21.8)	17 (30.9)
Family History of Tobacco Use	20 (36.3)	34 (61.8)	27 (49)	36 (65.4)

Data is presented as Mean ± SEM. Number in parenthesis are percentages.

RESULTS

All experimental groups were matched for age distribution. In subjects of group II, the average duration of smoke was 18 years with an average of 20 cigarettes / day whereas for subjects of group III, average amount of tobacco consumed was 4.8 g /day and the mean duration of use was 16 years. In group IV subjects (smokers + tobacco chewers) mean consumption of cigarettes was 18 / day with 3.2 g of chewable tobacco and average duration of use was 15 years. Present study showed that tobacco chewing as well as smoking was more prevalent among the subjects of middle class socioeconomic status in Pakistan (Table 1). A large number of subjects in all experimental groups completed college level education and were aware of health consequences of tobacco use. There was also a

greater incidence of family history of tobacco use among subjects of tobacco groups. Low body mass index was (non significant; P=0.41) observed in smokers group (table II) as compared to control, tobacco chewers and group IV subjects. Prevalence of obesity (BMI $\geq$ 25 kg/m^2) was high in control subjects (36%) as compared to three tobacco groups. Waist hip ratio was almost same in the three groups and no significant differences were observed. Systolic as well as diastolic blood pressure was greater in tobacco consuming groups. The changes in blood pressure were almost same in smokers and the group of tobacco chewers but in group IV subjects (smokers + tobacco chewers) the values were significantly (P<0.05) high (table II). Prevalence of systolic as well as diastolic hypertension (HTN) was almost same in smokers and tobacco chewers but was high (systolic HTN = 61.8%; diastolic HTN = 58%) in group IV subjects (smokers + tobacco chewers) (Table 2).

Table 2. Comparison of cardiovascular risk factors in subjects of experimental groups.

	EXPERIMENTAL GROUPS			
Variables	**Control Group**	**Smokers**	**Tobacco Chewers**	**Smokers + Tobacco chewers**
	N = 55	**N = 55**	**N = 55**	**N = 55**
Body Weight (Kg)	66.5 ± 1.881	63.85 ± 0.85*	61.65 ± 1.31*	65.18 ± 0.75 ^{NS}
Height (meters)	1.67 ± 0.009	1.69 ± 0.007	1.66 ± 0.009	1.69 ± 0.005
BMI (Kg/m^2)	23.62 ± 0.65	21.88 ± 0.41*	22.24 ± 0.42^{NS}	21.94 ± 0.24*
Overweight / Obesity BMI $\geq$ 25 Kg/m^2	20 (36.3)	3 (5.4)	4 (7.2)	2(3.6)
Waist-Hip ratio	0.87 ± 0.1	0.82 ± 0.1	0.88 ± 0.02	0.84 ± 0.1
Systolic BP (mmHg)	118 ± 1.76	132.03 ± 1.8***	129.47 ± 2.3***	138.76 ± 1.7***
Diastolic BP (mmHg)	77.8 ± 0.99	84.4 ± 1.08***	83.14 ± 1.2***	87.47 ± 0.9***
Systolic hypertension ≥140mmHg	2 (3.6)	22 (40)	21 (38.1)	34 (61.8)
Diastolic hypertension ≥ 90mmHg	2 (3.6)	18 (32.7)	22 (40)	32 (58.1)

BMI = Body mass index; BP = Blood pressure.
Data is presented as Mean ± SEM. Numbers in parenthesis are percentages.
* P < 0.05; ** P < 0.01; ***P < 0.005; NS = non significant (as compared to control).

Biochemical estimations showed that plasma concentrations of total cholesterol, triglyceride and LDL cholesterol were high in smokers, tobacco chewers and group IV subjects (smokers + tobacco chewers) (Table 3). However among group II and III subjects significant (P<0.05) lipid profile elevations were found in smokers group. Plasma HDL cholesterol concentrations were low in the three tobacco groups, but significantly low values were observed in group III (P<0.05) and IV subjects (P<0.05) as compared to controls. Prevalence of hypercholesterolemia and hypertriglyceridemia was also high in the three tobacco groups (table III). Plasma glucose concentrations were not significantly different in experimental groups except in group IV (smokers + tobacco chewers) where the value comes significantly higher (P<0.05) than control group (Table 3). Blood glutathione concentrations in the three groups of tobacco users were low as compared to control groups but most significant reduction (P<0.05) was observed in group IV subjects (smokers + tobacco chewers) (Table 3).

Table 3. Biochemical estimations in subjects of experimental groups.

Variable	EXPERIMENTAL GROUPS			
	Control Group	**Smokers**	**Tobacco Chewers**	**Smokers + Tobacco chewers**
	N = 55	**N = 55**	**N = 55**	**N = 55**
Total Cholesterol (mg/dl)	165.30 ± 4.2	194 ± 6.9***	188.12 ± 7.9**	200.4 ± 8.42***
Hypercholesterolemia; Cholesterol ≥200	10 (18)	23 (41.8)	15 (27.2)	27 (49.0)
Triglyceride (mg/dl)	164.0 ± 10.6	139.0 ± 10.4NS	185.54 ± 8.5NS	190.7 ± 11.6NS
Hypertriglyceridemia; Triglyceride ≥ 150	28 (50.9)	20 (36.3)	37 (67.2)	32 (58.1)
HDL Cholesterol (mg/dl)	54.50 ± 1.5	50.15 ± 1.9NS	45.74 ± 2.1***	44.28 ± 2.1***
Low HDL < 40	04 (7.2)	11 (20)	14 (25.4)	22 (40)
LDL Cholesterol (mg/dl)	77.99 ± 2.6	116.15 ± 5.0***	105.2 ± 6.5***	118.05 ± 6.7***
High LDL ≥ 150	0	21 (38.1)	9 (16.3)	14 (25.4)
Glucose (mg/dl)	79.52 ± 1.9	83.29 ± 1.8NS	81.8 ± 1.8NS	85.63 ± 1.7*
Glutathione (umol /g of Hb)	4.59 ± 0.19	2.18 ± 0.1***	2.89 ± 0.2***	1.72 ± 0.1***

HDL=high density lipoprotein; LDL=low density lipoprotein.
Data is presented as Mean ± SEM. Number in parenthesis are percentages.
* P < 0.05; ** P < 0.01; ***P < 0.005; NS = non significant.(as compared to control)

DISCUSSION

Tobacco is the most important cause of death worldwide (Brundtland, 2000) and by 2030, it is estimated to cause over 10 million annual deaths globally (John, 2005; Warnakulasuriya *et al*., 2005), out of which 70% will be in the developing world. Smokeless tobacco use could be as harmful as smoked tobacco (Behera *et al*., 2003) and owing to its prolonged absorption chewing tobacco could produce significantly greater cardiovascular effects than smoked tobacco (Pais *et al*., 2001). Results of present study showed that use of all types of tobacco products was more prevalent among subjects of middle class socioeconomic status in Pakistan (Table I). Prevalence of family history of tobacco use in present study was found to be high in the three tobacco groups and the result is in accordance of other studies (Gupta, 1996; Gupta *et al*., 2003). Results of present study were showing that BMI in smokers was lower as compared to tobacco chewers and as compared to control subjects (table II). This is because of the fact that smoked tobacco interferes more adversely with eating habits as compared to smokeless tobacco (Gupta *et al*., 2007). Prevalence of obesity (BMI ≥25 kg/m^2) was also high in non tobacco users as compared to other experimental groups. High systolic and diastolic blood pressures were observed in the three tobacco groups but significant increase was in group IV subjects. Prevalence of systolic as well as diastolic hypertension was also high in group IV subjects. Sympathomimetic effect of nicotine on cardiovascular system can explain this increase in blood pressure in our experimental groups. Increased plasma total cholesterol, triglyceride and LDL-C levels were observed in subjects of group II, III and IV. Tobacco based stimulation of free fatty acid metabolism in peripheral

tissues could explain this increase in plasma levels of lipids in tobacco users (Bartecchi *et al*., 1994). Khurana *et al*., (2000) also reported similar results in his study. Increased plasma LDL concentration in animal model of monkeys with nicotine feeding was reported by Brown *et al*. (1986) and the mechanism is identified as impaired clearance and accelerated synthesis of LDL through lipolysis of HDL. In late 1980s, Feskens and Kromhou (1989) first pointed out use of tobacco as a risk factor for type II diabetes in men, later it is confirmed in both men and women and among heavy smokers by Will *et al.* (2001) and Manson *et al.* (2000). Eliasson *et al.* (1993; 1991) in his study of university students reported that blood glucose concentration was same between smokers, snus users and non users but they had higher serum insulin levels. The exact relationship between smoking and insulin resistance is still obscure but muscle biopsies in smokers show that insulin based glucose transport is impaired (Rincon *et al.*, 1999). Present study also showed non significant changes in plasma glucose concentration in the three tobacco groups. Use of both smoked and smokeless tobacco products is associated with buildup of oxidative stress. Many research studies has confirmed that cigarette smoke contains oxidant gases that are responsible for increased oxidative stress together with increased lipid peroxidation and endothelial dysfunction (Morrow *et al*., 1995; Duthie *et al*., 1993). Yildiz *et al*., (1999) showed that smokeless tobacco extract can increase oxidative stress more than pure nicotine. Avti *et al*., (2006) in animal models (rats) demonstrated that oral administration of aqueous extract of smokeless tobacco at a low dose of 96mg/kg of body weight per day for 2-32 weeks significantly decrease hepatic GSH and glutathione peroxidase (GPx) levels and increase lipid peroxidation. Samal *et al* (2006) in his study demonstrated that the use of oral smokeless tobacco decreases erythrocyte superoxide dismutase (SOD) and glutathione reductase levels in humans. Blood glutathione concentration in the three groups of tobacco users studied were low as compared to control groups but most significant reduction was observed in group IV subjects (smokers + tobacco chewers). Present study concludes that prevalence of multiple cardiovascular risk factors is high in both tobacco chewers and smokers and they are at high risk of mortality from cardiovascular diseases Although the changes in tobacco chewers were not as much significant as in smokers but are significant as compared to controls.

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