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EFFECT OF CIGARETTE SMOKING ON SERUM HOMOCYSTEINE AND FOLIC ACID LEVELS IN APPARENTLY HEALTHY MALE SMOKERS

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ABSTRACT

Background: Globally, smoking cigarette is one of the most common reason for demise which is preventable. In those who smoke, altered levels of serum homocysteine and that of folic acid have been noted to aggravate the development of atherosclerosis and cardiovascular complications. Therefore the level of these two sensitive biomarkers may aid in detecting early the changes leading up to such complications in those who smoke. **Aim:** The aim of the study was to observe the serum levels of homocysteine and folic acid in smokers and compare these parameters with that of non smokers. **Materials and Method:** This research work (cross sectional in nature) was conducted on 90 apparently healthy male recruits (age between 20-60 years) in Sir Salimullah Medical College (SSMC), Dhaka. The department in which the study took place was the Physiology department. The duration of the research was one year (July 2019 – June 2020).Sixty out of the ninety recruits were considered as group A and those included in this group were smokers. This group A was further split in to 2 groups (Group A_1 and A_2) in accordance to the pack-years of smoking. The A^1 group consisted of those having history of 5-10 pack years of smoking and the A^2 group included those having >10 pack-years history of smoking. Thirty non smokers with matching age and body mass index (BMI) were included as the control group for making comparison with the study group and was termed as group B.The parameters assessed were levels of homocysteine and folic acid in the serum. **Results:** The study observed the level of homocysteine in serum was significantly greater in recruits who smoke than those recruits who do not smoke with p value <0.001.The levels of folic acid in serum noted to be lower significantly (p<0.001) in smoking recruits when compared to non smoking recruits. Such alterations were more profound in the smokers with >10 pack-year of smoking history. Besides this, positive correlation between pack year history of smoking and level of homocysteine in serum (r = 0.948) and the relationship was highly significant statistically (p<0.001) .Levels of folic acid in serum were negatively correlated (r = - 0.844 and r = - 0.863) with pack-year of smoking history which were significant statistically(p<0.001 and p<0.001). **Conclusion:** The present study reveals that serum homocysteine level is significantly higher whereas levels of folic acid in serum are significantly lower among smokers and these changes are more marked in the smokers with >10 pack-years of smoking history.

Keywords: Cigarette smoking, Duration of smoking, Homocysteine,Folic acid, Smoker and non-smoker.

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INTRODUCTION

Smoking has been described as a form of chemical toxicosis that has the ability of causing acute or chronic detriment to various body structures as for example epithelial glands, respiratory system , and cardiovascular system. Another grave outcome of smoking is physical addiction, primarily due to nicotine, that adversely influences smoking cessation[1].

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An individual is termed as a smoker when he smokes any product of tobacco occasionally or on a daily basis while a non smoker is an individual not smoking at all[2].

Smoking cigarette is leading globally as a major reason for demise .It is responsible for a majority of cases of chronic obstructive pulmonary disease and lung cancer and most smokers die either from these or from ischemic heart disease. Smoking also causes cancers of the upper respiratory and gastrointestinal tracts, pancreas, urinary bladder and kidney. There is also increased risk of peripheral vascular disease, stroke and peptic ulceration[3].

Tobacco products contain 50 established carcinogens that raise cancer risk. Smoking attributes to 20% of the causes resulting in cancer [4].The chief pharmacologically active ingredients present in the smoke of cigarette are nicotine, responsible for acute effects (1-2 mg per cigarette) and tars responsible for chronic effects (10-15 mg per cigarette).Tobacco smoke also contains carbon monoxide (1-5%) and carcinogenic substances (polycyclic hydrocarbons and nicotine derived N-nitrosamines)[5] .The form of tobacco smoking which is most common are cigarettes . Other smoking implements include pipes, cigars, bidis and hookahs[6]. The prevalence rate of smoking cigarette at present in our country is 14 %.Males currently smoke cigarette far more when compared to females[7].

Homocysteine (Hcy) is a nonessential sulfur-containing amino acid derived from essential amino acid methionine[8]. Smokers, when compared to non smokers,have significantly increased plasma homocysteine level[9]. Smokers of cigarette with increased plasma homocysteine are at greater risk of developing complications of cardiovascular system[10]. Elevated levels of homocysteine in plasma promote oxidative damage, inflammation, as well as, dysfunction of endothelium.Raised levels of this parameter acts as an independent risk factor that aggravate occlusive vascular disease such as cardiovascular disease (CVD) and stroke[11].

Folatein serum has been found to be lower in smokers as compared to non-smokers[12]. Folate is essential for remethylation pathway of homocysteine which converts homocysteine into methionine[11]. Research works have reported supplementing individuals suffering from hyperhomocysteinaemia (HHcy) with folic acid could reduce homocysteine levels[13] .Folic acid supplementation is not only useful in reducing homocysteine level in a patients with hyperhomocysteinemia[14] but also can significantly improve dysfunction of endotheliumin those having disease of coronary artery[15]. On the other hand, deficiency of folic acid may promote development of hyperhomocysteinemia[16].

Several studies have previously reported alterations in serum folic acid and hcy levels among smokers [9,10,12] .However, research regarding changes in these parameters in this country is sparse and hence this research work was performed to observe whether smoking has effect on serum folic acid and hcy levels. Such research may help contribute towards building knowledge about that impact that smoking has on human health and aid in policy making to encourage smokers to adopt healthy lifestyle.

MATERIALS AND METHOD

This research work which is cross sectional in nature was conducted on 90 apparently healthy male recruits (age between 20-60 years) in Sir Salimullah Medical College (SSMC), Dhaka and the department in which the study took place was the Physiology department. The duration of the research was one year (July 2019 – June 2020) .The participants were enrolled purposively on the basis of the inclusion and exclusion criteria. Criteria of inclusion into the study group (smokers): Male subjects, who appeared to be healthy,

giving history of ≥ 5 pack-years of smoking or smokers of a minimum of 10 sticks of cigarette / day for the last 10 years. Comparison group (Non-smokers): Male subjects, who appeared to be healthy, and do not smoke at all. Criteria of exclusion for the 2 groups: 1. BMI ≥ 30 kg/m^2 2. History of preexisting hypertension, diabetes mellitus, heart disease, chronic hepatic dysfunction, renal disease, nutritional derangements, malignancy, acute infection,pernicious anemia, celiac disease, inflammatory bowel disease, malabsorption, biliary or pancreatic disease. 3. History of alcoholism or drug addiction or ex-smoker.4. History of taking multivitamins, metformin and other drugs affecting homocysteine and folate levels.

Sixty out of the ninety recruits were considered as group A and those included in this group were smokers. This group A was further split in to 2 groups (Group A_1 and A_2) in accordance to the pack-years of smoking. The A^1 group consisted of those having history of 5-10 pack years of smoking and the A^2 group included those having >10 pack-years history of smoking. Thirty non smokers with matching age and BMI were included as the group for making comparison with the study group and was termed as group B. Recruits were selected from the hospital staffs of SSMC and Mitford hospital and hospital of Bangladesh Medical University (BMU), Dhaka as well as through personal contact smokers.

Study Procedure

Institutional Review board of SSMC, Dhaka provided the ethical clearance to go forward with the study. Individuals who fulfilled the abovementioned criteria were informed of the details of the research work. They were enrolled through voluntary participation and were free to withdraw from the research at any time during the study period. Only positive respondents were recruited as research participants after they gave their informed consent in written format.Face-face interviews were conducted with the recruits and for the smokers, information was taken regarding the smoking duration and average number of sticks of cigarette they smoke in a day. pack-year was estimated in order to determine exposure to smoking. Detailed history about personal, family, dietary, medical and occupation were taken from the recruits.Thorough physical examination of all participants were done and all of these information were gathered in a information sheet of data.

Samples of blood were collected from the recruits which were then sent to the Biochemistry and Molecular Biology department of BMU, Dhaka for biochemical analysis. The samples were tested for serum creatinine and serum alanine aminotransferase and fasting blood glucose levels for exclusion of diabetes mellitus, kidney disease and liver disease respectively. Then homocysteine and folate levels in the serum were estimated.

All the data were presented as mean ± SD (Standard deviation). The statistical analysis was done by using Statistical Package of Social Science (SPSS) windows version-22. ANOVA test was performed for comparison among the groups and then Bonferroni test was done to compare between the groups. Unpaired t-test and Pearson's Correlation coefficient test were also performed. Level of significance was taken at p value ≤ 0.05 .

RESULTS

Table 1 shows there were no difference that was significant for age and BMI between group A (smoker) and comparison group B (non-smoker). So, all the subjects were age and BMI matched.

Table 1: Age and BMI of the subjects in both groups (N=90)

Variables	Group A(smoker) (n=60)	Group B(non-smoker) (n=30)	*p*-value
Age (years)	42.85 ± 9.59 (25 - 60)	42.00 ± 12.44 (25 - 60)	0.721^{ns}
BMI (kg/m^2)	23.05 ± 0.91 (20.06 - 24.60)	22.67 ± 1.26 (20.57 - 24.69)	0.113^{ns}

N=total number of recruits; n=number of subjects in each group; ns=not significant; BMI=body mass index

Table 2 shows the values of all the subjects were within the normal reference range. So all the subjects were non diabetic and had normal renal and liver function.

Table 2: Mean fasting blood glucose, serum creatinine and serum ALT levels in both groups (N=90)

Variables	Group A(smoker) (n=60)	Group B(non-smoker) (n=30)	*p*-value
Fasting blood glucose (mmol/L)	4.96 ± 0.52 (4.00 - 5.80)	4.87 ± 0.47 (4.00 - 5.60)	0.462^{ns}
Serum creatinine (mg/dL)	0.89 ± 0.08 (0.75 - 1.10)	0.87 ± 0.09 (0.72 - 1.10)	0.254^{ns}
ALT (U/L)	22.67 ± 6.96 (10 - 36)	21.50 ± 7.21 (10 - 36)	0.461^{ns}

N=total number of recruits; n=number of subjects in each group;ns=not significant; ALT= Alanine amino transferase

Table 3 shows the values of all the recruits were within the normal reference range. So,They were all normotensive and normal pulse rate.

Table 3: Blood pressure and pulse rate of the recruits in both groups (N=90)

Variables	Group A(smoker) (n=60)	Group B(non-smoker) (n=30)	*p*-value
Pulse rate (beats/min)	77.70 ± 6.30 (68 - 90)	78.27 ± 6.12 (68 - 90)	0.686^{ns}
Systolic BP (mm of Hg)	117.33 ± 9.09 (100 - 130)	117.00 ± 9.15 (100 - 130)	0.870^{ns}
Diastolic BP (mm of Hg)	75.08 ± 7.04 (60 - 85)	74.83 ± 7.37 (60 - 85)	0.876^{ns}

N=total number of recruits; n=number of subjects in each group;ns=not significant; BP=blood pressure

Table 4: Mean homocysteine and folic acid levels in serum of both groups (N=90)

Variables	**Group A (n=60)**	**Group B (n=30)**	***p*-value**
Serum homocysteine (µmol/L)	22.52 ± 3.80 (15.20 - 28.80)	11.08 ± 0.94 (9.80 - 13.36)	$<0.001^{***}$
Serum folic acid (ng/mL)	4.87 ± 1.94 (2.00 - 9.60)	13.72 ± 1.19 (11.60 - 15.80)	$<0.001^{***}$

N=total number of recruits; n=number of subjects in each group;***=statistically significant

Table 4 displays the mean (±SD) level of homocysteine in serumof the recruits of group A and group B (22.52 ± 3.80 and 11.08 ± 0.94 μmol/L respectively). In this study the mean (±SD) level of homocysteine in serumwas significantly (p<0.001) higher in group A when compared to group B. The mean (±SD) serum folic acid level of the recruits were 4.87 ± 1.94 and 13.72 ± 1.19 ng/mL in group A and group B respectively. In this study the mean (±SD) serum folic acid level was significantly (p<0.001) lower in group A in comparison to that of group B.

Table 5 : Mean levels of homocysteine and folic acid in serum of different groups (N=90)

Variables	Group A_1 (n=30)	Group A_2 (n=30)	Group B (n=30)
Serum homocysteine (μmol/L)	19.54 ± 2.67 (15.20 - 22.50)	25.49 ± 2.00 (21.90 - 28.80)	11.08 ± 0.94 (9.80 - 13.36)
Serum folic acid (ng/mL)	6.31 ± 1.63 (4.50 - 9.60)	3.43 ± 0.82 (2.00 - 4.90)	13.72 ± 1.19 (11.60 - 15.80)

Multiple comparisons

	Serum homocysteine	Serum folic acid
	p-value	*p*-value
A_1 vs A_2 vs B	0.000***	0.000***
A_1 vs A_2	0.000***	0.000**
A_1 vs B	0.000***	0.000***
A_2 vs B	0.000***	0.000***

N=total number of recruits; n=number of subjects in each group;***=statistically significant

The mean (±SD) level of homocysteine in serum of the recruits were 19.54 ± 2.67, 25.49 ± 2.00 and 11.08 ± 0.94 μmol/L in group A_1 , group A_2 and group B respectively. In this study, themean (±SD) level of homocysteine in serum was higher significantly in group A_1 (p<0.001) and group A_2 (p<0.001) in comparison to that of group B. Again mean serum homocysteine level was significantly (p<0.001) higher in group A_2 than that of group A_1. The mean (±SD) levels of serum folic acid of the recruits were6.31 ± 1.63, 3.43 ± 0.82 and 13.72 ± 1.19 ng/mL in group A_1, group A_2 and group B respectively. Themean (±SD) serum folic acid level was significantly lower in group A_1 (p<0.001) and groupA_2 (p<0.001) when compared tothat of group B. Again mean levels of folic acid in serumwas significantly (p<0.001) lower in group A_2 than that of group A_1 (Table 5).

Table 6: Correlation of levels of homocysteine and folic acid in serum with smoking pack-year for the study group (N=60)

	r value	*p* - value
Serum homocysteine (μmol/L)	0.948	<0.001***
Serum folic acid (ng/mL)	-0.863	<0.001***

N=total number of recruits; n=number of subjects in each group;***= statistically significant
Positive correlation between smoking pack-years and homocysteine levels in serum was noted (r=0.948) and was highly significant statistically (p<0.001). On the other hand, a negative correlation was found to exist between the pack-years of smoking and levels of folic acid in the serum of the study group (r=-0.863). This relationship was highly significant statistically (p<0.001)as can be seen in Table 6.

DISCUSSION

This research work observed the homocysteine and folic acid levels in serum of smokers of cigarette who were apparently healthy males. Beside this, correlation of pack-year duration of smoking and serum homocysteine, folic acid was done in smokers to observe the relationship among them. Comparison of the parameters of smokers were done with that of non-smokers.

Mean homocysteine concentration in serum of the smokers were significantly (p<0.001) higher than that of non-smokers. These findings were similar to that of the studies of many researchers of different countries [17-18].Moreover, the homocysteine levels in serum was more marked in smokers with higher duration of smoking (duration of more than ten pack-year). Such finding was congruous with research work by Bandarian et al[19].Whereas, Haj Mouhamed et al. reported that there were no significant alterations in the levels of homocysteine in serum of smokers[9]. On the contrary, Al-Daghri and Al-Attas observed that there was significant rise in level of homocysteine in serum of hypertensive non-smoker and lower in smokers with family history of diabetes[20].

Our research noted a significantly lower levels of folic acid in serum (p<0.001) in smokers than that in serum of non smokers. Callaghan et al.[10] and Bansal et al.[21] found similar observations in their studies.Upon performing comparison of the parameter level with smoking duration,we noted a more pronounced decrease in folic acid concentration in serum of those with history of smoking for ten pack-years which is again similar to the finding of Saini et al.[22] .

Positive correlation noted in our research between homocysteine level in serum with pack-years of duration of smoking was significant statistically (p<0.001).Chen et al observed similar outcome[13]. However, Burke et al., observed negative, insignificant correlation between homocysteine levels in serum and pack-years of duration of smoking[23].

Folic acid concentration in serum of the smokers in our study correlated negatively with duration of smoking which was significant statistically (p<0.001) .Similar observation was noted by Saini et al. [22]. Whereas, Tastekin et al found that folic acid concentration had no significant correlation with pack-year of smoking duration[24].

The lifestyle of smokers differ from that of non-smokers and the decease in folic acid levels in smokers may be attributed certain factors including those related to the style of living of smokers. The factors affecting folic acid levels include consumption of diets with less health benefits, and poor in folic acid content, impaired absorption of polyglutamyl folic acid, reduced uptake and retention by hepatic cells, raised folic acid excretion through urine, hampered polyglutamates production or hydrolysis and raised catabolism of folic acid[25]. The tobacco's chemical components (hundreds in number) and folic acid coenzymes interact and lead to formation of inactive compounds. This may also alter the cell's ability to metabolize and store folate[26]. Such interactions may explain the diminished folic acid levels in smokers[9].Such mechanisms may be the underlying cause for the finding of lower folic acid levels in smokers observed in this study.

LIMITATIONS

Due to time and financial constraint the effect of supplementation with folic acid in smokers with folic acid deficiency could not be carried out. The effect of smoking on other related parameter like serum thiocyanate levels could not be assessed.

CONCLUSION

Through this research it may be concluded that the level of homocysteine in serum is significantly higher whereas serum folic acid levels is significantly lower among smokers which are more profound in the smokers with >10 pack-years of smoking history. Ideally, quitting of smoking should be promoted. However, in reality it is not always achievable. Thus, strategies that aid in prevention of deteriorating effects of smoking needs to be focused on. Smoking individuals consuming inadequate amounts of folic acid in their diet should be encouraged to improve their diet quality and consume supplements containing such nutrients.

CONFLICT OF INTEREST

There is no conflict of interest.

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