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Research Article

Fasting Plasma Glucose May Behave as a Positive in Mild but as a Negative Acute Phase Reactant in Moderate and Severe Inflammatory Disorders

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Abstract

Background: There may be significant relationships between fasting plasma glucose (FPG) and severity of inflammations.

Method: All cases with the digital clubbing were included.

Results: The study included 104 cases with clubbing detected among 2.428 cases (1.044 males). So clubbing was higher in males (8.1% versus 1.3%, p<0.001). Mean age of clubbing cases was 49.2 years, and there was a male predominance (81.7%), again. Parallel to the male predominance, there were higher prevalences of smoking (69.2% versus 41.6%, p<0.001), chronic obstructive pulmonary disease (COPD) (27.8% versus 10.8%, p<0.001), and coronary heart disease (CHD) and/or peripheric artery disease (PAD) (7.6% versus 0.0%, p<0.01) in the clubbing cases. Whereas the body weight, body mass index (BMI), and FPG were lower in the clubbing cases but the differences were nonsignificant probably due to the small sample size. But diabetes mellitus (DM) (12.5% versus 21.6%, p<0.05) and systolic blood pressure (BP) (127.6 versus 136.9 mmHg, p= 0.011) were lower in the clubbing cases, significantly.

Conclusion: There are significant relationships between smoking, digital clubbing, COPD, CHD, and PAD probably due to strong atherosclerotic effects of smoking. Similarly, the body weight, BMI, FPG, systolic BP, and DM are inversely related with the clubbing probably due to the severe inflammatory effects of smoking on the vascular endothelium, again. 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.

Key words: fasting plasma glucose; diabetes mellitus; irritable bowel syndrome; smoking; digital clubbing; sickle cell diseases; atherosclerosis

Introduction

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 [1]. Schamroth's window test is a popular test for the diagnosis of digital clubbing [2].

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. Although many disorders may be associated with the clubbing, the reports are mostly anecdotal, and prospective studies of patients with the clubbing have not been performed, yet. The clubbing may be associated with pulmonary, cardiac, and hepatic diseases 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 [3-7]. But there was not any underlying disorder in 60% of cases [8]. Additionally, the exact prevalence of digital clubbing in the population is not known. 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 [8]. Probably due to the higher prevalence of smoking in males [9], the great gender differences were observed in the clubbing. We tried to understand whether or not there are some relationships between fasting plasma glucose (FPG) and severity of inflammations in human body.

Material and methods

The study was performed in the Internal Medicine Clinic of the Mustafa Kemal University between March 2007 and May 2011 on all patients applying for any complaint. Their medical histories including smoking, claudication, angina pectoris, and already used medications were learnt, and a routine check-up procedure including FPG, total cholesterol, high density lipoproteins (HDL), triglycerides, an electrocardiography, and a Doppler echocardiogram just in suspected cases was performed. Digital clubbing is diagnosed by determining ratio of the distal phalangeal diameter to the interphalangeal diameter which is required to be greater than 1.0, and with the presence of the Schamroth sign [2, 8]. Current daily smokers at least for the last six months and cases with a history of five pack-years were accepted as smokers. Body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions (10). Office blood pressure (BP) was checked after a five-minute of rest in seated position with the mercury sphygmomanometer (ERKA, Germany). Cases with an overnight FPG level of 126 mg/dL or higher on two occasions or already using antidiabetic medications were defined as diabetics [10]. An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 100 and 125 mg/dL, and diagnosis of cases with a two-hour plasma glucose level of 200 mg/dL or greater was diabetes mellitus (DM) [10]. An exercise electrocardiogram was performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography was taken just for exercise electrocardiogram positive cases. So coronary heart disease (CHD) was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of the cardiac walls. A colored Doppler ultrasonograpy of arterial system of the lower extremities were obtained just in cases with a history of claudication for the diagnosis of peripheric artery disease (PAD). Chronic obstructive pulmonary disease (COPD) was diagnosed by means of spirometric measurements. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% [11]. Eventually, all cases with the clubbing were collected into the first, and age- and sex-matched control cases 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.

Results

The study included 104 patients (85 males) with the digital clubbing and 120 control cases. The clubbing cases were detected among 2.428 cases (1.044 males), totally. So clubbing was higher in males, significantly (8.1% versus 1.3%, $p<0.001$). The mean age of clubbing cases was 49.2 years, and there was a male predominance in them (81.7%), again. Parallel to the male predominance, there were higher prevalences of smoking (69.2% versus 41.6%, $p<0.001$), COPD (27.8% versus 10.8%, $p<0.001$), and CHD and/or PAD (7.6% versus 0.0%, $p<0.01$) in the clubbing cases. Whereas the body weight, BMI, and FPG were lower in the clubbing cases, but the differences were nonsignificant probably due to the small sample size. But DM (12.5% versus 21.6%, $p<0.05$) and systolic BP (127.6 versus 136.9 mmHg, $p= 0.011$) were lower in the clubbing cases, significantly. The mean pack-years were similar both in the clubbing and control groups (28.5 versus 28.0 years, respectively, $p>0.05$). On the other hand, low density lipoproteins (LDL) (130.0 versus 126.9 mg/dL, $p>0.05$) and triglycerides (152.5 versus 143.4 mg/dL, $p>0.05$) were higher in the digital clubbing cases but the differences were nonsignificant probably due to the small sample size of the study, again. There were seven cases with CHD and one case with PAD in the clubbing group, whereas no case could be detected in the control group (Table 1).

Variables	Cases with clubbing	*p*-value	Control cases
Number	104		120
Age (year)	49.2 ± 15.2 (21-81)	Ns*	49.3 ± 16.2 (21-82)
Male ratio	***81.7% (85)***	Ns	81.6% (98)
Smoking	***69.2% (72)***	***≤0.001***	41.6% (50)
COPD†	***27.8% (29)***	***≤0.001***	10.8% (13)
BMI‡ (kg/m^2)	26.4 ± 4.9 (16.1-40.5)	Ns	***27.3 ± 4.6 (17.1-39.2)***
Weight (kg)	74.3 ± 14.0 (38-120)	Ns	***77.9 ± 13.6 (45-116)***
FPG§ (mg/dL)	113.7 ± 43.5 (73-301)	Ns	***120.8 ± 40.8 (68-271)***
DM‖	12.5% (13)	***≤0.05***	***21.6% (26)***
LDL¶ (mg/dL)	***130.0 ± 38.0 (10-237)***	Ns	126.9 ± 35.7 (54-265)
Triglycerides (mg/dL)	***152.5 ± 79.3 (55-438)***	Ns	143.4 ± 79.8 (49-383)
Systolic BP** (mmHg)	127.6 ± 25.6 (80-200)	***0.011***	***136.9 ± 28.0 (80-220)***
Diastolic BP (mmHg)	88.0 ± 12.5 (60-120)	Ns	88.3 ± 12.2 (50-120)
CHD and/or PAD****	***7.6% (8)***	***≤0.01***	0.0% (0)

Table 1: Characteristics features of the study cases.

*Nonsignificant (p>0.05) †Chronic obstructive pulmonary disease ‡Body mass index §Fasting plasma glucose ‖Diabetes mellitus ¶Low density lipoproteins **Blood pressure ***coronary heart disease ****Peripheric artery disease

Discussion

Recurrent upper abdominal discomfort may be the cause of nearly half of applications to the Internal Medicine Clinics (12), and irritable bowel syndrome (IBS) and chronic gastritis may be the most commonly 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 by the patients with IBS. Although many patients relate onset of symptoms to intake of food, and often incriminate specific food items, a meaningful dietary role is doubtful in the IBS. According to the literature, nearly 20% of general population have IBS, and it is more common in females with unknown causes, yet [13]. 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 [14]. 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 [15]. 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 [16-18]. Similarly, some authors studied the role of inflammation in IBS via colonic biopsies in 77 patients [19]. 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 killer cells. All of 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 [19]. A direct link between the immunologic activation and IBS symptoms was shown by some other authors, too [20]. 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 [20]. In addition to above findings, there are some evidences for 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 obtained via laparoscopy [21]. 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 [21]. Nine patients had hypertrophy of longitudinal muscles, and seven had abnormalities in number and size of interstitial cells of Cajal [21]. The finding of intraepithelial lymphocytosis was also consistent with some other reports in the colon [19] and duodenum [22]. So, IBS may have more complex mechanisms affecting various systems of the body by means of a low-grade inflammatory process [23]. Beside that mean values of FPG (111.9 versus 105.4 mg/dL, p= 0.002) and plasma triglycerides (167.0 versus 147.3 mg/dL, p= 0.013) were higher in the IBS cases (24). Because plasma triglycerides are well-known acute phase reactants (APRs), the additionally increased FPG in the IBS cases may show the fact that FPG may behave as a positive APR in the IBS case (24).

Sickle cell diseases (SCDs) are chronic inflammatory process on vascular endothelium, initiated at birth and terminated with an accelerated

atherosclerosis induced end-organ failures in early years of life [25, 26]. Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity is the main problem instead of the shape 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, depression, and various stresses of the body. The hardened RBCs induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body [27]. As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level [28, 29], 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 narrowings 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 [26]. Due to the severity of inflammation in the SCDs, the body weight, BMI, FPG, LDL, HDL, systolic and diastolic BPs, and hematocrit values decreased as some negative APRs in the body, significantly [30].

The monolayer of endothelial cells that forms the inner lining of arteries, veins, capillaries, and lymphatics is called as the 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 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 BP 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 (31). The much higher BPs 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. Thus the term of venosclerosis 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 consequences of the systemic inflammatory process are obesity, hypertension (HT), DM, cirrhosis, PAD, COPD, CHD, chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, aging, and death (32). 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 end-points are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome, extensively [33, 34].

Obesity may be one of the irreversible end-points of the metabolic syndrome. Although some transient successes can be achieved, nonpharmaceutical approaches provide limited benefit to reverse the 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 [35]. The chronic low-grade inflammation may even cause genetic changes of 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 (36). 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%, $p<0.001$) [36], and 52.8% of patients with HT had obesity against 14.5% of patients with the sustained NT ($p<0.001$) (37). So, the major underlying cause of the metabolic syndrome appears as weight gain that may be the main cause of insulin resistance, impaired fasting glucose, impaired glucose tolerance, hyperlipoproteinemias, and white coat hypertension (WCH) [38]. Interestingly, weight gain before the development of an obvious overweight or obesity may even 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 [36, 37]. On the other hand, prevention of the weight gain with physical activity even in the absence of a prominent weight loss usually results with resolution of many parameters of the syndrome [39]. According to our experiences, excess weight may actually be a result of physical inactivity instead of an excessive eating habit. In another word, there is a problem with burning of calories instead of getting them. Thus prevention of weight gain cannot be achieved by diet, alone [40]. 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 [41]. 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 end-points of the metabolic syndrome [10].

Smoking may be the second common cause of disseminated vasculitis in human body. It may cause a low-grade systemic inflammation on vascular endothelium terminating with an accelerated atherosclerosis-induced end-organ insufficiencies all over the body [42]. 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. Plasma triglycerides, LDL, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) may be positive whereas HDL and FPG may be negative APRs indicating such inflammatory effects of smoking in the body [43]. Parallel to the systemic inflammatory and atherosclerotic effects of smoking, smoking in human being and nicotine administration in animals were associated with the lower values of BMI in some studies [44]. Some evidences revealed an increased energy expenditure during smoking both on the rest and light physical activity [45]. Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [46]. According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten [47]. Smoking may be associated with a postcessation weight gain, but the risk is the highest during the first year, and decreases with the following years [48]. As the opposite findings to the above studies, the mean weight and BMI were similar both in the smokers and non-smokers in the other study [43]. 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 [49]. 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 [50]. 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 [51]. 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. Several toxic substances found in the cigarette smoke get into the circulation, and cause the vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually reported together with depression, IBS, chronic gastritis, hemorrhoids, and urolithiasis in the literature (16, 52). There may be several underlying mechanisms to explain these associations in the smokers [52]. First of all, smoking may have some additional 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 the IBS including loose stool, diarrhea, and constipation. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis [16, 17]. 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. Actually, 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 ($p<0.01$) [16].

Alcohol may be the third common cause of systemic vasculitis in 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 [53]. 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 [54]. People with AUD have three-fold higher mortality in men and four-fold in women [55]. Similar to smoking, alcohol may be more dangerous for women about the atherosclerotic end-points 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 [54]. 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 barrier by means of the 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 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 the plasma (38). Although regular alcohol consumers were excluded, plasma triglycerides were higher in the smokers (163.1 versus 151.3 mg/dL, $p<0.05$), indicating the inflammatory effects of smoking in the other study [56].

The acute phase response occurs in case of infection, infarction, cancer, trauma, depression, and burn-like inflammatory conditions of the body. Certain mediators known as APRs are increased or decreased during the response [57, 58]. These markers are commonly used in the clinical practice 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 platelet counts may also behave as some other positive APRs in the body [59]. 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 in the body. 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 the smokers in the above study (56), production of HDL may also be suppressed in the liver during the acute phase response [60]. Similarly, triglycerides, DM, and CHD were all higher in patients with plasma HDL values of lower than 40 mg/dL, significantly [60]. So, HDL may actually 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 in the other study (38). Additionally, plasma triglycerides increased whereas HDL decreased during infections [61]. On the other hand, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke [62]. 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 [63]. 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 [38]. Parallel to ESR and CRP, plasma triglycerides and LDL may behave as positive whereas FPG and HDL negative APRs in smokers [56]. In another word, lower HDL values should alert clinicians for researching of any acute phase response in the body [64, 65].

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 mjor 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 uptaken 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. For example, 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 [66]. 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 (66). 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 [67]. 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 [68]. Similar to the above study [56], HDL and FPG values were also suppressed in the SCDs, probably due to the severe inflammatory nature of the diseases [30]. Smoking may reduce HDL and FPG by means of the inflammatory effects on the vascular endothelium all over the body [43]. On the other hand, triglycerides may be the most sensitive APRs indicating the metabolic syndrome [69]. Although ATP II determined the normal plasma triglycerides as lower than 200 mg/dL in 1994 [70], World Health Organisation in 1999 [71] and ATP III in 2001 reduced the normal limits as lower than 150 mg/dL [10]. But there are still suspicions about the safest values of triglycerides in the plasma [69]. Beside that triglyceride are the only lipids which were not suppressed with the pathological weight losses [72]. For example, plasma triglycerides increased in contrast to the suppressed body weight and BMI in the SCDs [72]. Similarly, prevalences of excess weight, DM, HT, and smoking were higher in the hypertriglyceridemia group (200 mg/dL and higher) in the other study [73]. Interestingly, the greatest number of deteriorations in the metabolic parameters was observed with triglycerides values of 60 mg/dL and higher [69].

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 [74]. The four grams of glucose circulate in the blood of a person with the 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 400 grams of glycogen stored in the skeletal muscles and liver, respectively [74]. The brain consumes about 60% of the blood glucose during fasting. FPG is the most commonly 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 [75]. Similarly, smokers have a lower likelihood of newly-diagnosed DM in Chinese men with a lower BMI in the other study [76]. Parallel to the above studies, FPG and DM were also lower in smokers in the other study (102.3 versus 111.6 mg/dL, p=0.007 and 8.9% versus 14.3%, p<0.05, respectively), and although majority of the smokers were male again (70.0%), BMI of the smokers was higher (26.6 kg/m2) in contrast to the above studies [56].

As a conclusion, there are some significant relationships between the digital clubbing, smoking, COPD, CHD, and PAD probably due to strong atherosclerotic effects of smoking. Similarly, the mean weight, BMI, FPG, systolic BP, and DM are inversely related with the clubbing probably due to the severe inflammatory effects of smoking on the vascular endothelium all over the body, again. FPG may behave as a positive APR in mild inflammatory disorders such as IBS but as a negative APR in moderate and severe inflammatory disorders such as smoking, digital clubbing, and SCDs.

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