Article

Association Between Electronic Cigarette Use and Levels of High-Sensitivity C-Reactive Protein and Uric Acid

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Abstract

The present study investigated whether electronic cigarette use, which is becoming increasingly common, was related to systemic inflammation that may lead to cardiovascular disease, similar to conventional cigarette smoking. The study included 1208 men (19-65 years old) who participated in the 7th Korean National Health and Nutrition Examination Survey (2016). The participants were categorized as electronic cigarette users, conventional cigarette users, and nonsmokers. Serum high-sensitivity C-reactive protein was used as an inflammatory index, and uric acid level was used as a metabolic indicator. After adjusting for confounding factors, electronic cigarette use was significantly associated with elevated serum high-sensitivity C-reactive protein levels ($\beta = 1.326$, $P = .002$), uric acid levels ($\beta = 0.400$, $P = .042$), and hyperuricemia (uric acid level of >7 mg/mL; odds ratio = 2.67, 95% confidence interval = 1.27-5.58). These findings suggest that electronic cigarette use may be associated with systemic inflammation markers, similar to conventional cigarette use.

Keywords

electronic cigarette, inflammatory marker, hs-CRP, uric acid, KNHANES

What We Already Know

Electronic cigarrettes use is increasing recently. Several studies have investigated about the association with elecronic cigarettes use and cardiovascular disease, but the results have been inconsistent.

What This Article Adds

Our study suggests that electronic cigarrettes use may be associated with systemic inflammation markers (uric acid, and hs-CRP) which is thought to be a major mechanism involved in the developement of cardiovasuclar diseae. The results indicate that electonic cigarettes are not a harmless substitute for conventional cigarettes.

Introduction

Electronic cigarettes or electronic nicotine delivery systems generally refer to refillable products that vaporize nicotine, concentrated flavor, and fillers (including propylene glycol and glycerin), which are inhaled by the user.[1] Electronic cigarettes were introduced in China during 2004 and quickly spread to American and European markets in 2007, with rapidly increasing usage rates. For example, the rate of any electronic cigarette use among American adults has increased by nearly 3-fold from 3.3% in 2010 to 8.5% in 2013, and a similar trend has been observed in England, with the rate increasing from 5.7% in 2010 to 16.2% in 2012.[2] Electronic cigarette use is also increasing in South Korea, with data from the 2016 Korean National Health and Nutrition Examination Survey (KNHANES) revealing rates of 4.2% among men and 0.4% among women, relative to fairly stable conventional smoking rates of 40.7% among men (1.3% annual increase) and 6.4% among women (0.9% annual increase).[3] In this context, a 2015 report from the South Korean Ministry of Health and Welfare suggested that electronic cigarettes still contain carcinogens, similar to conventional cigarettes, which may be concerning given the difficulty of altering a

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smoking habit, despite the relatively small amounts of these carcinogens in electronic cigarettes.[4] Conventional cigarettes contain carcinogens that are generated by incomplete combustion, which has led some to believe that electronic cigarettes do not contain carcinogens because of the vaporization mechanism. Nevertheless, electronic cigarettes contain nicotine and other toxic substances, such as nitrosamine, formaldehyde, acetaldehyde, and metals.[1,4]

Studies are ongoing regarding the effects of electronic cigarettes on cardiovascular disease (CVD). Animal studies have indicated that nicotine use reduces cardiovascular protection by increasing the levels of triglycerides (TGs) and very low-density lipoprotein-cholesterol, while decreasing the level of high-density lipoprotein (HDL)-cholesterol. Moreover, electronic cigarette solutions that do not contain nicotine still increase blood sugar levels.[5] Using electronic cigarettes may also cause elevated blood pressure (BP) due to increased aortic stiffness,[6] and venous endothelial cells exhibit blocked proliferation and induced apoptosis because of morphological changes after exposure to cytotoxic electronic cigarette vapor.[7] Moreover, similar to conventional cigarettes, electronic cigarettes cause sympathetic hyperactivity that leads to increased oxidative stress and an increased risk of CVD.[8] Nevertheless, some studies have suggested that electronic cigarettes are safe because their vapor does not contain substantial amounts of harmful substances ($<$5% of the contents of conventional cigarettes).[9] In addition, the major chemicals used in electronic cigarettes are not thought to be associated with a risk of serious diseases, as any effect on the cardiovascular system would be related to sympathetic hyperactivity caused by nicotine.[9,10] Other studies have indicated that conventional cigarette use causes delayed relaxation of the left ventricular cardiac muscle, whereas electronic cigarette use does not have an immediate effect, although those studies were based on short-term observations.[11] Thus, it remains unclear whether long-term electronic cigarette use has any effects on the cardiovascular system. The present study aimed to examine the relationship between electronic cigarette use and systemic inflammation, which is thought to be a major mechanism involved in the development of CVD. This relationship was evaluated based on blood levels of high-sensitivity C-reactive protein (hs-CRP) as an inflammatory index[12,13] and uric acid as a metabolic indicator.[13,14]

Methods

Subjects and Study Design

This study evaluated the associations of electronic cigarette use with inflammatory and metabolic markers in Korean men (19-65 years old) who participated in the first year of the 7th KNHANES (2016). The KNHANES is a nationwide representative cross-sectional survey conducted by the Korea Centers for Disease Control and Prevention, which uses a stratified multistage probability sampling design to select household units. Participants are then selected from the sampling units based on age, sex, and geographic area. The KNHANES involves a health examination and self-administered versions of a health interview survey, health behavior survey, and nutrition survey. Details regarding the study design and methods have been previously described.[15] All the participants provide informed consent and data are de-identified before being uploaded to a publicly available database. Ethical approval was not required based on the secondary analyses of de-identified data.

The present study evaluated participants in the first year of the 7th KNHANES (2016) who completed questionnaires regarding their smoking habits. We initially identified 1863 Korean men (19-65 years old), although 638 participants were excluded because they were ex-smokers. In addition, we excluded 17 participants with myocardial infarction,[16] stroke,[17] gastric cancer, liver cancer, colorectal cancer, and lung cancer,[18] because these diseases might have influenced their serum hs-CRP and uric acid levels. Therefore, the present study included a total of 1208 Korean men: 430 nonsmokers, 63 current electronic cigarette users, and 715 current conventional cigarette users.

Electronic and Conventional Cigarette Use

Current electronic cigarette users were defined as participants who answered "Yes" to the question, "Have you used electronic cigarettes in the past 1 month?" Among participants who indicated that they had smoked at least 100 cigarettes (5 packs) in their lifetime, current conventional cigarette users were defined as participants who answered "Everyday" or "Sometimes" to the question, "Do you currently smoke cigarettes?"

Inflammatory and Metabolic Markers

Blood samples were obtained for hs-CRP and uric acid testing from the antecubital vein or cephalic vein during the morning after a $>$8-hour overnight fast. Samples were collected in 8.5-mL serum separator tubes by trained medical staff, and were stored at 2°C to 8°C until testing. All laboratory analyses were performed within 24 hours after sample collection. Serum hs-CRP levels were analyzed using the immunoturbidimetric method with a Cobas analyzer (Roche, Germany), which provides a minimum detection level of 0.1 mg/L and a maximum detection level of 20.0 mg/L. Blood uric acid levels were analyzed using uricase colorimetry with a Hitachi 7600 analyzer (Hitachi, Japan). Based on previously reported values, we defined the high hs-CRP group as having levels of $>$3 mg/L,[19] and the hyperuricemia group as having uric acid levels of $>$7 mg/dL.[20]

Other Variables

Height was measured in 0.1-cm increments using an automatic height meter (Seca225, Hamburg, Germany), and weight was measured in 0.1-kg increments using a scale (GL-6000-20,

South Korea). Body mass index (BMI) was calculated using the measured weight and height values as kg/m^2. Blood pressure (BP) was measured using a mercury sphygmomanometer (Baumanometer wall unit 33, Baum, WA) after ≥5 minutes of rest to stabilize the subjects. Mean systolic BP (SBP) and diastolic BP (DBP) values were calculated using the average of 3 repeated measurements. Blood testing was performed using venous blood that was collected after confirming that the subject had fasted for ≥ 8 hours. The blood tests collected data regarding fasting blood sugar (FBS), glycated hemoglobin, total cholesterol, HDL-cholesterol, TG, low-density lipoprotein-cholesterol, and white blood cell count (WBC).

Data regarding the subjects' age and health behaviors were collected through personal interviews conducted by an experienced interviewer. Health behaviors included alcohol consumption and physical activity. High-risk drinking was defined as drinking two to three times or more per week. Levels of physical activity were measured using the Global Physical Activity Questionnaire,[21] and aerobic physical activity status was determined based on a total activity level of ≥600 MET-minutes in accordance with the Global Physical Activity Questionnaire analysis guidelines from the World Health Organization.[21] Based on these guidelines, appropriate physical activity is considered present at ≥150 minutes of moderate-intensity physical activity per week, ≥75 minutes of high-intensity physical activity per week, or an equivalent mixture of moderate-intensity and high-intensity physical activities (1 minute of high-intensity activity equals 2 minutes of moderate-intensity activity). Comorbidities were identified based on a questionnaire regarding the presence of hypertension, diabetes, or hyperlipidemia.

Statistical Analyses

All statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corporation, Armonk, NY), and differences were considered statistically significant at 2-sided P values of $<.05$. The subjects were categorized as nonsmokers, conventional cigarette users, and electronic cigarette users for the different analyses. Results were expressed as number of subjects (percentage) or mean ± standard deviation. Intergroup differences were evaluated using the χ^2 test for categorical variables and analysis of variance for continuous variables. Regression and logistic regression analyses were performed to evaluate the associations of electronic cigarette use (vs nonsmokers) with levels of hs-CRP and uric acid. Linear regression analysis was performed to assess the associations with blood hs-CRP and uric acid levels, while multivariate logistic regression analysis was performed to assess whether risks of high hs-CRP and hyperuricemia were associated with electronic cigarette use. The regression analyses were performed using 3 models that were adjusted in a stepwise manner for variables that might affect serum hs-CRP and uric acid levels. Model 1 was adjusted for age and BMI. Model 2 was adjusted for age, BMI, high-risk drinking, and physical activity level. Model 3 was adjusted for age, BMI, high-risk drinking, physical activity level, and various comorbidities (hypertension, diabetes, and hyperlipidemia). The variance inflation factor was calculated to identify any multicollinearity between the variables included in the multivariate analyses. Last, adjusted mean blood hs-CRP and uric acid levels were compared between the 3 smoking groups after adjusting for age.

Results

Participants' Characteristics

The present study included 1208 subjects: 430 nonsmokers (35.6%), 715 current conventional cigarette users (59.2%), and 63 current electronic cigarette users (5.2%). Table 1 shows the three groups' anthropometric characteristics, blood test results, and comorbidities. The mean age was highest in the conventional cigarette user group (conventional cigarettes = 42.25 ± 11.27 years, nonsmoker = 38.42 ± 13.25 years, and electronic cigarettes = 37.08 ± 11.54 years; $P < .001$). Relative to the nonsmokers and electronic cigarette users, conventional cigarette users also had significantly poorer values for mean FBS level (98.15 ± 23.23 mg/dL vs 98.79 ± 17.24 mg/dL vs 102.20 ± 27.32 mg/dL; $P = .029$) and mean HbA1C level (5.51 ± 0.76% vs 5.60 ± 0.58% vs 5.64 ± 0.81%; $P = .016$). Relative to the conventional and electronic cigarette users, nonsmokers had the best lipid profiles in terms of HDL-cholesterol level (48.51 ± 10.49 mg/dL vs 46.44 ± 12.41 mg/dL vs 43.27 ± 9.81 md/dL; $P < .001$) and TG level (136.33 ± 100.72 mg/dL vs 205.79 ± 192.17 mg/dL vs 189.67 ± 113.29 md/dL; $P < .001$).

Relative to the nonsmokers and conventional smokers, the electronic cigarette users had the highest values for mean hs-CRP level (1.25 ± 2.50 mg/L vs 1.37 ± 2.46 mg/L vs 2.10 ± 4.14 mg/L; $P = .053$) and mean uric acid level (5.94 ± 1.19 mg/dL vs 5.91 ± 1.32 mg/dL vs 6.35 ± 1.32 mg/dL; $P = .079$). When we performed 2-group comparisons to the electronic cigarette users, the uric acid levels were significantly lower in the nonsmoker group ($P = .049$) and the conventional cigarette user group ($P = .026$). Moreover, the electronic cigarette user group had the highest proportion of participants with hyperuricemia (n = 21, 33.3%).

Associations of Electronic Cigarette Use With Levels of hs-CRP and Uric Acid

The results of the linear regression analyses are shown in Table 2, and we confirmed that there was no multicollinearity present (variance inflation factor <10). The results indicate that electronic cigarette use was positively correlated with hs-CRP levels ($\beta = 1.326$, $P = .02$) and with uric acid levels ($\beta = 0.4$, $P = .042$). Furthermore, we evaluated the associations of electronic cigarette use with high hs-CRP levels and hyperuricemia, which only revealed a

Table 1. Baseline Participant Characteristics According to Smoking Status*,†.

Characteristics	Non-Smoker (n = 430)	Conventional Cigarette User (n = 715)	Electronic Cigarette User (n = 63)	*P*
Age (years)	38.42 ± 13.25[b]	42.25 ± 11.27[a]	37.08 ± 11.54[b]	<.001
BMI (kg/m^2)	24.64 ± 3.63	24.52 ± 3.53	25.38 ± 3.36	.185
WC (cm)	85.46 ± 9.91	86.11 ± 9.27	88.48 ± 8.13	.054
SBP (mm Hg)	118.37 ± 12.47	119.10 ± 13.76	117.95 ± 11.75	.587
DBP (mm Hg)	78.86 ± 9.31	79.68 ± 10.05	78.71 ± 9.73	.338
FBS (mg/dL)	98.15 ± 23.23[b]	102.20 ± 27.32[a]	98.79 ± 17.24[b]	.029
HbA1c (%)	5.51 ± 0.76[b]	5.64 ± 0.81[a]	5.60 ± 0.58[ab]	.016
Total cholesterol (mg/dL)	192.41 ± 33.60	195.57 ± 37.95	199.68 ± 37.24	.194
HDL-cholesterol (mg/dL)	48.51 ± 10.49[a]	46.44 ± 12.41[b]	43.27 ± 9.81[b]	<.001
TG (mg/dL)	136.33 ± 100.72[b]	205.79 ± 192.17[a]	189.67 ± 113.29[a]	<.001
LDL-cholesterol (mg/dL)	121.57 ± 32.17	115.75 ± 35.13	122.75 ± 26.21	.337
WBC (10^3/μL)	6.35 ± 1.46[b]	7.39 ± 1.93[a]	7.74 ± 1.81[a]	<.001
Uric acid (mg/dL)	5.94 ± 1.19	5.91 ± 1.32	6.35 ± 1.32	.079
hs-CRP (mg/L)	1.25 ± 2.50	1.37 ± 2.46	2.10 ± 4.14	.053
High CRP, n (%)[b]	33 (7.7)	66 (9.2)	8 (12.7)	.362
Hyperuricemia, n (%)[b]	85 (19.8)	154 (21.5)	21 (33.3)	.047
Hypertension, n (%)	87 (20.3)	205 (28.8)	12 (19.4)	.012
Diabetes mellitus, n (%)	26 (6.2)	65 (9.4)	4 (6.6)	<.001
Hyperlipidemia, n (%)	47 (15.8)	144 (30.9)	14 (33.3)	<.001
Problematic drinking, n (%)	71 (16.5)	364 (50.9)	19 (30.2)	<.001
Sufficient physical activity, n (%)[b]	239 (58.2)	318 (47.1)	29 (49.2)	.002

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; TG, triglyceride; LDL, low-density lipoprotein; WBC, white blood cells; hs-CRP, high-sensitivity C-reactive protein.

*Values are presented as mean ± standard deviation or number (%), and analyses were performed using analysis of variance for continuous variables and the χ^2 test for categorical variables. Multiple comparisons are shown as follows: a > b > c, a = ab, ab = b.

†Definitions: High CRP = hs-CRP of ≥3.0 mg/L; hyperuricemia = uric acid of ≥7.0 mg/dL, sufficient physical activity = met the aerobic physical activity recommendations of the World Health Organization.

Table 2. Linear and Logistic Regression Analysis of Current Electronic Cigarette Use on hs-CRP and Uric Acid Levels.

	Linear Regression Coefficients			
	hs-CRP		Uric Acid	
	β ± SE	*P*	β ± SE	*P*
Model 1[a]	0.796 ± 0.348	.022	0.328 ± 0.166	.049
Model 2[b]	0.942 ± 0.359	.009	0.292 ± 0.172	.090
Model 3[c]	1.326 ± 0.429	.002	0.400 ± 0.071	.042
	Logistic regression OR (95% CI)			
	High hs-CRP		Hyperuricemia	
	OR (95 % CI)	*P*	OR (95 % CI)	*P*
Model 1[a]	1.67 (0.72-3.85)	.232	1.90 (1.05-3.45)	.034
Model 2[b]	1.89 (0.81-4.41)	.142	2.00 (1.08-3.71)	.027
Model 3[c]	2.41 (0.86-6.75)	.093	2.67 (1.27-5.58)	.009

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; SE, standard error; OR, odds ratio; CI, confidence interval.

[a]Model 1: adjusted for age and body mass index.

[b]Model 2: adjusted for age, body mass index, alcohol use, and physical activity.

[c]Model 3: adjusted for age, body mass index, alcohol use, physical activity, and comorbidities (hypertension, diabetes, and hyperlipidemia).

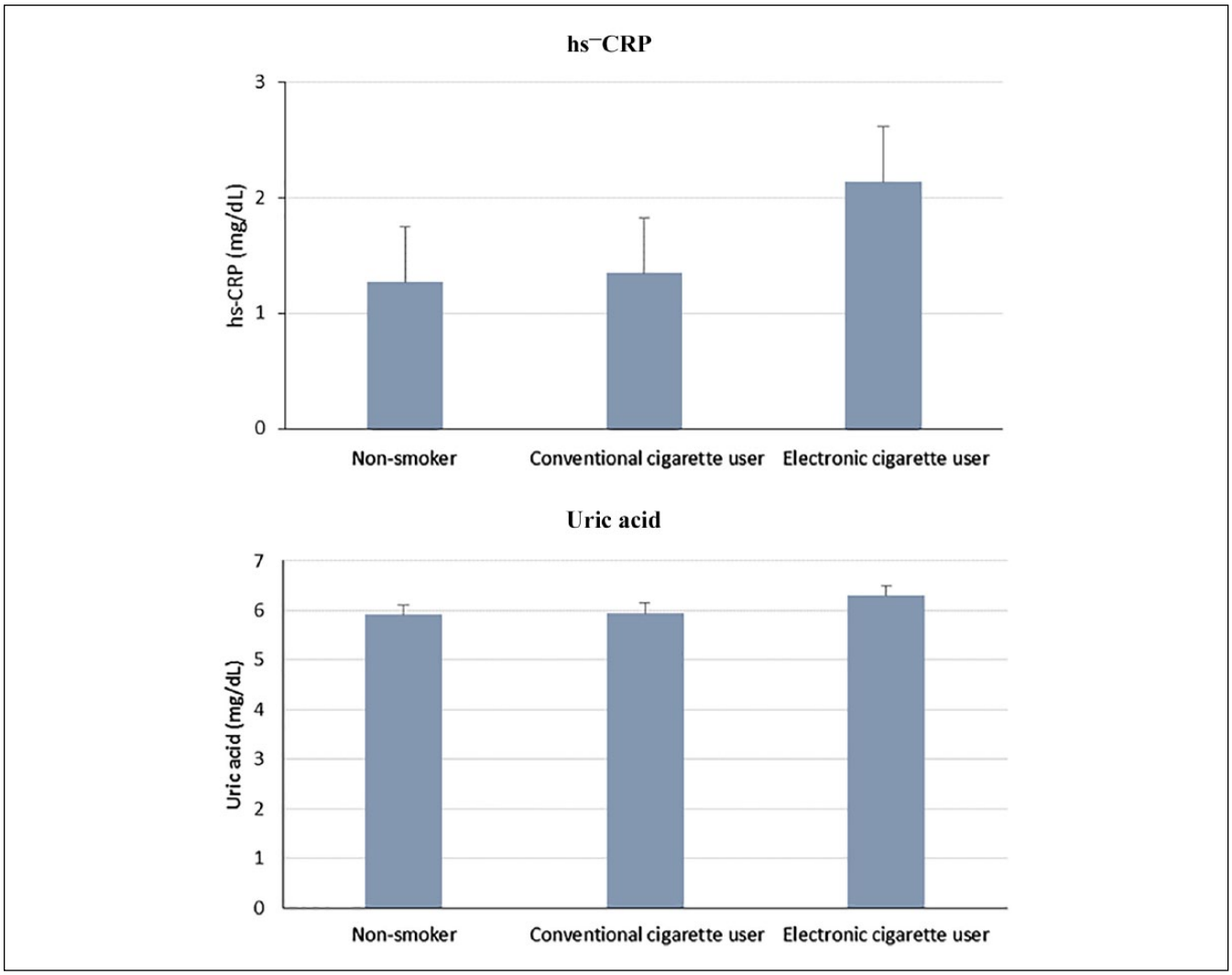

Figure 1. Comparing the adjusted mean levels of high-sensitivity C-reactive protein (hs-CRP) and uric acid among nonsmokers, conventional cigarette users, and electronic cigarette users.

significantly increased risk of hyperuricemia (odds ratio = 2.67, 95% confidence interval = 1.27-5.58).

Distributions of hs-CRP and Uric Acid Levels According to Smoking Type

Median and adjusted mean values for hs-CRP and uric acid levels were compared between the three smoking groups (Figure 1). The results revealed that the electronic cigarette users had the highest median hs-CRP level (0.5 mg/L vs 0.69 mg/L vs 0.80 mg/L) and the highest mean hs-CRP level (1.25 ± 2.50 mg/L vs 1.37 ± 2.46 mg/L vs 2.10 ± 4.14 mg/L; $P = .047$). These results also indicated that nonsmokers tended to have the lowest values for these markers. While not statistically significant, the electronic cigarette users also had the highest median uric acid level (5.9 mg/dL vs 5.8 mg/dL vs 6.3 mg/dL) and the highest adjusted mean uric acid level (5.91 ± 1.32 mg/dL vs 5.94 ± 1.19 mg/dL vs 6.35 ± 1.32 mg/dL; $P = .077$).

Discussion

Electronic cigarettes are currently used indiscriminately, despite their potential risks not being clearly understood. Thus, the present study aimed to evaluate whether their use was associated with systemic inflammation markers, which might indicate an elevated risk of CVD. The results suggest that male Korean electronic cigarette users had significantly higher levels of hs-CRP and uric acid than nonsmokers, as well as higher levels of uric acid than even conventional cigarette users. Even after adjusting for variables that might affect these inflammatory markers, electronic cigarette use remained positively correlated with levels of hs-CRP and uric acid, as well as with an elevated risk of developing hyperuricemia. These results agree with previous research

linking conventional cigarette smoking to elevated levels of inflammatory markers. For example, one study compared levels of CRP and uric acid in active smokers, passive smokers, and nonsmokers, which revealed that active smokers had higher CRP and uric acid levels than nonsmokers and passive smokers.[22] A Brazilian study also revealed that smokers had higher blood levels of hs-CRP than nonsmokers, and smokers with metabolic syndrome were more than twice as likely to have high hs-CRP levels (>3 mg/L), relative to nonsmokers with metabolic syndrome.[23]

There are a few potential mechanisms through which electronic cigarette use may lead to CVD. First, nicotine is an addictive substance that can cause atherosclerosis by facilitating angiogenesis and inhibiting apoptosis, and potentially influences CVD risk based on its associations with endothelial dysfunction and insulin resistance.[24] The aerosol generated during the vaporization process is also thought to contain carbonyls, which may cause inflammation in the body. For example, formaldehyde is known to lower BP by affecting smooth muscle cells, and in chronic smokers may cause thrombotic disorders by increasing platelet count and triggering oxidative stress in the heart.[25] Acrolein is an unsaturated and highly toxic compound that may cause dyslipidemia, vascular injury, and endothelial dysfunction, which may impair the inflammatory response and vascular regeneration.[26] Exposure to particulate matter with a diameter of <2.5 μm ($PM_{2.5}$) may also affect the regulation of the autonomic nervous system, which can alter heart rate and directly or indirectly cause oxidative stress that potentially leads to local inflammation and thrombosis.[25] Moreover, the effects of these molecules on the cardiovascular organs may be more pronounced than on other organs, as the cardiovascular tissues have less ability to manage toxic nonbiological components, which would suggest that even small amounts of these molecules might cause cancer and CVD. A recent study also revealed that the association between cigarette smoking and lung cancer was a simple linear relationship without a threshold value, while the risk of CVD increased steeply after exposure to a small amount of cigarette smoke and gradually plateaued at higher concentrations. These results suggest that cigarette use affects the heart and lungs via different mechanisms.[10]

Study Limitations

The present study involved a cross-sectional analysis of the relationship between electronic cigarette use and inflammation markers, which precluded an analysis of temporal changes and made it difficult to confirm a causal relationships. In addition, the study might be limited by inaccuracies regarding the measurements of nicotine addiction, actual smoking amount, and smoking duration. Furthermore, the present study was not able to account for the varying amounts of carbonyl emissions from different electronic cigarette types, as well as the potential for environmental exposure to secondhand smoke, which would vary from individual to individual. Therefore, future well-designed prospective studies are needed to examine the relationship between electronic cigarette use and systemic inflammation, which should include quantitative assessments of electronic cigarette types and usage levels.

Conclusion

This study revealed that, among Korean men, electronic cigarette use was closely linked to levels of hs-CRP and uric acid, which are known CVD markers. These results suggest that electronic cigarettes are not a harmless substitute for conventional cigarettes, and that practical efforts are needed to target smoking cessation rather than substitution.

Authors' Note

This study conducted secondary data analysis using raw data from the 7th KNHANES (2016). The data used in the present study were downloaded from the website site with open access. The raw data can be downloaded from following website: https://knhanes.cdc.go.kr/knhanes/sub03/sub03_02_02.do.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the independent Institutional Review Board of Jeju National University Hospital, Jeju, Republic of Korea (Approval Number: 2019-07-008).

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