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TOBACCO USE AND ITS RELATION TO RAISED TOTAL IGE CONCENTRATION AND INCREASED RISK OF TYPE 1 HYPERSENSITIVITY REACTION AMONG MALES IN KHARTOUM, SUDAN

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ABSTRACT

Background: Continued tobacco use has been shown to affect both humoral and cellular immune responses. Cigarette smoke as well as other tobacco forms impairs the integrity of the lung epithelial layer and facilitates the penetration of allergens by compromising the innate defense mechanisms in the lungs. Thus, smoking may be stated to induce predisposition to atopy. Symptoms of cigarettes allergy are similar to asthma which includes, shortness of breath, wheezing, coughing and impaired lung function. **Objectives:** To investigate the effect of different tobacco products on serum total IgE concentration among healthy males in Khartoum, Sudan. **Materials and methods:** This prospective case control study was conducted in Khartoum, Sudan and involved 119 healthy males who age between (18-35) years. Study subjected were classified into five groups: 19active smokers, 13water pipe smokers, 18 smokeless tobacco users, 22 passive smokers and 35 non-tobacco users (controls). Demographic data was collected from each participant in a data collection sheet and a written informed consent was obtained from all participants. Serum samples were analyzed quantitatively using The ELISA test kit for detection of human antibodies of the IgE

class. **Results**: A tremendous increase in IgE mean SD level have been demonstrated among tobacco consumers (302±154) compared to non-users, mean SD level (120.5±143), and this elevation was more obvious among males who use combination of all three forms of tobacco (415±500). **Conclusion:** This study concluded that tobacco use among Sudanese males could be on of today's leading public health problems and may play a major role on the progression of hyper sensitivity reactions and allergic responses.

KEYWORDS: shortness of breath, wheezing, coughing and impaired lung function.

INTRODUCTION

Tobacco use is one of the major leading causes of death and essential public health challenge in world over. Previous studies have estimated that each year tobacco causes about 6 million deaths (about 10% of all deaths) around the world (Gadalla, *et al*, 2012; Elamin, *et al*, 2013). Chronic inhalation of tobacco smoke and waterpipe (hookah, shisha) alters a wide range of immunological functions, including innate and adaptive immune responses (Sopori, 2002). It has been speculated that many of the health consequences of chronic inhalation of cigarettes and/or water pipe smoke might be due to its adverse effects on the immune system (Farhang, *et al*, 2013).

Water pipe, also known as shisha and hookah is a pipe used to smoke a combination of tobacco and fruit. Even after passing through water it still contains high levels of toxic compounds, including carbon monoxide, heavy metals and cancer-causing chemicals (carcinogens) which has a more harmful effect than cigarettes smoke (Morris, *et al*, 2012). Another form of tobacco which contains nicotine includes smokeless tobacco which is a pinch is placed between the lower lip and gum or cheek and gum. The body may actually absorb more nicotine from chewing tobacco or snuff than it does from a cigarette smoke (O'Connor, 2012).

All tobacco forms include many harmful chemical compounds in the particulate and vapor phases. These compounds comprise five known human carcinogens and many toxic agents, including carbon monoxide, ammonia, acrolein, acetone, nicotine, benzopyrenes, hydroquinone and nitrogen oxides (Davis and Nielson, 1999; Sopori, 2002; Carson and Mumford, 2002). Many of these agents are known to be carcinogenic and toxic to the cells however; tar and nicotine have shown to be the most dangerous compounds (Richter, *et al*, 2008). Continued tobacco use has been shown to affect both humoral and cellular immune

responses. This causes a decreased response to antigens and reduced serum concentration of IgG, IgM and IgA, and also increased levels of IgE, autoantibodies notably; anti-nuclear and rheumatoid factors (Dinas, *et al*, 2013).

The qualitative and quantitative effects of smoking on the immune system might depend on the duration of smoking, as well as the sex and ethnicity of the subjects that are studied (Sopori, 2002; Sood, *et al*, 2014; Borish, *et al*, 2005).

Several factors, including age, sex and atopic status have been reported to influence levels of serum IgE. Studies have shown higher total serum IgE levels in smokers, and increased risk of developing respiratory illness, asthma and allergy (Mohammed, 2013). Cigarette smoke impairs the integrity of the lung epithelial layer and facilitates the penetration of allergens by compromising the innate defense mechanisms in the lungs. Symptoms of cigarettes allergy are similar to asthma which includes, shortness of breath, wheezing, coughing and impaired lung function (Sherrill, *et al*, 1994; Abdulhamid, *et al*, 2015). It has been recorded that cigarettes smoke increases mucosal permeability allowing easier and greater access of allergens to sub epithelial lymphoid tissue (Chhabra,*et al*, 2001). Thus, smoking may be stated to induce predisposition to atopy (Shirakawa, *et al*, 1992). This effect seems to be more common in males than in females and there is a dose-response relationship in the sense that increased pack-years correlate with increased IgE levels (Criqui, *et al*, 1990; Jenson, *et al*, 1992).

This study aims to reflect a closer image on the effect of tobacco use among males at different ages by looking into IgE antibody levels and other behavioral aspects in addition to the possible influences of this on further capacity at the immune system in terms of hypersensitivity reactions.

MATERIALS AND METHODS

Study design and population

This prospective case control study involving tobacco user males was conducted in Khartoum, Sudan and samples were collected from males attending different universities and water pipe cafes. Eligible subjects selected in the study were119 healthy males who age between (18-35) years. Tobacco users whom were included in the study were classified into five groups: 19active smokers, 13water pipe smokers, 18 smokeless tobacco users and 22 passive smokers. Another 35 samples were collected from non-tobacco users (controls).

Smokers with acute illness, history of chronic illness, any previous history of hypersensitivity reaction disease, atopic, previous infection, parasitic infection and history of heavy alcohol consumption were excluded from the study.

Data collection

Demographic data was collected from each participant in a data collection sheet. Furthermore information's about age, type of tobacco used, as well as the duration and frequency of tobacco use were obtained. The results of laboratory investigation were also included in the sheet.

Sample collection

Five milliliters (5 ml) of venous blood was collected from each participant into a plain containers and the serum was separated by centrifugation at 2000 rpm for 15 minutes. Serum was transferred into clean vials and stored at (-20°C) for further investigation.

Detection of anti IgE antibody in serum

Principle of the test

The ELISA test kit provides a quantitative in vitro assay for human antibodies of the IgE class in serum or plasma. The test kit contained microtiltre strips each with 8 break-off reagent wells coated with polyclonal antibodies against human IgE. In the first reaction step, diluted patient samples were incubated in the wells. IgE included in the sample was bound to antibodies. To detect bound IgE a second incubation was carried out using an enzyme labeled anti human IgE (enzyme conjugate) catalyzing a color reaction. The determination of the IgE concentrations was measured by means of calibration curve using the calibration sera 1 to 4.

Manual test performance

IgE antibody was measured using ELISA (Enzyme linked immunosorbent assay) a commercially purchased kit and the test were performed according to manufactured instructions. Briefly, 100 µL of diluted serum samples, standards and controls were added into appropriate wells. The incubation mixture was removed by flicking plate content into waste container, and then the microtitre plate was rinsed with distilled water. After that the microtiter plate was stroked sharply onto absorbent paper to remove all residual water droplets. Next 100 µL of enzyme conjugate reagent was dispensed into each well, gently mixed for 10 seconds and incubated at room temperature for 1 hour. The incubation mixture again was removed by flicking well contents into a suitable waste container and the wells

were rinsed with distilled water. 100 µL of TMB Substrate was added into each well, gently mixed for 5 seconds and incubated at room temperature for 30 minutes. The reaction was stopped by adding 100µL of stop solution (1N HCl) into each well and mixing gently for 30 seconds. Finally, the optical density was read using ELISA reader at wavelength 450 nm.

CALCULATION OF RESULTS

The stander curve from which the IgE concentration in serum samples was obtained by point to point plotting of the extinction values measured for the 4 calibration sera against the corresponding units (liner/liner). Participants samples which lied above the value of calibrator 1 (500 IU/ml, the result were reported as >500 IU/ml.

Normal IgE antibody level, titre (0-100 IU/ml).

Data analysis

Results were expressed as mean SD, and fisher's test of two-tailed p value was used to measure the significance of association between groups and outcomes.

Ethical consideration

Written informed consent was obtained from all males who were selected to participate in this study.

RESULTS

This study comprised 119 male participants who were among the age of (18-35 years) and live in Khartoum, Sudan. The study groups were divided in to four categories, 19 (31%) active cigarettes smokers, 13 (21%) waterpipe smokers, 18 (30%) snuff users and 22 passive smokers. Whereas 10 (16%) of participants were cigarettes and water pipe smokers and only 2 (3%) of them were using all the three types of tobacco. Another 35 subjects who never smoked before were included as control group.

Personal interviews of cigarettes smokers revealed that all of them were using Bringi brand while only 2 participants (10%) were using combination of Bringi with other brands. According to data sheet information all smokers were not previously diagnosed with any type of allergy, still 4 (21%) of them were experiencing various allergic symptoms such as itchy nose, sneezing, runny or stuffy nose, itchy eyes, coughing and skin problems. On the other hand 95% of tobacco users have pointed to the fact that they either live or work around smokers and they are usually exposed to smoke most of the day. Apart from that all tobacco

consumers were well educated and in deep knowledge about the risks of nicotine products and all dangerous disease caused by it, therefore 52% of tobacco users declared that they had intend to quit.

Mean levels of total IgE were increased among all males under study who use various tobacco types compared to control group, (titer > 100 IU/ml). The highest IgE levels were detected among those who use combination of all three types of tobacco which ranged between 415±500 IU/ml. Comparing over all the IgE levels of tobacco users indicated that, 17(89.4%) cigarettes smokers have had an increased IgE levels which range between 96±500 IU/ml. While smokeless tobacco users showed the lowest mean levels among studied participants with a range of 60±500, figure 1.

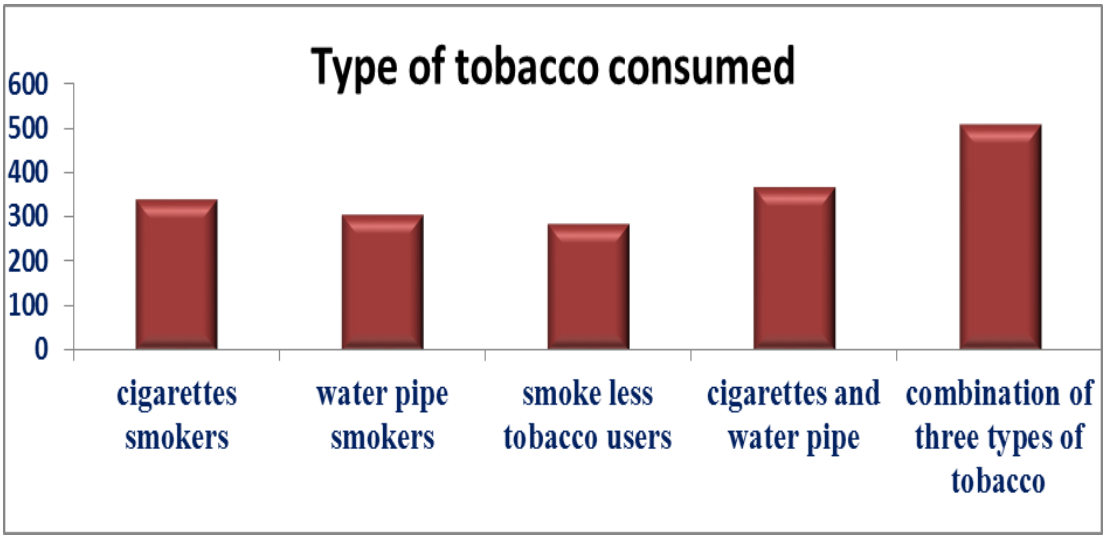

Figure 1: Comparison between total IgE mean levels of participants using different tobacco products.

Tobacco users were originally subdivided according their duration of tobacco use into less than 5 years, 5-10 years, 11-15 years and > 16 years. However, there was a relation between the duration of tobacco use and IgE level, in which the highest level of IgE was found among those who were using tobacco for 11-15 years except the water pipe smokers were lower, and those who were using tobacco for less than 5 years recorded the lowest IgE levels, table 1.

Table 2: Association of IgE means levels and duration of tobacco use

Duration of smokeless tobacco use	**Using frequency**		**IgE mean levels SD±**
Less than 5 years	9	50%	306±155
5-10 years	6	33%	253±199
11-15 years	2	12%	462±194
More than 16 years	1	5%	340
Duration of cigarette smoke	**using frequency**		**IgE mean levels**
less than 5 years	12	63%	313±208
5-10 years	6	31%	393±180
11-15 years	1	5%	350
Duration of water pipe use	**Using frequency**		**IgE mean levels**
Less than 5 years	11	84%	258±243
5-10 years	2	16%	>500
Duration of cigarette and water pipe smoking	**Using frequency**		**IgE mean levels**
Less than 5years	6	60%	297±210
5-10years	3	30%	446±135
11-15 years	1	10%	249

Results of IgE levels by ELISA of tobacco users' volunteers revealed an obvious relation between the rate of tobacco consumption per day and the elevation of IgE levels in which those who consumed tobacco more frequently had the most increased IgE levels compared to those who use it less frequently, table 2.

Table 3: The correlation between the rate of tobacco consumption/day and IgE mean levels among the studied groups.

Cigarette smoked per day	**frequency**	**IgE mean levels**
Less than 5	6	356
5-10 cigarettes	10	339
10-15 cigarettes	2	249
More than 15	1	350
Water pipe smokers	**frequency**	**IgE mean levels**
Once in month	2	175
1-3 in weak	1	398
Once a day	7	282
More than once a day	3	440
Smokeless tobacco users	**Frequency**	**IgE mean levels**
3 times/day	1	430
More than 3 times/day	17	306

In 42.1% of passive smokers there were more than two persons with smoking habits in their living surroundings, while 57.8% of passive smokers had one person using tobacco products. Difference in mean standard deviation of total IgE levels between this two investigated groups among passive smokers were 408±91.9, 247±167.3 respectively.

Statistically significant higher total IgE (IU/ml) was higher in all tobacco consumers compared to non-smokers (p=0.0001).

DISCUSSION

Nowadays, sales and advertising of tobacco smoke in Sudan are increasingly targeting individuals among their younger ages which in turn resulted in a sharp increase of smoking habit in the community (Sudan hub group, 2015). Even though most of tobacco consumers have a general knowledge of the impact of smoking, they may not know that smoking both cigarettes and shisha as well as snuff use may also increase IgE immunoglobulin level which is an indication of an increased probability of an IgE mediated hypersensitivity reaction (Salih, *et al*, 2009; Mohamed, 2013).

In this study the tobacco user males were mostly between the ages of 18-35 years, this age group seems to be the most susceptible age to be attracted to this habit. Such finding has been reported in a recent research study in Sudan by (Khidr, *et al*, 2015) who pointed to the fact that nearly all first use of tobacco takes place before high school graduation and people at younger age are easy targets for the tobacco industry.

The study revealed that cigarettes and smokeless tobacco seems to be the most types of tobacco consumed among participants representing 31% and 30% respectively. This result agrees with previous studies which indicated that cigarettes and smokeless tobacco are the most popular type of tobacco and are widely used among males during their younger ages (Idris, *et al*., 1998; Salih, *et al*, 2009).

The present study also demonstrated that Bringi was the most type of brand used by smoker males when compared to other cigarettes brands, including all participants in the study. This might be explained by a recent study done in 2015, in which the reason that makes this brand so special are the strength of them, they are quite strong and considered much stronger than Marlborough reds. So once a person is used to such heavy cigarettes such as Bringi, nothing else will do (Khidr, *et al*, 2015).

A tremendous increase in IgE mean SD level have been demonstrated among tobacco consumers (302±154) compared to nonsmokers mean SD level (120.5±143), and this elevation was more obvious among males who use combination of all three types. This result has been previously investigated and proven by (Chhabra, *et al*, 2001) in which they he explained this elevation among tobacco users and reported that nicotine the main component in tobacco products increases mucosal permeability allowing easier and greater access of allergens to sub epithelial lymphoid tissue and this elevation in IgE level indicates an increased probability of type 1 hypersensitivity reaction (allergy), which also explains the allergy symptoms experienced by 21% of tobacco users.

On the other hand, the lowest IgE SD mean levels were revealed among participants who use smokeless tobacco. However the result of this study is contrary to (Mlinaric, *et al*, 2011) who reported that nicotine levels were found to be similar in smokeless tobacco and cigarettes smoke.

The study also showed an increased IgE levels among passive smokers. This agrees with number of studies which found a greater prevalence of allergic diseases and increased IgE levels in passive smoker's subjects. Also impact of passive tobacco consumption on the severity of asthma was found to be very similar to the impact of active tobacco consumption smoke (Milnaric, *et al*, 2011).

The study revealed an association between the duration of tobacco use and increased IgE level, in which those who used tobacco for longer duration appear to have the highest IgE levels when compared to others. This result have also been proven by (Abdulhamid, *et al*, 2015) who reported in a recent research study that there is a dose-response relationship in the sense that increased back- years correlate with increased IgE levels.

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