Thromboangiitis obliterans (TAO) or Buerger’s disease, the aetiology of which is still largely unknown, is a non-arteriosclerotic, non-inflammatory, segmentally occlusive disease involving medium- and small-sized arteries and veins. It mainly affects young male smokers, although very few cases have been reported in ex-smokers and smokeless tobacco users, in those over 50 years old, and women. A definite relationship was reported between cigarette smoking and exacerbation and remissions of the disease. Thromboangiitis obliterans is rare in western countries but common in south and southeast Asia, the Middle East, and eastern European countries. Besides smoking, lifestyle habits in Bangladesh such as not wearing shoes, cultivating rice and jute fields in ankle deep mud and water, and the squatting posture of farmers while working in the field, have been reported as possible aetiological or aggravating factors.

Bidi smoking is a popular habit in Bangladesh, especially in rural areas and among the urban poor. Bidi is the cheapest substitute for a cigarette and is generally available in filterless form in Bangladesh. It is a crude form of smoking, smaller than a cigarette in size, home-made, and consists of about 0.5 g of raw, dried and crushed tobacco flakes, hand-rolled in a dried leaf of Tendu (Diospyros melanoxylon or Diospyros ebenum) or white paper. The Tendu leaf itself is responsible for 60% of the

Association of thromboangiitis obliterans with cigarette and bidi smoking in Bangladesh: a case-control study

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Background
In addition to cigarettes, bidi, made of unprocessed and low-grade tobacco, is being smoked widely in Bangladesh and in other south Asian countries. The cause-and-effect relationship is established between thromboangiitis obliterans (TAO) and smoking. However, type of smoking material(s) most strongly related to TAO is not yet determined.

Methods
We conducted a hospital-based case-control study in Rajshahi, Bangladesh, to examine the relationship of type of smoking materials (cigarette versus bidi) with TAO on 103 pairs of cases and controls matched by age and sex during the period 1995 to 1996. The inclusion criteria for cases were newly diagnosed TAO and current smoker, while those for controls were current smokers admitted to the hospital due to non-cardiovascular diseases.

Results
Among the cases 35.0% and 65.0% were cigarette and bidi smokers, while among the controls 69.9% and 30.1%, respectively. Using logistic regression approach, considering cigarette smoking ~10 per day as reference, bidi smoking ~20 per day (odds ratio [OR] = 34.76, 95% CI: 6.11–197.67) and 11–20 per day (OR = 7.12, 95% CI: 2.35–21.63) had greater risk of TAO after adjusting confounding factors. Respective OR for bidi smoking ~10 per day, cigarette smoking 11–20 per day and cigarette smoking ~20 per day, were 2.18 (95% CI: 0.64–7.51), 3.81 (95% CI: 1.37–10.57) and 6.88 (95% CI: 1.87–25.30).

Conclusion
Within the limits inherent to case-control study, our findings suggest that bidi smoking may well play a more important role in causing TAO than cigarettes. It leads to the speculation that unprocessed and low-grade tobacco used for producing bidi might play a more potent role to initiate TAO than cigarettes.

Keywords
Thromboangiitis obliterans, smoking, tobacco, bidi, cigarette, Bangladesh

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weight of bidi\textsuperscript{14} and the tobacco used is less refined and sun-cured (naturally cured) and thereby low-grade. The total mean nicotine and total dry particulate materials per unit weight are higher in bidi compared to cigarettes.\textsuperscript{15} The prevalence of smoking in different urban and semi-urban settings was 39–73\% among adult males and 0–28\% among females.\textsuperscript{16–18} In a rural setting, however, these were 67\% and 1\%, respectively.\textsuperscript{19} Among urban smokers in the low socioeconomic group, 36\% smoked bidi.\textsuperscript{18}

So far, smoking is widely regarded to be the most important initiating factor for TAO. However, the type of smoking material(s) most strongly related to TAO is not yet determined. The present investigation aimed to assess the risk of TAO associated with bidi and cigarette smoking.

 Subjects and Methods

Cases

Cases were 103 clinically confirmed TAO patients (distal extremity ischaemic symptoms in the absence of trauma, diabetes and hyperlipidaemia) diagnosed in 1995 and 1996, and admitted to Rajshahi Medical College Hospital (RMCH), situated in the biggest city (Rajshahi) of northern Bangladesh. Inclusion criteria for cases were: (1) newly diagnosed TAO, and (2) smoking either cigarettes or bidi. Four cases who smoked both were excluded from the study.

Controls

Patients, admitted to the same hospital, matched to the case by age and sex (1:1 ratio), were recruited as controls. Inclusion criteria for controls were: (1) being hospitalized due to non-cardiovascular diseases, and (2) smoking either cigarettes or bidi. After interviewing newly diagnosed TAO patients, controls were chosen randomly from the list of inpatients of different units of the same hospital. Patients closest to the age of the cases (± 5 years) who were current smokers of either cigarettes or bidi were then chosen as controls. All the cases and controls who were asked agreed to participate.

Data collection

Historical information on cases and controls was obtained by interviewer-administered (ASC) questionnaire. The interviewer as well as cases and controls were blinded regarding the hypothesis of this study. In addition to sociodemographic variables, the items of interest were bidi smoking, cigarette smoking, betel-nut chewing, and tobacco chewing with respect to daily frequency, total duration in years, and age when these habits started.

Statistical methods

Considering bidi smoking as the main exposure of interest, given an estimated 36\%\textsuperscript{18} exposure rate in the control group, we calculated that 86 pairs cases and controls would be required, at the $P < 0.05$ level, to yield a 90\% chance of detecting 60\% exposure rate among the cases.\textsuperscript{20} The association between cigarette and bidi smoking and TAO was assessed by computing the odds ratio (OR) as an estimate of the relative risk (RR). Odds ratios were calculated using conditional logistic regression approach. The 95\% CI were calculated using standard error of the regression estimates. All the statistical procedures were performed by SPSS\textsuperscript{21} and MINITAB.\textsuperscript{22} A two-sided $P$-value of 0.05 was used as the criterion for statistical significance. The Mann Whitney U test and $\chi^2$ test or Fisher’s exact test were used for comparing continuous and categorical data, respectively. Dose response was evaluated by Mantel extension test\textsuperscript{23} both for frequency and duration.

Results

Comparative features of cases and controls are listed in Table 1. The ages of cases and controls were nearly identical ($P < 0.38$) and all of them were male and current smokers. More cases were married ($P < 0.025$) and illiterate (43 versus 15, $P < 0.0001$) compared to controls. There was no significant difference between cases and controls regarding the religion ($P < 0.60$) and occupation ($P < 0.20$). More controls were cigarette smokers than bidi smokers.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years)</td>
<td>38.6</td>
<td>39.5</td>
<td>0.38</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Muslim</td>
<td>96</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Hindu</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Married (%)</td>
<td>92.2</td>
<td>80.6</td>
<td>0.025</td>
</tr>
<tr>
<td>Mean schooling (years)</td>
<td>4.9</td>
<td>8.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Proportion of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smokers (%)</td>
<td>35.0</td>
<td>69.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bidi smokers (%)</td>
<td>65.0</td>
<td>30.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Betel-nut chewers (%)</td>
<td>60.2</td>
<td>43.7</td>
<td>0.025</td>
</tr>
<tr>
<td>Tobacco leaf chewers (%)</td>
<td>20.4</td>
<td>15.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean age at starting (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>18.0</td>
<td>18.9</td>
<td>0.11</td>
</tr>
<tr>
<td>Bidi smoking</td>
<td>16.9</td>
<td>16.5</td>
<td>0.77</td>
</tr>
<tr>
<td>Betel-nut chewing</td>
<td>18.3</td>
<td>17.4</td>
<td>0.56</td>
</tr>
<tr>
<td>Tobacco leaf chewing</td>
<td>17.4</td>
<td>19.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean duration of smoking (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette</td>
<td>23.0</td>
<td>19.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Bidi</td>
<td>20.7</td>
<td>23.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean duration of chewing (years)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Betel nuts</td>
<td>19.8</td>
<td>22.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Tobacco</td>
<td>21.2</td>
<td>21.5</td>
<td>1</td>
</tr>
<tr>
<td>Frequency per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette</td>
<td>15.6</td>
<td>11.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Bidi</td>
<td>18.1</td>
<td>11.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Betel-nut</td>
<td>4.8</td>
<td>4.7</td>
<td>0.94</td>
</tr>
<tr>
<td>Chewing tobacco</td>
<td>6.1</td>
<td>7.0</td>
<td>0.20</td>
</tr>
</tbody>
</table>
than bidi smokers ($P < 0.0001$) while the reverse was true for cases ($P < 0.0001$). More cases chewed betel-nut ($P < 0.025$) than controls while there was no difference regarding tobacco leaf chewing ($P < 0.40$). Mean duration of cigarette smoking was significantly longer ($P < 0.04$) among cases than controls. However, no significant differences were found regarding mean duration of bidi smoking ($P < 0.08$), betel-nut chewing ($P < 0.22$), and tobacco leaf chewing ($P < 1$). Mean ages of starting both smoking and chewing habits were not significantly different among the cases and controls. Figure 1 shows the proportion of cases based on frequency of bidi and cigarette smoking per day. For both cigarette and bidi smokers, the higher the frequency of smoking per day, the higher the proportion of cases. On average, cases smoked more cigarettes (15.6 versus 11.0, $P < 0.01$) or bidi (18.1 versus 11.4, $P < 0.0001$) per day than controls.

Table 2 summarizes the OR for TAO in relation to the type of smoking based on frequency per day. Using a conditional logistic regression approach and considering cigarette smoking ~10 per day as reference, smoking >20 bidi per day (OR = 34.76, 95% CI: 6.11–197.67) and 11–20 per day (OR = 7.12, 95% CI: 2.35–21.63) had greater risk of TAO after adjusting confounding factors. The OR for TAO for bidi smoking ~10 per day, cigarette smoking 11–20 per day and cigarette smoking >20 per day, were 2.18 (95% CI: 0.64–7.51), 3.81 (95% CI: 1.37–10.57) and 6.88 (95% CI: 1.87–25.30), respectively. The Mantel extension test for dose response showed statistical significance for both frequency and duration regarding cigarette smoking ($\chi^2 = 12.19, P < 0.0005$ for frequency and $\chi^2 = 6.39, P < 0.025$ for duration), but only for frequency for bidi smoking ($\chi^2 = 15.69, P < 0.0005$ for frequency and $\chi^2 = 1.43, P < 0.25$ for duration).

The combined effects of bidi and betel-nut, cigarette and betel-nut, bidi and chewing tobacco, and cigarette and chewing tobacco were not significantly different between cases and controls.

**Discussion**

This study demonstrated that risk of TAO is greater among bidi smokers (11–20, and >20 per day) than cigarette smokers (11–20, and >20 per day) within the limits inherent in a case-control study. Recall bias is one of the limitations of a case-control study. Since all the cases and controls were smokers and admitted to the hospital for some clinical condition, there might be underreporting of the exposure as a whole both for cases and controls, because they may simply try to label the disease as natural rather than caused by their own habit. Since all consecutive TAO patients were included in the study, only selection bias might work for controls, not for cases. The diagnoses of controls included, in decreasing order, anaemia (7.8%), hydrocele (5.8%), enteric fever (4.9%), nephrotic syndrome (4.9%), kala-azar (4.9%), pleural effusion (4.9%), viral hepatitis A (3.9%), peptic ulcer (3.9%) and 39 other diseases for which there was no prior indication of relation with the smoking. Thus, the variety of diagnoses would certainly dilute any bias from including a specific diagnostic group.

In Bangladeshi conditions the referral system cannot be properly maintained. All academic hospitals are public hospitals and the services there are provided almost free of charge so these are invariably used by all the lower socioeconomic groups. Rajshahi Medical College Hospitals, the biggest public hospital for Rajshahi city and adjacent areas, is the sole healthcare centre for the lower socioeconomic groups of that region irrespective of the type of clinical problem. Therefore, the source population for both cases and controls seems to be the same.

![Figure 1 Proportion of cases based on frequency of cigarette and bidi smoking per day](image)

**Table 2** Odds ratios (OR) for thromboangiitis obliterans by cigarette and bidi smoking based on frequency per day

<table>
<thead>
<tr>
<th>Smoking category</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Crude OR</th>
<th>Adjusted OR (95% CI)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cigarettes (per day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>~10</td>
<td>7</td>
<td>34</td>
<td>1a</td>
<td>1a</td>
<td>0.0102</td>
</tr>
<tr>
<td>11–20</td>
<td>20</td>
<td>30</td>
<td>3.23</td>
<td>3.81 (1.37–10.57)</td>
<td>0.0003</td>
</tr>
<tr>
<td>&gt;20</td>
<td>9</td>
<td>8</td>
<td>5.46</td>
<td>6.88 (1.87–25.30)</td>
<td>0.0037</td>
</tr>
<tr>
<td><strong>Bidi (per day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>~10</td>
<td>9</td>
<td>14</td>
<td>3.12</td>
<td>2.18 (0.64–7.51)</td>
<td>0.2150</td>
</tr>
<tr>
<td>11–20</td>
<td>34</td>
<td>15</td>
<td>11.01</td>
<td>7.12 (2.35–21.63)</td>
<td>0.0005</td>
</tr>
<tr>
<td>&gt;20</td>
<td>24</td>
<td>2</td>
<td>98.28</td>
<td>34.76 (6.11–197.67)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

a Reference value.

The OR and 95% CI were calculated with conditional logistic regression where smoking of cigarette and bidi considered as a single categorical variable, with smokers of ~10 cigarettes per day as reference category, adjusted for number of years of education, marital status, betel-nut chewing, tobacco chewing, and duration of smoking (~15 years, >15 years).
Socioeconomic status (SES) is a potential source of bias in this study. Education and occupation were the main indicators of SES in this study. Although there is a significant difference in mean schooling years (4.9 versus 8.3) between cases and controls emphasized by the greater number of illiterate cases than controls (43 versus 15), no such difference was found in respect of occupation. Since the number of years of education was adjusted in the logistic model, higher OR found for bidi smokers were not due to the difference of SES between cases and controls. Besides, the proportion of bidi smoking among the controls (30.1%) was comparable to that among the lower socioeconomic group which was 36% in another study.18

A standard diagnostic procedure for TAO based on clinical, pathological and arteriographic criteria24 is not maintained in Bangladesh due to limited resources and facilities. The sensitivity of the diagnostic method based on clinical findings is not known, but in the absence of bias, one expects that the odds of exposure among the false-positive cases will equal the odds of exposure among the controls as reported in a recent study.25 In this study any such false-positive cases would lead to a reduction in the differences regarding exposure status between case and controls. In that case the OR for bidi could be greater than that found in this study.

Patients with TAO invariably smoked cheaper brand cigarettes or bidi. These are made of unprocessed and unrefined tobacco (naturally cured) and it can be presumed that they contain larger amounts of the substance(s) which initiate the pathological changes in arterioles and veins leading to TAO. While unprocessed and low-grade tobacco may be one of the strongest triggering factors for developing TAO in Bangladesh, autoimmunity could be the another factor.26

Bidi needs to be smoked at a minimum of two puffs per min to keep it burning. It has been reported, however, that bidi smokers actually smoke at 4.75 puffs per min27 compared to two puffs among cigarette smokers.28 The puff frequency is positively related to inhalation of tar and nicotine. Bidi smoking would therefore cause more than double tar and nicotine intake compared to cigarette smoking. Thus, the fact that the majority of the TAO patients were bidi smokers in our study may show high nicotine and tar content work as triggering factors for TAO. Future studies on animal models are required to prove this hypothesis.

It has already been suggested that bidi smoking leads to a greater risk of developing cancer of the tongue, floor of the mouth, buccal and labial mucosa, gingiva, oral cavity, oropharynx, oesophagus, larynx, and lung than cigarette smoking, although the differences were not statistically different.29–38 Such carcinogenic substances as steam-volatile phenol, hydrogen cyanide, benzo[a]pyrene, and radioactive uranium were also detected in greater amount in bidi than cigarettes.39,40 Another study also showed that bidi contained 1.5 times more carcinogenic hydrocarbons than a filterless popular American cigarette.41 In an experimental study in Swiss mice where bidi and cigarette smoke condensates were used as initiating factors for tumour growth, the bidi smoke condensate induced liver angioma, forestomach papilloma and cancer, and cancer of the oesophagus in 7 of the 15 mice while at the same dose the cigarette smoke condensate failed to produce any tumour in the mice.42

There used to be sizeable numbers of TAO patients in the developed world. However, TAO is now almost eradicated from the developed countries following the establishment of a tobacco processing standard and a reduction in nicotine in cigarettes. Thus, the high incidence in the Indian subcontinent and other parts of the developing world is contrast to the rarity of TAO in the western world strongly suggests the relationship of unprocessed tobacco products with high nicotine and tar content and TAO. Thromboangiitis obliterans is the most prevalent vascular disease not only in Bangladesh but also in India where bidi smoking is also very popular among lower socioeconomic groups.43

In conclusion, our results reinforce the evidence for a greater risk of developing TAO from bidi smoking compared to cigarette smoking.

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References


