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CIGARETTE SMOKE-INDUCED VITAMIN A DEFICIENCY CONTRIBUTES TO EMPHYSEMA PROGRESSION IN RATS

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Abstract

Emphysema and lung inflammation can be accelerated by a lack of vitamin A, an important nutrient. Vitamin A levels were shown to be lower in rats that were given benzopyrene, a component of cigarette smoke. Two separate groups of rats served as experimental subjects for the length of the study. The first group, known as the experimental group, was subjected to daily, unfiltered cigarette smoke exposure for fifteen sessions, while the second group, called the control group, was exposed just to outside air. An assessment was conducted to measure the levels of retinol and vitamin A in the blood, liver, and lungs six weeks after the investigation began. Vitamin A levels were found to be lower in the group of rats that were exposed to cigarette smoke. Additionally, amounts of pulmonary vitamin A were positively correlated with emphysema severity, indicating a negative connection. Hyperplasia of the tracheal epithelium and the development of hepatic vacuoles were also noted**.**

Keywords: *smoking, vitamin A, Emphysema Progression, inflammation, and cigarette*.

Introduction

Different types of vitamins contribute to a person's health in their own special ways. It is imperative that doing researches to learn about the significance of various vitamins, to recognize the symptoms of deficiency, and to investigate ways to increase their levels [1].

Vitamins are well-known for their critical roles in promoting wound healing and immune system strengthening, among other crucial physiological functions, and their relevance in health maintenance is well acknowledged. Several symptoms, such as fatigue, mental difficulties, physical weakness, and gastrointestinal issues, might arise from an individual's dietary habits not consuming enough vitamins [2].

Vitamins can be either fat-soluble. Vitamins are divided into two categories according to how well they dissolve in various substances. The fat-soluble vitamins (A, D, E, and K) are essential nutrients. In order to facilitate their optimal absorption into the bloodstream,

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fat-soluble vitamins exhibit a limited capacity to dissolve in water-based environments. The human body stores these particular vitamins in its adipose tissue and skeletal muscles [3].

The B vitamins and water-soluble vitamins, such vitamin C and vitamin A, are essential nutrients that dissolve easily in water. Some vitamins, known as water-soluble vitamins, are soluble in water and are not normally stored in large quantities by the human body. It is extremely important to maintain constant intake in order to prevent deficiency of this vitamin because it is not bio-stored but is instead excreted in urine [5].

People require trace amounts of vitamins, which are significant bioactive substances. Maintaining general health and physiological functions relies on each component performing its own specific function. The amount of vitamin that various species require varies. Dogs, for instance, may produce sufficient amounts of vitamin C internally, even though humans must get their vitamin C from food. Because the body can only synthesize a small fraction of the vitamins it needs, getting enough of these nutrients from food is essential [6].

Recognizing that dietary sources do not deliver an adequate amount of vitamin D is critical within the field of human nutrition. Natural sunshine is the most important source of vitamin D because it triggers vitamin D production in the human body [7].

For optimal health and well-being, it's best to consume the recommended daily allowance (RDA) of each vitamin, as they all play unique roles in the human body. On top of that, vitamins perform a plethora of roles in the human body and include a diverse array of chemical components that are crucial for homeostasis maintenance in minute amounts. Vitamins are essential for good health, but the human body can't make them on its own. The availability of vitamins has been a growing concern, with more and more people looking to dietary supplements and nutritionally dense foods and drinks for their vitamin needs (Nutraceutical and Functional Food Components, 153-181, 2022). Based on their solubility properties and modes of action, vitamins are categorized into two main groups: water-soluble and fat-soluble [8].

One feature of the fat-soluble vitamins is their solubility in organic solvents. This is especially true of vitamins A, K, E, and K. Vitamin absorption and dietary fat accumulation in adipose tissue, mainly in the liver, occur simultaneously. The B vitamin complex and vitamin C are examples of water-soluble vitamins; the body is unable to retain these nutrients. Therefore, if these vitamins aren't consumed, they're excreted from the body by means of urine (Semba RD, 2012, p. 310) [9].

Among the many cellular processes that it regulates, vitamin A is one of the fat-soluble nutrients. Certain food sources can be consumed to provide vitamin A. It is possible to get synthetic vitamin A through fortified foods and pills, though [10]

Two primary groups of vitamin A exist. In medicine, "preformed vitamin A" refers to a type of vitamin A that is already physiologically active and easily absorbed by humans.

Animal products like liver, eggs, fish, and dairy are the main sources of preformed vitamin A, which includes retinol [11].

Vitamin A can be produced internally from the molecule provitamin A. Vitamin A, in its biologically active form as retinol, is synthesized in the human body from provitamin A, which is derived from plants and goes through metabolic transformation. Many foods are known to be rich in provitamin A, including tomatoes, sweet potatoes, carrots, melons, and leafy greens [12].

Maintaining peak health and wellness requires a vitamin A diet rich in the nutrient. The majority of people get enough vitamin A from food alone, however those who suffer from specific medical issues might do better with supplemental vitamin A [13].

The medical disorder is marked by insufficient intake or absorption of essential vitamins. Most people in industrialized nations get enough vitamin A from food, therefore cases of vitamin A deficiency are uncommon. Several symptoms have been associated with vitamin A deficiency, including lethargy, dry eyes, infertility, and vision problems that can lead to blindness [14].

The context here is the contagious illness measles. The risk of developing vitamin A insufficiency is higher in areas where measles is prevalent. A lower mortality rate has been reported in children with measles when vitamin A is given to them, according to previous research. The digestive and respiratory systems are severely affected by cystic fibrosis, a hereditary genetic disorder. Vitamin A deficiency is more likely to arise in patients with cystic fibrosis because of the prevalence of pancreatic issues in this disease [15].

It is mostly in the small intestine that vitamins are absorbed. One thing to keep in mind is that water-soluble vitamins are more easily absorbed than fat-soluble ones. The absorption rates of water-soluble vitamins, however, may vary [16].

Vitamin absorption is influenced by a multitude of circumstances, including but not limited to: alcohol consumption, smoking, stomach acids, inadequate food intake, and the route of distribution. The efficiency of these nutrients in the human body is thus affected by these factors [17].

A vital vitamin, vitamin A is involved in many bodily functions, including development and growth, immunity, eye health, and cell proliferation, to name a few. The heart, lungs, kidneys, and other vital organs and systems are able to function at their best because of it. In addition, some have speculated that it could improve skin and hair health while simultaneously decreasing the risk of some types of cancer. In addition to their many other beneficial effects on human health, vitamin A and related retinoids are essential for regulating lung growth. Among other possible consequences, night blindness can serve as an indication of vitamin A deficiency [18].

Naturally occurring forms of vitamin, A can be found in a variety of foods, including dairy products, eggs, meat, fish, and other seafood. The main form of vitamin A found in the bloodstream, retinol, can only be sourced from animals. One of the main ways that vitamin

A is stored is by retinyl palmitate. Many different types of fruits, vegetables, and other foods made from plants contain provitamin A [19].

An essential role in animals' normal metabolic processes is played by vitamins, which are significant chemical compounds. But because they can't be made internally or only in small enough amounts, these compounds must be obtained through food. Vitamin absorption primarily takes place in the small intestine [20].

In order to avoid vitamin shortages, it is crucial to understand how the gastrointestinal tract absorbs vitamins. Impaired vitamin absorption inside the gastrointestinal tract can be caused by a number of things, such as gastrointestinal disease, genetic problems affecting transport molecules, heavy alcohol consumption, and drug interactions [21].

When the foods were eaten that are rich in water-soluble vitamins, the bodies are able to absorb these nutrients more easily. Another way that the body gets these vitamins is through the microbes that live in the large intestines, specifically in the rumen of ruminant animals. Among the vitamins that have two places of origin are thiamin, biotin, pantothenic acid, riboflavin, and folic acid. Although some animals can make their own ascorbic acid, it is essential for monkeys and guinea pigs to consume it because it is a real vitamin. Unique characteristics of niacin are its ability to be synthesized internally from tryptophan and its absorption through the intestines from food sources [22].

While most absorption of vitamins produced by bacteria in the large intestine happens there, the small intestine is where water-soluble vitamins consumed in food are absorbed. Vitamins can enter the enterocyte from the gut lumen and exit it from the basolateral surface via their own unique carrier-mediated transport pathways, according to research. Said (2004) states that while certain transporters are salt-dependent, others are not.

1.2. Absorption of Fat-soluble Vitamins

The intestinal lumen facilitates the absorption of fat-soluble vitamins A, D, E, and K by mechanisms similar to those involved in the absorption of other lipids. To summarize, these substances are combined with various lipids and bile acids inside the small intestinal lumen and then enter the enterocyte primarily through diffusion. Enterocytes take in chylomicrons, which they then expel into the lymphatic system by means of exocytosis [23].

1.3. Effects of smoking on vitamins A

Even if many people continue to smoke, the habit itself is a major influence on people's health and a major component in defining their lifestyle. Several serious health issues, including atherosclerosis, emphysema, and coronary pulmonary obstructive disease, are more likely to occur in people who smoke cigarettes [23].

If you smoke, the body won't be able to absorb the vitamins and minerals as well. The main reason for this phenomenon is that blood vessels contract, which causes lipid deposits

to be deposited along the walls of these channels. Research has shown that smoking reduces vitamin A absorption and its physiological effects on humans.

In addition, a separate case about protecting the alveolar epithelium and regulating healthy lung growth was put up by Miura (1993). He claimed that retinoids and vitamin A have a significant impact on this procedure. A study conducted by Edes and T.E. (1997) found that rats' lung and liver vitamin A concentrations were reduced when exposed to benzo(a)pyrene, a chemical component often found in cigarette smoke. Vitamin A deficiency can cause emphysema in rats.

It has also been shown that alveoli in the lungs can be helped along in their maturation process by giving an active metabolic product of vitamin A, particularly all-trans-retinoic acid. McSorley et al. (2000) stated that in the medical field, the indicated phenomena have been found to have therapeutic effects on elastase-induced emphysema (Med, 657). Physio (265) reports that prior studies have directly linked the addition of retinoic acid to the growing medium of rat lung fibroblasts to the development of stretchable lung tissue. All things considered; these studies provide credence to the idea that vitamin A plays a significant role in warding off the onset of emphysema.

Therefore, it is believed that emphysema may develop in those who inhale cigarette smoke and have a vitamin A deficit. There is a lack of consistent and comprehensive data about the effects of cigarette smoking on trace components, according to Bashar and Mitra (2004). It was set out to determine whether and how smoking affects the levels of trace elements in the blood of men with heart disease diagnoses. Following the specified approach, it was surveyed 100 adult patients hospitalized in Bangladesh for cardiac issues using a cross-sectional design. The percentage of individuals showing bacterial growth on throat swab culture and the mean serum concentrations of trace elements are the major parameters being investigated. The results showed that retinol, alpha-tocopherol, zinc, and selenium concentrations in the serum of smokers were much lower, whereas copper concentrations were much higher. Compared to the control group, smokers had a higher prevalence of Streptococcus β-hemolyticus in throat swab cultures, according to the study. Scientific studies have linked smoking to negative effects on blood concentrations of trace components. Improving the health and nutritional well-being of those who are already confronting nutritional deficits in Bangladesh requires the implementation of a smoking control plan [24].

Despite the abundance of literature linking smoking to diseases like cancer, emphysema, and cardiovascular illness, very little is known about how smoking affects the body's macro- and micronutrient levels, as pointed out by Preston AM (1991). There is little doubt that differences in the amounts of these essential nutrients may contribute to the development of numerous smoking-related health problems. A large percentage of the gaseous chemicals and condensed tar particles that make up tobacco smoke have oxidant and prooxidant characteristics. These compounds can trigger the production of free radicals, which in turn can cause lipid peroxidation in living cell membranes. The cellular

antioxidant defense mechanism helps to reduce the harmful effects of reactive oxygen species; key components of this mechanism include selenium, B-carotene, vitamin C, and vitamin E [25]. Vitamin C and B-carotene plasma concentrations are known to drop during smoking, according to a number of studies. The presence of cadmium in tobacco has been found to reduce selenium bioavailability and show antagonistic effects towards zinc, which is a necessary component for the superoxide dismutase antioxidant enzyme. It is possible that cigarette smokers' tissue quantities of vitamin E, the main lipid-soluble antioxidant, will be lower than ideal. In addition, research has demonstrated that some compounds included in tobacco might lower levels of certain B-complex vitamins. People who smoke may already be in a worse nutritional position due to their poor food consumption. The results of the Second National Health and Nutrition Examination Survey show that the consumption of fruits and vegetables, especially those rich in carotene and vitamin C, is inversely related to smoking behavior. Quitting smoking is a clear and well-established way to effectively address the issues associated with cigarette consumption. The current state of affairs demands that the medical community take on the responsibility of proposing solutions to reduce the number of tobacco-related diseases among smokers [26]. Nutritionists can make a significant impact in this particular procedure. Appropriate nutrition level determination is a topic of ongoing academic controversy. People who smoke might think about taking a vitamin C supplement, as it has been suggested before. It is advised to try taking more antioxidants [27].

In order to determine whether there is a correlation between cigarette smoking and lung vitamin A concentrations and the development of emphysema, this study set out to test this hypothesis. This study aims to compare the levels of vitamin A (retinol) in serum and lung tissue after exposure to smoking with those after exposure to room air. It is well-known that the liver is the primary site for vitamin A deposition. Therefore, it is crucial to assess vitamin A concentrations in the liver to find out how exposure to cigarette smoke affects these levels.

2. MATERIALS AND METHODS

Utilizing male Sprague-Dawley weanling rats, the present experiment was conducted. Separated from one another, these rats were kept in stainless steel cages at the standard room temperature of 25°C. In accordance with the AIN-83 protocol, the researchers repeatedly recorded the rats' weights once a week and methodically recorded data on their food intake every day.

In order to begin the experiment, the rats were divided into two groups. One group was given daily smoke from 15 unfiltered cigarettes, while the other group was given no smoke at all (called air exposure).

The living quarters for these rodents are a 75 cm x 60 cm x 55 cm plastic rectangle. A pair of holes, one on each side of this cellular structure, are present. The first one is a

cigarette holder, while the second one is connected to a tube that lets air in. The rats were first exposed to three minutes of cigarette smoke and subsequently to three minutes of room air as part of the experiment. It took an estimated 1.25 to 1.5 hours of repeating the aforementioned technique to smoke all fifteen cigarettes. Using data obtained from two 20 mm Gelman filters, the rats' smoke particle consumption was measured using accurate quantification procedures. The other group of rats, called the CT rats, are kept in a separate room where they are only exposed to outside air. After inhaling all fifteen cigarettes, the rats in the control group had a mean concentration of 12.4-4.3 (standard error of the mean) mcg/L of smoke particles, according to the study.

2.1. Serum collection

An intraperitoneally anesthesia was injected to the rats at the ending of the day, an abdominal aorta blood was drawn and stored at low temperature.

3. Result

General observations.

The absence of recorded instances of rat mortality for vitamin A previous to the designated cutoff date was demonstrated. In terms of daily nutrient intake, there was no statistically significant difference between the cigarette smoke group and the ambient air group of rats. The cigarette-exposed experimental group showed signs of pulmonary haemorrhaging and vasculitis in the third week of the trial. But these side effects were no longer noticeable by week six. Lung, liver, and heart weights as a percentage of body weight were noticeably higher in the smoke-exposed group of rats.

The following graphs show the association between the following weight variables for two separate groups, SM and CT: body weight, lung weight, heart weight, and liver weight. The results indicate that the two groups of rats, one exposed to air CT and the other to SM, differ significantly from one another.

The figures below summaries the results of quantifying these vitamin A variances in relation to damage severity. No deaths occurred in the rat population before the vitamin A experiment was scheduled to end. The daily food consumption of the SM and CT groups did not differ statistically. Additionally, the average weekly weight gain (CT = 34.75 +/- 6.05 g/wk; SM = 31.07 +/- 5.33 g/wk) did not differ significantly between the two groups. Vasculitis and haemorrhaging were observed in the pulmonary area of SM rats after 4 weeks. However, hidden data reveal that the aforementioned clinical indications were not discovered after six weeks. The study found that compared to CT rats, SM rats had significantly higher lung, heart, and liver to body weight ratios. The correlation between weight and the CT and SM vitamin A groups is illustrated in figure (1). According to the results, the vitamin A-normal group had a higher body weight than the smoking group. Figure 2 shows that the smoking group had larger lung weights when compared to the normal vitamin A group. Figure (3) shows that when comparing the normal vitamin, A group

to the smoking group, the latter had a larger heart. Figure 4 shows the correlation between smoking and normal liver weight groups. The heart weights of the smoking group were found to be higher than those of the normal group. You can see the correlation between vitamin A normalcy and liver weight in the smoking group in figure (4). The normal vitamin A group was thought to have a smaller heart, liver, and lung mass than the smoking group.

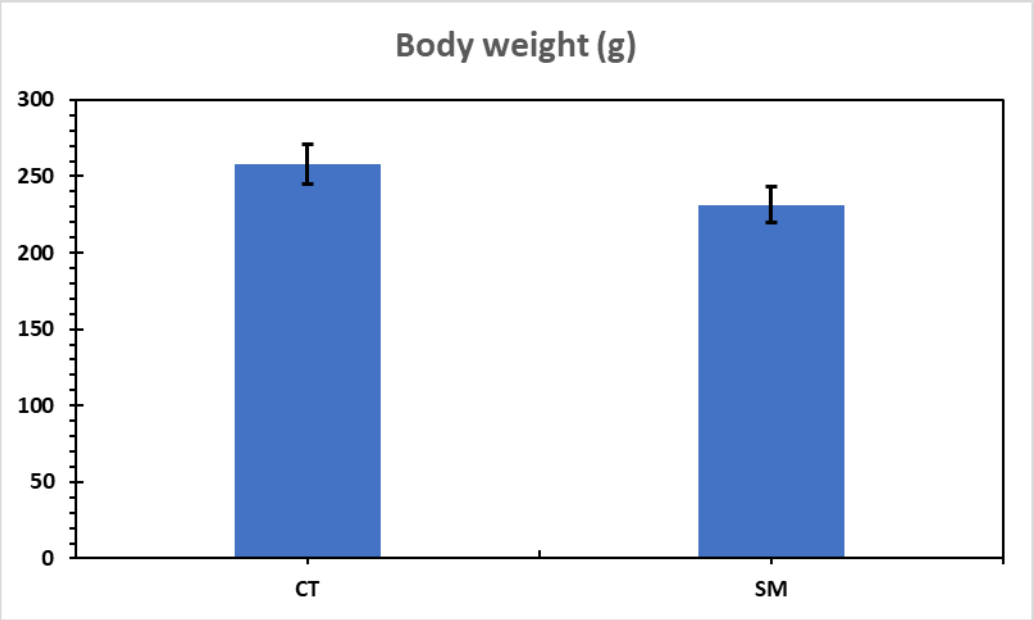

Figure (1). The relation between body weight and groups of both CT and SM for vitamin A.

Figure (2). The relation between groups with lung weight for vitamin A.

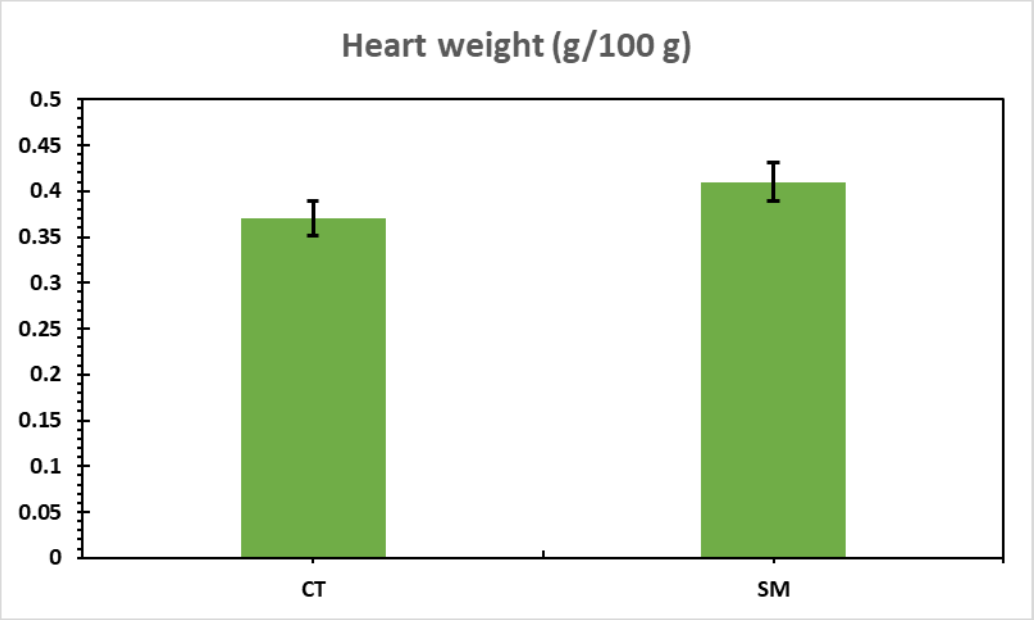

Figure (3). The relation between groups and heart weight for vitamin A.

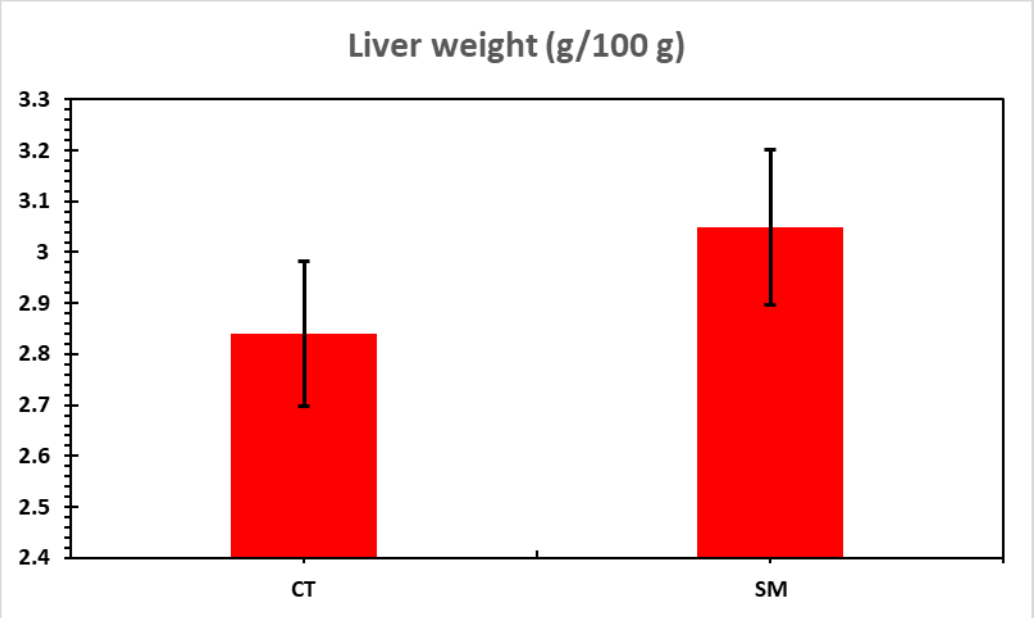

Figure (4). The relation between liver weight and groups for vitamin A.

3.1. Lung, liver and serum levels of retinol:

The retinol concentrations in the lung, liver, and serum of the group exposed to cigarettes for vitamin A decreased significantly after a 6-week exposure test. Additionally, the incidence of emphysema in rats was found to be inversely related to the level of retinol in the pulmonary system. Figure 5 displays the outcomes. The severity of emphysema in the total rat population was shown to be significantly inversely correlated ($r = -0.73$, $P < 0.03$, n

= 10) with the retinol content in the lung, as shown in Figure 6.

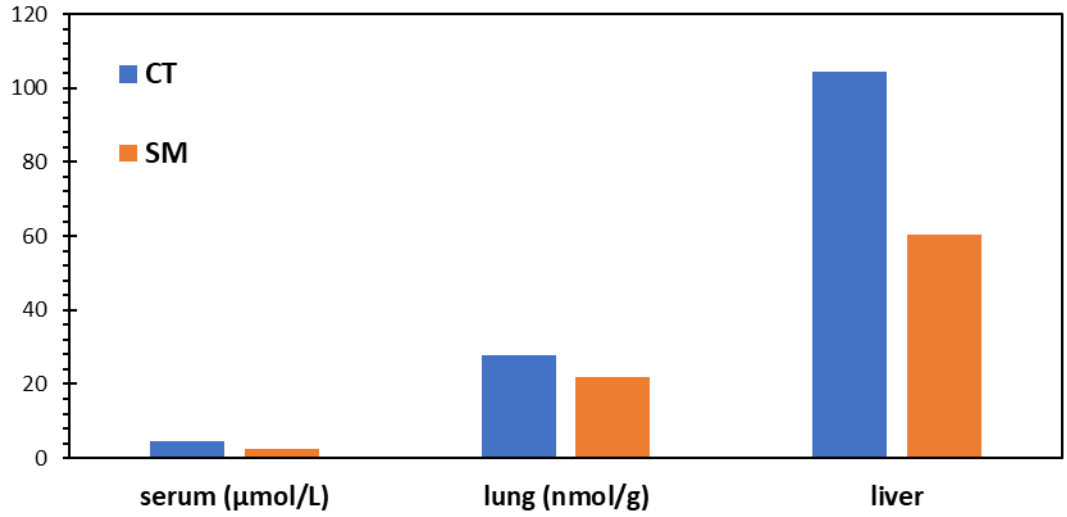

Figure (5). The retinol concentrations of serum, lung and liver of rats exposed to cigarette smoke (SM) or air (CT) for 6 wk1 for vitamin A.

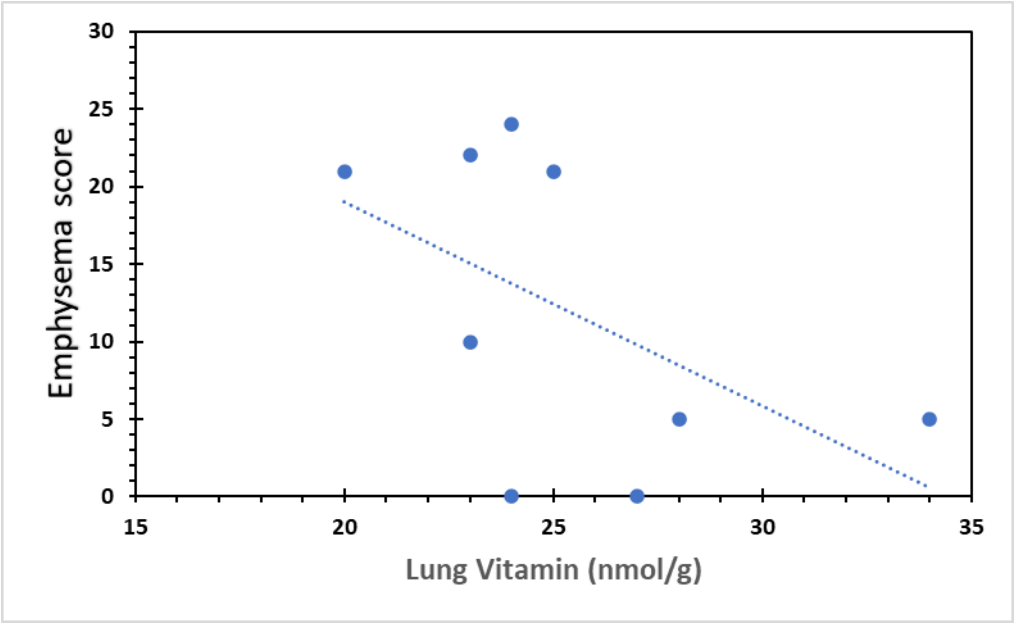

Figure (6). Correlation between lung vitamin A concentration and emphysema evaluation score of a rat exposed to cigarette smoke for 6 wk (r =- 0.69, P < 0.03).

Enhanced vacuole development, also known as fatty infiltration, is observed in the liver. Contributing significantly to what is already known, it was reported novel data showing that cigarette smoke reduces retinol concentrations in rats' lungs, serum, and liver. Since there were no significant differences in food consumption between the groups, it follows that cigarette smoke is the primary cause of the observed decrease in resources.

These results are in line with those of previous studies [5, 16] that found that exposing rats to BP—a component of tobacco smoke—caused a deficiency of vitamin A in the liver and lungs of the rats. The amount of vitamin A stored in the liver was shown to decrease after administering tobacco extract or a specific tobacco component, N-nitrosonornicotine, to the abdomen, according to previous research [17]. It has also been found that breathing in cigarette smoke can cause the liver and respiratory system to produce cytochrome P450 isoforms, specifically CYP1A1 and CYP1A2 [18, 19]. It has been found that the aforementioned isoforms can increase the breakdown of retinoic acid (RA) (18, 20), which could cause vitamin A levels to drop. It is acknowledged that any of these factors could lead to a decrease in vitamin A levels, but the exact process behind this has to be fully understood. Results from previous investigations on the effects of smoke exposure are consistent with the current finding that weanling rats exposed to smoke had lower vitamin A levels. Cigarette smoke significantly reduced retinoic acid (RA) concentrations in the lungs of adult ferrets by increasing the breakdown of retinoids [21, 22]. The investigation failed to find any statistically significant changes in lung retinol concentrations, even though there was an increase in catabolic activity. While RA was not measured in this experiment, the results of lower tissue retinol concentrations point to a faster rate of retinoid catabolism. However, differences in the individuals' ages could be a possible explanation for this discrepancy. The hepatic stocks of vitamin A in adult ferrets are far higher, and they may have better compensatory mechanisms to make up for any lung system deficiencies. It is important to take into account the possible effects of smoke exposure on the loss of vitamin A due to smoking. For six weeks, researchers in an experiment subjected young guinea pigs to a modest dose of six cigarettes daily. A statistically significant increase in retinol concentrations within the pulmonary tissue was shown in this investigation [23]. Conversely, lung retinol levels were much lower in weanling rats that were exposed to a greater dosage of 20 cigarettes daily for 6 weeks.

3.2. Biochemical analysis of serum:

After a duration of 4 weeks, a decrease in the levels of Aspartate Transferase (AST) and Gamma-Glutamyl Transferase (GGT) was observed in the serum of rats exposed to air (CT group) compared to the group exposed to cigarette smoke. However, these decreases returned to normal levels after a duration of 6 weeks. Throughout the study, there were no significant differences observed in the values of Alanine Transaminase (ALT) and Lactate Dehydrogenase (LDH) between the group of rats exposed to cigarette smoke and the CT group.

4. DISCUSSION

This research set out to quantify the effects of secondhand smoke on vitamin A concentrations in rats, particularly how it might affect the liver, serum, and lungs.

Emphysema and pulmonary inflammation are conditions that are likely to appear in the lungs. Hepatocytes that have vacuolation, or fatty infiltration, The broadening of the tracheal epithelial cells is a hallmark of hyperplasia.

Lung, liver, and serum vitamin A levels are less affected by cigarette smoke. Vitamin A levels are unaffected by changes in food consumption or other variables that may affect them. Previous work by Moulder and Carine (1996), who used the chemical compound benzo(a)pyrene to create vitamin A insufficiency through cigarette administration, lends credence to the aforementioned conclusions. Moreover, prior studies by Ross et al. (1986) have shown that intraperitoneal administration of tobacco extracts significantly reduces vitamin A storage in the liver [26].

Cigarette smoking is also associated with vitamin A deficiency [27]. Researchers found that all-trans retinoic acid prevented emphysema from developing in rats that were exposed to cigarette smoke in a study conducted by Magdula (1988). In addition, several explanations have been put out, suggesting that vitamin A could potentially reduce the occurrence of emphysema.

McSclory and Daley (2003) stated that the emphysema that develops in the lungs is caused by the elastic fibers in the alveoli gradually wearing down.

Cigarette smoke is responsible for the suppression of elastic re-synthesis in an elastase-induced emphysema model [28]. Conversely, research has shown that vitamin A can help facilitate elastin formation, which in turn reduces its degradation and provides protection against elastic fibre degradation. In contrast to retinol, Massaro (2001) stated that the retinoic acid is responsible for the increase of elastin transcription [29]. There is also an active induction of the elastin protein manufacturing process.

Hayashi and Suzuki (1995) expressed that there is evidence that shows a correlation between neutrophil elastase activity and elastin breakdown. Furthermore, metalloproteinases have been associated with this hyperactivity (McGowan, 1997, p. 410). Human leukocyte elastase activity is decreased in the presence of retinoic acid, as stated by Sklan (1999). Burmesiter (1998) also found that human leukocyte elastase activity is similarly affected by metalloproteinase activity.

The reverse impact on the trachea was described by Lasnitzki (1987) in his work as tracheal squamous metaplasia, which developed as a result of vitamin A therapy.

Leo (1983) stated that it should also be noted that vitamin A levels might be negatively impacted by liver impairment. The main location for vitamin A storage, the hepatic stellate cells, are stimulated, and this is the main source of the condition. This activation process may cause vitamin A to degrade since it lowers the total concentration of the vitamin. There

are a number of liver diseases that are linked to low vitamin A levels, and one of these is the development of vacuoles [30].

5. Conclusion

In conclusion, this study lends credence to the idea that third-party exposure to cigarette smoke may reduce vitamin A levels in the blood, lungs, and liver. Additionally, it has been found that the start of emphysema is linked to lower vitamin A levels. This is supported by the fact that there is a negative link between lung vitamin A levels and the incidence of this medical illness. The potential of increasing vitamin A levels in rats to slow or stop the progression of emphysema is the focus of a current investigation. Overall, vitamin A levels in the blood, liver, and lungs are significantly affected by breathing in cigarette smoke. Reduced vitamin A levels, brought on by the aforementioned exposure, increase the risk of developing emphysema.

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