



Case-controlled Study

Evaluation of exposure to secondhand smoke and serum level of interleukin 18 in non-smokers

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ABSTRACT

Objective: Smoking is one significant global health care problems, that not only affects the users but also endangers the health of people inhaling the smoke (passive smoking/secondhand smoke). The serum level of IL-18, an important regulator of inherent and acquired immune response, is affected by cigarette smoking. The aim of this study was to evaluate the effect of secondhand smoke (SHS) exposure on IL-18 serum level in non-smoker adults.

Methods: In a case-control study, using easy sampling method, 76 non-smokers who were exposed to cigarette smoke for at least 1 h daily during the past year were considered as exposure group, while 76 of their companions without exposure to cigarette smoke (after matching age) were considered as non-exposure group. Serum IL-18 levels were measured for all participants and finally compared between the two groups using Chi-square test. P value < 0.05 was considered to be statistically significant.

Results: The exposure and non-exposure groups included 58 (76.3%) and 25 (32.9%) males, respectively ($P < 0.001$). The mean $\pm$ SD of age for the exposure and non-exposure groups was 35.42 ± 10.37 and 38.47 ± 12.49 years, respectively ($P = 0.102$). There was no significant difference between the mean serum levels of IL-18 in the exposure (54.81 ± 57.03 ng/ml) and non-exposure (41.49 ± 42.14 ng/ml) groups ($P = 0.104$).

Conclusion: The exposure to secondhand smoke has no significant effect on serum level of IL-18 in exposed adult individuals. However, more studies with larger sample sizes on different populations are required to confirm these results.

1. Introduction

Approximately, 1 billion people are smokers, globally and the health-related burden associated with smoking in smokers and secondhand smokers (passive smokers) imposes myriad of problems [1]. Every 10 s, an individual is reported to die because of tobacco-related complications and diseases [2]. Smoking causes exposure of non-smokers to secondhand smoke (SHS) [3], exposure to cigarette smoke, also known as passive smoking, threatens the health of 40% of children and 34% of non-smoker adults and is a major health concern in the world [4,5]. SHS is defined as smoke that comes out from the burning tip of a cigarette and/or the smoke of the tobacco cigarette that is exhaled from the lungs of the smoker [6]. The smoke that is inhaled by the people around the

smokers is several times more dangerous and more toxic than the smoke passed through the filter [7]. Studies have indicated that the use of air filters does not reduce the risk of exposure to SHS. A short-term exposure to SHS is enough to alter the inflammatory cytokine response [8]. Tassa et al. examined the toxic effects of SHS on vascular endothelial cells using endothelial biopsy. The study reported that an increase of inflammation as well as reduction of active endothelial nitric oxide synthase (eNOS) in passive smokers was similar to active smokers [9]. Common immune response to cigarette smoking include increased number of leukocytes, decreased secretion of immunoglobulin A (IgA) and change in cytokines and inflammatory mediators production [2]. In a systematic study conducted in 2017, children with asthma who were exposed to SHS had a greater asthma severity [10].

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Interleukin 18 (IL-18) is a pro-inflammatory cytokine and a member of the Interleukin-1 family, which is produced by many cells including macrophages, monocytes, epithelial cells, and dendritic cells [11]. Produced mainly by antigen-presenting cells, IL-18 is a pleiotropic factor involved in the regulation of both innate and acquired immune responses, playing a key role in autoimmune, inflammatory, and infectious diseases [10]. In a study, it has been reported that IL-18 levels are higher in children with allergic rhinitis and asthma compared to control healthy subjects [12].

Some studies have shown that IL-18 concentration has increased in mouse lung tissues exposed to SHS, and this increase in concentration has led to lung tissue destruction and enhanced emphysema [13]. Another study showed that in the mouse model, IL-18 receptor signaling (IL-18R) was involved in the pathogenesis of inflammation caused by cigarette smoke and emphysema [14,15]. In a study by Kratzer et al., in 2013, IL-18 was reported to be involved in the death of endothelial cell lung cells and the development of emphysema after exposure to cigarette smoke. It has also been shown that this cytokine results in cell death of capillary endothelial cells [16]. Similar has been suggested in animal models of water pipe tobacco smoking [17].

In spite of existence of several studies showing the impact of exposure to cigarette smoke on the imbalance of some interleukins effective in the progression of diseases, there are few human studies about the effects of passive exposure (SHS). A recent nationwide study reported that approximately 31.5% of Iranians are exposed to SHS, regardless of the location [18]. Therefore, we studied the effect of exposure to secondhand smoke on the serum level of interleukin-18 in non-smoker adults.

2. Materials and methods

This was case-control study performed at (XXX) over past one-year. Patients were selected from those who are non-smokers. The inclusion criteria were age of 20–60 years; no current use of any drug; non-exposure to narcotic smoke (opium, sap, heroin, etc.); no underlying inflammatory, pulmonary, cardiovascular, rheumatologic, or renal diseases and diabetes; no recent surgery; no history of hospitalization in the recent year. The following data was obtained through interview or examination of medical history, if any.

It is indicated in studies that 1 h exposure to secondhand smoking can significantly reduce lung function and increase inflammation and induce depressive symptoms [19–21]. Using sequential sampling method, 76 non-smokers who were exposed to cigarette smoke for at least 1 h daily during the past year were considered as exposure group, while 76 of their companions without exposure to cigarette smoke (after matching age) were considered as non-exposure group. Non-smokers were also defined as serum cotinine ≤ 15 ng/ml, as reported in other studies [22]. Blood samples (5 ml) were collected from the participants and, after centrifugation for 5 min (2000 rpm, Kubota, Japan), their serum IL-18 levels were measured using the ELISA kits purchased from the Eastbiopharm company (China).

2.1. Statistical analysis

SPSS software version 19 (SPSS Inc., USA) was used for statistical analysis. For quantitative data, the results were reported as mean SD and for qualitative data, the results were reported as (%). Chi-square test was used to evaluate homogeneity of the two groups and the results were reported at the significant level of 0.05.

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The methods have been presented in parallel with STROCSS guidelines 2021 [23].

3. Results

The exposure group included 58 men (76.3%) men and 18 women

(23.7%), while the non-exposure group included 25 men (32.9%) men and 51 women (67.1%), the results showed that the two groups were not sex-matched ($P < 0.001$) (Table 1).

The mean $\pm$ SD of age for the exposure and non-exposure groups was 35.42 ± 10.37 and 38.47 ± 12.49 years, respectively, there was no significant difference between the mean age of the two groups according to ($P = 0.102$) (Table 2).

There was no significant difference between the mean serum levels of IL-18 in the exposure (54.81 ± 57.03 ng/ml) and non-exposure (41.49 ± 42.14 ng/ml) groups ($P = 0.104$) (Table 3).

The comparison of mean serum IL-18 levels between the two groups by gender is shown in Table 4. As shown, there was no significant difference between the groups according to gender.

4. Discussion

Many studies have shown important effects of smoking on immune responses in active and passive smokers such as some of this effects include increasing the number of T cells and neutrophils, reducing the activity of natural killer cells, production of certain immunoglobulin classes, and changing the production of several inflammatory cytokines and mediators [24]. One of these cytokines is IL-18, which is recognized as an important regulator of inherent and acquired immune response [25]. Today, finding the role of IL-18 in other immune activities is rapidly expanding.

The aim of this study was to determine the effect of exposure to secondhand smoke (SHS) on the serum level of IL-18 in nonsmokers. According to our results, the mean serum IL-18 level in subjects with exposure to SHS was higher than those without exposure; however, this difference was not statistically significant. This is consistent with the results of several studies and in contrast to some others.

In the study of Tariq et al., long-term exposure to SHS increased the levels of inflammatory cytokines such as IL-17A and IL-6 in the lungs and also caused a defect in adaptive immune response to infection or P6vaccination [26].

A study by Gaschler et al. found that exposure to cigarette smoke could reduce the production of cytokines in mouse alveolar macrophages [27]. Another study by Dinarello et al. showed that exposure to SHS leads to reduction of most cytokines; but at the same time, significant increase in IL-18 concentration was seen in bronchoalveolar lavage fluid (BALF) in exposed rats [28]. Jordan and colleagues showed that almost all cells express IL-18 in low level and following intense pulmonary damage, the expression of its active form in macrophages is greatly increased [29]. Sugawara et al. stated that cigarette smoke exposure induces the release of active IL-18 from alveolar macrophages by activating Caspase-1 enzyme [30]. According to studies, IL-18 is present in cigarette-derived pulmonary responses and a high concentration of IL-18 is present in patients with chronic obstructive pulmonary disease (COPD). Smoke exposure is known to activate IL-18, caspases 1 and 11 mediated IL-18R α (IL-18 receptor alpha) that leads to endothelial apoptosis, chemokine upregulation and protease production [31,32]. Evidence suggests that about half of the population in the United States is at risk for COPD because they are unwittingly exposed to SHS [33]. Kearley and colleagues in 2015 showed that cigarette smoke increases the IL-33-dependent inflammatory response that leads to COPD exacerbation. The onset of this inflammatory response occurs by altering the micro-environment of the lung tissue [34]. According to

Table 1

Comparison of the frequency and percentage of people in the two groups exposed and not exposed to cigarette smoke by gender.

Groups	Male	Female	Total	p-value
Exposed to cigarette smoke	58(76.3%)	18(23.7%)	76	$p < 0.001$
Non-exposed to cigarette smoke	25(32.9%)	51(67.1%)	76	
Total	54.6%	45.4%	152	

Table 2

Comparison of the average age between people exposed and not exposed to cigarette smoke.

Groups	Mean	Standard deviation± average	Number	p-value
Exposed to cigarette smoke	33 (17)	35.42 ± 10.37	76	P = 0.102
Non-exposed to cigarette smoke	37 (20)	38.47 ± 12.40	76	

Table 3

Comparison of mean serum levels of interleukin 18 between exposed and non-smokers.

Groups	Mean	Standard deviation± average	Number	p-value
Exposed to cigarette smoke	26.6 (50.1)	41.49 ± 42.14	76	P = 0.104
Non-exposed to cigarette smoke	24.3 (29.6)	54.81 ± 57.03	76	

Table 4

Comparison of mean serum IL-18 levels between exposed and non-exposed groups to cigarette smoke by sex.

Sex	Group	Median (Interquartile range)	Standard deviation± average	Number	P value
Female	Exposed to cigarette smoke	32.4 [35]	57.8 ± 62.1	18	P = 0.08
	Non-exposed to cigarette smoke	23.6 (24.6)	37.63 ± 35.8	51	
Male	Exposed to cigarette smoke	26.1 (56.1)	53.8 ± 55.9	58	P = 0.73
	Non-exposed to cigarette smoke	30.3 (31.4)	49 ± 52.7	25	

Suffwan et al., some of the proteins involved in the formation of inflammasome such as NALP3 (NACHT, LRR and PYD domains-containing protein 3), ASC (apoptosis-associated speck-like protein containing CARD), and alscaspase1/11, are involved in the secretion of IL-1 β /IL-18 induced by cigarette smoke and airway inflammation [35].

In a study by Rovina et al., in 2009, it was shown that IL-18 concentrations were diminished in the humor of active smokers. They also found a significant correlation between the concentration of IL-18 and the severity of asthma in smokers with asthma(15). Jefferis, Lowe [22] reported that IL-18 is not significantly different among smokers and passive smokers. Nonetheless, other biomarkers like white blood cells, c-reactive protein, fibrinogen, albumin and triglycerides are significantly different among the two groups.

In our study, 45.4% and 54.6% of participants were female and male, respectively. According to the statistical analysis, the two groups were not gender matched in spite of random selection. This is because smoking is more common in the environments where men are present, such as the workplace. However, according to the analysis, gender had no confounding effect on the observed results.

5. Conclusion

The exposure to secondhand smoke has no significant correlation with serum level of IL-18 in exposed adult individuals. However, more

studies with larger sample sizes on different populations are required to confirm or rule out this result.

Several limitations of the present study include small sample size and data regarding diet and physical activity were not compared among the two groups, which can affect IL-18 levels. Duration of SHS can affect the level of inflammation and IL-18, which is also not presented in our study. We did not obtain data regarding the exposure to smoke for less than 1 h and effects of other cytokines, that might cause immune dysfunction in these individuals are also not evaluated in our study. The data provided here implies only for individuals expose to tobacco smoke for 1 h or more and its effects on levels of IL-18. Furthermore, data regarding the type of cigarettes used in terms of filter/no-filter, manufacturer, and chemical composition could not be obtained as non-smokers did not have this information. Therefore, more studies are needed to better define the role second-hand smoke on the production of interleukin 18 and secondary its effect on non-smoker adults.

Provenance and peer review

Not commissioned externally peer reviewed.

Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication

Informed consent was obtained from each participant.

Availability of data and materials

All relevant data and materials are provided with in manuscript.

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Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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No funding was secured for this study.

Author contribution

Ali Kharazmkia and Alireza Azargoon: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Samareh Mir and Mehdi Birjandi: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Nazanin Kordalivand: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to

be accountable for all aspects of the work.

Consent

Not applicable.

Registration of research studies

1. Name of the registry: N/a.

2. Unique Identifying number or registration ID: LUMS. REC.1396.322.

Hyperlink to the registration (must be publicly accessible):

Guarantor

Dr. Ali Kharazmkia.

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study. All the fees provided by research center fund and deployed accordingly.

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