

POSITIVE AND NEGATIVE ACUTE PHASE REACTANTS IN SMOKERS

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Received: May 2022; Accepted: June 2022; Published: July 2022

Citation: Helvaci M R et al. Positive and negative acute phase reactants in smokers. Middle East Journal of Nursing 2022; 16(2): 42 - 48. DOI: 10.5742/MEJN2021.9378026

Abstract

Background: We tried to understand whether or not there are some positive and negative acute phase reactants (APR) indicating the possible inflammatory effects of smoking on vascular endothelium.

Method: Consecutive daily smokers at least with a history of one pack-year 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, or heart failure were excluded.

Results: The study included 247 smokers (173 males) and 167 non-smokers. Interestingly, the mean age of the smokers was 46.2 years, and 70.0% of them were males. Although the mean body weight, body mass index, systolic and diastolic blood pressures, and hematocrit values were similar in both groups, plasma triglycerides (163.1 versus 151.3 mg/dL, p<0.05), low density lipoproteins (LDL) (123.8 versus 117.5 mg/dL, p<0.05), erythrocyte sedimentation rate (ESR) (10.6 versus 9.3 mm/h, p<0.05), and C-reactive protein (CRP) (2.3 versus 2.0 mg/L, p<0.05) values

were all higher in the smokers, significantly. On the other hand, high density lipoproteins (HDL) (40.9 versus 44.0 mg/dL, p<0.05) and fasting plasma glucose (FPG) (102.3 versus 111.6 mg/dL, p= 0.007) values and prevalence of diabetes mellitus (8.9% versus 14.3%, p<0.05) were all lower in the smokers, significantly.

Conclusion: Smoking may cause a low-grade systemic inflammation on vascular endothelium terminating with an accelerated atherosclerotic process-induced end-organ insufficiencies all over the body. Plasma triglycerides, LDL, ESR, and CRP may be positive whereas HDL and FPG may be negative APR indicating such inflammatory effects in the 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 builds up 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. They are also important for generation of vasoactive hormones such as angiotensin II. An endothelial dysfunction linked to an imbalance between the synthesis and release of these endothelial factors may explain the initiation of several cardiovascular pathologies including hypertension (HT) and atherosclerosis. On the other hand, overweight and obesity, smoking, and alcohol are well-known causes of chronic endothelial inflammation terminating with an accelerated atherosclerotic process-induced end-organ insufficiencies in the human body (1, 2). Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in the human being. 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. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical 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, and finally early aging and premature death (3). Although early withdrawal of the accelerating factors may delay such 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 titles of the metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the medical literature, extensively (4, 5). We tried to understand whether or not there are some positive and negative acute phase reactants (APR) indicating the possible inflammatory effects of smoking on the vascular endothelium all over the body.

Material and methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupınar University between August 2005 and March 2007. Consecutive daily smokers at least with a history of one pack-year 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. Cases with an overnight FPG level of 126 mg/dL or higher on two occasions were defined as diabetics. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 125 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM (6). Eventually, all smokers were collected into the first, and age and sex-matched non-smokers were collected into the second groups. Mean body weight, BMI, systolic and diastolic BP, triglycerides, LDL, HDL, FPG, ESR, CRP, and hematocrit values and prevalences of DM 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 247 smokers (74 females and 173 males) and 167 non-smokers (55 females and 112 males). Interestingly, the mean age of the smokers was 46.2 years, and 70.0% of them were males. Although the mean body weight, BMI, systolic and diastolic BP, and hematocrit values were similar in both groups, mean triglycerides (163.1 versus 151.3 mg/dL, $p<0.05$), LDL (123.8 versus 117.5 mg/dL, $p<0.05$), ESR (10.6 versus 9.3 mm/h, $p<0.05$), and CRP values (2.3 versus 2.0 mg/L, $p<0.05$) were all higher in the smokers, significantly. On the other hand, mean HDL (40.9 versus 44.0 mg/dL, $p<0.05$) and FPG values (102.3 versus 111.6 mg/dL, $p=0.007$) and prevalences of DM (8.9% versus 14.3%, $p<0.05$) were lower in the smokers, significantly (Table 1). The smokers had a mean smoking history of 20.5 ± 15.0 (1-100) pack years.

Table 1: Comparison of smokers and non-smokers

Variables	Smokers	p-value	Non-smokers
Number	247		167
<u>Male ratio</u>	<u>70.0% (173)</u>	Ns*	67.0% (112)
Mean age (year)	46.2 ± 13.4 (19-76)	Ns	44.8 ± 15.7 (13-77)
Weight (kg)	76.1 ± 13.8 (44-118)	Ns	74.7 ± 13.0 (45-122)
BMI† (kg/m ²)	26.6 ± 4.4 (16.2-39.4)	Ns	26.5 ± 4.5 (16.6-41.1)
Systolic BP‡ (mmHg)	127.5 ± 23.7 (80-200)	Ns	130.0 ± 22.6 (80-200)
Diastolic BP (mmHg)	88.0 ± 12.4 (60-130)	Ns	88.5 ± 11.9 (60-130)
<u>Triglycerides (mg/dL)</u>	<u>163.1 ± 101.4 (40-585)</u>	<u><0.05</u>	<u>151.3 ± 86.2 (20-410)</u>
<u>LDL§ (mg/dL)</u>	<u>123.8 ± 34.3 (10-282)</u>	<u><0.05</u>	<u>117.5 ± 29.0 (43-185)</u>
<u>HDL (mg/dL)</u>	<u>40.9 ± 9.6 (26-70)</u>	<u><0.05</u>	<u>44.0 ± 9.4 (24-70)</u>
<u>FPG** (mg/dL)</u>	<u>102.3 ± 25.5 (70-309)</u>	<u>0.007</u>	<u>111.6 ± 37.6 (74-327)</u>
<u>ESR*** (mm/h)</u>	<u>10.6 ± 10.2 (1-51)</u>	<u><0.05</u>	<u>9.3 ± 8.0 (1-35)</u>
<u>CRP**** (mg/L)</u>	<u>2.3 ± 2.6 (0-13)</u>	<u><0.05</u>	<u>2.0 ± 2.5 (0-12)</u>
Hematocrit (%)	41.9 ± 4.6 (28-60)	Ns	41.0 ± 3.7 (31-49)
<u>DM*****</u>	<u>8.9% (22)</u>	<u><0.05</u>	<u>14.3% (24)</u>

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

*****Diabetes mellitus

Discussion

Excess weight may be the most common cause of vasculitis all over the world. Obesity may be one of the terminal consequences of the metabolic syndrome. It usually starts to develop just after infancy (7), and after such a long period of development, pharmaceutical and nonpharmaceutical approaches provide transient benefits 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 (8). The chronic low-grade inflammation may cause genetic changes on the endothelial cells, and additionally the systemic atherosclerotic process may even decrease clearance of the malignant cells. The effects of excess weight on the BP were shown in the medical literature, extensively (9). For instance, 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) (10). So the dominant underlying cause of the metabolic syndrome appears as gaining weight, 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 (11). 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 metabolic syndrome (12-15). According to our experiences, excess weight may actually be a consequence of physical inactivity instead of an

excessive eating habit, thus prevention of weight gain can not be achieved by diet alone (16). Additionally, limitation of excess weight as an excessive fat tissue around the abdomen under the heading of abdominal obesity is meaningless. Actually, it should be defined as overweight or obesity via the BMI since adipocytes function as an endocrine organ, and they release leptin, tumour necrosis factor (TNF)-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines into the plasma (17). The eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with chronic endothelial inflammation, insulin resistance, and elevated BP. 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 terminal consequences of the metabolic syndrome (6).

Smoking may be the second common cause of vasculitis all over the world. It is one of the major risk factors for the atherosclerotic end-organ insufficiencies (18). 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 (19). Some evidences revealed an increased energy expenditure during smoking both on rest and light physical activity (20), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (21). According to an animal study, nicotine may lengthen

intermeal time, and simultaneously decrease amount of meal eaten (22). Additionally, the BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers (23). Smoking may be associated with a postcessation 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 (24). Interestingly, the mean body 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 prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females (25). Beside that, the incidence of myocardial infarction is increased six-fold in women and three-fold in men who smoked at least 20 cigarettes per day (26). 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 (18). 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 by means of several underlying mechanisms (27). 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 (28, 29). 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 urease. Similarly, urolithiasis was detected in 17.9% of cases with the IBS, whereas this ratio was just 11.6% in cases without the IBS ($p<0.01$) (28).

Alcohol may be the third common cause of vasculitis all over the world. It is addictive to humans, and can result in alcohol use disorder (AUD), dependence, and withdrawal. 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 and injuries (30). For instance, people hospitalized with AUD have an average life expectancy of 47-53 years in men and 50-58 years in women (31). In another definition, they die 24-28 years earlier than the general population (31). People with AUD have three-fold higher mortality in men and four-fold higher mortality in women (32). 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 consumption (8). Women are generally more sensitive to the harmful effects of alcohol, primarily due to the lower body weight, lower capacity to metabolize alcohol, and higher body fat. Alcohol can damage the liver and brain, and it is one of the major leading causes of cancers all over the world (30). Continued alcohol consumption leads to cell death in liver, scarring, cirrhosis, and hepatocellular carcinoma. Prolonged heavy consumption may even cause permanent brain damage. Alcohol may even cause loss of consciousness and rapid death in high amount. 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 of the brain. Alcohol causes happiness and euphoria, decreases anxiety, increases sociability, and induces sedation, impairment of cognitive, memory, motor, and sensory functions, and terminates with generalized depression of the central nervous system. Drinking in pregnancy may terminate with fetal disorders, since ethanol is classified as a teratogen. Similarly, alcohol is a major contributing factor of elevated triglycerides in the plasma. Plasma triglycerides may be one of the most sensitive APR in the body (9). Although the cases with regular alcohol consumption were excluded, plasma triglycerides were higher in the smokers in the present study (163.1 versus 151.3 mg/dL, $p<0.05$), indicating the inflammatory effects of smoking in the human body.

The acute phase response occurs in case of infections, infarctions, foreign bodies, autoimmune disorders, allergies, neoplasms, traumas, or burn-like stresses of the body. Certain mediators known as APR are increased or decreased during the acute phase response (33, 34). These mediators are frequently used in the 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. Plasma concentrations of the positive and negative APR increase or decrease during an acute phase response, respectively. The acute phase response is predominantly mediated by the pro-inflammatory cytokines including TNF-alpha, interleukin (IL)-1, and IL-6 secreted by immune cells. In case of inflammations, infections, or tissue damages, neutrophils and macrophages release such cytokines into the circulation. The liver and various organs respond to the cytokines by producing several positive APR.

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 inflammations were resolved. Measurement of CRP is a useful indicator of inflammations in the body. It correlates with ESR, but not always sensitively. 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 inflammatory or infectious stimulus in the body. 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 negative APR is also used as an indicator of inflammations in the body. Suppression of the synthesis of such negative APR may actually 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 (35). Similarly, triglycerides, DM, and CHD were higher in patients with plasma HDL values of lower than 40 mg/dL, significantly (35). 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 (9). Additionally, plasma triglycerides increased whereas HDL decreased during infections (36). On the other hand, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke in the other study (37). Similarly, the highest prevalences of HT and DM parallel to the increased values of LDL and HDL, and the highest prevalences 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 (38). 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 (9). The increased plasma LDL, parallel to the triglycerides, ESR, and CRP, in contrast to the decreased HDL and FPG may also be an indicator of the low-grade nature of smoking-induced inflammation in the present study. According to the above observations, if the smoking-induced inflammation has been severe enough, plasma LDL values had been suppressed, too. In another definition, HDL and FPG may be more sensitive than LDL for suppression in the acute phase response.

Lower HDL values should alert physicians about searching of additional inflammatory pathologies (39-41). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (40). However, HDL may become 'dysfunctional' in pathologic conditions in which relative compositions of lipids and proteins, as well

as the enzymatic activities of HDL are altered (40). For example, properties of HDL are compromised in patients with DM via the oxidative modification, glycation, 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, and stroke (42). In other definition, HDL may just be 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 (43). Similar to the present study, FPG and HDL were also suppressed in sickle cell diseases (SCD), probably due to the severe inflammatory nature of such diseases (44). Smoking may reduce HDL due to the systemic inflammatory effects on vascular endothelium. On the other hand, plasma triglycerides are the only lipids those are not suppressed in pathological weight losses (45). For example, plasma triglycerides were not decreased, instead increased in contrast to the suppressed body weight and BMI in the SCD (45). Similarly, prevalences of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) (46). 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 (47).

The body's homeostatic mechanism keeps blood glucose levels within a narrow range. There are two groups of mutually antagonistic hormones affecting the blood glucose levels. Glucagon, cortisol, and catecholamines are the catabolic hormones increasing the blood glucose, whereas insulin is the anabolic hormone decreasing the blood glucose levels. Glucagon is secreted from the alpha cells, while insulin is secreted from the beta cells of pancreatic islets which are the bundles of endocrine tissues. They regulate the blood glucose levels together through a negative feedback mechanism. When the blood glucose level is too high, insulin tells muscles to take up excess glucose for storage. When the blood glucose level is too low, glucagon informs the tissues to produce more glucose. Glucagon and insulin are secreted into the portal vein, and extracted from the portal vein by the liver. Epinephrine prepares the muscles and respiratory system for a 'fight to fight' response. Cortisol prepares the body for the stresses. Glucose is stored in the skeletal muscles and hepatocytes in the form of glycogen. There are approximately 100 and 400 grams of glycogen stored in the skeletal muscles and liver in the human body, respectively (48). A blood glucose level of four grams, or about a teaspoon, is critical for the normal function of millions of cells in the body (48). The brain consumes about 60% of the blood glucose in fasting. The four grams of glucose circulates in the blood stream of a person with a body weight of 70 kg. This amount is kept constant with a sophisticated control mechanism in the body. The constant blood glucose levels are maintained via the hepatic and muscular glycogen stores at fasting. FPG, which is measured after a fast of 8 hours, is the most commonly used indication of overall

glucose homeostasis. Infections, inflammations, surgical operations, depressions, alcohol, smoking, and various stresses may affect the blood glucose homeostasis. For example, smoking was negatively associated with FPG and type 2 DM in Chinese men of normal weight, but no significant association was found in men with excess weight or in women (49). On the other hand, smoking was positively associated with nonfatal stroke, particularly in patients with type 2 DM (49). Similarly, smokers have a lower likelihood of newly-diagnosed DM among Chinese males with a lower BMI (50). Parallel to the above results, mean FPG value (102.3 versus 111.6 mg/dL, p= 0.007) and prevalence of DM (8.9% versus 14.3%, p<0.05) were also lower in the smokers in the present study.

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

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