"Is Smokeless Tobacco use a risk factor for Coronary artery disease? A comparative study of smokers and smokeless tobacco users”.

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Abstract:
Coronary artery disease (CAD) is a major cause of premature death and disability throughout the world. Tobacco use is an important and avertable cause of CAD. The use of tobacco is on the rise worldwide especially among the youth. So the present study was carried out in 400 young males to evaluate & compare the cardio vascular disease risk factors in smokers & smokeless tobacco users- tobacco chewers & Kharra chewers. Tobacco users had significantly higher cardiovascular disease risk factors- C reactive protein & lipid profile (except HDL) than non users. The C reactive protein & lipid profile differences between smokers & tobacco chewers were found to be non significant while Kharra chewers had significantly lower values than smokers & tobacco chewers. The deleterious cardiovascular risk factors were considerably less in Kharra chewers than cigarette smokers & tobacco chewers. Excessive risks in tobacco users than non users bestow grounds to initiate and strengthen the programs to inform the public of the harmful nature of all forms of tobacco use.

Key words: C reactive protein (CRP), lipid profile, cardio vascular disease, Tobacco, Smokeless tobacco.
INTRODUCTION: Coronary heart disease is a leading cause of morbidity & mortality in developed countries & is emerging as an epidemic in developing countries. [1] A substantial proportion of population in India is exhibiting increasing prevalence of cardio-vascular disease and associated risk factors.

Trends are believed to be due to influence of life style habits like sedentary life style, dietary patterns, alcohol abuse and tobacco use. Both the smoking and the nonsmoking forms of tobacco use are common in India. 30% of population, 15 years or older - 47% men & 14 % women either smoke or chew tobacco [2]. Prevalence of smokeless tobacco consumption in India is 20%. [3] According to recent reports, by year 2030 the developing world is expected to have 7 million deaths annually from tobacco use [4]. Previous studies have found the association of tobacco with the increased rates of traditional cardiovascular risk factors like hypercholesterolemia, hypertension, obesity etc. In addition, novel nontraditional cardiovascular risk factor related to chronic subclinical inflammation like C - reactive protein was further contributing to burden of cardiovascular diseases [5, 6]. Increased serum concentrations of C-reactive protein, considered as an independent predictor of ischemic heart disease, have been documented in adult Oji-Cree of the sandy lake First national community in northwestern Ontario [7].

The increased appeal and use of smokeless tobacco has generated considerable public health concern because research indicates that chewing tobacco can be significant health hazard. Detrimental cardiovascular effects of smoking are well documented; possible health hazards of smokeless tobacco remain controversial. Tucker, Benowitz & Russel have studied the effect of smokeless form of tobacco association with cardiovascular risk factors [8, 9, 10]

In India very few studies have been done to gauge the effects of smokeless form of tobacco use on cardio-vascular risk factors and its comparison with tobacco smoking. So we undertook the cross sectional study to explore and compare cardiovascular risk factors in young men with different pattern of tobacco use like smokeless tobacco use and smoking.

MATERIALS AND METHODS: A total four hundred male volunteers of age group 20-30 yrs were studied. The study groups were selected from the employee of Indira Gandhi Govt. Medical College, Nagpur and community dwellers from the Nagpur & periphery of Nagpur in India. Considering the objectives of study, selection criteria were formed & accordingly the groups of the study were defined. The groups were as follows:

All the subjects were not suffering from any known cardiovascular and medical problems, were not taking hypolipidemic drugs & had no acute illness symptoms at the point of entry. Then the study groups were divided into four groups according to
following criteria:

**Group I: Smokers (100 subjects)**
Those who smoke ≥ 10 cigarettes per day, regularly at least for last 10 years were selected & included in the study.

**Group II: Tobacco chewers (100 subjects)**
Those who chew tobacco regularly two packets (10gm) per day for last 10 years were selected & included in the study. Tobacco is dried crushed leaves powder mixed with lime.

**Group III: Kharra chewers (100 subjects)**
Those who chew Kharra regularly, 5 packets (10 gm) per day, for last 10 years were selected and included in the study. Kharra is homogenous mixture of dried crushed leaves with areca nut and slacked lime.

**Group IV: Controls (100 subjects)**
Those who have never chewed or smoked tobacco were selected for the study.

The institutional ethics committee approved the study. Experimental protocol was fully explained to all the subjects and written consent was obtained. Detailed medical history, family history and personal history with special reference to the history of tobacco use at present and past was recorded. Height & weight were recorded. BMI was calculated.

Under all the aseptic precautions, 5ml fasting blood sample was obtained from each subject with the help of disposable syringe and needle. Serum was separated. Lipid profile estimation was done by enzyme kit method. Readings were taken on semi auto analyzer. C-reactive protein estimation was done by turbimetric method.

**STATISTICAL ANALYSIS:**
All the data was expressed in mean ± SD format. The groups were compared by using ANOVA test. Post hoc comparison by Bonferroni’s multiple comparison tests using Graph Pad 5.1 software.

**OBSERVATIONS & RESULTS :**
The anthropometric parameters of various groups are given in table I. The results of ANOVA test are depicted in table II.

The mean age of smokers (Group I), Tobacco chewers (Group II), Kharra chewers (Group III), and Control group (Group IV) were 25.34, 25.39, 25.3 & 25.04 years respectively and the statistical difference was found to be non significant (table II). The prevalence of tobacco use is more in early to middle age groups, so we selected this age group.

No significant difference in age, height or BMI was found among the various groups studied, indicating that the samples were homogenous in this respect. (table II)

However, the lipid profile parameters like serum cholesterol, Triglyceride (TG), Very Low Density Lipoprotein (VLDL), Low Density Lipoprotein (LDL) showed increasing trends in their means from controls → Kharra chewers → Tobacco
chewers → smokers. Highest values were found in the smokers and lowest for the controls. Similar trend was observed for the C reactive protein (CRP) values. Highest values were found in the smokers (16.33 ± 12.74 g %) and lowest for the controls (3.56 ±1.3 g %). While for the High Density Lipoprotein (HDL) values, trend was found to be reverse i.e. Smokers had the lowest value (29.14±4.7 mg %) and controls had the highest value (46.26±6.7 mg %) and decreasing trend was observed from controls → Kharra chewers → Tobacco chewers → Smokers.

These trends were found to be statistically significant when compared amongst various groups. However the difference between Group I & Group II (smoker and tobacco chewer) was found to be statistically non significant .(table II)

The findings of our study were-
1. Tobacco users (smokers & smokeless tobacco users) had significantly higher lipid profile (except HDL) values than controls.
2. Tobacco users (smokers & smokeless form of tobacco users) had significantly higher C- reactive protein levels than controls.
3. The lipid profile & C- reactive protein level differences between smokers & tobacco chewers were found to be non significant.

**DISCUSSION:** Nicotine is a principle component of all forms of tobacco use. Nicotine poses considerable risk of many health related problems. Smoking or Smokeless tobacco acts as a medium to transport nicotine to the body. Both Smoking and Smokeless tobacco use leads to almost equal blood nicotine levels. [10,11, 12] Nicotine’s effect on cardiovascular disease is by affecting lipid metabolism, coagulation & hemodynamic status. [12]

In support to these clinical observations, Brischetto et al [13] proposed a mechanism to explain the link between smoking and some of the observed changes in serum lipid profile and lipoprotein concentrations. (a) Nicotine stimulates release of adrenaline by the adrenal cortex, leading to the increased serum concentrations of free fatty acids (FFAs) observed in smokers. [14, 15, 16] (b) Free fatty acids are well known stimulants of hepatic secretion of VLDL and hence TG. HDL concentration varies inversely with VLDL concentration in serum. [17] Complementary to these mechanisms is the finding that free fatty acids (FFAs) also stimulate hepatic synthesis and secretion of cholesterol. [18]

Tobacco users had significantly higher C-reactive protein levels than controls. Recent studies provide evidence that inflammation plays a role in pathogenesis of cardiovascular disease. Circulating level of C-reactive protein may constitute an independent risk factor for cardiovascular disease.
C-reactive protein may directly interact with atherosclerotic vessels of ischemic myocardium by activation of complement system, thereby promoting inflammation & thrombosis. Acute phase responses are induced by cytokines released from jeopardized tissue which stimulate liver to synthesize acute phase protein including C-reactive protein.

Tobacco users - smokers & smokeless tobacco users (Tobacco chewer & Kharra chewers) face significantly higher risk of cardiovascular disease than non users. G Bolinder et al, F Huhtasari & K Asplund reported higher risk of death from cardiovascular disease in smokers & smokeless tobacco users than non users. Statistically no significant difference was found in lipid profile parameters (Serum Cholesterol, TG, LDL, and VLDL) & C-reactive protein in Smokers & Tobacco chewers. However Kharra chewers had significantly lower lipid profile parameters & C-reactive protein than smokers & tobacco chewers.

D Siegel & Benowitz NL suggested similar cardiovascular hazards in smokers & smokeless tobacco users. They reported maximum level of nicotine is achieved because of prolonged absorption by single exposure to smokeless tobacco, was twice as large as compared to cigarette smoking.

G Bolinder et al, F Huhtassari & K Asplund suggested lower risk in smokeless tobacco users than smokers. Smokeless tobacco is associated with less serious health hazards than cigarette smoking. Carbon monoxide or aromatic hydrocarbon toxicity induce damage to vessels wall or enhance the probability of coronary thrombosis by inducing hypercoagulable state.

Overall goal to improve the public health should address the issue of tobacco consumption. Prevention of tobacco consumption both in smoking and smokeless forms could be an important intervention in preventing ongoing upswing in prevalence of coronary heart disease that is throttling to engulf every region of the world.

REFERENCES:

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16. Kershbaum A, Khorsandian R, Caplan RF, Bellet S, Feinberg LJ. The role of catecholamines in the free fatty acid response to...
Table I. Table showing mean and standard deviations of various parameters:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Smokers</th>
<th>Group II Tobacco chewers</th>
<th>Group III Kharra chewers</th>
<th>Group IV Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>25.34 ± 5.45</td>
<td>25.39 ± 3.53</td>
<td>25.30 ± 8.04</td>
<td>25.04 ± 6.47</td>
</tr>
<tr>
<td>Height (Meters)</td>
<td>1.63 ± 0.08</td>
<td>1.66 ± 0.04</td>
<td>1.64 ± 0.04</td>
<td>1.63 ± 0.02</td>
</tr>
<tr>
<td>Weight (Kilogram)</td>
<td>56.21 ± 14.1</td>
<td>58.04 ± 0.7</td>
<td>55.2 ± 6.28</td>
<td>55.73 ± 4.91</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>21.16 ± 7.09</td>
<td>21.06 ± 0.37</td>
<td>20.52 ± 3.16</td>
<td>20.98 ± 2.5</td>
</tr>
<tr>
<td>Serum cholesterol (mg%)</td>
<td>228.2 ± 38.6</td>
<td>215 ± 18.3</td>
<td>185.1 ± 38.8</td>
<td>145.7 ± 23.6</td>
</tr>
<tr>
<td>Serum TG (mg%)</td>
<td>113.4 ± 18.7</td>
<td>102.8 ± 2.8</td>
<td>96.8 ± 10.1</td>
<td>72.3 ± 7.5</td>
</tr>
<tr>
<td>Serum VLDL (mg%)</td>
<td>22.68 ± 3.4</td>
<td>20.56 ± 0.5</td>
<td>19.36 ± 2</td>
<td>14.45 ± 1.5</td>
</tr>
<tr>
<td>Serum LDL (mg%)</td>
<td>159.26 ± 31.4</td>
<td>152.13 ± 14.1</td>
<td>128.72 ± 31.3</td>
<td>102.13 ± 19</td>
</tr>
<tr>
<td>Serum HDL (mg%)</td>
<td>29.14 ± 4.7</td>
<td>37.02 ± 7.7</td>
<td>43.17 ± 3.6</td>
<td>46.26 ± 6.7</td>
</tr>
<tr>
<td>C–reactive protein (g%)</td>
<td>16.33 ± 12.7</td>
<td>13 ± 1.4</td>
<td>11.25 ± 2.3</td>
<td>3.56 ± 1.3</td>
</tr>
</tbody>
</table>
Table II. Table showing results of ANOVA test:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Vs. Group IV (t-value)</th>
<th>Group II Vs. Group IV (t-value)</th>
<th>Group III Vs. Group IV (t-value)</th>
<th>Group I Vs. Group II (t-value)</th>
<th>Group I Vs. Group III (t-value)</th>
<th>Group II Vs. Group III (t-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.53 NS</td>
<td>1.66 NS</td>
<td>1.05 NS</td>
<td>1.07 NS</td>
<td>1.11 NS</td>
<td>1.21 NS</td>
</tr>
<tr>
<td>Height</td>
<td>1.11 NS</td>
<td>2.11 NS</td>
<td>2.37 NS</td>
<td>2.01 NS</td>
<td>1.98 NS</td>
<td>1.24 NS</td>
</tr>
<tr>
<td>Weight</td>
<td>2.41 NS</td>
<td>2.44 NS</td>
<td>2.04 NS</td>
<td>2.33 NS</td>
<td>1.88 NS</td>
<td>2.03 NS</td>
</tr>
<tr>
<td>BMI</td>
<td>1.75 NS</td>
<td>2.23 NS</td>
<td>2.21 NS</td>
<td>2.17 NS</td>
<td>1.94 NS</td>
<td>1.61 NS</td>
</tr>
<tr>
<td>Sr. cholesterol</td>
<td>10.37***</td>
<td>8.82***</td>
<td>5.16***</td>
<td>5.21 NS</td>
<td>5.21***</td>
<td>3.65**</td>
</tr>
<tr>
<td>Sr. TG</td>
<td>9.77***</td>
<td>7.25***</td>
<td>5.88***</td>
<td>2.57 NS</td>
<td>3.89***</td>
<td>3.59**</td>
</tr>
<tr>
<td>Sr. VLDL</td>
<td>9.77***</td>
<td>7.25***</td>
<td>5.88***</td>
<td>2.52 NS</td>
<td>3.88**</td>
<td>3.61**</td>
</tr>
<tr>
<td>Sr. LDL</td>
<td>11.46***</td>
<td>9.39***</td>
<td>5.50***</td>
<td>2.07 NS</td>
<td>4.54***</td>
<td>3.89**</td>
</tr>
<tr>
<td>Sr. HDL</td>
<td>8.88**</td>
<td>7.77***</td>
<td>4.34**</td>
<td>1.11 NS</td>
<td>4.52**</td>
<td>3.43**</td>
</tr>
<tr>
<td>Sr. CRP</td>
<td>6.45**</td>
<td>4.76***</td>
<td>3.98**</td>
<td>1.687 NS</td>
<td>2.478**</td>
<td>3.54**</td>
</tr>
</tbody>
</table>

(***: Highly significant; **: Moderate significant; NS : Not significant; Significance set at P<0.05.)

This original research work was conducted in Department of Physiology, Indira Gandhi Govt. Medical College, Nagpur, Maharashtra by Dr. Prathmesh Kamble with Dr. Mamta V Rode, Dr. Mrunal S Phatak and Dr. Prashant Tayade.

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