American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Research Article

Smoking Causes a Moderate or Severe Inflammatory Process in Human Body

Mehmet Rami Helvaci[1]*, Yasemin Kayabasi[2], Ozlem Celik[3], Huseyin Sencan[4], Abdulrazak Abyad[5] and Lesley Pocock[6]

[1]*Specialist of Internal Medicine, Turkey*

[2]*Manager of Writing and Statistics, Turkey*

[3]*Ministry of Health of Turkey, Turkey*

[4]*Middle-East Academy for Medicine of Aging, Turkey*

[5]*Medi-WORLD International, Turkey*

[6]*Mehmet Rami Helvaci, Turkey*

***Corresponding author:** Mehmet Rami Helvaci, Specialist of Internal Medicine, 07400, ALANYA, Turkey.

To Cite This Article: *Mehmet Rami H, Yasemin K, Ozlem C, Huseyin S, Abdulrazak A, et al. Smoking Causes a Moderate or Severe Inflammatory Process in Human Body. Am J Biomed Sci & Res. 2023 17(6) AJBSR.MS.ID.002416,* DOI: 10.34297/AJBSR.2023.17.002416

Received: December 29, 2022; **Published:** January 26, 2023

Abstract

Background: We tried to understand severity of smoking-induced inflammation on vascular endothelium in the process of metabolic syndrome.

Methods: Current daily smokers at least for the last six months and age and sex-matched non-smokers were included into the study. Patients with current alcohol consumption (one drink a day) and patients with malignancies or inflammatory, infectious, or devastating disorders were excluded from the study.

Results: The study included 247 smokers (173 males) and 167 non-smokers. The mean age of smokers was 46.2 years, and 70.0% 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, fasting plasma glucose (FPG) (102.3 versus 111.6mg/dL, p= 0.007) and high-density lipoproteins (40.9 versus 44.0mg/dL, p<0.05) were lower in the smokers, significantly. Whereas triglycerides (163.1 versus 151.3mg/dL, p<0.05), low density lipoproteins (123.8 versus 117.5mg/dL, p<0.05), erythrocyte sedimentation rate (10.6 versus 9.3mm/h, p<0.05), and C-reactive protein (2.3 versus 2.0mg/L, p<0.05) were higher in the smokers, significantly.

Conclusion: FPG may behave as a positive acute phase reactant (APR) in mild inflammatory disorders such as irritable bowel syndrome but as a negative APR in moderate and severe inflammatory disorders such as smoking, digital clubbing, and sickle cell diseases in human body.

Keywords: ASmoking, Fasting plasma glucose, High density lipoproteins, Triglycerides, Low density lipoproteins, Irritable bowel syndrome, Digital clubbing, Sickle cell diseases

Introduction

The monolayer of endothelial cells that forms the inner lining of arteries, veins, capillaries, and lymphatics is called endothelium. Probably, the whole endothelium all over the body may act as a private organ that may be the largest organ of the body. It may contract vasculature of the peripheral organs while relaxing the internal ones during cold, anxiety, and depression-like stresses. Because we measure the systolic and diastolic blood pressures (BPs) of the arms and legs, they may not show the actual BPs of the brain, heart, lung, liver, and kidney-like internal organs. The endothelium may be the main organ in the control of blood fluidity, platelets aggregation, and vascular tone in the body. It may control vascular tone and blood flow by releasing nitric oxide, reactive oxygen species, and metabolites of arachidonic acid into the circulation. It may also be important for synthesizing of vasoactive hormones such as angiotensin II. An endothelial dysfunction-induced

accelerated atherosclerosis all over the body may be the main cause of end-organ insufficiencies, aging, and death. Such a dysfunction may also be important in the development of cancers by preventing clearance of malignant cells by the natural killers in terminal points of the circulation. Similarly, physical inactivity, animal-rich diet, excess weight, higher BPs and glucose levels, chronic inflammations, prolonged infections, cancers, smoking, and alcohol may be accelerating factors of the chronic endothelial inflammation and dysfunction terminating with the accelerated atherosclerosis-induced end-organ insufficiencies [1]. The much higher BP of the afferent vasculature may be the major accelerating factor by inducing recurrent injuries on the vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore, the term Ven sclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, fibrosis, and dysfunction, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood flow to the terminal organs, and increase systolic and decrease diastolic BPs further. Some of the irreversible endpoints of the systemic inflammatory process are obesity, hypertension (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, aging, and death [2]. Although early withdrawal of the accelerating factors may delay terminal consequences, endothelial changes cannot be reversed, completely after development of the irreversible end-points due to their fibrotic natures. The accelerating factors and irreversible endpoints are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome, extensively [3,4]. We tried to understand severity of smoking-induced inflammation on vascular endothelium in the process of metabolic syndrome.

Material and Methods

The study was performed in the Internal Medicine Clinic of Dubliner University between August 2005 and March 2007. Current daily smokers at least for the last six months were included into the study. Patients with current 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, or heart failure were excluded from the study. A routine checkup procedure including hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting plasma glucose (FPG), total cholesterol, triglycerides, high density lipoproteins (HDL), albumin, creatinine, thyroid function tests, hepatic function tests, markers of hepatitis A, B, C, and human immunodeficiency viruses, a urinalysis, a posterior-anterior chest x-ray graphic, and an electrocardiogram was performed. An additional Doppler echocardiogram and/or abdominal ultrasonography were performed just in case of a requirement. The body mass index (BMI) of everyone was calculated by measurements of the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared [5]. Office BPs were checked after a 5-minute of rest in seated position with mercury sphygmomanometer (ERKA, Germany). Eventually, all smokers were collected into the first, and age and sex-matched non-smokers were collected into the second groups and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Table 1: Comparison of smokers and non-smokers.

Variables	Smokers	P-Value	Non-Smokers
Number	247		167
Male ratio	**70.00%**	Ns*	67.00%
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/m2)	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)
Hematocrit (%)	41.9±4.6 (28-60)	Ns	41.0±3.7 (31-49)
FPG§ (mg/dL)	102.3±25.5 (70-309)	**0.007**	**111.6±37.6 (74-327)**
HDL‖ (mg/dL)	40.9±9.6 (26-70)	**<0.05**	**44.0±9.4 (24-70)**
Triglycerides (mg/dL)	**163.1±101.4 (40-585)**	**<0.05**	151.3±86.2 (20-410)
LDL (mg/dL)**	**123.8±34.3 (10-282)**	**<0.05**	117.5±29.0 (43-185)
ESR* (mm/h)**	**10.6±10.2 (1-51)**	**<0.05**	9.3±8.0 (1-35)
CRP** (mg/L)**	**2.3±2.6 (0-13)**	**<0.05**	2.0±2.5 (0-12)

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

Results

The study included 247 smokers (173 males) and 167 non-smokers (112 males). The mean age of smokers was 46.2 years, and 70.0% of them were male. Although the mean body weight, BMI, systolic and diastolic BPs, and hematocrit values were similar both in smokers and non-smokers, FPG (102.3 versus 111.6mg/dL, p= 0.007) and HDL (40.9 versus 44.0mg/dL, p<0.05) were lower in the smokers, significantly. Whereas triglycerides (163.1 versus 151.3mg/dL, p<0.05), low density lipoproteins (LDL) (123.8 versus 117.5mg/dL, p<0.05), ESR (10.6 versus 9.3mm/h, p<0.05), and CRP (2.3 versus 2.0mg/L, p<0.05) were higher in the smokers, significantly (Table 1).

Discussion

Obesity may be one of the irreversible endpoints of the metabolic syndrome. Although some transient successes can be achieved, nonpharmaceutical approaches provide limited benefit to reverse obesity, permanently. Due to the excess weight-induced chronic low-grade inflammation on the vascular endothelium, the risk of death from all causes including cardiovascular diseases and cancers increases parallel to the range of excess weight in all age groups [6]. The chronic low-grade inflammation may even cause genetic changes in the endothelial cells, and the systemic atherosclerosis may prevent clearance of malignant cells, effectively. Similarly, the effects of excess weight on the BP were shown in the literature, extensively [7]. For example, prevalences of sustained normotension (NT) were higher in the underweight than the normal weight (80.3% versus 64.0%, p<0.05) and overweight groups (80.3% versus 31.5%, p<0.001) (7), and 52.8% of patients with HT had obesity against 14.5% of patients with the sustained NT (p<0.001) [8]. So, the major underlying cause of the metabolic syndrome appears to be weight gain that may be the main cause of insulin resistance, impaired fasting glucose, impaired glucose tolerance, hyperlipoproteinemia's, and white coat hypertension (WCH) [9]. Interestingly, weight gain even before the development of an obvious overweight or obesity may cause development of several components of the syndrome. For example, WCH alone may be a strong indicator of weight gain even before development of excess weight [7,8]. On the other hand, prevention of weight gain with physical activity even in the absence of a prominent weight loss usually results with resolution of many parameters of the syndrome [10]. According to our experiences, excess weight may be a result of physical inactivity instead of an excessive eating habit. Therefore, prevention of weight gain cannot be achieved by diet, alone [11]. On the other hand, limitation of excess weight as an excessive fat tissue around abdomen under the heading of abdominal obesity may be meaningless, instead it should be defined as overweight or obesity by means of the BMI. Because 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 [12]. Eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with insulin resistance, elevated BPs, and chronic endothelial inflammation and dysfunction. Similarly, the Adult Treatment Panel (ATP) III reported that although some people classified just as overweight with larger muscular masses, most of them also have excess fat tissue predisposing to the irreversible endpoints of the metabolic syndrome [5].

Smoking may be the second common cause of disseminated vasculitis in the human body. It may cause a systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies in whole body [13]. Its atherosclerotic effect is the most obvious in Buerger's disease. Buerger's disease is an obliterative vasculitis characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking. As also observed in the present study, FPG and HDL may be negative whereas triglycerides, LDL, ESR, and CRP positive acute phase reactants (APRs) indicating inflammatory effects of smoking on vascular endothelium in the metabolic syndrome. Parallel to the systemic inflammatory and atherosclerotic effects, smoking in human beings and nicotine administration in animals were associated with the lower values of BMI [14]. Some evidence revealed an increased energy expenditure during smoking both on the rest and light physical activity [15]. Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [16]. According to an animal study, nicotine may lengthen intermeal time, and decrease the amount of meal eaten [17]. Smoking may be associated with a post cessation weight gain, but the risk is the highest during the first year, and decreases with the following years [18]. As the opposite findings to the above studies, the body weight and BMI were similar both in the smokers and non-smokers in the present study. Similarly, prevalences of smoking were similar in the normal weight (35.9%), overweight (32.9%), and obesity groups (33.7%, p>0.05 between all) in another study [19]. 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 WCH, BMI, LDL, triglycerides, HT, and DM in females [20]. Beside that the prevalence of myocardial infarctions is increased three-fold in men and six-fold in women who smoked at least 20 cigarettes per day [21]. In another word, smoking may be more dangerous for women about the atherosclerotic endpoints probably due to the higher BMI in them. Several toxic substances found in the cigarette smoke get into the circulation and cause vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually associated with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature [22].

There may be several underlying mechanisms to explain these associations [23]. First, smoking may have some antidepressant properties with several potentially lethal side effects. Secondly, smoking-induced vascular endothelial inflammation may disturb epithelial functions for absorption and excretion in the gastrointestinal and genitourinary tracts which may terminate with urolithiasis and components of the IBS including loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis [24]. Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with the IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with the gastrointestinal and genitourinary tract infections causing loose stool, diarrhea, and urolithiasis, because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits in the urine. 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced during infections with the bacteria producing urease. Parallel to the results above, urolithiasis was detected in 17.9% of cases with the IBS and 11.6% of cases without in the other study ($p<0.01$) [22].

Alcohol may be the third common cause of systemic vasculitis in the human body. It is addictive to humans and can result in alcohol use disorder (AUD), dependence, and withdrawal. Alcohol is causally associated with more than 200 different pathologies including cancers in whole body [25]. Eventually, people hospitalized with 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 [26]. People with AUD have three-fold higher mortality in men and four-fold in women [27]. Like smoking, alcohol may be more dangerous for women about the atherosclerotic endpoints probably due to their lower body mass induced lower capacity to metabolize alcohol and higher body fat. A very substantial part of the Danish excess mortality and lower life expectancy compared to Sweden can be attributed to higher mortality related with alcohol and smoking [26]. It may even cause unconsciousness and sudden death if taken in high amounts. Hepatic alcohol dehydrogenase is the main enzyme to metabolize alcohol that requires the cofactor, nicotinamide adenine dinucleotide (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. Ethanol is the only alcohol that is found in alcoholic beverages. Ethanol crosses biological membranes and blood-brain barriers by means of passive diffusion, easily. Alcohol works particularly by increasing effects of the gamma aminobutyric acid that is the main inhibitory neurotransmitter of the brain. Alcohol causes happiness and euphoria, decreased anxiety, increased sociability, sedation, generalized depression of the central nervous system, and impairment of cognitive, memory, motor, and sensory functions. It may even cause fetal disorders in pregnancy since ethanol is classified as a teratogen. Regular alcohol consumption leads to cell death in the liver, scarring, cirrhosis, and hepatocellular carcinoma. Heavy consumption may even terminate with permanent brain damage. Alcohol is the major contributing factor of elevated triglycerides which are the sensitive APRs in plasma [9]. Although regular alcohol consumers were excluded, plasma triglycerides were higher in the smokers (163.1 versus 151.3mg/dL, $p<0.05$), indicating the inflammatory effects of smoking in the present study.

The acute phase response occurs in case of infection, infarction, cancer, trauma, depression, and burn-like inflammations of the body. Certain mediators known as APRs are increased or decreased during the response [28,29]. These markers are commonly used in clinics as the indicators of acute and chronic inflammations in the body. The terms of acute phase proteins and APRs are usually used synonymously, although some APRs are polypeptides rather than proteins. Positive and negative APRs are those whose concentrations increase or decrease during the acute phase response, respectively. The response is predominantly mediated by the pro-inflammatory cytokines including TNF, interleukin-1, and interleukin-6 secreted by neutrophils and macrophages into the circulation. The liver and other organs respond to the cytokines by producing many positive APRs. ESR, CRP, fibrinogen, ferritin, procalcitonin, hepcidin, haptoglobin, ceruloplasmin, complement proteins, and serum amyloid A are some of the well-known positive APRs. CRP is a useful indicator of the acute phase response, clinically. It is responsible for activation of the complement pathway. CRP reaches up to the maximum concentration within two days and decreases with the resolution of the inflammation with a half-life of 6-8 hours, rapidly. It correlates with ESR, but not simultaneously since ESR is 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.

Similarly, white blood cells and platelets may also behave as positive APRs in the body [30]. On the other hand, productions of the negative APRs are suppressed, simultaneously. Albumin, transferrin, retinol-binding protein, antithrombin, transcortin, alpha-fetoprotein, and hemoglobin are some of the well-known negative APRs in the body. Suppressions of such negative APRs are also used as the indicators of the acute phase response. Suppressions of such negative APRs may actually be secondary to the protection of amino acids and polypeptides required for the production of positive APRs, sufficiently. As also observed in smokers here, production of HDL may also be suppressed in the liver during the acute phase response [31]. Similarly, triglycerides, DM,

and CHD were higher in patients with plasma HDL values of lower than 40mg/dL, significantly [31]. So, HDL may behave as negative whereas triglycerides positive APRs 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 [9]. Additionally, triglycerides increased whereas HDL decreased during infections [32]. On the other hand, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke [33]. Similarly, the highest prevalences of HT and DM parallel to the elevated 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 APRs [34]. Probably, HDL turn to the negative direction much earlier than LDL in the plasma. 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]. Parallel to ESR and CRP, triglycerides and LDL may behave as positive whereas FPG and HDL as negative APRs in smokers in the present study. In another word, lower HDL should alert clinicians for researching of any acute phase response in the body [35,36].

Cholesterol, triglycerides, and phospholipids are the major lipids of the body. They do not circulate in the plasma, freely instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins in the plasma. Chylomicrons carry exogenous triglycerides to the liver via the thorasic duct. Very low density lipoproteins (VLDL) are produced in the liver, and carry endogenous triglycerides to the organs. VLDL are converted into the intermediate density lipoproteins (IDL) by removal of 90% of triglycerides by lipases in the capillaries of adipocytes and muscle tissues. Then the IDL are degraded into LDL by removal of more triglycerides. So VLDL are the main source of LDL in the plasma, and LDL deliver cholesterol from the liver to organs. Although the liver removes majority of LDL from the circulation, a small amount is up taken by scavenger receptors of the macrophages migrating into the arterial walls, and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells including the arterial wall atheroma, and carry the cholesterol back to the adrenals, ovaries, and testes-like steroidogenic organs and liver for excretion, re-utilization, or disposal. All of the carrier lipoproteins are under dynamic control, and are readily affected by diet, drugs, inflammations, infections, cancers, trauma, smoking, alcohol, and excess weight.

Thus lipid analysis should be performed during a steady state. The metabolic syndrome alone is a low-grade inflammatory process, and it may even cause abnormal lipoproteins levels in the plasma. HDL may normally show various anti-oxidative, anti-inflammatory, and anti-atherogenic properties including reverse cholesterol transport [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 the proinflammatory proteins. Additionally, the drugs increasing HDL values such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors cannot reduce all-cause mortality, CHD mortality, myocardial infarction, and stroke [38]. In other words, HDL may just be some indicators instead of being the main actors of the 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 [39]. Similar to the present study, HDL and FPG were also suppressed in the sickle cell diseases (SCDs), probably due to the moderate and severe inflammatory effects of the SCDs on the vascular endothelium in whole body [40]. On the other hand, triglycerides may be the most sensitive APRs in the body [41]. Although ATP II determined the normal plasma triglycerides as lower than 200mg/dL in 1994 [42], World Health Organization in 1999 [43] and ATP III in 2001 reduced the normal limits as lower than 150 mg/dL (5). But there are still suspicions about the safest values of triglycerides in plasma [41]. Besides that, triglycerides are the only lipids which were not suppressed with the pathological weight loss [44]. For example, plasma triglycerides increased in contrast to the decreased body weight and BMI in the SCDs [44]. Similarly, excess weight, DM, HT, and smoking were higher in the hypertriglyceridemia group (200mg/dL and higher) in the other study [45]. Interestingly, the greatest number of deteriorations in the metabolic parameters was observed with triglycerides values of 60mg/dL and higher [41].

The body's homeostatic mechanism keeps blood glucose levels within a narrow range with two groups of mutually antagonistic hormones. 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 through a negative feedback mechanism together. When the blood glucose levels are too high, insulin tells muscles to take up excess glucose for storage. When the blood glucose levels are too low, glucagon informs the tissues to produce more glucose. Catecholamines prepare the muscles and respiratory system for a 'fight to fight' response. Cortisol prepares the body for the various stresses. A blood glucose level of four grams, or about a teaspoon, is critical for the normal function of millions of cells in the body [46]. The four grams of glucose circulate in the blood of a person with a weight of 70 kg. The constant blood glucose levels are maintained via the hepatic and muscular glycogen stores during fasting since glucose is stored in the skeletal muscles and hepatocytes in the form of glycogen.

There are approximately 100 and 400grams of glycogen stored in the skeletal muscles and liver, respectively [46]. The brain consumes about 60% of the blood glucose during fasting. FPG is the most used indication of overall glucose homeostasis, and it is measured after a fasting period of 8 hours. Infections, inflammations, surgical operations, depression, alcohol, and smoking-like stresses may affect the blood glucose homeostasis. For example, smoking was negatively associated with FPG and DM just in Chinese men with the normal weight, but not in men with excess weight or in women [47]. Similarly, smokers have a lower likelihood of newly diagnosed DM in Chinese men with a lower BMI in the other study [48]. Parallel to the above studies, FPG and DM were also lower in the smokers (102.3 versus 111.6mg/dL, p=0.007 and 8.9% versus 14.3%, p<0.05, respectively) [49]. But although majority of the smokers were male, again (70.0%), BMI of the smokers was higher (26.6kg/m2) [49] in contrast to the above studies.

Recurrent upper abdominal discomfort may be the cause of nearly half of applications to the Internal Medicine Clinics [50], and IBS and chronic gastritis may be the most diagnosed disorders in such cases. Flatulence, periods of diarrhea and constipation, repeated toilet visits due to urgent evacuation or early filling sensation, excessive straining, feeling of incomplete evacuation, frequency, urgency, reduced feeling of well-being, and eventually disturbed social life are often reported in cases with IBS. A meaningful dietary role is suspicious in the IBS. Nearly 20% of general population have IBS, and it is more common in females [51]. Psychological factors seem to precede onset and exacerbation of gut symptoms, and many potentially psychiatric disorders including anxiety, depression, sleep disorders, illness fear, cancer fear, or death fear usually coexist with the IBS [52]. For example, thresholds for sensations of initial filling, evacuation, urgent evacuation, and utmost tolerance recorded via a rectal balloon significantly decreased by focusing the examiners' attention on gastrointestinal stimuli by reading pictures of gastrointestinal malignancies in patients with the IBS [53]. In other words, although IBS is described as a physical disorder according to Rome II guidelines, psychological factors may be crucial for triggering of these physical changes in the body. Eventually, IBS may even terminate with chronic gastritis, urolithiasis, and hemorrhoids [54]. Similarly, some authors studied the role of inflammation in the IBS via colonic biopsies in 77 patients [55]. Although 38 patients had normal histology, 31 patients demonstrated microscopic inflammation, and eight patients fulfilled criteria for lymphocytic colitis. However, immunohistology revealed increased intraepithelial lymphocytes as well as increased CD3 and CD25 positive cells in lamina propria of the group with "normal" histology. These features were more evident in the microscopic inflammation group who additionally revealed increased neutrophils, mast cells, and natural killers. All these immunopathological abnormalities were the most evident in the lymphocytic colitis group who also demonstrated HLA-DR staining in the crypts and increased CD8 positive cells in the lamina propria [55]. A direct link between the immunologic activation and IBS symptoms was shown by some other authors, too [56]. They demonstrated not only an increased mast cell degranulation in the colon but also a direct correlation between proximity of mast cells to neuronal elements and severity of pain in the IBS [56]. In addition to above findings, there are some evidence of extension of the inflammatory process behind the mucosa. Some authors addressed this issue in ten patients with severe IBS by examining full thickness jejunal biopsies [57]. They detected a low-grade infiltration of lymphocytes in myenteric plexus of nine patients, four of whom had an associated increase in intraepithelial lymphocytes and six demonstrated evidence of neuronal degeneration [57]. Nine patients had hypertrophy of longitudinal muscles, and seven had abnormalities in number and size of interstitial cells of Cajal [57]. The finding of intraepithelial lymphocytosis was also seen in the colon [55] and duodenum [58]. Beside that FPG (111.9 versus 105.4mg/dL, p= 0.002) and triglycerides (167.0 versus 147.3mg/dL, p= 0.013) were higher in the IBS cases [59]. Because plasma triglycerides are well-known APRs, the additionally increased FPG in the IBS cases may show the fact that FPG may behave as a positive APR in the body [59], and IBS may be a mild inflammatory process affecting various organ systems of the body [60].

Digital changes may help to identify some systemic disorders in human body. Digital clubbing is a deformity of the fingers and fingernails that is known for a long time. It is characterized by bulbous enlargement of the distal phalanges due to the increase in soft tissue. Digital clubbing develops in the following steps; fluctuation and softening of the nailbed, loss of normal angle between the nailbed and fold which is lower than 165°, increased convexity of the nail fold, thickening of the whole distal finger, and shiny aspect and striation of the nail and skin [61]. Schamroth's window test is a popular test for the diagnosis of digital clubbing [62]. When the distal phalanges of corresponding fingers of opposite hands are directly opposed, a small diamond-shaped 'window' is apparent between the nailbeds, normally. If this window is obliterated, the test is positive and digital clubbing is present. The clubbing may be associated with pulmonary, cardiac, and hepatic disorders that are featuring with chronic tissue hypoxia (tuberculosis, bronchiectasis), hypothyroidism, gastrointestinal and hepatobiliary disorders (malabsorption, Crohn's disease, ulcerative colitis, cirrhosis), thymoma, thalassemia, and human immunodeficiency virus infection [63-66]. But there was not any underlying diagnosis in 60% of cases [67]. Additionally, the exact prevalence of digital clubbing in the population is unknown. The above study detected digital clubbing just in 0.9% of all patients admitted to the Department of Internal Medicine, and 66.6% of the clubbing cases were male [67]. Probably due to the higher

prevalence of smoking in males [68], the great gender differences were observed in the clubbing. Interestingly, prevalences of cirrhosis (25.0% versus 1.6%, p<0.001), leg ulcers (33.3% versus 11.9%, p<0.001), pulmonary hypertension (27.7% versus 9.6%, p<0.001), COPD (38.8% versus 12.1%, p<0.001), CHD (27.7% versus 12.1%, p<0.01), and stroke (27.7% versus 6.9%, p<0.001) were all higher in the digital clubbing group in patients with the SCDs [69]. So digital clubbing is an indicator of a severe inflammatory process in the body.

SCDs are chronic inflammatory processes on vascular endothelium, initiated at birth and terminated with an accelerated atherosclerosis induced end-organ failures in early years of life [70,71]. Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of the shape is the main problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, and depression-like various stresses of the body. The hardened RBCs induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body [72]. As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level [73,74] since the capillary system is the main distributor of the hardened RBCs into the tissues. The hardened RBCs induced chronic endothelial damage builds up an advanced atherosclerosis in early years of life. Vascular narrowing and occlusions induced tissue ischemia and infarctions are the final consequences, so the mean life expectancy is decreased by 25 to 30 years in both genders in the SCDs [71]. Due to the severity of inflammation of the SCDs, the weight, BMI, FPG, HDL, LDL, systolic and diastolic BPs, and hematocrit values suppressed as some negative APRs, significantly [40].

Conclusion

As a conclusion, FPG may behave as a positive APR in mild inflammatory disorders such as the IBS but as a negative APR in moderate and severe inflammatory disorders such as smoking, digital clubbing, and SCDs in human body.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Helvaci MR, Kaya H, Borazan A, Ozer C, Seyhanli M, et al. (2008) Metformin and parameters of physical health. Intern Med 47(8): 697-703.
2. Helvaci MR, Algin MC, Abyad A, Pocock L (2018) Physical inactivity or an excessive eating habit. Middle East J Nursing 12(1): 14-18.
3. Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. Lancet 365(9468): 1415-1428.
4. Helvaci MR, Ayyildiz O, Muftuoglu OE, Yaprak M, Abyad A (2017) Aging syndrome. World Family Med 15(3): 39-42.
5. (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106(25): 3143-3421.
6. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr (1999) Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 341(15): 1097-1105.
7. Helvaci MR, Kaya H, Yalcin A, Kuvandik G (2007) Prevalence of white coat hypertension in underweight and overweight subjects. Int Heart J 48(5): 605-613.
8. Helvaci MR, Kaya H, Duru M, Yalcin A (2008) What is the relationship between white coat hypertension and dyslipidemia? Int Heart J 49(1): 87-93.
9. Helvaci MR, Yapyak M, Tasci N, Abyad A, Pocock L (2020) The most desired values of high and low density lipoproteins and triglycerides in the plasma. World Family Med 18(8): 21-27.
10. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi T, Azizi F (2005) Beneficial effects of a Dietary Approaches to Stop Hypertension eating plan on features of the metabolic syndrome. Diabetes Care 28(12): 2823-2831.
11. Helvaci MR, Ayyildiz O, Gundogdu M, Aydin Y, Abyad A (2019) Body mass and blood pressure. World Family Med 17(1): 36-40.
12. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, et al. (1999) Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 38(2): 202-206.
13. Fodor JG, Tzerovska R, Dorner T, Rieder A (2004) Do we diagnose and treat coronary heart disease differently in men and women? Wien Med Wochenschr 154(17-18): 423-425.
14. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, et al. (1992) National working conference on smoking and body weight. Task Force 1: Mechanisms relevant to the relations between cigarette smoking and body weight. Health Psychol 11: 4-9.
15. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ (1999) The effect of smoking on energy expenditure and plasma catecholamine and nicotine levels during light physical activity. Nicotine Tob Res 1(4): 365-370.
16. Hughes JR, Hatsukami DK (1997) Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. J Subst Abuse 9: 151-159.
17. Miyata G, Meguid MM, Varma M, Fetissov SO, Kim HJ (2001) Nicotine alters the usual reciprocity between meal size and meal number in female rat. Physiol Behav 74(1-2): 169-176.
18. Froom P, Melamed S, Benbassat J (1998) Smoking cessation and weight gain. J Fam Pract 46(6): 460-464.
19. Helvaci MR, Altintas E, Yalcin A, Muftuoglu OE, Abyad A (2023) Smoking may not prevent overweight or obesity. World Family Med.
20. Helvaci MR, Kaya H, Gundogdu M (2012) Gender differences in coronary heart disease in Turkey. Pak J Med Sci 28(1): 40-4.
21. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J (1998) Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 316(7137): 1043-1047.

22. Helvaci MR, Kabay S, Gulcan E (2006) A physiologic events' cascade, irritable bowel syndrome, may even terminate with urolithiasis. J Health Sci 52(4): 478-481.

23. Helvaci MR, Dede G, Yildirim Y, Salaz S, Abyad A (2019) Smoking may even cause irritable bowel syndrome. World Family Med 17(3): 28-33.

24. Helvaci MR, Algin MC, Kaya H (2009) Irritable bowel syndrome and chronic gastritis, hemorrhoid, urolithiasis. Eurasian J Med 41(3): 158-161.

25. Rehm J (2014) Alcohol and mortality. Alcohol Res 35(2): 174-83.

26. Juel K (2008) Life expectancy and mortality in Denmark compared to Sweden. What is the effect of smoking and alcohol? Ugeskr Laeger 170(33): 2423-2427.

27. Westman J, Wahlbeck K, Laursen TM, Gissler M, Nordentoft M, et al. (2015) Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland, and Sweden. Acta Psychiatr Scand 131(4): 297-306.

28. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340(6): 448-454.

29. Wool GD, Reardon CA (2007) The influence of acute phase proteins on murine atherosclerosis. Curr Drug Targets 8(11): 1203-1214.

30. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I (2014) Platelet and white blood cell counts in severity of sickle cell diseases. Health MED 8(4): 477-482.

31. Helvaci MR, Abyad A, Pocock L (2020) High- and low-density lipoproteins may be negative acute phase proteins of the metabolic syndrome. Middle East J Nursing 14(1): 10-16.

32. Pirillo A, Catapano AL, Norata GD (2015) HDL in infectious diseases and sepsis. Handb Exp Pharmacol 224: 483-508.

33. Ma C, Na M, Neumann S, Gao X (2019) Low-density lipoprotein cholesterol and risk of hemorrhagic stroke: a systematic review and dose-response meta-analysis of prospective studies. Curr Atheroscler Rep 21(12): 52.

34. Helvaci MR, Abyad A, Pocock L (2020) The safest values of low density lipoproteins in the plasma. World Family Med 18(4): 18-24.

35. Toth PP (2005) Cardiology patient page. The good cholesterol: high-density lipoprotein. Circulation 111(5): 89-91.

36. Ertek S (2018) High-density lipoprotein (HDL) dysfunction and the future of HDL. Curr Vasc Pharmacol 16(5): 490-498.

37. Femlak M, Gluba Brzózka A, Cialkowska Rysz A, Rysz J (2017) The role and function of HDL in patients with diabetes mellitus and the related cardiovascular risk. Lipids Health Dis 16(1): 207.

38. Keene D, Price C, Shun Shin MJ, Francis DP (2014) Effect on cardiovascular risk of high-density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. BMJ 349: 4379.

39. Helvaci MR, Abyad A, Pocock L (2020) What a low prevalence of diabetes mellitus between the most desired values of high-density lipoproteins in the plasma. World Family Med 18(7): 25-31.

40. Helvaci MR, Altintas E, Yalcin A, Muftuoglu OE, Abyad A (2022) Positive and negative acute phase reactants in sickle cell diseases. World Family Med 20(3): 36-42.

41. Helvaci MR, Abyad A, Pocock L (2020) The safest upper limit of triglycerides in the plasma. World Family Med 18(1): 16-22.

42. (1994) National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 89(3): 1333-1445.

43. (1999) World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation.

44. Helvaci MR, Salaz S, Yalcin A, Muftuoglu OE, Abyad A (2021) Cholesterol may be a negative whereas triglycerides positive acute phase reactants in the plasma. Asclepius Med Res Rev 4(1): 1-8.

45. Helvaci MR, Aydin LY, Maden E, Aydin Y (2011) What is the relationship between hypertriglyceridemia and smoking? Middle East J Age and Ageing 8(6).

46. Wasserman DH (2009) Four grams of glucose. Am J Physiol Endocrinol Metab 296(1): E11-21.

47. Wang S, Chen J, Wang Y, Yang Y, Zhang D, et al. (2019) Cigarette smoking is negatively associated with the prevalence of type 2 diabetes in middle-aged men with normal weight but positively associated with stroke in men. J Diabetes Res:1853018.

48. Hou X, Qiu J, Chen P, Lu J, Ma X, et al. (2016) Cigarette smoking is associated with a lower prevalence of newly diagnosed diabetes screened by OGTT than non-smoking in Chinese Men with normal weight. PLoS One 11(3): e0149234.

49. Helvaci MR, Kayabasi Y, Celik O, Dede G, Abyad A, et al. (2023) What a lower prevalence of diabetes mellitus but higher incidence of dyslipidemia in smokers. World Family Med (in press).

50. Valenkevich LN, Iakhontov OI (2004) Modern myths of clinical gastroenterology. Eksp Klin Gastroenterol 105(3): 72-74.

51. Rhee PL (2006) Definition and epidemiology of irritable bowel syndrome. Korean J Gastroenterol 47(2): 94-100.

52. Lee OY (2006) Psychosocial factors and visceral hypersensitivity in irritable bowel syndrome. Korean J Gastroenterol 47(2): 111-119.

53. Wang W, Pan G, Qian J (2002) Effect of psychological factors on visceral sensation of patients with irritable bowel syndrome. Zhonghua Yi Xue Za Zhi 82(5): 308-311.

54. Helvaci MR, Kaya H, Algin MC, Yalcin A (2008) A physiologic events' cascade: irritable bowel syndrome may even terminate with chronic gastritis. Med J Malaysia 63(2): 140-142.

55. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, et al. (2002) Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology 122(7): 1778-1783.

56. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, et al. (2004) Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 126(3): 693-702.

57. Tornblom H, Lindberg G, Nyberg B, Veress B (2002) Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 123(6): 1972-1979.

58. Wahnschaffe U, Ullrich R, Riecken EO, Schulzke JD (2001) Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. Gastroenterology 121(6): 1329-1338.

59. Helvaci MR, Kayabasi Y, Celik O, Dede G, Abyad A, et al. (2023) Fasting plasma glucose may initially behave as a positive but eventually negative acute phase reactant in the body. World Family Med.

60. Park H (2006) The pathophysiology of irritable bowel syndrome: inflammation and motor disorder. Korean J Gastroenterol 47(2): 101-110.

61. Myers KA, Farquhar DR (2001) The rational clinical examination. Does this patient have clubbing? JAMA 286(3): 341-347.

62. Schamroth L (1976) Personal experience. S Afr Med J 50(9): 297-300.

63. Sridhar KS, Lobo CF, Altman RD (1998) Digital clubbing and lung cancer. Chest 114(6): 1535-1537.

64. Goodyer MJ, Cronin MC, Ketsitlile DG, O Reilly SP, Moylan EJ, et al. (2009) Hodgkin's lymphoma with digital clubbing. J Clin Oncol 27(26): 95-96.

65. Mathur SK, Sharma BB, Choudhary D, Rao RS, Shibin TS, et al. (2008) Clubbing in a case of hypothyroidism. J Assoc Physicians India 56: 241.

66. Ddungu H, Johnson JL, Smieja M, Mayanja Kizza H (2006) Digital clubbing in tuberculosis--relationship to HIV infection, extent of disease and hypoalbuminemia. BMC Infect Dis 6: 45.

67. Vandemergel X, Renneboog B (2008) Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 19(5): 325-329.

68. Ferrari R, Tanni SE, Lucheta PA, Faganello MM, do Amaral RA, et al. (2010) Gender differences in predictors of health status in patients with COPD. J Bras Pneumol 36(1): 37-43.

69. Helvaci MR, Ayyildiz O, Muftuoglu OE, Pocock L (2016) Digital clubbing may be a pioneer sign of cirrhosis in sickle cell patients. Middle East J Intern Med 9(3): 12-17.

70. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, et al (2015) Mortal quintet of sickle cell diseases. Int J Clin Exp Med 8(7): 11442-11448.

71. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, et al. (1994) Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 330(23): 1639-1644.

72. Helvaci MR, Yaprak M, Abyad A, Pocock L (2018) Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 16(3): 12-18.

73. Helvaci MR, Kaya H (2011) Effect of sickle cell diseases on height and weight. Pak J Med Sci 27(2): 361-364.

74. Helvaci MR, Aydin Y, Ayyildiz O (2013) Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 7(8): 2327-2332.