ORIGINAL ARTICLE

IMPACT OF SMOKELESS TOBACCO USE ON DISTRIBUTION OF VESSEL INVOLVEMENT IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Objectives: Despite widespread use of smokeless tobacco (ST) in Pakistan, a very limited empirical evidence have been reported regarding its impact on the coronary anatomy and obstructions. Therefore, this study was conducted to compare the coronary angiographic profile of smokeless tobacco (ST) users and smokers with non-tobacco users presented with acute myocardial infarction (AMI).

Methodology: Consecutive patients with AMI were stratified in to four groups as tobacco non-users (G1), solo ST users (G2), both smoking and ST users (G3), and solo smokers (G4). Coronary angiographic findings regarding number of diseases vessels and infarct related artery were recorded.

Results: Out of 326 patients, ST users were 28.2%(92), 6.4%(21) in conjunction with smoking and reaming 21.8%(71) without smoking. Females were 19.7%(14/71) of G2, 4.8%(1/21) of G3, 0% in G4. Young patients (≤ 40 years) were 3.4%(5/149) of G1, 9.9%(7/71) of G2, 14.1%(12/85) of G4, and 23.8%(5/21) of G3 cumulatively making 82.8%(24/29) of the young patients. Single vessel disease (SVD) and left anterior descending artery (LAD) were significantly higher among ST user as compared to non-users with distribution of 46.7% vs. 34.2% and 70.7% vs. 56.4% respectively.

Conclusion: The distribution and localization of involved vessels among ST users with AMI are same as that of smokers with SCD and LAD as infarct artery as the common findings. Tendency of ST use is also high among female patients and Tobacco use in either form, smoking or smokeless, is alarmingly high (>80%) among young (≤40 years) patients with AMI.

Keywords: smokeless; tobacco; South Asian; Pakistan; cardiovascular diseases; acute coronary syndrome

INTRODUCTION

Nearly 80% of the world's smokeless tobacco (ST) users are from South Asian region comprises of around 300 million individuals.[1] Smokeless tobacco use is estimated to be associated with loss of at least 2.5 million disability adjusted life years and over 90,791 deaths worldwide for the year 2017 and more than 85% of the this burden is shared by the South Asian countries namely Pakistan, India, and Bangladesh.[2] Various smokeless tobacco compounds consumed in this region are highly addictive, all of these compounds contain nicotine along with heavy metals and carcinogens.[1] ST use not only leads to various types of cancers, an increased risk of cardiovascular diseases (CVD) among ST users has been reported.[3-5]

Literature regarding tobacco consumption in the form of smoking and increased risk of ischemic heart disease (IHD) is well documented, however, due to conflicting evidence the relationship between use ST products and risk of CVD is shrouded with controversy.[6] Therefore, smoking has been considered as one of the major modifiable CVD risk factor but ST has not been given due attention.[3,7] The INTERHEART study reported an increased risk of first myocardial infarction, with an odds ratio of 2.23, among ST users as compared to non-users.[8] A very limited literature are available especially for Pakistan, prevalence of ST use among young adults has been reported to be 16 to 20% in Pakistani population.[9] A case control study of 300 cases of CVD and 300 healthy individuals in Pakistani population reported six times higher risk of CVD among betel nut chewers as compared to non-chewers, study further reported eight fold increase in risk of CVD development for individuals with more than 10 years of betel nut consumption duration.[10] Despite its widespread use in Pakistan, little empirical research has been carried out on the prevalence and determinants of smokeless tobacco consumption and how use of smokeless tobacco effects the coronary anatomy and

obstructions. Therefore, aim of this study was to compare the coronary angiographic profile of smokers, smokeless tobacco users, and non-tobacco users presented with acute myocardial infarction at a tertiary care cardiac center.

METHODOLOGY

This cross-sectional study was conducted at one of largest cardiac care center of Pakistan between the study periods of October 2020 to March 2021. Study was approved by the ethical review board of the institution and written consent was waived due to observational nature of the study. Verbal informed consent was obtained from all the participants of the study. Consecutive patients admitted to the inpatient department with the diagnosis of ST-elevation myocardial infarction (STEMI) were included. Diagnosis of STEMI was made based on duration of chest pain and electrocardiographic (ECG) finding at presentation as per the 4th universal definition of myocardial infarction (MI). Inclusion criteria for the study were patients diagnosed of STEMI, undergone left heart catheterization (LHC), and age between 18 and 80 years. Patients with prior history of diagnosed coronary artery diseases were excluded.

Data regarding demographic data and conventional risk factors were collected for all the participating patients using a pre-designed structured questionnaire. Conventional risk factors included history of hypertension; defined as on antihypertensive medications for at least six months, diabetes mellitus; defined as on antihyperglycemic medications/insulin for at least six months, obesity; defined as body mass index ≥ 30 kg/m^2, and family history of ischemic heart diseases (IHD) in first degree blood relatives (male $\leq$ 55 years and female $\leq$ 65 years). Tobacco users were categorized into two groups, smokers and smokeless tobacco users. Active smokers were defined as history of smoking 10 or more cigarettes per day for at least 2 years or equivalent. Study participants with at least twice a day intake/chewing frequency of any of the available smokeless tobacco products were categorized were categorized as smokeless tobacco users. Such products consisted of Paan; a chewable combination of tobacco with betel leaves and areca nut as main ingredients, Naswar; a moist combination of heat- or sun-dried tobacco leaves with slaked lime and ash from tree bar as main ingredients along with coloring and flavoring agents, and other regional variants namely Guttka, Mainpuri, or Mawa which are chewable tobacco products with crushed or thin shavings of areca nut as main ingredient along with slaked lime and tobacco and other flavoring ingredients such as cinnamon, catechu, and clove.

All the enrolled patients were managed as per the current clinical practice guidelines. Coronary angiography procedures were performed and interpreted by the consultant cardiologists. Collected angiographic data consisted of burden of diseases (number of vessels with $\geq 70\%$ stenosis in luminal diameter or $\geq 50\%$ stenosis in left main) and involved coronary territory.

Collected data were analyzed with IBM SPSS version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Patients were categorized as smokeless tobacco users and non-users and users were further categorized as smokeless tobacco users in conjunction with smoking or without smoking. These groups were compared for various demographic, clinical, and angiographic characteristics by applying appropriate independent sample t-test or chi-square test. Situations where expected cell frequency is less than 5, Likelihood Ratio test or Fisher's Exact test was preferred over Chi-square test. Two sided p-value of ≤ 0.05 will be taken as significant.

RESULTS

A total of 326 patients were included in this study, out of which 80.1% (261) were male and mean age of the study participants was 57.48 ± 10.84 years. Smokeless tobacco users were 28.2% (92) of the total sample, 21 (6.4%) in conjunction with smoking and reaming 71 (21.8%) patients without smoking. The proportion of young patient (≤ 40 years) was found to be higher among smokeless tobacco users, 13.0% (12) vs. 7.3% (17); p = 0.099, as compared to non-users. Current smokers were significantly higher among non-users of smokeless tobacco, 36.3% (85) vs. 22.8% (21); p = 0.019, as compared to user. Smokeless tobacco users had significantly higher proportion of single vessel disease (SVD) and left anterior descending artery (LAD) involvement as compared to non-users with frequency of 46.7% (43) vs. 34.2% (80); p = 0.035 and 70.7% (65) vs. 56.4% (132); p = 0.018 respectively. Comparison of demographic, clinical, and angiographic characteristics of smokeless tobacco users and non-users are presented in Table 1.

Female participants were found to have higher tendency of smokeless tobacco use as compared to smoking with female proportion of 16.3% (15/92) among smokeless tobacco users and 0.9% (1/106) among smokers. Tendency of use of tobacco products, either in the form of smoking or smokeless, was found to be higher among young patients with distribution of 3.4% (5/149) young patients among tobacco non-users and 13.6% (24/177) among tobacco users. Among these young tobacco users, 7 (29.2%) were smokeless

tobacco users, 12 (50.0%) were smokers, while, 5 (20.8%) were both smokers and smokeless tobacco users. Hypertension was more common among smokeless tobacco users as compare to smokers (62% vs. 41.2%) but less prevalent as compared to tobacco non-users (62% vs. 71.8%). Similarly, diabetes was also more prevalent among smokeless tobacco users as compare to smokers (33.8% vs. 21.2%) but less common as compared to non-users (47% vs. 33.8%).

Single vessel disease was significantly higher among smokeless tobacco user as compared to non-users with distribution of 46.7% vs. 34.2%. LAD was involved vessel among significantly higher number of smokeless tobacco users as compared to non-users with distribution of 70.7% vs. 56.4%. Comparison of demographic, clinical, and angiographic among the patient groups based on tobacco usage are presented in Table 2.

Table 2: Demographic, clinical, and angiographic characteristics stratified by smokeless tobacco usage

Characteristics	Total	Smokeless Tobacco Users		P-value
		Non-users	Users	
Total (N)	**326**	**234 (71.8%)**	**92 (28.2%)**	**-**
Gender				
Male	80.1% (261)	78.6% (184)	83.7% (77)	0.303
Female	19.9% (65)	21.4% (50)	16.3% (15)	
Age (years)	57.48 ± 10.84	57.44 ± 10.51	57.61 ± 11.69	0.897
≤ 40 years	8.9% (29)	7.3% (17)	13% (12)	0.099
41 to 65 years	73.3% (239)	74.4% (174)	70.7% (65)	0.496
> 65 years	17.8% (58)	18.4% (43)	16.3% (15)	0.660
Body mass index (kg/m^2)	25.44 ± 3.07	25.51 ± 3.03	25.26 ± 3.16	0.500
Smoking				
Never smoked	55.2% (180)	53% (124)	60.9% (56)	0.198
Ex-smoker	12.3% (40)	10.7% (25)	16.3% (15)	0.164
Current smoker	32.5% (106)	36.3% (85)	22.8% (21)	0.019*
Co-morbid Conditions				
Hypertension	59.5% (194)	60.7% (142)	56.5% (52)	0.491
Diabetes mellitus	37.4% (122)	37.6% (88)	37% (34)	0.913
Obesity	6.4% (21)	7.3% (17)	4.3% (4)	0.334
Family History of CAD	3.7% (12)	3.8% (9)	3.3% (3)	0.801
Number of vessels involved				
Single vessel disease	37.7% (123)	34.2% (80)	46.7% (43)	0.035*
Two vessel disease	28.2% (92)	29.9% (70)	23.9% (22)	0.279
Three vessel disease	34% (111)	35.9% (84)	29.3% (27)	0.261
Infarct Related Artery				
Left main	2.1% (7)	2.1% (5)	2.2% (2)	0.983
LAD	60.4% (197)	56.4% (132)	70.7% (65)	0.018*
Right coronary artery	27% (88)	29.9% (70)	19.6% (18)	0.058
Left circumflex	8.9% (29)	9.8% (23)	6.5% (6)	0.345
Obtuse marginal	0.6% (2)	0.9% (2)	0% (0)	-
Diagonal	0.6% (2)	0.9% (2)	0% (0)	-
Ramus	0.3% (1)	0% (0)	1.1% (1)	-

CAD = coronary artery diseases, LAD = left anterior descending artery
*significant at 5%

Table 2: Demographic, clinical, and angiographic characteristics stratified by the form of tobacco usage

Characteristics	Form of Tobacco Use				P-value
	Non-users	Smokeless Alone	Both	Smoking Alone	
Total (N)	**149 (45.7%)**	**71 (21.8%)**	**21 (6.4%)**	**85 (26.1%)**	**-**
Daily frequency of use	-	7.62 ± 9.99	10.57 ± 6.38	14.99 ± 7.82	<0.001*
Duration of use (year)	-	19.76 ± 14.61	25.71 ± 11.53	18.89 ± 11.04	0.087
Gender					
Male	66.4% (99)	80.3% (57)	95.2% (20)	100% (85)	<0.001*
Female	33.6% (50)	19.7% (14)	4.8% (1)	0% (0)	
Age (years)	59.21 ± 10.1	58.66 ± 10.84	54.05 ± 13.91	54.33 ± 10.57	0.003*
≤ 40 years	3.4% (5)	9.9% (7)	23.8% (5)	14.1% (12)	0.002*
41 to 65 years	73.2% (109)	74.6% (53)	57.1% (12)	76.5% (65)	0.347
> 65 years	23.5% (35)	15.5% (11)	19% (4)	9.4% (8)	0.053
BMI(kg/m^2)	25.74 ± 3.16	25.28 ± 3.27	25.2 ± 2.84	25.11 ± 2.77	0.426
Co-morbid Conditions					

Hypertension	71.8% (107)	62% (44)	38.1% (8)	41.2% (35)	<0.001*
Diabetes mellitus	47% (70)	33.8% (24)	47.6% (10)	21.2% (18)	0.001*
Obesity	6.7% (10)	4.2% (3)	4.8% (1)	8.2% (7)	0.765
Family History of CAD	4.7% (7)	4.2% (3)	0% (0)	2.4% (2)	0.633
Number of vessels involved					
Single vessel disease	29.5% (44)	45.1% (32)	52.4% (11)	42.4% (36)	0.035*
Two vessel disease	30.9% (46)	21.1% (15)	33.3% (7)	28.2% (24)	0.466
Three vessel disease	39.6% (59)	33.8% (24)	14.3% (3)	29.4% (25)	0.089
Infarct Related Artery					
Left main	2.7% (4)	0% (0)	9.5% (2)	1.2% (1)	0.055
LAD	54.4% (81)	73.2% (52)	61.9% (13)	60% (51)	0.066
Right coronary artery	32.9% (49)	19.7% (14)	19% (4)	24.7% (21)	0.143
Left circumflex	8.7% (13)	5.6% (4)	9.5% (2)	11.8% (10)	0.613
Obtuse marginal	1.3% (2)	0% (0)	0% (0)	0% (0)	-
Diagonal	0% (0)	0% (0)	0% (0)	2.4% (2)	-
Ramus	0% (0)	1.4% (1)	0% (0)	0% (0)	-

BMI = body mass index, CAD = coronary artery diseases, LAD = left anterior descending artery
significant at 5%

DISCUSSION

Ischemic heart diseases (IHD) remains a leading cause of mortality and morbidity worldwide, South Asian region is most effected region with around 73% increase in healthy life-years lost as compared to 30% global increase between 1990 and 2010.[11] Hence it is important to explore not only the biological factors but also behavioral, environmental, and social factors indigenous to the region. Smokeless tobacco use is one such globally lesser recognized factor indigenous to the South Asian Region.[1] Unlike smoking problem, due to lack of proper regulation in manufacturing and distribution process of these products, it has become particular public health concern and a difficult task to control and regulate.[3,12,13]

Although in our population smoking among female is not as common as western world,[14] but higher tendency of smokeless tobacco use was observed among female participants in our study with almost equal proportion of female smokeless tobacco users as compared to their male counterpart (23.1% (15/65) vs. 29.5% (77/261); p=0.303). Nearly half (12/29) of young (≤ 40 years) patients were ST users, seven were solo ST users and five were conjunction users of ST and smoking along with 12 solo smokers. Collectively, 82.8% (24/29) young patients were found to be tobacco users in either smokeless or smoking form. While, data regarding conventional risk factors among young patients in this populations does not account for the ST use, tobacco use in the form of smoking is reported to be 30.4% among patients with STEMI.[15] Hence, considering the higher odds of tobacco use, regardless of its form, among young patients with ACS, it is important to explore the possible causative linkage between tobacco use and premature coronary artery diseases in our population.

Previously, a study by Karim MT et al.[16] reported a strong association between ST (areca nut) use and early re-hospitalization (≤30 days) after ACS event with adjusted hazard ratio of 2.09 [95% CI; 1.37, 3.18]. Another study from the same region have reported strong association of ST use with hyperhomocysteinemia, a well-recognized risk factor for CAD, with odds ratio of 11.34 [95% CI; 7.58, 16.96; p=0.001].[17] When it comes to impact of smokeless tobacco use on angiographic profile, when compared non-tobacco users (in either form) to the solo smokeless tobacco users, single vessel disease was more common among users as compared to non-users (45.1% (32/71) vs. 29.5% (44/149); p=0.023) and LAD was the most commonly observed infarct artery among solo smokeless tobacco users, 73.2% (52/71) vs. 54.4% (81/149); p=0.007. Similar, observation can be made for solo smokers too with single vessel disease in 42.4% (36/85) vs. 29.5% (44/149) and LAD as infarct artery in 60.0% (51/85) vs. 54.4% (81/149) for solo smokers and non-tobacco users respectively. Hence, probably smokeless tobacco use has equal impact on angiographic profile as smoking. Smokeless tobacco use need to be recognized as one of the major risk factor for coronary artery diseases and should be given equal attention as smoking problem in our population.

Due to wide regional variations in formulation of smokeless tobacco products, research efforts on smokeless tobacco use in the context of coronary artery diseases also suffers from varying results. Such as Frobert O et al.[18] conducted a registry based study in Swedish population to evaluate the risk of death and future cardiac events after PCI among snus (a regional smokeless tobacco product) users. They reported no increased risk of all-cause mortality, re revascularization or hospitalization for heart failure, however, time to subsequent event (PCI) was reported to be longer among snus quitters. However, three

major systematic reviews by Gupta R et al.[6], Gupta R et al.[7], and Rostron BL et al.[19] have reported increased risk of fatal cardiovascular diseases and stroke. The American Heart Association in there policy statement regarding impact of use of smokeless products on cardiovascular diseases summarized available evidence and also concluded increased risk of fatal myocardial infarction (MI) and stroke and reduced survival after fatal event among patients who used smokeless tobacco for a longer duration. In this policy statement AHA also emphasis on discouraging ST alternative or smoking cessation product.[20]

Smoking is considered to be a major confounder in research efforts on smokeless tobacco use in the context of cardiovascular diseases, here in this study we have stratified and compared solo as well as conjunction users in either form to the tobacco non-users to minimize confounding effect of smoking. However, our study has certain limitations which includes, smoking and smokeless tobacco use status was assessed based on self-reporting of the patients this may have induced bias into estimates. Also single center coverage, cross-sectional study design with small sample size, and unequal group size may have limit the generalizability of the study results. Further studies with larger sample size are needed to ascertain the said associations and to further investigate impact of smokeless tobacco use on other anatomical features and severity of lesion such as SYNTAX score, legion length, type of lesion, presence/absence of calcification, or bifurcation lesions etc.

CONCLUSION

The patterns of coronary angiographic findings among smokeless tobacco users are same as that of smokers with single vessel disease and LAD as infarct artery as the common findings. Unlike smoking, tendency of smokeless tobacco use is also high among female patients along with male patients. Tobacco use in either form, smoking or smokeless, is alarmingly high (>80%) among young (≤40 years) patients with AMI. Hence, smokeless tobacco use can also be considered as one of risk factors and along with policies regarding smoking cessation appropriate efforts are needed to promote tobacco free lifestyle.

AUTHORS' CONTRIBUTION:

GSS, TS, and BH: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. HI, MK, SK, DQ: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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