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What a Lower Value of Fasting Plasma Glucose in Smokers

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Abstract

There may be a significant relationship between smoking and fasting plasma glucose (FPG) in the human body. Consecutive daily smokers at least for a period of six months and age and sex-matched non-smokers were included 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 from the study. The study included 150 smokers (99 males) and 162 non-smokers. The mean age of smokers was 45.9 years, and 66.0% of them were male. Although the mean body weight, body mass index, systolic and diastolic blood pressures, and hematocrit values were similar in both groups, FPG value was lower in the smokers (101.9 versus 111.9 mg/dL, $p<0.01$), significantly. Similarly, high density lipoproteins (HDL) value was lower in the smokers (41.1 versus 44.0 mg/dL, $p<0.05$), again. On the other hand, 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. Smoking causes a low-grade systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies all over the body. FPG and HDL may be negative whereas triglycerides, LDL, ESR, and CRP positive acute phase reactants indicating the inflammatory effects of smoking in the human body.

Keywords: *smoking; fasting plasma glucose; high density lipoproteins; triglycerides; low density lipoproteins; erythrocyte sedimentation rate; C-reactive protein*

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 main actor in immunology, inflammation, angiogenesis, and 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 may also be important for generation of vasoactive hormones such as angiotensin II. An endothelial dysfunction linked to the imbalance between the synthesis and release of these endothelial factors may explain initiations of hypertension (HT) and atherosclerosis. On the other hand, excess weight, smoking, and alcohol are obvious causes of chronic endothelial inflammation terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in the body (1). Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies (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. 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, 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 is a significant relationship between smoking and fasting plasma glucose (FPG) in the present study.

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 hypothyroidism, or heart failure were excluded. A routine checkup procedure including hemogram, chronic renal failure, cirrhosis, COPD, hyper- or erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 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 cases with 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 body 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 (99 males and 51 females) and 162 non-smokers (107 males and 55 females). The mean age of the smokers was 45.9 years, and 66.0% of them were male. Although the mean body weight, BMI, systolic and diastolic BP, and hematocrit values were similar in both groups, the mean FPG value was lower in the smokers (101.9 versus 111.9 mg/dL, p<0>p<0> On the other hand, mean triglycerides (163.3 versus 151.8 mg/dL, p<0>p<0>p<0>p<0>Table 1).

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 all over the body, 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). Because the chronic low-grade inflammation may cause genetic changes on the endothelial cells, and the systemic atherosclerosis may decrease clearance of malignant cells, effectively. The effects of excess weight on BP were shown in the medical literature, extensively (8). For instance, prevalence of sustained normotension (NT) was higher in the underweight than the normal weight (80.3% versus 64.0%, *p*<0>p<0>p<0>.

After the excess weight, smoking may be the second common cause of vasculitis all over the body. It is one of the major risk factors for the atherosclerotic end-organ insufficiencies (14). 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 in the medical literature.

Table 1: Comparison of cases with smoking and without

Variables	Smokers	p-value	Non-smokers
Number	*150*		*162*
Male ratio	*66.0%*	*Ns**	*66.0%*
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/m^2)	*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)*
Hematocrit (%)	*41.6 ± 5.1 (28-60)*	*Ns*	*41.0 ± 3.7 (31-49)*
FPG§ (mg/dL)	*101.9 ± 25.8 (70-309)*	*<0.01*	*111.9 ± 38.1 (74-327)*
HDL‖ (mg/dL)	*41.1 ± 9.5 (26-70)*	*<0.05*	*44.0 ± 9.5 (24-70)*
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)*
*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)*

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

Besides the obvious atherosclerotic effects of smoking, some studies reported that smoking in human being and nicotine administration in animals are associated with lower BMI values (15). Some evidences revealed an increased energy expenditure during smoking both on rest and light physical activity (16), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (17). According to an animal study, nicotine may lengthen intermeal time, and simultaneously decrease amount of meal eaten (18). Additionally, the BMI seems to be the highest in the former, the lowest in the current, and medium in never smokers (19). Smoking may be associated with a postcessation weight gain, but evidences suggest that risk of weight gain is the highest during the first year after quitting, and decreases with the following years (20). 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 (21). 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 (22). In another word, smoking may be more dangerous for women about the atherosclerotic end-points probably due to the higher BMI and its consequences in them. As also observed in the present study, smoking is consistently higher in men in the medical literature (14). Several toxic substances found in cigarette smoke get into the circulation mainly by means of the respiratory tract, and cause a vascular endothelial inflammation all over the body. On the other hand, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis (23-25). There may be several underlying mechanisms to explain these associations in smokers (23). First of all, smoking may have some antidepressant properties with several side effects. Secondly, 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 urolithiasis and components of IBS including loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis, too (24, 25). Fourthly, smoking-induced sympathetic nervous system activation may cause motility disorders in the gastrointestinal and genitourinary tracts terminating with IBS and urolithiasis. 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. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with bacteria those have the enzyme, urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with IBS and in 11.6% of cases without in the other study (p<0>

After the excess weight and smoking, alcohol may be the third common cause of vasculitis all over the body. Alcohol is the only drug that mostly damaged the other people. It is causally associated with more than 200 different pathologies (26). For instance, 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 others (27). People with AUD have three-fold higher mortality in men and four-fold in women (28). Similar to the smoking, alcohol may be more dangerous for women about the atherosclerotic end-points probably due to the higher BMI and its consequences in them, again. 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 (27, 28). Women are generally more sensitive to the harmful effects of alcohol, primarily due to their smaller body weight, lower capacity to metabolize alcohol, and higher proportion of fat in the body. Its consumption is one of the major leading causes of cancers all over the body (26). Alcohol can cause unconsciousness and death in high amounts. Hepatic alcohol dehydrogenase is the main enzyme to metabolize alcohol that requires the cofactor, nicotinamide adenine dinucleotide (NAD). 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. Eventually, prolonged exposure of alcohol causes fatty liver. Acetaldehyde is subsequently metabolized by the aldehyde dehydrogenase into acetate that in turn is broken down into carbon dioxide and water. Ethanol is the only alcohol that is found in alcoholic beverages. Ethanol crosses biological membranes and blood-brain barrier by means of passive diffusion, easily. Alcohol works by increasing effects of the gamma aminobutyric acid in the brain, primarily. This is the major inhibitory neurotransmitter of the brain. Alcohol induces happiness and euphoria, decreased anxiety, increased sociability, sedation, generalized depression of central nervous system, and impairment of cognitive, memory, motor, and sensory functions. It may cause fetal disorders in pregnancy because ethanol is classified as a teratogen. Alcohol is addictive to humans, and can result in AUD, dependence, and withdrawal. Regular alcohol consumption leads to cell death in liver, scarring, cirrhosis, and hepatocellular carcinoma. Heavy alcohol consumption may even terminate with permanent brain damage. Similarly, alcohol is a major contributing factor of elevated triglycerides. It is obvious that triglycerides are sensitive acute phase reactants (APR) in the plasma (10). Although the cases with regular alcohol consumption were excluded, plasma triglycerides were higher in the smokers in the present study (163.3 versus 151.8 mg/dL, $p<0>$

An 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 response (29, 30). 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 the 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 inflammation, clinically. It correlates with ESR, but not always simultaneously, since ESR is largely dependent upon elevation of fibrinogen with a half-life of one week, approximately. Therefore 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 suppressions of such APR are also used as the indicators of inflammation 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 (31). Similarly, triglycerides, DM,

and CHD were all higher in patients with plasma HDL values of lower than 40 mg/dL, significantly (31). 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 (10). Additionally, plasma triglycerides increased whereas HDL decreased during infections (32). On the other hand, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke (33). 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 (34). 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 (10). Parallel to ESR and CRP, plasma triglycerides and LDL may behave as positive whereas FPG and HDL 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 in the body (35, 36).

Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (37). 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 (37). 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 (38). 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

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