KEMAS
JURNAL KESEHATAN MASYARAKAT

Editorial Policies

Focus and Scope

KEMAS: Jurnal Kesehatan Masyarakat is an international, peer-reviewed journal. It publishes original papers, reviews and short reports on all aspects of the science, philosophy, and practice of public health.

It is aimed at all public health practitioners and researchers and those who manage and deliver public health services and systems. It will also be of interest to anyone involved in provision of public health programmes, the care of populations or communities and those who contribute to public health systems in any way.

Published twelve times a year, KEMAS: Jurnal Kesehatan Masyarakat considers submissions on any aspect of public health across age groups and settings.

These include:

Public health practice and impact
Epidemiology and Biostatistic
Applied EpidemiologyÂ
Need or impact assessments
Health service effectiveness, management and re-design
Health Protection including control of communicable diseasesÂ
Health promotion and disease prevention
Evaluation of public health programmes or interventions
Public health governance, audit and quality
Public health law and ethics
Health policy and administration
Capacity in public health systems and workforce
Public health nutrition
Environmental health
Occupational health and safety
Reproductive health
Maternal and child health

This is not an exhaustive list and the Editors will consider articles on any issue relating to public health.

KEMAS: Jurnal Kesehatan Masyarakat also publishes invited articles, reviews and supplements from leading experts on topical issues.

Section Policies

Articles

☑ Open Submissions ☑ Indexed ☑ Peer Reviewed

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Both the reviewer and the author are anonymous.

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- Make sure that figures and tables do not contain any reference to author affiliations
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The journal was first published in July 2005 and subsequently published twice per year, in July and January

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KEMAS: Jurnal Kesehatan Masyarakat [P-ISSN 1858-1196 | E-ISSN 2355-3596 | DOI 10.15294/kemas] publised by Universitas Negeri Semarang in collaboration with Ikatan Ahli Kesehatan Masyarakat Indonesia (IAKMI Tingkat Pusat) and Jejaring Nasional Pendidikan Kesehatan (JNPK). KEMAS publishes the article based on research or equivalent to research results in public health or other disciplines related to public health that has not been loaded/published by other media. The journal contains articles about epidemiology and biostatistics, health policy and administration, public health nutrition, environmental health, occupational health and safety, health promotion, reproductive health, maternal and child health, and other related articles in public health. The journal can be used by health practitioners, health caregivers, teachers, medical students, and people who are interested in public health issues. The journal was first published in July 2005 and subsequently published twice a year, in July and January. KEMAS has been accredited by DIKTI starting in 2014 with an Accreditation Letter Number: 212/P/2014 and indexed by Sinta 2nd. Since 2017, the journal were published 3 times a year in July, November and March. In 2019, KEMAS has been acredited with Accreditation Letter Number : 10/E/KPT/2019.

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The Expression Change of MMP-8 and Collagen Type-2 Intracell in Lung Tissue Due to Electronic Smoke Exposure

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Abstract

The number of electronic smokers has increased annually. Exposure to electronic cigarette will increase free radicals in the body and result in oxidative stress occurrence causing lung tissue damage. The severity degree of lung tissue damage caused by electronic smoke exposure depends on the duration of electronic cigarette smoke exposure and is going to affect Matrix Metalloproteinase-8 and collagen type-2 in the cells. The study aims to understand the change degree of Matrix Metalloproteinase-8 and collagen type-2in lung tissue due to electronic cigarette smoke exposure. This study applied experimental method with post control group design. The male wistar rats were used as the animal models in this research in order to asses cell damage through the expression of Matrix Metalloproteinase-8 and collagen type-2 in the lung tissue using immunohistochemical staining. Exposure to electronic smoke cigarette was given to each group of animal models with difference in amount and time duration. The expression of Matrix Metalloproteinase-8 indicated that there was a significant increase due to electronic smoke exposure (ANOVA, p=0.000). Meanwhile, the expression of collagen type-2 showed that there was a significant decrease because of electronic smoke exposure (ANOVA, p=0.000). Besides, MMP-8 and collagen type-2 manifested relationship existence and strong impact (r=0.948, p=0.000). The negative impact of exposure to electric cigarette smoke causes increased expression of Matrix Metalloproteinase-8 and decreased expression of type-2 collagen in lung tissue.

Introduction

In the recent years, the number of electronic cigarette smoker has significantly increased. It is caused by lack of knowledge about the long-term effects caused by the electronic cigarette as well as limited amount of research data indicating the negative impacts of long-term use of electronic cigarette. Moreover, the rule regulating the use of electronic cigarette has become a growing controversy. (Cherng, Tam, Christine, & Meza, 2016) Most people assume electronic cigarette as one of ways to reduce addiction to tobacco cigarette and the electronic cigarette is considered safer because it only contains nicotine (Vardavas, Filippidis, & Agaku, 2015). However, for most people electronic cigarette is assumed as a way of legalizing smokers to smoke in public and in working places and it can negatively affect teenagers to smoke (Martínez-Sánchez et al., 2015). People's perception related to electronic cigarette use also influences the increasing number of smokers. The use of electronic cigarette considered safe by some people can influence teenagers to start smoking the electronic cigarette (Amrock, Lee, & Weitzman, 2016). Electronic cigarette has become more popular in society through massive marketing system via several media such as television, print publication, radio and internet. The promotion budget of electronic cigarette in the United States in 2012 had increased almost

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double the same budget in 2011. In the second quarter of 2013, it increased more than eight times compared to the second quarter of 2012 (Xu, Guo, Liu, Liu, & Wang, 2016).

The increasing number of electronic cigarette smokers does not only happen in several developing countries, but also in developed countries. In 2011, the prevalence of electronic cigarette in young adult age (18-28 years old) was the highest compared to the other age groups, reaching 4.9%-7%, with all age groups reaching 0.6% until 6.2%. The user prevalence of electronic cigarette in the United States in adult age group also increased 2 until 4 times higher in 2012 (Jaber et al., 2018). Meanwhile in senior high school students, the use of electronic cigarette was approximately 1.5% which later consistently increased in 2014 reaching 13.4%. New Zealand had also experienced an increasing number of electronic cigarettes in teenagers (14-15 years old) reaching almost 3 times higher than 7% in 2012 into 20% in 2014 (Thrasher et al., 2016). In the recent years, Australia had also demonstrated an increase of electronic cigarette smokers. In the adult age group, the increase reached twice of 4% in 2013 into 9% in 2016. The scores were obtained from two groups, which were active smokers having an increase from 18% to 31%, while the non-smokers had an increase from 2% into 5%. However, this is inversely proportional to the use of cigarettes which decreases every year (Jongenelis, Kameron, Rudaizky, & Pettigrew, 2019). Policies on tobacco control such as an increase in cigarette taxes, smoke-free laws, limiting cigarette advertisements and normalizing the behavior of smokers in active smokers are the most influential factors in reducing the number of smokers. But all these things have not been applied to users of e-cigarettes (Voigt, 2015).

The increase in the use of e-cigarettes does not only occur in high-income countries, but also occurs in countries with medium and low incomes. In developing countries, electronic cigarette has been used both individually and in pairs along with tobacco cigarette (Palipudi et al., 2016). In Greece and Qatar, more than 60% of electronic cigarette smokers also use tobacco cigarette concurrently, while the electronic cigarette smokers originating from non-smokers have reached 35.6% in Greece and 15% in Qatar (Palipudi et al., 2016).

Electronic cigarettes are battery powered cigarettes operating through a heating process of an element (metal coil) by evaporating propylene glycol solvent, vegetable glycerin, and flavoring which sometimes contain nicotine (Grana, Benowitz, & Glantz, 2014). Electronic cigarettes are considered to have less side effects for the health compared to the tobacco cigarettes. Besides, more modern packaging and better marketing strategies have made electronic cigarettes a lifestyle choice for both smokers and teenager group (Canistro et al., 2017). Electronic cigarette is always claimed as one of effective ways to stop smoking or as a substitute of cigarette because it does not contain tar, carbon monoxide, and other chemical compounds. This has led to an annual increasing rate of electronic cigarette smokers (Polosa et al., 2011).

The cigarette smoke contains several types of high number of free radicals, estimated reaching more than 1016 for every inhalation, including Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) (Dellinger, Khachatryan, Masko, & Lomnicki, 2011). Reactive Oxygen Species (ROS) consists of superoxide anion (O2•-), hydrogen peroxide (H2O2), and hydroxyl radical (OH•) as normal products of oxygen molecule reduction. Radical oxygen is not only produced by mitochondria, but neutrophils and macrophages can also produce ROS through the plasma membrane (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010; Herlina, Riyanto, Martono, & Rohman, 2018). In hypoxic conditions, mitochondria produce Nitric Oxide (NO), which can produce other Reactive Nitrogen Species (RNS), for example aldehydes-malondialdehyde and 4-hydroxinonenal (Arulselvan et al., 2016) .In a normal condition and a balance between free radicals and antioxidants, the free radicals serve as the body defense mechanism (Ravipati et al., 2012). A significant increase of the number of free radicals due to electronic cigarette smoke exposure can cause occurrence of oxidative stress in lung tissue (Zhang et al., 2018). Oxidative stress is triggered by imbalance between the number of free radicals entering the lung tissue and antioxidants in the

body which can result in injury in all cellular components such as lipid, protein, and DNA so that causing cells' death (R. V. Suryadinata, Wirjatmadi, & Adriani, 2017; Sagor, Reza, Tabassum, Rahman, & Alam, 2017). Some diseases can also be caused by cigarettes, such as cancer, cardiovascular diseases, and Chronic Obstructive Pulmonary Disease (COPD) (Goel et al., 2015).

The number and size of particles generated from electronic cigarettes are the same as the ones produced by tobacco cigarettes. Even, some types of electronic cigarettes can produce more particles compared to the tobacco cigarettes (Grana et al., 2014). Particles produced from e-cigarettes cause irritation of the airways so that mucous hypersecretion occurs in the bronchi (R. V. Suryadinata, Wirjatmadi, & Adriani, 2016). The number increase of free radical particles can trigger inflammation reaction in the lung tissue (Pratiwi, Lorensia, & Suryadinata, 2018). Inflammation reaction is a lung defense mechanism against dangerous stimulus such as pathogen, cell damage, and harmful chemical compounds. Moreover, acute inflammation response can minimize injury or infection caused in the lung tissue. The inflammatory process changes in blood vessel permeability, leukocyte movement and the release of inflammatory mediators (Chen et al., 2018).

However, a prolonging inflammation process in airways can result in lung cell damage. This can cause cell lysis occurrence impacting in deteriorating lung cell function (Levy & Serhan, 2014). In a pathological condition or cell damage, there is an increase of productivity and activity of Matrix Metalloproteinase-8, while collagen type-2will experience an intracellular decrease (Asano et al., 2010). The change of Matrix Metalloproteinase-8 and collagen type-2 can trigger fibrosis formation in the lung (McKleroy, Lee, & Atabai, 2013).

Electronic cigarette is always considered as containing less chemical compound compared to tobacco cigarettes. The fact of the matter is that the safety of electronic cigarette has not yet been proven and the side effects of its long-term use on the lung tissue has not yet been known (Jensen et al., 2015; Suryadinata & Wirjatmadi, 2020). As a consequence, verification of histology aspects of the levels of Matriks Metalloprotein-8 and collagen type 2 as a parameter of lung tissue damage due to the use of electronic cigarettes in male wistar rat models is required. These parameters can provide a direct picture of lung tissue damage compared to the use of malondialdehyde levels (Wirjatmadi & Suryadinata, 2020).

Methods

This study is an experimental research using post test control group design. The samples of the study used male wistar rats (Rattus novergicus). This research was divided into 6 groups with different time duration of administration treatment of electronic cigarette smoke exposure for each group. The smoke exposure was done for 5 minutes during each intervention administration. The differing aspect of each group was the total amount of administration per day and the time duration per week. The first group was the negative control group which was not exposed to electronic cigarette and used as a comparison to treatment groups, while the rest, in each group there was exposure of electronic cigarette smoke for several time duration and observation of lung tissue using immunohistochemical staining (HIS) was conducted to see the tissue damage.

Samples of experimental animals Wistar rats (Rattus novergicus) aged 2-3 months with a weight of 200-250 grams, move actively, macroscopically found no abnormalities and have never been the object of research. Before the treatment is carried out, all animals try to do the adaptation process first for 5-7 days. The study was conducted at the Laboratory of the Faculty of Medicine, Airlangga University based on the 3R principle (Replacement, Reduce and Refinement). Experimental animals were placed in cages measuring 800 cm2 per 5 animals with ventilation and room temperature around 25oC. Cleaning the cage and providing drinking water is done periodically as well as providing food as much as 20-30 grams / day. Each group will be given exposure to electric cigarette smoke that is different in time, amount and duration of administration in accordance with research procedures. Sample replication using is used to compare between treatment

groups.

Based on the results of the calculation of the minimum sample in this study amounted to 5 male Wistar rats in each group. The solution of the electric cigarette used in this study contained 6 mg of nicotine. The room where the exposure to electric cigarette smoke measures 50 cm x 40 cm x 20 cm. In this space a pipe will be passed through which can flow e-cigarette smoke. Provision of exposure to cigarette smoke is adjusted to the length of administration planned in the study

Samples were assessed semiquantitatively according to the modified Remmele method, where the Remmele scale index (Immuno Reactive Score / IRS) is the result of multiplying the percentage score of immunoreactive cells with the color intensity score on immunoreactive cells. The data for each sample is the average value of the IRS that was observed in 5 (five) Field View (LP) different at 1000x magnification. All of these examinations use a light microscope

The male Wistar rats were divided into 6 groups, including negative control and treatment group. The first group as the negative control group was a group that given no intervention for 4 weeks. While the second group as the treatment group I was given the e-cigarette smoke intervention once every 5 minutes per day in a week. The third group or the treatment group II was given e-cigarette smoke exposure intervention twice every 5 minutes per day in a week. The treatment group III was given intervention of e-cigarette smoke exposure once every 5 minutes per day in 2 weeks. The treatment group IV was given e-cigarette smoke exposure twice every 5 minutes per day in 2 weeks. The last control group was given intervention of e-cigarette smoke exposure once every 5 minutes per day in 3 weeks.

The data that has been collected perform statistical tests using ANOVA test analysis with SPSS version 20 to see the difference between Metalloprotein 8 matrix and collagen type 2 in lung tissue in all groups. Then the Least Significant Differences (LSD) test is performed to compare between groups. In addition, a trial was conducted to see the existence of a relationship between the two groups. Data will be presented in average numbers from the Immuno Reactive Score (IRS)

Results and Discussion

The results of the study were carried out by comparing the Metalloprotein 8 (MMP-8) matrix and the collagen type 2 average in each group per 5 visual fields. Based on Figure 1. the average value and Standard Deviation of the Metalloprotein 8 (MMP-8) matrix can be seen in each group. These results show the increasing Metalloprotein 8 (MMP-8) matrix in each group which is directly proportional to the length of time of exposure to cigarette smoke. In group I, the mean value of Metalloprotein 8 (MMP-8) matrix reached 2.00 ± 0.17, which is the lowest mean value in all groups. While the highest mean value was obtained in group VI which reached 7.48 ± 0.34.

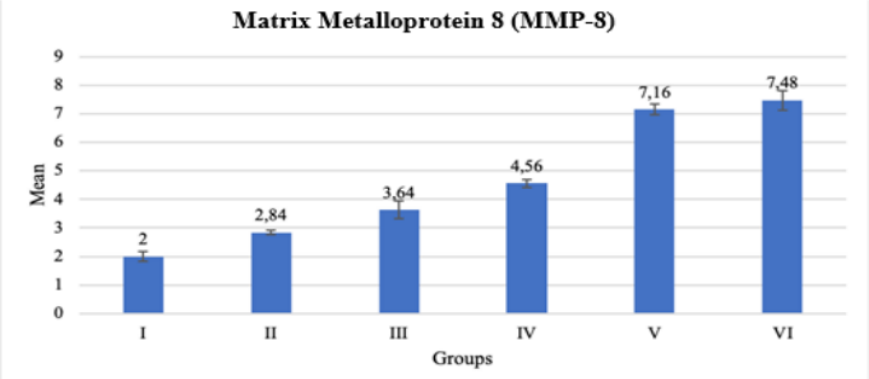

Figure 1. The Mean Value of Matrix Metalloprotein 8 (MMP-8) in Each Group

ANOVA analysis of the Metalloprotein 8 (MMP-8) matrix shows the difference in the Metalloprotein 8 (MMP-8) matrix in various groups (p = 0,000), then analyzed using Least Significance Different (LSD) to see the difference in Metalloprotein 8 (MMP-8) -8) between groups (Table 1). Based on Table 1 there was a significant difference (p <0.05) of the average Metalloprotein 8 (MMP-8) matrix between all groups, except group 5 and group 6 which showed no difference (p> 0.05).

Tabel 1. Least Significant Difference (LSD) test on Matrix Metalloprotein 8 (MMP-8) in Each Group

Groups	I	II	III	IV	V	VI
I	-	-	-	-	-	-
II	0,014	-	-	-	-	-
III	0,000	0,019	-	-	-	-
IV	0,000	0,000	0,008	-	-	-
V	0,000	0,000	0,000	0,000	-	-
VI	0,000	0,000	0,000	0,000	0,322	-

Source: Pimary Data

Based on the picture 2. Shows the mean value of collagen type 2 is inversely proportional to the duration of exposure to cigarette smoke. In group VI type 2 collagen reached the lowest value of 2.84 ± 0.15, while the highest value was obtained in group I which was 10.04 ± 0.75.

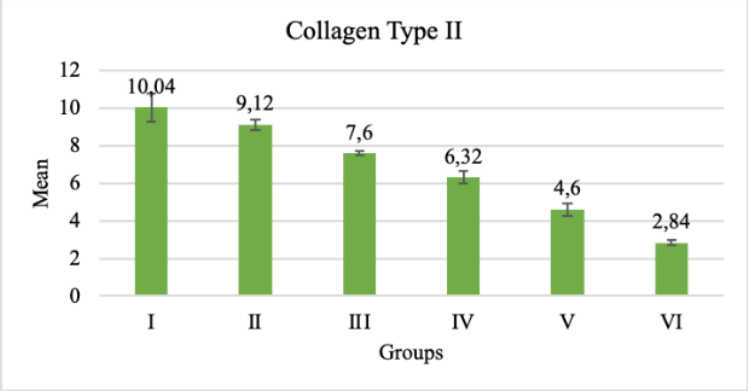

Figure 2. The Mean Value of Collagen Type 2 in Each Group

ANOVA analysis results on collagen type 2 showed differences in average collagen type 2 in various groups (p = 0,000), then analyzed using the least significance different (LSD) to see differences in collagen type 2 between groups (Table 4). Based on Table 2 there was a significant difference (p <0.005) of collagen type 2 between the negative control group, and all treatment groups

Table 2. Least Significant Difference (LSD) Test Results on Collagen Type 2 in Each Group

Groups	I	II	III	IV	V	VI
I	-	-	-	-	-	-
II	0,012	-	-	-	-	-
III	0,000	0,003	-	-	-	-
IV	0,000	0,000	0,001	-	-	-
V	0,000	0,000	0,000	0,000	-	-
VI	0,000	0,000	0,000	0,000	0,000	-

Source: Pimary Data

The results of the correlation test analysis showed a strong relationship between Metalloprotein 8 matrix and collagen type 2 (r = 0.948). In addition, the two groups had a significant relationship (p <0.05).

This research indicates that administration of electronic cigarette exposure will result in lung tissue damage. In the group without administration of electronic cigarette smoke exposure, it does not show any lung tissue damage marked by the expression of low level of Matrix Metalloproteinase-8 and high level of collagen type-2. Meanwhile, the most severe lung tissue damage is exhibited in the group receiving 3-week exposure of cigarette smoke, where there is an increase of Matrix Metalloproteinase-8 and a decrease of collagen type-2.

Lung inflammation occurs because of electronic cigarette exposure containing several harmful compounds entering airways and can result in an increase of free radicals in the body (R. V. Suryadinata, Lorensia, & Sari, 2017). The number increase of free radicals entering the body can cause antioxidant imbalance problem in the body. This can trigger the occurrence of lipid peroxidation causing cells undergone oxidative stress. The content of cigarette smoke can be divided into free radicals and non-radical oxidants. The type of free radical that plays the most role in cigarette smoke is superoxide anion (O2•-). These free radicals can be directly neutralized by enzymatic antioxidants namely Superoxide Dismutase. The result of this reaction is hydrogen peroxide (H2O2) which is a non-radical oxidant. Furthermore, the radical Hydrogen peroxide (H2O2) will be neutralized by enzymatic antioxidants Gluthation peroxidase (GSH-Px) and catalase to be converted into water (H2O) and oxygen (O2) (Karmaker, Lira, Das, Kumar, & Rouf, 2017). Radicals Hydrogen peroxide (H2O2) can also react again with superoxide anion (O2•-) to hydroxyl radicals (OH-) called the Haber-Weiss reaction. In addition, if the Hydrogen Peroxide Radical (H2O2) reacts with pheton (Fe2+) or known as pheton reaction, it can also produce hydroxyl radicals (OH). Increased hydroxyl radicals (OH-) in the body will aggravate the occurrence of lipid peroxidation. Malondialdehyde (MDA) is the final result most widely used as a measure of the increase in free radicals in the body (Marrocco, Altieri, & Peluso, 2017).

Lipid peroxidase undergone by the cells will cause cell rupture or necrosis which is often called as Damage-associated molecular patterns (DAMPs) or more commonly known as cell debris (Virlando Suryadinata, 2018). Cell debris exiting the cell can cause disruption in microenvironment and is regarded as a foreign object by the body. The reaction will improve macrophage activities to reach the cell debris and do phagocytosis process which becomes one of macrophage's roles as a non-specific immune system.

The phagocytosis process carried out by macrophages is carried out with the help of lysosomes or better known as phagolisosomes. in the body, macrophages do not only act as a non-specific immune system. In addition, macrophages as well as Antigen Presenting Cell (APC) which can present major histocompatibility complex (MHC) class1 or class II which play an important role in the adaptive immune system. Class I major histocompatibility complex (MHC) will be recognized by cytotoxic CD 8+ T cells, while class II major histocompatibility complex (MHC) will be recognized by CD 4+ T cells (Wieczorek et al., 2017).

The phagocytosis of cell debris conducted by macrophage will trigger several types of inflammation mediators such as Interleukin 1 (IL-1), interleukin-6 (IL-6), interleukin 8 (IL-8) and Tumor Necrosis Factor-α (TNF-α). (Wojdasiewicz, Poniatowski, & Szukiewicz, 2014) Interleukin-8 has a role of stimulating neutrophil movement or more commonly known as Neutrophil Chemotactic Factor (NFC) to fight against pathogen or foreign objects through recognition of several receptors (de Oliveira et al., 2013).

Neutrophil increase will cause the damage of Matrix Metalloproteinase (MMPs). This is because Matrix Metalloproteinase (MMPs) is responsible for maintenance of extracellular matrix (ECM) protein surrounding endothelial in the whole body. Besides, Matrix Metalloproteinase also has

a role in inflammation process which will increase more inflammation process in the tissue. Moreover, matrix metalloproteinase (MMPs) serves to balance homeostasis of several collagen types. One type of matrix metalloproteinase which is in the airways and has a role during inflammation in the lung tissue is matrix metalloproteinase-8 (MMP-8) (Basu, Donaworth, Siroky, Devarajan, & Wong, 2015).

Matrix Metalloproteinase-8 is initially called as Neutrophil Collagenase because there was specific grains obtained in the neutrophil and is also expressed in epithelial cells, fibroblast, macrophage, and endothelial. Several studies also show existence of MMP-8 activities in tumor and metastasis (Thirkettle et al., 2013). But later on, MMP-8 is linked with inflammation process and fibrosis in lung. This is because Matrix Metalloproteinase-8 has a direct impact on collagen type-2 existing in the lung tissue. The expression of MMP-8 which occurs due to inflammation reaction is influenced by secretion of Interleukin 6 and Interleukin 8 as proinflammation cytokins (Rathnayake, Gieselmann, Heikkinen, Tervahartiala, & Sorsa, 2017).

Collage is the main part of extracellular matrix and contains a high level of protein. Collagen in tissues also serves as mechanical defense and organism. Besides, collagen can also serve as signaling molecules for cellular shape and behavior. The body has 16 types of collagen, but the most prominent are collagen types I, II and III. Collagen is produced by various types of cells according to their morphology, distribution, function and pathogenesis (Deshmukh, Dive, Moharil, & Munde, 2016). The type of collagen existing in the lung tissue is collagen type-2 and plays a role in fibrosis formation in the lung tissue. A damage to collagen type-2 in the lung tissue will result in cell damage as well as cell death. The content of collagen type-2 in the lung tissue which is influenced by MMP-8 will show a relationship existence that an increase of MMP-8 will cause a decrease of collagen type-2, hence causing lung tissue damage, further triggering fibrosis tissue formation in the lung (Pardo, Cabrera, Maldonado, & Selman, 2016).

Lung fibrosis is a pathological syndrome as a result of lung injury. The pathobiological mechanism of pulmonary fibrosis produces a different remodeling response in the lungs. Lung fibrosis is a chronical, progressive, and severe lung disease. This is because disruption of Extracellullar Matrix (ECM) which is irregular. The smoke of electronic cigarette is one of main factors of lung fibrosis occurrence. Besides, the reason of lung fibrosis is caused by job exposure, dust, and smoke of motor vehicles (Awadalla, Hegazy, Elmetwally, & Wahby, 2012). Lung fibrosis disease is often associated to environmental disturbance (Chilosi, Poletti, & Rossi, 2012).

Conclusion

According to conducted research, it can directly provide some information related to negative impacts caused by electronic cigarettes. Some misconception popular among people related to the safety of electronic cigarette must be addressed properly as soon as possible. A perception viewing electronic cigarette is safer than the tobacco cigarette in reducing addiction to tobacco cigarette of active smokers must be reconsidered. This study has shown that the negative impacts of free radicals caused by electronic cigarette smoke exposure has directly influenced the intracellular lung tissue. The inflammation process contributes to lung tissue through some inflammation mediators. This will result in an intracell increase of Matrix Metalloproteinase-8, which later will reduce the collagen type-2 in the lung tissue.

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The Expression Change of MMP-8 and Collagen Type-2 Intracell in Lung Tissue Due to Electronic Smoke Exposure

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Abstract

The number of electronic smokers has increased annually. Exposure to electronic cigarette will increase free radicals in the body and result in oxidative stress occurrence causing lung tissue damage. The severity degree of lung tissue damage caused by electronic smoke exposure depends on the duration of electronic cigarette smoke exposure and is going to affect Matrix Metalloproteinase-8 and collagen type-2 in the cells. The study aims to understand the change degree of Matrix Metalloproteinase-8 and collagen type-2in lung tissue due to electronic cigarette smoke exposure. This study applied experimental method with post control group design. The male wistar rats were used as the animal models in this research in order to asses cell damage through the expression of Matrix Metalloproteinase-8 and collagen type-2 in the lung tissue using immunohistochemical staining. Exposure to electronic smoke cigarette was given to each group of animal models with difference in amount and time duration. The expression of Matrix Metalloproteinase-8 indicated that there was a significant increase due to electronic smoke exposure (ANOVA, p=0.000). Meanwhile, the expression of collagen type-2 showed that there was a significant decrease because of electronic smoke exposure (ANOVA, p=0.000). Besides, MMP-8 and collagen type-2 manifested relationship existence and strong impact (r=0.948, p=0.000). The negative impact of exposure to electric cigarette smoke causes increased expression of Matrix Metalloproteinase-8 and decreased expression of type-2 collagen in lung tissue.

Introduction

In the recent years, the number of electronic cigarette smoker has significantly increased. It is caused by lack of knowledge about the long-term effects caused by the electronic cigarette as well as limited amount of research data indicating the negative impacts of long-term use of electronic cigarette. Moreover, the rule regulating the use of electronic cigarette has become a growing controversy. (Cherng, Tam, Christine, & Meza, 2016) Most people assume electronic cigarette as one of ways to reduce addiction to tobacco cigarette and the electronic cigarette is considered safer because it only contains nicotine (Vardavas, Filippidis, & Agaku, 2015). However, for most people electronic cigarette is assumed as a way of legalizing smokers to smoke in public and in working places and it can negatively affect teenagers to smoke (Martínez-Sánchez et al., 2015). People's perception related to electronic cigarette use also influences the increasing number of smokers. The use of electronic cigarette considered safe by some people can influence teenagers to start smoking the electronic cigarette (Amrock, Lee, & Weitzman, 2016). Electronic cigarette has become more popular in society through massive marketing system via several media such as television, print publication, radio and internet. The promotion budget of electronic cigarette in the United States in 2012 had increased almost

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double the same budget in 2011. In the second quarter of 2013, it increased more than eight times compared to the second quarter of 2012 (Xu, Guo, Liu, Liu, & Wang, 2016).

The increasing number of electronic cigarette smokers does not only happen in several developing countries, but also in developed countries. In 2011, the prevalence of electronic cigarette in young adult age (18-28 years old) was the highest compared to the other age groups, reaching 4.9%-7%, with all age groups reaching 0.6% until 6.2%. The user prevalence of electronic cigarette in the United States in adult age group also increased 2 until 4 times higher in 2012 (Jaber et al., 2018). Meanwhile in senior high school students, the use of electronic cigarette was approximately 1.5% which later consistently increased in 2014 reaching 13.4%. New Zealand had also experienced an increasing number of electronic cigarettes in teenagers (14-15 years old) reaching almost 3 times higher than 7% in 2012 into 20% in 2014 (Thrasher et al., 2016). In the recent years, Australia had also demonstrated an increase of electronic cigarette smokers. In the adult age group, the increase reached twice of 4% in 2013 into 9% in 2016. The scores were obtained from two groups, which were active smokers having an increase from 18% to 31%, while the non-smokers had an increase from 2% into 5%. However, this is inversely proportional to the use of cigarettes which decreases every year (Jongenelis, Kameron, Rudaizky, & Pettigrew, 2019). Policies on tobacco control such as an increase in cigarette taxes, smoke-free laws, limiting cigarette advertisements and normalizing the behavior of smokers in active smokers are the most influential factors in reducing the number of smokers. But all these things have not been applied to users of e-cigarettes (Voigt, 2015).

The increase in the use of e-cigarettes does not only occur in high-income countries, but also occurs in countries with medium and low incomes. In developing countries, electronic cigarette has been used both individually and in pairs along with tobacco cigarette (Palipudi et al., 2016). In Greece and Qatar, more than 60% of electronic cigarette smokers also use tobacco cigarette concurrently, while the electronic cigarette smokers originating from non-smokers have reached 35.6% in Greece and 15% in Qatar (Palipudi et al., 2016).

Electronic cigarettes are battery powered cigarettes operating through a heating process of an element (metal coil) by evaporating propylene glycol solvent, vegetable glycerin, and flavoring which sometimes contain nicotine (Grana, Benowitz, & Glantz, 2014). Electronic cigarettes are considered to have less side effects for the health compared to the tobacco cigarettes. Besides, more modern packaging and better marketing strategies have made electronic cigarettes a lifestyle choice for both smokers and teenager group (Canistro et al., 2017). Electronic cigarette is always claimed as one of effective ways to stop smoking or as a substitute of cigarette because it does not contain tar, carbon monoxide, and other chemical compounds. This has led to an annual increasing rate of electronic cigarette smokers (Polosa et al., 2011).

The cigarette smoke contains several types of high number of free radicals, estimated reaching more than 1016 for every inhalation, including Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) (Dellinger, Khachatryan, Masko, & Lomnicki, 2011). Reactive Oxygen Species (ROS) consists of superoxide anion (O2•-), hydrogen peroxide (H2O2), and hydroxyl radical (OH•) as normal products of oxygen molecule reduction. Radical oxygen is not only produced by mitochondria, but neutrophils and macrophages can also produce ROS through the plasma membrane (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010; Herlina, Riyanto, Martono, & Rohman, 2018). Hypoxic conditions, mitochondria produce Nitric Oxide (NO), which can produce other Reactive Nitrogen Species (RNS), for example aldehydes-malondialdehyde and 4-hydroxinonenal (Arulselvan et al., 2016) .In a normal condition and a balance between free radicals and antioxidants, the free radicals serve as the body defense mechanism (Ravipati et al., 2012). A significant increase of the number of free radicals due to electronic cigarette smoke exposure can cause occurrence of oxidative stress in lung tissue (Zhang et al., 2018). Oxidative stress is triggered by imbalance between the number of free radicals entering the lung tissue and antioxidants in the

body which can result in injury in all cellular components such as lipid, protein, and DNA so that causing cells' death (R. V. Suryadinata, Wirjatmadi, & Adriani, 2017; Sagor, Reza, Tabassum, Rahman, & Alam, 2017). Some diseases can also be caused by cigarettes, such as cancer, cardiovascular diseases, and Chronic Obstructive Pulmonary Disease (COPD) (Goel et al., 2015).

The number and size of particles generated from electronic cigarettes are the same as the ones produced by tobacco cigarettes. Even, some types of electronic cigarettes can produce more particles compared to the tobacco cigarettes (Grana et al., 2014). Particles produced from e-cigarettes cause irritation of the airways so that mucous hypersecretion occurs in the bronchi (R. V. Suryadinata, Wirjatmadi, & Adriani, 2016). The number increase of free radical particles can trigger inflammation reaction in the lung tissue (Pratiwi, Lorensia, & Suryadinata, 2018). Inflammation reaction is a lung defense mechanism against dangerous stimulus such as pathogen, cell damage, and harmful chemical compounds. Moreover, acute inflammation response can minimize injury or infection caused in the lung tissue. The inflammatory process changes in blood vessel permeability, leukocyte movement and the release of inflammatory mediators (Chen et al., 2018).

However, a prolonging inflammation process in airways can result in lung cell damage. This can cause cell lysis occurrence impacting in deteriorating lung cell function (Levy & Serhan, 2014). In a pathological condition or cell damage, there is an increase of productivity and activity of Matrix Metalloproteinase-8, while collagen type-2will experience an intracellular decrease (Asano et al., 2010). The change of Matrix Metalloproteinase-8 and collagen type-2 can trigger fibrosis formation in the lung (McKleroy, Lee, & Atabai, 2013).

Electronic cigarette is always considered as containing less chemical compound compared to tobacco cigarettes. The fact of the matter is that the safety of electronic cigarette has not yet been proven and the side effects of its long-term use on the lung tissue has not yet been known (Jensen et al., 2015; Suryadinata & Wirjatmadi, 2020). As a consequence, verification of histology aspects of the levels of Matriks Metalloprotein-8 and collagen type 2 as a parameter of lung tissue damage due to the use of electronic cigarettes in male wistar rat models is required. These parameters can provide a direct picture of lung tissue damage compared to the use of malondialdehyde levels (Wirjatmadi & Suryadinata, 2020).

Methods

This study is an experimental research using post test control group design. The samples of the study used male wistar rats (Rattus novergicus). This research was divided into 6 groups with different time duration of administration treatment of electronic cigarette smoke exposure for each group. The smoke exposure was done for 5 minutes during each intervention administration. The differing aspect of each group was the total amount of administration per day and the time duration per week. The first group was the negative control group which was not exposed to electronic cigarette and used as a comparison to treatment groups, while the rest, in each group there was exposure of electronic cigarette smoke for several time duration and observation of lung tissue using immunohistochemical staining (HIS) was conducted to see the tissue damage.

Samples of experimental animals Wistar rats (Rattus novergicus) aged 2-3 months with a weight of 200-250 grams, move actively, macroscopically found no abnormalities and have never been the object of research. Before the treatment is carried out, all animals try to do the adaptation process first for 5-7 days. The study was conducted at the Laboratory of the Faculty of Medicine, Airlangga University based on the 3R principle (Replacement, Reduce and Refinement). Experimental animals were placed in cages measuring 800 cm2 per 5 animals with ventilation and room temperature around 25oC. Cleaning the cage and providing drinking water is done periodically as well as providing food as much as 20-30 grams / day. Each group will be given exposure to electric cigarette smoke that is different in time, amount and duration of administration in accordance with research procedures. Sample replication using is used to compare between treatment

groups.

Based on the results of the calculation of the minimum sample in this study amounted to 5 male Wistar rats in each group. The solution of the electric cigarette used in this study contained 6 mg of nicotine. The room where the exposure to electric cigarette smoke measures 50 cm x 40 cm x 20 cm. In this space a pipe will be passed through which can flow e-cigarette smoke. Provision of exposure to cigarette smoke is adjusted to the length of administration planned in the study

Samples were assessed semiquantitatively according to the modified Remmele method, where the Remmele scale index (Immuno Reactive Score / IRS) is the result of multiplying the percentage score of immunoreactive cells with the color intensity score on immunoreactive cells. The data for each sample is the average value of the IRS that was observed in 5 (five) Field View (LP) different at 1000x magnification. All of these examinations use a light microscope

The male Wistar rats were divided into 6 groups, including negative control and treatment group. The first group as the negative control group was a group that given no intervention for 4 weeks. While the second group as the treatment group I was given the e-cigarette smoke intervention once every 5 minutes per day in a week. The third group or the treatment group II was given e-cigarette smoke exposure intervention twice every 5 minutes per day in a week. The treatment group III was given intervention of e-cigarette smoke exposure once every 5 minutes per day in 2 weeks. The treatment group IV was given e-cigarette smoke exposure twice every 5 minutes per day in 2 weeks. The last control group was given intervention of e-cigarette smoke exposure once every 5 minutes per day in 3 weeks.

The data that has been collected perform statistical tests using ANOVA test analysis with SPSS version 20 to see the difference between Metalloprotein 8 matrix and collagen type 2 in lung tissue in all groups. Then the Least Significant Differences (LSD) test is performed to compare between groups. In addition, a trial was conducted to see the existence of a relationship between the two groups. Data will be presented in average numbers from the Immuno Reactive Score (IRS)

Results and Discussion

The results of the study were carried out by comparing the Metalloprotein 8 (MMP-8) matrix and the collagen type 2 average in each group per 5 visual fields. Based on Figure 1. the average value and Standard Deviation of the Metalloprotein 8 (MMP-8) matrix can be seen in each group. These results show the increasing Metalloprotein 8 (MMP-8) matrix in each group which is directly proportional to the length of time of exposure to cigarette smoke. In group I, the mean value of Metalloprotein 8 (MMP-8) matrix reached 2.00 ± 0.17, which is the lowest mean value in all groups. While the highest mean value was obtained in group VI which reached 7.48 ± 0.34.

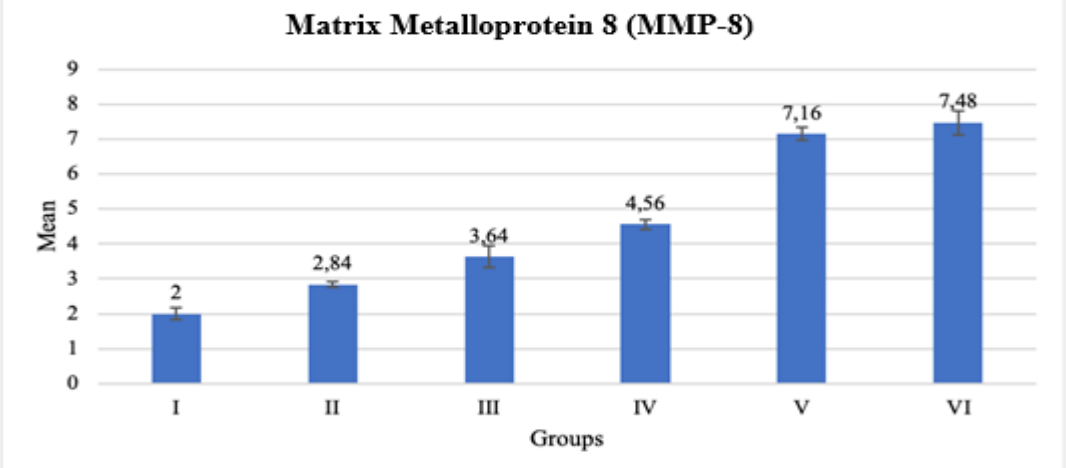

Figure 1. The Mean Value of Matrix Metalloprotein 8 (MMP-8) in Each Group

ANOVA analysis of the Metalloprotein 8 (MMP-8) matrix shows the difference in the Metalloprotein 8 (MMP-8) matrix in various groups (p = 0,000), then analyzed using Least Significance Different (LSD) to see the difference in Metalloprotein 8 (MMP-8) -8) between groups (Table 1). Based on Table 1 there was a significant difference (p <0.05) of the average Metalloprotein 8 (MMP-8) matrix between all groups, except group 5 and group 6 which showed no difference (p> 0.05).

Tabel 1. Least Significant Difference (LSD) test on Matrix Metalloprotein 8 (MMP-8) in Each Group

Groups	I	II	III	IV	V	VI
I	-	-	-	-	-	-
II	0,014	-	-	-	-	-
III	0,000	0,019	-	-	-	-
IV	0,000	0,000	0,008	-	-	-
V	0,000	0,000	0,000	0,000	-	-
VI	0,000	0,000	0,000	0,000	0,322	-

Source: Pimary Data

Based on the picture 2. Shows the mean value of collagen type 2 is inversely proportional to the duration of exposure to cigarette smoke. In group VI type 2 collagen reached the lowest value of 2.84 ± 0.15, while the highest value was obtained in group I which was 10.04 ± 0.75.

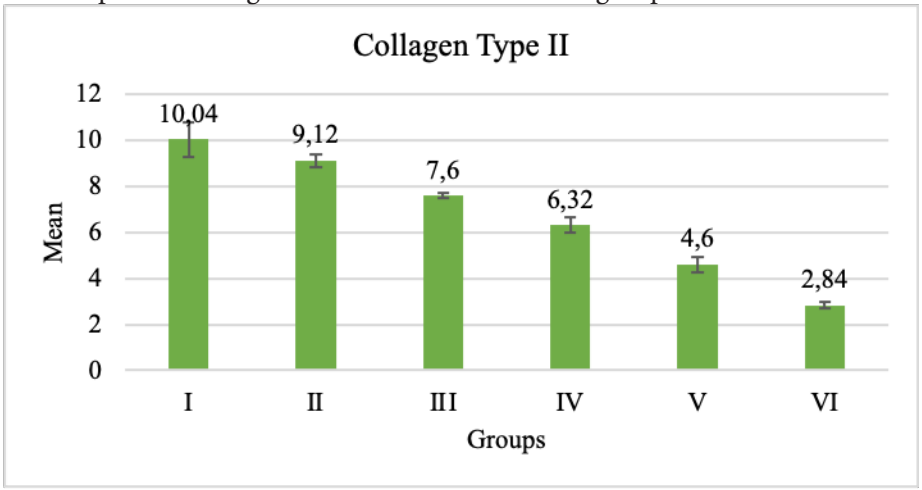

Figure 2. The Mean Value of Collagen Type 2 in Each Group

ANOVA analysis results on collagen type 2 showed differences in average collagen type 2 in various groups (p = 0,000), then analyzed using the least significance different (LSD) to see differences in collagen type 2 between groups (Table 4). Based on Table 2 there was a significant difference (p <0.005) of collagen type 2 between the negative control group, and all treatment groups

Table 2. Least Significant Difference (LSD) Test Results on Collagen Type 2 in Each Group

Groups	I	II	III	IV	V	VI
I	-	-	-	-	-	-
II	0,012	-	-	-	-	-
III	0,000	0,003	-	-	-	-
IV	0,000	0,000	0,001	-	-	-
V	0,000	0,000	0,000	0,000	-	-
VI	0,000	0,000	0,000	0,000	0,000	-

Source: Pimary Data

The results of the correlation test analysis showed a strong relationship between Metalloprotein 8 matrix and collagen type 2 (r = 0.948). In addition, the two groups had a significant relationship (p <0.05).

This research indicates that administration of electronic cigarette exposure will result in lung tissue damage. In the group without administration of electronic cigarette smoke exposure, it does not show any lung tissue damage marked by the expression of low level of Matrix Metalloproteinase-8 and high level of collagen type-2. Meanwhile, the most severe lung tissue damage is exhibited in the group receiving 3-week exposure of cigarette smoke, where there is an increase of Matrix Metalloproteinase-8 and a decrease of collagen type-2.

Lung inflammation occurs because of electronic cigarette exposure containing several harmful compounds entering airways and can result in an increase of free radicals in the body (R. V. Suryadinata, Lorensia, & Sari, 2017). The number increase of free radicals entering the body can cause antioxidant imbalance problem in the body. This can trigger the occurrence of lipid peroxidation causing cells undergone oxidative stress. The content of cigarette smoke can be divided into free radicals and non-radical oxidants. The type of free radical that plays the most role in cigarette smoke is superoxide anion (O2•-). These free radicals can be directly neutralized by enzymatic antioxidants namely Superoxide Dismutase. The result of this reaction is hydrogen peroxide (H2O2) which is a non-radical oxidant. Furthermore, the radical Hydrogen peroxide (H2O2) will be neutralized by enzymatic antioxidants Gluthation peroxidase (GSH-Px) and catalase to be converted into water (H2O) and oxygen (O2) (Karmaker, Lira, Das, Kumar, & Rouf, 2017). Radicals Hydrogen peroxide (H2O2) can also react again with superoxide anion (O2•-) to hydroxyl radicals (OH-) called the Haber-Weiss reaction. In addition, if the Hydrogen Peroxide Radical (H2O2) reacts with pheton (Fe2+) or known as pheton reaction, it can also produce hydroxyl radicals (OH). Increased hydroxyl radicals (OH-) in the body will aggravate the occurrence of lipid peroxidation. Malondialdehyde (MDA) is the final result most widely used as a measure of the increase in free radicals in the body (Marrocco, Altieri, & Peluso, 2017).

Lipid peroxidase undergone by the cells will cause cell rupture or necrosis which is often called as Damage-associated molecular patterns (DAMPs) or more commonly known as cell debris (Virlando Suryadinata, 2018). Cell debris exiting the cell can cause disruption in microenvironment and is regarded as a foreign object by the body. The reaction will improve macrophage activities to reach the cell debris and do phagocytosis process which becomes one of macrophage's roles as a non-specific immune system.

The phagocytosis process carried out by macrophages is carried out with the help of lysosomes or better known as phagolisosomes. in the body, macrophages do not only act as a non-specific immune system. In addition, macrophages as well as Antigen Presenting Cell (APC) which can present major histocompatibility complex (MHC) class1 or class II which play an important role in the adaptive immune system. Class I major histocompatibility complex (MHC) will be recognized by cytotoxic CD 8+ T cells, while class II major histocompatibility complex (MHC) will be recognized by CD 4+ T cells (Wieczorek et al., 2017).

The phagocytosis of cell debris conducted by macrophages will trigger several types of inflammation mediators such as Interleukin 1 (IL-1), interleukin-6 (IL-6), interleukin 8 (IL-8) and Tumor Necrosis Factor-α (TNF-α). (Wojdasiewicz, Poniatowski, & Szukiewicz, 2014) Interleukin-8 has a role of stimulating neutrophil movement or more commonly known as Neutrophil Chemotactic Factor (NFC) to fight against pathogen or foreign objects through recognition of several receptors (de Oliveira et al., 2013).

Neutrophil increase will cause the damage of Matrix Metalloproteinase (MMPs). This is because Matrix Metalloproteinase (MMPs) is responsible for maintenance of extracellular matrix (ECM) protein surrounding endothelial in the whole body. Besides, Matrix Metalloproteinase also has

a role in inflammation process which will increase more inflammation process in the tissue. Moreover, matrix metalloproteinase (MMPs) serves to balance homeostasis of several collagen types. One type of matrix metalloproteinase which is in the airways and has a role during inflammation in the lung tissue is matrix metalloproteinase-8 (MMP-8) (Basu, Donaworth, Siroky, Devarajan, & Wong, 2015).

Matrix Metalloproteinase-8 is initially called as Neutrophil Collagenase because there was specific grains obtained in the neutrophil and is also expressed in epithelial cells, fibroblast, macrophage, and endothelial. Several studies also show existence of MMP-8 activities in tumor and metastasis (Thirkettle et al., 2013). But later on, MMP-8 is linked with inflammation process and fibrosis in lung. This is because Matrix Metalloproteinase-8 has a direct impact on collagen type-2 existing in the lung tissue. The expression of MMP-8 which occurs due to inflammation reaction is influenced by secretion of Interleukin 6 and Interleukin 8 as proinflammation cytokins (Rathnayake, Gieselmann, Heikkinen, Tervahartiala, & Sorsa, 2017).

Collage is the main part of extracellular matrix and contains a high level of protein. Collagen in tissues also serves as mechanical defense and organism. Besides, collagen can also serve as signaling molecules for cellular shape and behavior. The body has 16 types of collagen, but the most prominent are collagen types I, II and III. Collagen is produced by various types of cells according to their morphology, distribution, function and pathogenesis (Deshmukh, Dive, Moharil, & Munde, 2016). The type of collagen existing in the lung tissue is collagen type-2 and plays a role in fibrosis formation in the lung tissue. A damage to collagen type-2 in the lung tissue will result in cell damage as well as cell death. The content of collagen type-2 in the lung tissue which is influenced by MMP-8 will show a relationship existence that an increase of MMP-8 will cause a decrease of collagen type-2, hence causing lung tissue damage, further triggering fibrosis tissue formation in the lung (Pardo, Cabrera, Maldonado, & Selman, 2016).

Lung fibrosis is a pathological syndrome as a result of lung injury. The pathobiological mechanism of pulmonary fibrosis produces a different remodeling response in the lungs. Lung fibrosis is a chronical, progressive, and severe lung disease. This is because disruption of Extracellullar Matrix (ECM) which is irregular. The smoke of electronic cigarette is one of main factors of lung fibrosis occurrence. Besides, the reason of lung fibrosis is caused by job exposure, dust, and smoke of motor vehicles (Awadalla, Hegazy, Elmetwally, & Wahby, 2012). Lung fibrosis disease is often associated to environmental disturbance (Chilosi, Poletti, & Rossi, 2012).

Conclusion

According to conducted research, it can directly provide some information related to negative impacts caused by electronic cigarettes. Some misconception popular among people related to the safety of electronic cigarette must be addressed properly as soon as possible. A perception viewing electronic cigarette is safer than the tobacco cigarette in reducing addiction to tobacco cigarette of active smokers must be reconsidered. This study has shown that the negative impacts of free radicals caused by electronic cigarette smoke exposure has directly influenced the intracellular lung tissue. The inflammation process contributes to lung tissue through some inflammation mediators. This will result in an intracell increase of Matrix Metalloproteinase-8, which later will reduce the collagen type-2 in the lung tissue.

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