SMOKING CAUSES A LOW-GRADE SYSTEMIC INFLAMMATION IN HUMAN BODY

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Abstract

Background: There may be some positive and negative acute phase reactants (APR) indicating the possible inflammatory effects of smoking on vascular endothelium all over the body.

Method: Consecutive daily smokers at least for a period of six months and age and sex-matched non-smokers were taken into the study. Cases with regular alcohol consumption (one drink a day) and patients with inflammatory, infectious, or devastating disorders including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, chronic obstructive pulmonary disease, hyper- or hypothyroidism, or heart failure were excluded.

Results: The study included 150 smokers (99 males) and 162 non-smokers. Interestingly, the mean age of the smokers was 45.9 years, and 66.0% of them were male. Although the mean weight, body mass index, systolic and diastolic blood pressures, and hematocrit values were similar in both groups, triglycerides (163.3 versus 151.8 mg/dL, $p<0.05$), low density lipoproteins (LDL) (126.1 versus 117.4 mg/dL, $p<0.05$), erythrocyte sedimentation rate (ESR) (10.8 versus 9.4 mm/h, $p<0.05$), and C-reactive protein (CRP) (2.5 versus 2.1 mg/L, $p<0.05$) values were all higher in the smokers, significantly. On the other hand, high density lipoproteins (HDL) (41.1 versus 44.0 mg/dL, $p<0.05$) and fasting plasma glucose (FPG) (101.9 versus 111.9 mg/dL, $p<0.01$) values were lower in the smokers, significantly.

Conclusion: Smoking causes a low-grade systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in the body. Plasma triglycerides, LDL, ESR, and CRP may be positive whereas HDL and FPG negative APR indicating the inflammatory effects of smoking in the human body.

Key words: Smoking, triglycerides, low density lipoproteins, erythrocyte sedimentation rate, C-reactive protein, high density lipoproteins, fasting plasma glucose

Introduction

The endothelium is a monolayer of endothelial cells which constitutes the inner cellular lining of arteries, veins, capillaries, and lymphatics. It may be the major player in the control of blood fluidity, platelets aggregation, and vascular tone. It may be the major actor in immunology, inflammation, and angiogenesis. It may also be important in the endocrinology. The endothelial cells control vascular tone and blood flow by synthesizing and releasing nitric oxide, metabolites of arachidonic acid, and reactive oxygen species. Additionally, they are also important for generation of vasoactive hormones such as angiotensin II. An endothelial dysfunction linked to an imbalance in the synthesis and/or release of these endothelial factors may explain the initiation of several cardiovascular pathologies including hypertension (HT) and atherosclerosis. On the other hand, excess weight, smoking, and alcohol are well-known causes of chronic endothelial inflammation terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in human body (1). Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human being (2). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, animal-rich diet, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, HT, diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, early aging, and premature death (3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes can not be reversed completely due to their fibrotic natures. The accelerating factors and terminal consequences are researched under the headings of the metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome, extensively (4, 5). We tried to understand whether or not there are some significant relationships between smoking and some acute phase reactants (APR) in the body.

Material and methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive daily smokers at least for a period of six months were taken into the study. Cases with regular alcohol consumption (one drink a day) and patients with inflammatory, infectious, or devastating disorders including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, COPD, hyper- or hypothyroidism, and heart failure were excluded. A routine check up procedure including hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting plasma glucose (FPG), triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL), albumin, creatinine, thyroid function tests, hepatic function tests, markers of hepatitis A, B, C, and human immunodeficiency viruses, urinalysis, a posterior-anterior chest x-ray graphy, and an electrocardiogram was performed. An additional Doppler echocardiogram and/or an abdominal ultrasonography were performed just in case of requirement. Body mass index (BMI) of each case was calculated by measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (6). Office BP were checked after a 5-minute of rest in seated position with mercury sphygmomanometer. Eventually, all smokers were collected into the first, and age and sex-matched non-smokers were collected into the second groups. Mean weight, BMI, systolic and diastolic BP, triglycerides, LDL, HDL, FPG, ESR, CRP, and hematocrit values were detected in each group, and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 150 smokers (51 females and 99 males) and 162 non-smokers (55 females and 107 males). Interestingly, the mean age of the smokers was 45.9 years, and 66.0% of them were male. Although the mean weight, BMI, systolic and diastolic BP, and hematocrit values were similar in both groups, mean triglycerides (163.3 versus 151.8 mg/dL, $p<0.05$), LDL (126.1 versus 117.4 mg/dL, $p<0.05$), ESR (10.8 versus 9.4 mm/h, $p<0.05$), and CRP values (2.5 versus 2.1 mg/L, $p<0.05$) were all higher in the smokers, significantly. On the other hand, mean HDL (41.1 versus 44.0 mg/dL, $p<0.05$) and FPG values (101.9 versus 111.9 mg/dL, $p<0.01$) were lower in the smokers, significantly (Table 1).

Table 1: Comparison of smokers and non-smokers

Variables	Smokers	*p*-value	Non-smokers
Number	150		162
Male ratio	*66.0% (99)*	Ns*	66.0% (107)
Mean age (year)	45.9 ±13.4 (19-76)	Ns	45.2 ±15.7 (13-77)
Weight (kg)	75.6 ±14.5 (44-118)	Ns	74.6 ±13.0 (45-122)
BMI† (kg/m²)	26.7 ±4.5 (16.7-39.4)	Ns	26.5 ±4.5 (18.1-41.1)
Systolic BP‡ (mmHg)	128.0 ±25.0 (90-200)	Ns	130.2 ±22.7 (80-200)
Diastolic BP (mmHg)	88.1 ±12.7 (60-120)	Ns	88.4 ±12.0 (60-130)
Triglycerides (mg/dL)	*163.3 ± 83.1 (45-385)*	*<0.05*	*151.8 ± 86.9 (20-410)*
LDL§ (mg/dL)	*126.1 ± 35.4 (10-282)*	*<0.05*	*117.4 ± 28.8 (43-185)*
HDL‖ (mg/dL)	*41.1 ± 9.5 (26-70)*	*<0.05*	*44.0 ± 9.5 (24-70)*
*FPG** (mg/dL)*	*101.9 ± 25.8 (70-309)*	*<0.01*	*111.9 ± 38.1 (74-327)*
*ESR*** (mm/h)*	*10.8 ± 9.7 (1-51)*	*<0.05*	*9.4 ± 8.0 (1-35)*
*CRP**** (mg/L)*	*2.5 ± 2.7 (0-13)*	*<0.05*	*2.1 ± 2.6 (0-12)*
Hematocrit (%)	41.6 ±5.1 (28-60)	Ns	41.0 ±3.7 (31-49)

*Nonsignificant (p>0.05) †Body mass index ‡Blood pressures §Low density lipoproteins
‖High density lipoproteins **Fasting plasma glucose ***Erythrocyte sedimentation rate ****C-reactive protein

Discussion

Obesity may be one of the terminal consequences of the metabolic syndrome since after development of the obesity, nonpharmaceutical approaches provide limited benefit either to heal obesity or to prevent its complications. Excess weight may cause a chronic low-grade inflammation on vascular endothelium, and risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups (7). The chronic low-grade inflammation may even cause genetic changes on the endothelial cells, and the systemic atherosclerosis may decrease clearance of malignant cells. The effects of excess weight on BP were shown in the literature, extensively (8). For example, incidence of sustained normotension (NT) was higher in the underweight (80.3%) than the normal weight (64.0%, p<0.05) and overweight groups (31.5%, p<0.05), and 52.8% of patients with HT had obesity against 14.5% of patients with the sustained NT (p<0.001) (9). So the dominant underlying cause of the metabolic syndrome appears as weight gain, which may be the main cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose, impaired glucose tolerance, and white coat hypertension (WCH) via the prolonged low-grade inflammation on vascular endothelium in whole body (10). Prevention of the weight gain with physical activity, even in the absence of a prominent weight loss, will probably result with resolution of many parameters of the syndrome (11-14). According to our experiences, excess weight may actually be a consequence of physical inactivity instead of an excessive eating habit therefore prevention of weight gain cannot be achieved by diet, alone (15). Additionally, limitation of excess weight as an excessive fat tissue around abdomen under the title of abdominal obesity is meaningless instead it should be defined as overweight or obesity via the BMI since adipocytes function as an endocrine organ, and they produce leptin, tumour necrosis factor (TNF)-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines in the plasma (16). The eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with elevated BP, insulin resistance, and chronic endothelial inflammation. Similarly, the Adult Treatment Panel III reported that although some people classified as overweight with larger muscular masses, most of them also have excessive fat tissue predisposing to the end-points of the metabolic syndrome (6).

Just after the excess weight, smoking may be the second common cause of vasculitis in the world. It is one of the major risk factors for the atherosclerotic end-organ insufficiencies (1, 17). Its atherosclerotic effect is the most obvious in Buerger's disease. Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. Beside the well-known atherosclerotic effects of smoking, some studies reported that smoking in human being and nicotine administration in animals are associated with lower BMI values (18). Some evidences revealed an increased energy expenditure during smoking both on rest and light physical activity (19), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (20). According to an animal study, nicotine may lengthen inter-meal time, and simultaneously decrease amount of meal eaten (21). Additionally, the BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers (22). Smoking may be associated with a post cessation weight gain, but evidences suggest that risk of the weight gain is the highest during the first year after quitting, and decreases with the following years (23).

Interestingly, the mean weight and BMI were similar both in the smokers and non-smokers in the present study (p>0.05 for both). On the other hand, although the CHD was detected with similar prevalence in both genders, prevalences of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females (24). Beside that, the incidence of myocardial infarctions is increased six-fold in women and three-fold in men who smoked at least 20 cigarettes per day (25). In another word, smoking may be more harmful for women about the atherosclerotic end-points probably due to the higher BMI and its consequences in them. Similarly, smoking is consistently higher in men in the literature (17). Several toxic substances found in cigarette smoke get into the circulation via the respiratory tract, and cause a vascular endothelial inflammation in all systems of the body. For example, smoking may even terminate with irritable bowel syndrome (IBS) and its consequences including chronic gastritis, hemorrhoids, and urolithiasis. There may be several underlying mechanisms terminating with the IBS and its consequences in smokers (26). First of all, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts. These functional problems may terminate with the symptoms and components of the IBS including loose stool, diarrhea, constipation, and urolithiasis. Secondly, diarrheal losses-induced urinary changes may even cause urolithiasis (27, 28). Thirdly, smoking-induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts. Finally, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis since some types of bacteria can provoke urinary supersaturation and modify the environment to form crystal deposits in the urine. In fact, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infection with bacteria that possess the enzyme, urease. Similarly, urolithiasis was detected in 17.9% of cases with the IBS, whereas this ratio was 11.6% in cases without the IBS (p<0.01) (27).

After the excess weight and smoking, alcohol may be the third common cause of vasculitis in the world. Alcohol is the most dangerous drug, and the only drug that mostly damaged the others. It is causally linked to more than 200 different diseases, conditions, and injuries (29). For example, people hospitalized with alcohol use disorder (AUD) have an average life expectancy of 47-53 years in men and 50-58 years in women, and die 24-28 years earlier than the general population (30). People with AUD have three-fold higher mortality in men and four-fold higher mortality in women (31). A very substantial part of the Danish excess mortality and lower life expectancy compared to Sweden can be attributed to higher mortality related to alcohol and tobacco consumption (7). Women are generally more sensitive than men to the harmful effects of alcohol, primarily due to their smaller body weight, lower capacity to metabolize alcohol, and higher proportion of body fat. Alcohol can cause liver and brain damages, and its consumption is one of the major leading causes of cancers all over the world (29). Alcohol may even cause loss of consciousness and death in high amounts. Hepatic alcohol dehydrogenase is the main enzymatic system to metabolize alcohol that requires the cofactor nicotinamide adenine dinucleotide (NAD), and the products are acetaldehyde and reduced NAD. Normally, NAD is used to metabolize fats in the liver but alcohol competes with these fats for the use of NAD in drinkers. In another definition, prolonged exposure of alcohol means that fats accumulate in the liver, leading to the term of fatty liver. Acetaldehyde is subsequently metabolized by the aldehyde dehydrogenase into acetate which in turn is broken down into carbon dioxide and water. Ethanol is the only type of alcohol that is found in alcoholic beverages. Ethanol crosses biological membranes and blood-brain barrier via passive diffusion, easily. Alcohol works in the brain primarily by increasing the effects of the gamma aminobutyric acid. This is the major inhibitory neurotransmitter in the brain. Alcohol produces happiness and euphoria, decreased anxiety, increased sociability, sedation, impairment of cognitive, memory, motor, and sensory functions, and generalized depression of central nervous system. Drinking in pregnancy may terminate with fetal disorders, since ethanol is classified as a teratogen. Alcohol is addictive to humans, and can result in AUD, dependence, and withdrawal. Continued alcohol consumption leads to cell death in liver, scarring, cirrhosis, and hepatocellular carcinoma. Prolonged heavy consumption may even cause permanent brain damage. Similarly, alcohol is a major contributing factor of elevated triglycerides in the plasma. It is well-known that plasma triglycerides are sensitive APR in the body (8). Although the cases with regular alcohol consumption were excluded, plasma triglycerides were higher in smokers in the present study (163.3 versus 151.8 mg/dL, p<0.05), indicating the inflammatory properties of smoking in the human body.

The acute phase response occurs in case of infection, infarction, foreign body, autoimmune disorder, allergy, neoplasm, trauma, or burn-like stresses of the body. Certain mediators known as APR are increased or decreased during the acute phase response (32, 33). These markers are commonly measured in clinical practice as indicators of acute inflammation in the body. The terms of acute phase proteins and APR are usually used synonymously, although some APR are polypeptides rather than proteins. Positive and negative APR are those whose concentrations increase or decrease during an acute phase response, respectively. The acute phase response is predominantly mediated by the pro-inflammatory cytokines including TNF, interleukin (IL)-1, and IL-6 secreted by immune cells. In case of inflammation, infection, or tissue damage, neutrophil and macrophages release such cytokines into the circulation. The liver and some other organs respond by producing many positive APR to the cytokines. Some of the well-known positive APR are ESR, CRP, fibrinogen, ferritin, procalcitonin, hepcidin, haptoglobin, ceruloplasmin, complement proteins, and serum amyloid A. CRP is

responsible for activation of the complement pathway. Serum CRP rises rapidly, with a maximal concentration reached within two days, and falls quickly once the inflammation has resolved. Measurement of CRP is a useful indicator of inflammations in the clinics. It correlates with ESR, but not always directly. This is due to the ESR being largely dependent upon elevation of fibrinogen with a half-life of one week, approximately. Thus ESR remains higher for a longer period of time despite the removal of the inflammatory stimulus. Whereas CRP rises with a half-life of 6-8 hours rapidly, and then returns to normal in case of a successful treatment, quickly. On the other hand, productions of the negative APR are suppressed at the same time. Some of the well-known negative APR are albumin, transferrin, retinol-binding protein, antithrombin, transcortin, alpha-fetoprotein, and hemoglobin. The suppression of such APR is also used as an indicator of inflammation. Suppression of the synthesis of such negative APR may be due to the protection of amino acids for the production of positive APR, sufficiently. As also observed in the present study, productions of HDL may also be suppressed in the liver during the acute phase responses (34). Similarly, triglycerides, DM, and CHD were higher in patients with plasma HDL values of lower than 40 mg/dL, significantly (34). So HDL may actually behave as negative and triglycerides behave as positive APR in the plasma. Similarly, the highest CHD of the group with HDL values of lower than 40 mg/dL can also be explained by the same hypothesis in the other study (8). Additionally, plasma triglycerides increased whereas HDL decreased during infections (35). On the other hand, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke (36). Similarly, the highest prevalence of HT and DM parallel to the increased values of LDL and HDL, and the highest prevalence of COPD, CHD, and CRD in contrast to the lowest values of LDL and HDL may show initially positive but eventually negative behaviors of LDL and HDL as the APR (37). Interestingly, the most desired values were between 80 and 100 mg/dL for LDL, between 40 and 46 mg/dL for HDL, and lower than 60 mg/dL for triglycerides in the plasma (8). Parallel to ESR and CRP, plasma triglycerides and LDL may behave as positive whereas HDL and FPG behave as negative APR in smokers in the present study. In another definition, low HDL values should alert clinicians about searching of additional inflammatory pathologies (38-40).

Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (39). However, HDL may become 'dysfunctional' in pathologic conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (39). For example, properties of HDL are compromised in patients with DM by means of the oxidative modification, glycation, and/or transformation of HDL proteomes into proinflammatory proteins. Additionally, the drugs increasing HDL values in the plasma such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, or stroke (41). In other definition, HDL may just be some indicators instead of being the main actors of the human health. Similarly, BMI, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence of DM was only 3.1% between these values against 22.2% outside these limits (42). Similar to the present study, FPG and HDL were also suppressed in sickle cell diseases (SCD), probably due to the severe inflammatory nature of the diseases (43). Smoking may reduce HDL in the plasma due to the systemic inflammatory effects on vascular endothelium. On the other hand, plasma triglycerides were the only lipids those were not suppressed in pathological weight losses in the body. For example, plasma triglycerides were not decreased instead increased in contrast to the suppressed body weight and BMI in the SCD (44). Similarly, prevalences of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in the other study (45). On the other hand, the greatest number of deteriorations in the metabolic parameters was observed just above the plasma triglycerides value of 60 mg/dL (46).

As a conclusion, smoking causes a low-grade systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in the body. Plasma triglycerides, LDL, ESR, and CRP may be positive whereas HDL and FPG negative APR indicating the inflammatory effects of smoking in the human body.

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