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LETTER TO THE EDITOR

Aggravation of Inflammation by Smokeless Tobacco in Comparison of Smoked Tobacco

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Dear Sir,

We have come across an article entitled "Comparison of the Carcinogenic Potential of Smokeless Tobacco and Smoked Tobacco by Quantifying the Excretion of Nicotine Metabolite NNAL in Patients with Oral Leukoplakia Indian J Clin Biochem. 2014; 29(2):246–9" authored by Mohamed Anser S et al. in April–June 2014 issue. The published study reported significant difference of NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] in smokeless tobacco users than tobacco smokers. Thus authors concluded that smokeless tobacco is more carcinogenic than smoked tobacco [1].

We have examined the inflammatory status in prostate carcinoma (PCa) patients who were exposed with same mode of abuse (smokers and chewers i.e. smokeless) by exploring pro-inflammatory (Interleukin-12, Interleukin-18) and anti-inflammatory (Interleukin-10) levels in north Indian population [2, 3]. It is now established that most of carcinogenic compound follow redox pathway and aggravate inflammation but at the same time inflammation also promotes the free radical generation and hence vicious cycle. With the relentless progress in cancer research the puzzle of carcinogenesis has been now simplified into few hallmarks. Important hallmarks included so far sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis. Recently inflammation is added as a new hallmark of carcinogenesis, which fosters other hallmark functions. It has been now established that inflammation contributes to proliferation, malignancy, angiogenesis, metastasis, adaptive immunity modulation, unresponsiveness to hormones and chemotherapeutic agents [4], never the less inflammation has also been reported in other diseases [5].

Our findings correlated the inflammatory status with various modes of tobacco smoking (bidi's, chillum, cigarette, Hookah) and chewing (smokeless forms–khaini > gutkha > betel quid) as shown in Table 1. We have found that levels of IL-12 (pro-inflammatory) showed unique trend in tobacco exposed groups (within groups), that is, the levels were highest in bidi's smokers, followed by chillum, cigarette, and hookah (bidi's smokers > chillum > cigarette smokers > Hookah). When we compared within cancer group's IL-12 levels differed significantly ($P < 0.05$) with cigarette, bidi, hookah, Chillum users than non-users cancer patients [2]. We also found that the IL-18 levels in tobacco smokers were high and IL-18 levels differed according to the mode of tobacco exposure and the highest level was seen in bidi smokers, followed by cigarette smokers, chillum, hookah (bidis > cigarette > chillum > Hookah). Similarly, significantly high levels of IL-18 were found in cigarette and bidi smokers as compared to non-users while it was not significant with chillum and hookah. In men with cancer, the IL-18 levels differed significantly ($P < 0.05$) among cigarette, bidi, hookah, chillum smokers as compared to non-users [3].

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Further we correlated the IL-12 levels with tobacco chewers (between groups) with betel quid, gutkha and khaini chewers of cancer have elevated levels than BPH and control group. Moreover, when comparison was made within same group again non users have their lowest expressions. Moreover, among tobacco exposure groups (within groups), the mean level of IL-12 showed a characteristic trend i.e. the levels were highest in khaini chewers, followed by gutkha, betel quid chewers (khaini > gutkha > betel quid chewers) [2]. Similarly the association of IL-18 levels among tobacco chewers groups showed that the mean IL-18 levels being highest in khaini chewers, followed by gutkha and betel quid chewers (khaini > gutkha > betel quid chewers). The levels of IL-18 were significantly raised in cancer patients (who chewed tobacco in any form) as compared to controls [3].

We have also observed the pro-inflammatory IL-12 with combined users (Tobacco consumed in more than one form) and found that the mean level of IL-12 showed highest levels in chewing and smoking with alcohol (CSA), followed by chewing with alcohol, smoking with alcohol, and alcohol alone (chewers and smokers with alcohol (CSA) > chewers with alcohol > smokers with alcohol > alcohol alone) [2]. Similarly the levels of IL-18 was highest in men who consumed all three [chewing, smoking and alcohol intake (CSA), this was followed by smokers and alcohol consumers (SA) followed by men was consumed alcohol alone and then followed by chewers and alcohol consumers (CA) [CSA > SA > alcohol (alone) > CA]. The IL-18 levels in cancer patients were significantly higher in CSA users, SA users and men who were drinkers as compared to cancer patients who were non-users [3].

Further, we have also observed association of elevated pro-inflammatory IL-18 levels with disease progression (TNM staging and stages I, II, III, IV) and also elevated in tobacco exposed patients of carcinoma [3, 6, 7]. Additionally, levels for stages III and IV were significantly higher in all modes except in tobacco chewers of stage III patients, although the levels were higher than stage II. The IL-12 levels were higher in men who were chewers and smokers as compared to nonusers in stages I and II; the results have shown their increased levels in all higher stages and within all groups and they were significantly differed ($P < 0.05$) in stages II, III, and IV within all exposure groups except in nonusers and chewers with alcohol group [2].

Further survival outcome of tobacco exposed population were also analyzed with all modes of exposure and our study found that the median survival of nonusers was better than all tobacco exposed subgroups (43.03 months; 95 % CI = 40.34–45.72). The median survival for various modes of

Table 1 Tobacco and alcohol exposure with various modes and their association with pro-(IL-12), anti-(IL-10) inflammatory cytokine and PSA in all groups [2]

Addiction	Interleukin-12 (pg/ml)			Interleukin-10 (pg/ml)			PSA (ng/ml)		
Tobacco chewing	BPH ($n = 94$)	Cancer ($n = 285$)	Controls ($n = 285$)	BPH ($n = 94$)	Cancer ($n = 285$)	Controls ($n = 285$)	BPH ($n = 94$)	Cancer ($n = 285$)	Controls ($n = 285$)
Betel quid	65.69 ± 2.84^{ns}	$164.64 \pm 6.27^{*}$	$54.39 \pm 2.55^{*}$	$3.56 \pm 0.57^{*}$	$13.41 \pm 1.90^{**}$	$3.30 \pm 0.36^{**}$	2.36 ± 0.20^{ns}	29.72 ± 18.22^{ns}	0.79 ± 0.28^{ns}
Khaini	$68.35 \pm 3.25^{*}$	$177.91 \pm 7.53^{**}$	$57.13 \pm 2.46^{**}$	2.29 ± 0.21^{ns}	$10.09 \pm 0.46^{**}$	$2.60 \pm 0.38^{**}$	2.42 ± 0.28^{ns}	28.26 ± 12.15^{ns}	0.63 ± 0.23^{ns}
Gutkha	66.79 ± 3.74^{ns}	$171.91 \pm 5.47^{**}$	$55.20 \pm 1.59^{**}$	2.62 ± 0.32^{ns}	$9.59 \pm 0.70^{*}$	$2.59 \pm 0.31^{**}$	2.31 ± 0.32^{ns}	25.99 ± 12.08^{ns}	0.66 ± 0.23^{ns}
Tobacco smoker Cigarette	65.57 ± 2.64^{ns}	$167.58 \pm 5.87^{**}$	53.11 ± 2.33^{ns}	2.36 ± 0.17^{ns}	$9.21 \pm 0.74^{*}$	$2.68 \pm 0.33^{**}$	2.23 ± 0.14^{ns}	26.83 ± 12.60^{ns}	0.58 ± 0.25^{ns}
Bidi	$68.97 \pm 2.25^{*}$	$183.81 \pm 8.64^{**}$	$57.25 \pm 4.08^{**}$	2.63 ± 0.22^{ns}	$9.59 \pm 0.73^{**}$	$2.86 \pm 0.25^{**}$	2.28 ± 0.18^{ns}	27.01 ± 9.76^{ns}	0.62 ± 0.31^{ns}
Hookah	63.59 ± 1.13^{ns}	$163.50 \pm 5.39^{**}$	53.33 ± 1.90^{ns}	2.60 ± 0.27^{ns}	8.97 ± 0.78^{ns}	2.58 ± 0.29^{ns}	2.24 ± 0.15^{ns}	28.63 ± 17.08^{ns}	0.67 ± 0.35^{ns}
Chillum	68.66 ± 3.47^{ns}	$183.81 \pm 3.97^{**}$	$56.79 \pm 2.50^{**}$	2.64 ± 0.25^{ns}	$9.92 \pm 0.64^{*}$	$2.74 \pm 0.30^{*}$	2.34 ± 0.20^{ns}	27.22 ± 12.91^{ns}	0.92 ± 0.68^{ns}
Smoker with alcohol	$70.03 \pm 3.83^{**}$	$189.56 \pm 6.27^{*}$	$58.09 \pm 2.55^{**}$	2.39 ± 1.62^{ns}	$11.70 \pm 1.16^{**}$	$2.97 \pm 0.28^{**}$	2.35 ± 0.27^{ns}	26.87 ± 9.41^{ns}	0.68 ± 0.27^{ns}
Chewing with alcohol	$72.38 \pm 3.16^{**}$	$194.90 \pm 6.03^{**}$	$59.32 \pm 2.58^{**}$	2.62 ± 0.19^{ns}	$11.84 \pm 1.20^{**}$	$3.08 \pm 0.33^{**}$	2.47 ± 0.28^{ns}	25.05 ± 10.11^{ns}	0.64 ± 0.28^{ns}
Alcohol alone	$71.20 \pm 2.63^{**}$	$187.25 \pm 5.38^{**}$	$55.2 \pm 1.20^{*}$	2.53 ± 0.36^{ns}	8.97 ± 0.76ns	$2.76 \pm 0.36^{**}$	2.35 ± 0.19^{ns}	25.13 ± 10.22^{ns}	0.62 ± 0.36^{ns}
Smoker & chewing and alcohol	$74.09 \pm 1.29^{**}$	$204.12 \pm 2.78^{**}$	$61.11 \pm 3.11^{**}$	2.52 ± 0.24^{ns}	$11.99 \pm 1.49^{**}$	3.22 ± 0.27	2.38 ± 0.30^{ns}	28.46 ± 12.32^{ns}	0.64 ± 0.31^{ns}
Non-users	62.04 ± 1.05	158.63 ± 4.32	51.46 ± 3.23	2.06 ± 0.51	8.47 ± 0.98	2.24 ± 0.31	2.27 ± 0.17	26.39 ± 11.63	0.61 ± 0.27

^{ns} $P > 0.05$, * $P < 0.05$, ** $P < 0.001$ comparison with non-users within same group

tobacco exposed subgroups versus nonusers has been shown as (a) tobacco smokers (29.17 months; 95 % CI = 27.80–30.54, $P < 0.0001$), (b) smoker with alcohol (28.40 months; 95 % CI = 24.79–45.72, $P = 0.001$), (c) chewers with alcohol (30.16 months; 95 % CI = 29.12–33.20, $P > 0.05$), and (d) with alcohol (28.90 months; 95 % CI = 26.01–31.79, $P = 0.01$), while in (e) smokers, chewers, and alcoholic users (27.01 months; 95 % CI = 21.40–32.62, $P < 0.0001$) and (f) tobacco chewers it was 30.93 months (95 % CI = 29.99–31.88) which was lower than the nonusers (nonsmokers + non chewers + nonalcoholic cancer patients); which was statistically significant [3].

So our study on larger sample size also validate the findings of Mohamed Anser S et al.; with advanced exploratory study based on the inflammation. Tobacco exposure has always been illustrated as main attributable risk factor in the development of various cancers; this study helps to understand the link between tobacco exposure-mediated inflammatory response and PCa development/progression.

Conflict of interest The authors declare that there is no conflict of interests regarding the publication of this paper.

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