

DEPRESSION CAUSES VARIOUS INFLAMMATORY PROCESSES IN HUMAN BODY

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Abstract

Background: We tried to understand whether or not there are some relationships between irritable bowel syndrome (IBS), chronic gastritis (CG), depression, and various inflammatory processes in the body.

Method: Consecutive patients with IBS and age and sex-matched control cases were included.

Results: The study included 936 patients with IBS (592 females) and 346 control cases. Mean age of the patients was 41.0 years, and 63.2% of them were female. Although gastric sample biopsies were taken just in suspected cases, CG was diagnosed nearly in all of the patients with the IBS (80.4% vs 15.0%, $p < 0.001$). Interestingly, prevalence of antidepressants use was also higher in the IBS cases, significantly (46.4% vs 16.1%, $p < 0.001$). Similarly, smoking (35.2% vs 20.8%, $p < 0.001$), hemorrhoids (37.1% vs 7.2%, $p < 0.001$), and urolithiasis (22.0% vs 9.5%, $p < 0.001$) were all higher in the IBS patients, again. Beside that the mean values of fasting plasma glucose (FPG) (111.9 vs 105.4 mg/dL, $p = 0.002$) and plasma triglycerides (167.0 vs 147.3 mg/dL, $p = 0.013$) were also higher in the IBS patients, significantly.

Conclusion: Because FPG and triglycerides are well-known acute phase reactants in the body, IBS and CG may be some low-grade inflammatory processes initiated with anxiety, depression, infection, inflammation, trauma, and cancer fear-like stresses of the body, and eventually terminate with hemorrhoids and urolithiasis. Due to the highly significant associations between IBS, CG, and depression, IBS and CG may actually be the two sides of the same paper, and just be two examples of depression-induced various inflammatory processes in human body.

Key words: Depression, irritable bowel syndrome, chronic gastritis, irritable gastrointestinal syndrome, smoking, fasting plasma glucose, triglycerides

Introduction

Recurrent upper abdominal discomfort may be the cause of nearly half of the applications to the Internal Medicine Clinics, and irritable bowel syndrome (IBS) and chronic gastritis (CG) may be the most commonly diagnosed disorders in such cases (1). 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 with the IBS. A meaningful dietary role is doubtful, and psychological factors seem to precede onset and exacerbation of gut symptoms. Many potentially psychiatric disorders including anxiety, depression, sleep disorders, cancer fear, or death fear usually coexist with the IBS (2). For example, thresholds for sensations of initial filling, evacuation, urgent evacuation, and utmost tolerance recorded via a rectal balloon decreased by focusing the examiners' attention on gastrointestinal stimuli by reading pictures of gastrointestinal malignancies in the IBS (3). 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. IBS may have a more complex mechanism by affecting various systems of the body with a low-grade inflammatory process (4). Eventually, IBS may even terminate with CG, urolithiasis, and hemorrhoids (5-7). Similarly, some authors studied the role of inflammation in the IBS by means of colonic biopsies in 77 patients (8). 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 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 (8). Some other authors 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 IBS (9). In addition to the above findings, there are some evidences for extension of the inflammatory process behind the mucosa. Some authors addressed this issue in ten patients with the severe IBS by examining full-thickness jejunal biopsies, laparoscopically (10). They detected a low-grade infiltration of lymphocytes into the myenteric plexus of nine patients, four of whom had an associated increase in intraepithelial lymphocytes and six demonstrated evidence of neuronal degeneration (10). Nine patients had hypertrophy of longitudinal muscles, and seven had abnormalities in the number and size of interstitial cells of Cajal (10). The finding of intraepithelial lymphocytosis was consistent with some other reports in the colon and duodenum, too (8, 11). We tried to understand whether or not there are some significant relationships between IBS,

CG, depression, and various inflammatory processes in the body.

Material and methods

The study was performed in the Internal Medicine Clinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients with upper abdominal discomfort were taken into the study. Their medical histories including smoking, alcohol, urolithiasis, and already used medications including antidepressants at least for a period of six months were learned. Patients with devastating illnesses including eating disorders, malignancies, acute or chronic renal failure, cirrhosis, hyper- or hypothyroidism, or heart failure were excluded. Current daily smokers at least for the last six months and cases with a history of five pack years were accepted as smokers. Patients with regular alcohol consumption (one drink a day) at least for the last six months and cases with a history of five drink years were accepted as drinkers. A routine check up procedure including fasting plasma glucose (FPG), total cholesterol, triglycerides, high density lipoproteins (HDL), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 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 graphy, an electrocardiogram, a Doppler echocardiogram in case of requirement, an abdominal ultrasonography, an abdominal x-ray graphy in supine position, a rectosigmoidoscopy just in patients symptomatic for hemorrhoids, and a questionnaire for the IBS was performed. IBS was diagnosed according to Rome II criteria in the absence of red flag symptoms including pain, nocturnal diarrhea, weight loss, fever, and any abnormal finding of the physical examination. An upper gastrointestinal endoscopy was performed, and sample biopsies were taken just in cases with suspicion. CG is diagnosed, histologically. Infiltrations of neutrophils and monocytes into the gastric mucosa is the hallmark of CG (12). An additional intravenous pyelography was performed according to the results of the urinalysis and abdominal x-ray graphy. So urolithiasis was diagnosed either by medical history or as a result of current clinical and laboratory findings. Body mass index (BMI) of each case was calculated by measurements of Same Physician instead of verbal expressions. Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (13). An oral glucose tolerance test with 75-gram glucose was performed in cases with FPG levels between 100 and 126 mg/dL, and diagnosis of cases with a two-hour plasma glucose level of 200 mg/dL or higher is diabetes mellitus (DM) (13). Office blood pressure (OBP) was checked after five minutes of rest in seated position with mercury sphygmomanometer on three visits, and no smoking was permitted during the previous two hours. Ten days twice daily measurements of blood pressure at home (HBP) were obtained in all cases, even in normotensives in the office due to the risk of masked hypertension after an education about proper blood pressure (BP) measurement techniques (14). The education included recommendation

of upper arm devices, using a standard adult cuff with bladder sizes of 12 x 26 cm for arm circumferences up to 33 cm in length and a large adult cuff with bladder sizes of 12 x 40 cm for arm circumferences up to 50 cm in length, and taking a rest for a period of five minutes in seated position before measurements (14). An additional 24-hour ambulatory blood pressure monitoring was not required due to the equal efficacy of the HBP measurements to diagnose hypertension (HT) (15). HT is defined as a mean BP of 140/90 mmHg or greater on HBP measurements, and white coat hypertension (WCH) is defined as an OBP of 140/90 mmHg or greater, but a mean HBP value of lower than 140/90 mmHg (14). Eventually, all patients with the IBS 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 936 patients with the IBS (592 females) and 346 control cases, totally. Mean age of the patients was 41.0 years, and 63.2% of them were female. Although gastric sample biopsies were taken just in suspected cases, CG was diagnosed nearly in all of the patients with the IBS (80.4% vs 15.0%, $p < 0.001$). Interestingly, prevalence of antidepressants use was also higher in the IBS cases, significantly (46.4% vs 16.1%, $p < 0.001$). Similarly, smoking (35.2% vs 20.8%, $p < 0.001$), hemorrhoids (37.1% vs 7.2%, $p < 0.001$), and urolithiasis (22.0% vs 9.5%, $p < 0.001$) were all higher in the IBS patients, again. Beside that the mean values of FPG (111.9 vs 105.4 mg/dL, $p = 0.002$) and plasma triglycerides (167.0 vs 147.3 mg/dL, $p = 0.013$) were also higher in the IBS patients, significantly (Table 1). Due to the limited number of cases with alcoholism among the study cases, regular alcohol consumption was not included in comparison.

Table 1: Comparison of patients with irritable bowel syndrome and without

| Variables | Patients with IBS* | p-value | Control cases |
|-----------------------------------|-------------------------------|------------------|------------------------|
| Number | 936 | | 346 |
| Mean age (year) | 41.0 ± 14.7 (13-86) | Ns† | 41.4 ± 14.4 (15-82) |
| Female ratio | 63.2% | Ns | 63.0% |
| CG‡ | 80.4% | <0.001 | 15.0% |
| Antidepressants use | 46.4% | <0.001 | 16.1% |
| Hemorrhoids | 37.1% | <0.001 | 7.2% |
| Smoking | 35.2% | <0.001 | 20.8% |
| Urolithiasis | 22.0% | <0.001 | 9.5% |
| Mean BMI‡ (kg/m ²) | 27.2 ± 5.6 (15.0-51.1) | Ns | 27.7 ± 5.9 (16.5-49.0) |
| WCH§ | 27.7% | Ns | 31.4% |
| HT | 12.8% | Ns | 14.7% |
| DM** | 8.3% | Ns | 10.0% |
| Mean FPG*** (mg/dL) | 111.9 ± 42.8 (66-392) | 0.002 | 105.4 ± 32.9 (70-323) |
| Mean TC**** (mg/dL) | 199.8 ± 43.9 (105-352) | Ns | 196.5 ± 43.6 (110-296) |
| Mean triglycerides (mg/dL) | 167.0 ± 106.5 (20-622) | 0.013 | 147.3 ± 102.9 (27-857) |
| Mean LDL***** (mg/dL) | 125.4 ± 35.8 (10-282) | Ns | 124.0 ± 32.5 (54-231) |
| Mean HDL***** (mg/dL) | 46.6 ± 13.5 (24-124) | Ns | 45.0 ± 10.3 (26-72) |

*Irritable bowel syndrome †Nonsignificant ($p > 0.05$) ‡Chronic gastritis ‡Body mass index

§White coat hypertension ||Hypertension **Diabetes mellitus ***Fasting plasma glucose

****Total cholesterol *****Low-density lipoprotein *****High-density lipoprotein

Discussion

IBS is a chronic low-grade inflammatory process affecting various organ systems of the body with an average world prevalence of 11.2% to 15.0% (16, 17). It is higher in females and under the age of 50 years (18). It has become a multifactorial disease that is characterized by visceral hypersensitivity, alteration of the gut microflora, an increased intestinal membrane permeability, a low-grade inflammation mainly affecting the gastrointestinal and genitourinary tracts, deterioration in gastroenteric physiology, gastrointestinal motor dysfunction, somatization, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, interstitial cystitis, sexual dysfunction, sleep disturbance, increased colonic motility, increased colonic bile acid concentration, epithelial barrier dysfunction, neurohormonal up-regulation, activation of secretory processes in the epithelial layer, immune activation, disordered bile salt metabolism, abnormalities in serotonin metabolism, and alterations in brain functions (19-24). The interface of IBS and psychiatry is well established with psychiatric comorbidities approaching 20% to 60% in IBS cases (25). For example, patients with IBS who asked for medical help because of their symptoms presented emotional problems such as anxiety, depression, and expressed neurotic personality (26). In another study, patients with IBS had a three-fold increased odds of either anxiety or depression (27). Similarly, IBS was also common in patients seeking treatment for major depression in another study (28), and symptoms of major depressive disorders occur in up to 90% of patients with IBS in the other study (16). The life time prevalence of major depressive and anxiety disorders increased up to 76% and 54% in cases with IBS, respectively (29). Particularly in diarrhea predominant type of IBS, the major depression was considered to be strongly involved in the onset and the clinical course of IBS (30). Anxiety disorders, depressive disorders, and somatoform disorders were the more frequently detected comorbid disorders with IBS in the other study (25). Lower socioeconomic status was associated with an increased prevalence of comorbid anxiety and depression in IBS (31). Similarly, the prevalences of both depression and insomnia were higher with IBS compared to each individual occurrence (32). Prevalences of IBS and abdominal/belly pain were greater among a sample of veterans with posttraumatic stress disorder (33). Additionally, the prevalences of IBS and depressive symptoms were higher in the fibromyalgia patients (34). Fibromyalgia alone and patients with fibromyalgia plus IBS averaged greater disability than those with IBS alone, and disability was correlated with anxiety and depression (35). Prevalences of fibromyalgia (30% vs 3%, $p < 0.001$), anxiety-disorder (39.7% vs 10.2%, $p < 0.001$), and depression (8.1% vs 4.9%, $p < 0.001$) were higher with IBS in another study, again (36). Eventually, 54% to 100% of patients with IBS may have associated psychiatric illnesses and personality pathologies according to the some authors (26).

Primary bacterial gut disturbances may be important for the development and severity of IBS (37). Dysbiosis, or alteration in the normal intestinal flora, modulates

intestinal permeability, inflammation, and gut motility (37). The severities of psychological and gastrointestinal symptoms in IBS have been linked with a distinct intestinal microbiota signature (37). Similarly, various psychiatric disorders including depression and posttraumatic stress disorder are associated with unique gut microbiota profiles, which could differentially affect the onset and progression of coincident IBS (38). But efforts to modulate intestinal dysbiosis in IBS have shown little improvement in large systematic reviews which means that the intestinal dysbiosis may actually be the result instead of the cause of IBS (37). On the other hand, IBS patients with a depression score on the Zung Depression Self-Rating Scale of 50 or more had a significantly lower number of total and T lymphocytes than the rest of IBS patients (39). The results may suggest a possible association between depression and indices of cellular immunity in IBS (39). An emerging role has been attributed to the importance of immune factors in the pathophysiology of IBS with evidence of altered cytokine profiles and increased levels of mucosal immune cells (40). These factors have also been shown to have direct effects on neuronal signalling (40). Pro- and anti-inflammatory cytokines are important modulators of the immune response, and may also play a major role in IBS (41). Cytokine production is regulated genetically, and imbalances in cytokine secretion may affect disease susceptibility and clinical outcomes of various conditions (41). Psychological stress, anxiety, and depression may also be involved in the altered profiles of pro- and anti-inflammatory cytokines leading to IBS (41). On the other hand, a maladaptive stress response, probably mediated by corticotropin-releasing hormone (CRH), contributes to the initiation, persistence, and severity of symptom flares in IBS (40). CRH is the stress hormone of the body, and a major mediator of stress response in the brain-gut axis (42). IBS is presumed to be a disorder of the brain-gut link associated with exaggerated response to stress (42). The previous study findings suggest the major role of CRH in stress-related pathophysiology of IBS, and possibly in inflammation of the gastrointestinal and genitourinary tracts mucosae (42). This inflammatory infiltrate is mainly represented by increased numbers of T lymphocytes and mast cells lying in the lamina propria (43). The close apposition of immunocytes to gut nerves supplying the mucosa provides a basis for neuroimmune cross-talk, which may explain gut sensorimotor dysfunction and related symptoms in IBS (43). Similarly, some other authors have also supported the idea that a low-grade inflammation, particularly mast cell activation, may be a contributory factor in IBS (44). As a result, it is not a surprising that IBS was an independent predictor ($p = 0.025$) of greater high-sensitive CRP levels in the plasma (45).

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 separate 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 all over 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 (46). 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. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical 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, HT, DM, cirrhosis, peripheral artery disease, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, early aging, and premature death (47). Although early withdrawal of the accelerating factors may delay terminal consequences, endothelial changes can not be reversed, completely after development of the irreversible end-points due to their fibrotic natures. The accelerating factors and irreversible consequences are researched under the titles of the metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (48).

Excess weight may be the most common cause of systemic vasculitis, and the major underlying cause of metabolic syndrome all over the world. Unfortunately, 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 (49). 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. The adverse effects of excess

weight on the BP were shown in the literature, extensively (50). For example, prevalences of sustained normotension (NT) were higher in the underweight than the normal weight (80.3% vs 64.0%, $p < 0.05$) and overweight groups (80.3% vs 31.5%, $p < 0.001$) (50), and 52.8% of patients with HT had obesity against 14.5% of patients with the sustained NT ($p < 0.001$) (51). So the major underlying cause of the metabolic syndrome appears as weight gain that may be the main cause of insulin resistance, hyperlipoproteinemias, impaired fasting glucose, impaired glucose tolerance, and WCH (52). Interestingly, weight gain before the development of an obvious overweight or obesity may even cause development of several components of the metabolic syndrome. For example, WCH alone may be a strong indicator of weight gain even before development of excess weight (50, 51). 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 (53). 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. Therefore prevention of weight gain can not be achieved by diet, alone (54). 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 (55). Eventual hyperactivities of sympathetic nervous system and renin-angiotensin-aldosterone system are probably associated with insulin resistance, elevated BP, and chronic endothelial inflammation and dysfunction. Similarly, the Adult Treatment Panel (ATP) III reported that although some people classified as overweight with larger muscular masses, most of them also have excessive fat tissue predisposing to the irreversible end-points of the metabolic syndrome (13).

Smoking may be the second common cause of systemic vasculitis all over the world. It is one of the major risk factors for the atherosclerotic end-organ insufficiencies (56). 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 up to now. Smoking may cause a moderate or severe inflammatory process in the vascular endothelium (57), and plasma triglycerides, low density lipoproteins (LDL), ESR, and CRP may be positive whereas HDL and FPG may be negative acute phase reactants (APRs) indicating such moderate or severe inflammatory effects in the plasma (58). Whereas FPG and plasma triglycerides were increased in the IBS cases in the present study, indicating that FPG may behave as a positive in mild but as a negative APR in moderate and severe inflammatory disorders in the body (59). In other words, IBS causes a mild, but smoking

causes a moderate or severe inflammatory process in the body. Beside the obvious atherosclerotic effects of smoking, some studies reported that smoking in human being and nicotine administration in animals are associated with the lower values of BMI (60). Some evidences revealed an increased energy expenditure during smoking both on the rest and light physical activity (61). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (62). According to an animal study, nicotine may lengthen intermeal time, and decrease amount of meal eaten (63). 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 (64). As the opposite findings to the above studies, the mean body weight and BMI were similar both in the smokers and non-smokers in the other study (58). 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 (65). 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 (66). 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 (67). In another words, 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 a vascular endothelial inflammation in all organ systems of the body. For example, smoking is usually reported together with depression, IBS, CG, hemorrhoids, and urolithiasis in the literature (5, 6). There may be several underlying mechanisms to explain these associations in the smokers (68). First of all, smoking may have some antidepressant properties and the most widely used antidepressant drug with several side effects in the body. 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 hemorrhoids. Thirdly, diarrheal losses-induced urinary changes may even cause urolithiasis (5, 6). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with urolithiasis and hemorrhoids. 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 IBS and 11.6% of cases without in the other study ($p<0.01$) (5).

Alcohol may be the third common cause of systemic vasculitis in the world. It is addictive to human being, and can result in alcohol use disorder (AUD), dependence, and withdrawal. Similar to the smoking, alcohol may have some antidepressant properties, and may be the second most widely used antidepressant drug with several side effects in the body. Alcohol is causally associated with more than 200 different pathologies including cancers in whole body (69). 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 (70). People with AUD have three-fold higher mortality in men and four-fold in women (71). 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. 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. Regular alcohol consumption leads to cell death in the liver, scarring, cirrhosis, and hepatocellular carcinoma. Heavy alcohol 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 (52). Although regular alcohol consumers were excluded, plasma triglycerides were higher in the smokers (163.1 vs 151.3 mg/dL, $p<0.05$), indicating the inflammatory effects of smoking (72).

The acute phase response occurs in case of infection, infarction, cancer, trauma, and burn-like inflammatory conditions of the body. Certain mediators known as APRs are increased or decreased during the response (73, 74). 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 (75). 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 (72), production of HDL may also be suppressed in the liver during the acute phase response (76). Similarly, triglycerides, DM, and CHD were all higher in patients with plasma HDL values of lower than 40 mg/dL, significantly (76). 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 (52). Additionally, plasma triglycerides increased whereas HDL decreased during infections (77). On the other hand, a 10 mg/dL increase of plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke (78). 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 (79). Probably, HDL turn to the negative direction much more 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 (52). Parallel to ESR and CRP, plasma triglycerides and LDL may behave as positive whereas FPG and HDL negative APRs in smokers in the above study (72). In another words, lower HDL values should alert clinicians for researching of any underlying pathology in the body (80, 81).

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 thoracic 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, drug, inflammation, infection, cancer, trauma, smoking, alcohol, and excess weight. Thus lipid analysis should be performed during a steady state, but 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 (82). 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 (82). 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 can not reduce all cause mortality, CHD mortality, myocardial infarction, and stroke (83). 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 (84). Similar to the above study (72), HDL and FPG values were also suppressed in the sickle cell diseases (SCDs), probably due to the severe inflammatory nature of the diseases (85). Smoking may reduce HDL and FPG by means of the moderate or severe inflammatory effects on the vascular endothelium all over the body (58). On the other hand, triglycerides alone may be one of the most sensitive APRs indicating the metabolic syndrome (86). Although ATP II determined the normal plasma triglycerides as lower than 200 mg/dL in 1994 (87), World Health Organisation in 1999 (88) and ATP III in 2001 reduced the normal limits as lower than 150 mg/dL (13). Although these cutpoints, there are still suspicions about the safest values of triglycerides in the plasma (86). Beside that triglycerides are the only lipids which were not suppressed with the pathological weight losses (89). For example, plasma triglycerides increased in contrast to the suppressed body weight and BMI in the SCDs (89). Similarly, prevalences of excess weight, DM, HT, and smoking were all higher in the hypertriglyceridemia group (200 mg/dL and higher) in the other study (90). Interestingly, the greatest number of deteriorations of the metabolic parameters was observed with the triglycerides values of 60 mg/dL and higher (86).

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. When the blood glucose levels are too high, insulin tells muscles to take up excess glucose for storage as glycogen. When the blood glucose levels are too low, glucagon informs the tissues to produce more glucose from the stores of glycogen. 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 of a person with the weight of 70 kg (91). The constant blood glucose levels are maintained via the hepatic and muscular glycogen stores on fasting. The brain consumes about 60% of the blood glucose on fasting. FPG is the most commonly used indication of overall glucose homeostasis, and it is measured after a fasting period of 8 hours. Infection, inflammation, surgical operation, depression, alcohol, and smoking-like stresses may affect the blood glucose homeostasis. For example, smoking was negatively associated with the FPG and DM in Chinese men with the normal weight, but not in men with excess weight or in women (92). Similarly, smokers have a lower likelihood of newly-diagnosed DM in Chinese men with a lower BMI in the other study (93). Parallel to the above studies, FPG and DM were also lower in the smokers (102.3 vs 111.6 mg/dL, $p=0.007$ and 8.9% vs 14.3%, $p<0.05$, respectively), and although majority of the smokers were male again (70.0%), BMI was relatively higher (26.6 kg/m²) in contrast to the above studies (72).

As a conclusion, because FPG and triglycerides are well-known APRs in the body, IBS and CG may be some low-grade inflammatory processes initiated with anxiety, depression, infection, inflammation, trauma, and cancer fear-like stresses of the body, and eventually terminate with hemorrhoids and urolithiasis. Due to the highly significant associations between IBS, CG, and depression, IBS and CG may actually be the two sides of the same paper, and just be two examples of depression-induced various inflammatory processes in human body.

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