MATHEWS

Review Article

Mathews Journal of Diabetes & Obesity

# What A Low Prevalence of Diabetes Mellitus in Digital Clubbing

**Mehmet Rami Helvaci[1,*], Yasemin Kayabasi[2], Ozlem Celik[3], Guner Dede[3], Abdulrazak Abyad[4], Lesley Pocock[5]**

[1]*Specialist of Internal Medicine, MD, Turkey*

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

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

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

[5]*Medi-WORLD International, Australia*

## ABSTRACT

**Background:** There may be some significant relationships between digital clubbing, fasting plasma glucose (FPG), and diabetes mellitus (DM). **Method:** All cases with digital clubbing were included. **Results:** The study included 104 patients (85 males) with digital clubbing detected among 2.428 cases (1.044 males), in total. 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 (81.7%), again. Parallel to the male predominance, there were higher prevalences of smoking (69.2% versus 41.6%, p<0.001) and chronic obstructive pulmonary disease (COPD) (27.8% versus 10.8%, p<0.001) in the clubbing cases. Although the mean body weight, body mass index (BMI), and FPG were lower in the clubbing cases, the differences were nonsignificant probably due to the small sample size of the study. Similarly, DM was lower in the clubbing cases, significantly (12.5% versus 21.6%, p<0.05). The systolic blood pressure (BP) was also lower in the clubbing cases, significantly (127.6 versus 136.9 mmHg, p= 0.011). On the other hand, coronary heart disease (CHD) and/or peripheric artery disease (PAD) were higher in the digital clubbing cases, significantly (7.6% versus 0.0%, p<0.01). **Conclusion:** There are some significant relationships between digital clubbing, smoking, COPD, CHD, and PAD probably due to the strong atherosclerotic effects of smoking. Similarly, the mean body weight, BMI, FPG, systolic BP, and DM are inversely related to digital clubbing probably due to the severe inflammatory effects of smoking on the vascular endothelium all over the body, again.

**Keywords:** Digital Clubbing, Smoking, Fasting Plasma Glucose, Diabetes Mellitus, Triglycerides, Acute Phase Reactants, Atherosclerosis.

## INTRODUCTION

Digital changes may help to identify some systemic disorders in the body. Digital clubbing is a deformity of the fingers and fingernails that is known for centuries. It is characterized by bulbous enlargement of the distal

**Vol No: 06, Issue: 01**

Received Date: March 30, 2023

Published Date: April 15, 2023

***Corresponding Author**

**Prof Dr. Mehmet Rami Helvaci, MD**

Specialist of Internal Medicine, 07400, ALANYA, Turkey, Phone: 00-90-506-4708759

**E-mail:** mramihelvaci@hotmail.com

**Citation:** Helvaci MR, et al. (2023). What A Low Prevalence of Diabetes Mellitus in Digital Clubbing. Mathews J Diabetes Obes. 6(1):15.

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 clubbing, the reports are mostly anecdotal, and prospective studies of patients with clubbing have not been performed, yet. The clubbing may be associated with pulmonary, cardiac, and hepatic disorders that are featuring with chronic hypoxia (tuberculosis, bronchiectasis), gastrointestinal and hepatobiliary dysfunctions (malabsorption, Crohn's disease, ulcerative colitis, cirrhosis), hypothyroidism, thymoma, thalassemia, and human immunodeficiency virus infection [3-7]. But there is not any underlying detected disorder in 60% of cases [8]. We tried to understand whether or not there are some significant relationships between digital clubbing, fasting plasma glucose (FPG), and diabetes mellitus (DM) in the present study.

## MATERIAL AND METHODS

The study was performed in the Internal Medicine Clinic of 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 checkup procedure including FPG, total cholesterol, high-density lipoproteins (HDL), triglycerides, 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 the last six months and cases with a history of five pack-years were accepted as smokers. The body mass index (BMI) of each case was calculated by the measurements of the Same Physician instead of verbal expressions [9]. 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 [9]. An oral glucose tolerance test with 75-gram glucose was performed in cases with an FPG level between 100 and 125 mg/dL, and the diagnosis of cases with a two-hour plasma glucose level of 200 mg/dL or greater is DM [9]. An exercise electrocardiogram was performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography was taken 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 ultrasonography 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% [10]. Eventually, all cases with the digital 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 clubbing and 120 control cases. The clubbing cases were detected among 2.428 cases (1.044 males), in total. 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 was a higher prevalence of smoking in the clubbing cases, significantly (69.2% versus 41.6%, $p<0.001$). The mean pack-years were similar both in the clubbing and control groups (28.5 versus 28.0 years, respectively, $p>0.05$). Similarly, there was a higher prevalence of COPD in the clubbing cases (27.8% versus 10.8%, $p<0.001$), again. Although the mean weight, BMI, and FPG were lower in the clubbing cases, the differences were nonsignificant probably due to the small sample size of the study ($p>0.05$ for all). Similarly, the prevalence of DM was lower in the clubbing cases, significantly (12.5% versus 21.6%, $p<0.05$). Besides that the systolic BP was lower in the clubbing cases, again (127.6 versus 136.9 mmHg, $p= 0.011$). 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 clubbing cases but

the differences were nonsignificant probably due to the small sample size of the study, again. As one of the most important results of the study, prevalences of CHD and/or PAD were higher in the clubbing cases, significantly (7.6% versus 0.0%, p<0.01). There were seven cases of CHD and one case of PAD in the clubbing group, whereas no case could be detected in the control group (Table 1).

**Table 1.** Characteristics features of the study cases.

| Variables | Cases with clubbing | *p*-value | Control cases |
|---|---|---|---|
| Number | 104 | | 120 |
| ***Male ratio*** | ***81.7% (85)*** | Ns* | 81.6% (98) |
| Age (year) | 49.2 ± 15.2 (21-81) | Ns | 49.3 ± 16.2 (21-82) |
| ***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)** |

*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

Digital clubbing remains as an unknown box in the medical field, and its possible association with significant health problems is still needed to be explained. Cardiac, pulmonary, and hepatic pathologies inducing chronic tissue hypoxia have been suspected [11-13]. Moreover, the significance of digital clubbing is not well-established, clinically. For example, only 40% of clubbing cases turned out to have significant underlying disorders, while 60% remained well over the subsequent years [8]. On the other hand, the exact prevalence of digital clubbing in the population is not known. Although the above study detected digital clubbing just in 0.9% of all patients admitted to the Department of Internal Medicine [8], its prevalence was detected as 4.2% in the Clinic of Internal Medicine in the present study. In the above study [8], 15 patients were diagnosed with digital clubbing among 1.511 admissions, and ten of them were male (66.6%). Whereas, the male ratio was 81.7% in the present study. Probably due to the greater prevalence of smoking in male gender [14], the great gender differences were observed in the digital clubbing cases. So smoking may take the main role in the etiology of clubbing probably due to the strong atherosclerotic effects on the vascular endothelium all over the body.

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, platelet 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 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 dysfunction may also be important in the development of cancers by preventing clearance of malignant cells by the natural killers in terminal points of 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 accelerated atherosclerosis-induced end-organ insufficiencies [15]. 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 [16]. 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 end-points are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome, extensively [17,18].

Obesity may be one of the irreversible end-points of metabolic syndrome. Although some transient successes can be achieved, nonpharmaceutical approaches provide limited benefits 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 [19]. Chronic low-grade inflammation may even cause genetic changes of the endothelial cells, and systemic atherosclerosis may prevent the clearance of malignant cells, effectively. Similarly, the effects of excess weight on BP were shown in the literature, extensively [20]. 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%, $p<0.001$) [20], and 52.8% of patients with HT had obesity against 14.5% of patients with the sustained NT ($p<0.001$) [21]. 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) [22]. 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 [20,21]. 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 [23]. 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 can not be achieved by diet, alone [24]. 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 [25]. 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 [9].

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 [26]. 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 acute phase reactants (APRs) indicating such inflammatory effects of smoking in the body [27]. Parallel to the systemic inflammatory and atherosclerotic effects of smoking, smoking in human being and nicotine administration in animals were associated with lower values of BMI in some studies [28]. Some evidences revealed an increased energy expenditure during smoking both on rest and light physical activity [29]. Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner [30]. According to an animal study, nicotine may lengthen intermeal time, and decrease the amount of meal eaten [31]. Smoking may be associated with post-cessation weight gain, but the risk is the highest during the first year, and decreases with the following years [32]. 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 [27]. 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 [33]. On the other hand, although 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 [34]. Besides that, the prevalence of myocardial infarctions increased threefold in men and sixfold in women who smoked at least 20 cigarettes per day [35]. In another word, smoking may be more dangerous for women with atherosclerotic end-points probably due to the higher BMI and its consequences in them. Several toxic substances found in cigarette smoke get into circulation and cause vascular endothelial inflammation in various organ systems of the body. For example, smoking is usually reported together with depression, irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, and urolithiasis in the literature [36-38]. There may be several underlying mechanisms to explain these associations in smokers [36]. 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 [37,38]. Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the gastrointestinal and genitourinary tracts terminating with IBS and urolithiasis. Eventually, immunosuppression secondary to smoking-induced vascular endothelial inflammation may even terminate with 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 ($p<0.01$) [37].

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 [39]. 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 [40]. People with AUD have three-fold higher mortality in men and four-fold in women [41]. 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 [40]. 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 to 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 passive diffusion, easily. Alcohol works particularly by increasing the 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 [22]. 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 [42].

The acute phase response occurs in cases 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 [43,44]. These markers are commonly used in clinical practice as 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 the 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 the 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 [45]. On the other hand, production 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 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 [42], production of HDL may also be suppressed in the liver during the acute phase response [46]. Similarly, triglycerides, DM, and CHD were all higher in patients with plasma HDL values of lower than 40 mg/dL, significantly [46]. 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 [22]. Additionally, plasma triglycerides increased whereas HDL decreased during infections [47]. On the other hand, a 10 mg/dL increase in plasma LDL values was associated with a 3% lower risk of hemorrhagic stroke [48]. 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 [49]. Probably, HDL turns 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 [22]. 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 [42]. In another word, lower HDL values should alert clinicians for researching any acute phase response in the body [50,51].

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 intermediate density lipoproteins (IDL) by the removal of 90% of triglycerides by lipases in the capillaries of adipocytes and muscle tissues. Then the IDL are degraded into LDL by the removal of more triglycerides. So VLDL are the main source of LDL in the plasma, and LDL delivers cholesterol from the liver to organs. Although the liver removes the majority of LDL from the circulation, a small amount is uptaken by scavenger receptors of the macrophages migrating into the arterial walls, and becoming the foam cells of atherosclerotic plaques. HDL removes fats and cholesterol from cells including the arterial wall atheroma and carries 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, 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 [52]. 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 [52]. For example, the properties of HDL are compromised in patients with DM by means of oxidative modification, glycation, and/or transformation of HDL proteomes into proinflammatory proteins. Additionally, the drugs increasing HDL values such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors can not reduce all causes of mortality, CHD mortality, myocardial infarction, and stroke [53]. In other words, HDL may just be some indicators instead of being the main actors of 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 [54]. Similar to the above study [42], HDL and FPG values were also suppressed in sickle cell diseases (SCDs), probably due to the severe inflammatory nature of the diseases [55]. Smoking may reduce HDL and FPG by means of the inflammatory effects on the vascular endothelium all over the body [27]. On the other hand, triglycerides alone may be one of the most sensitive APRs indicating metabolic syndrome [56]. Although ATP II determined the normal plasma triglycerides as lower than 200 mg/dL in 1994 [57], World Health Organisation in 1999 [58] and ATP III in 2001 reduced the normal limits to lower than 150 mg/dL [9]. Although these are cutpoints, there are still suspicions about the safest values of triglycerides in the plasma [56]. Besides, that triglycerides are the only lipids which were not suppressed with pathological weight losses [59]. For example, plasma triglycerides increased in contrast to the suppressed body weight and BMI in the SCDs [59]. 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 [60]. Interestingly, the greatest number of deteriorations in the metabolic parameters was observed with triglyceride values of 60 mg/dL and higher [56].

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 blood glucose, whereas insulin is the anabolic hormone decreasing 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 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 [61]. The four grams of glucose circulating 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 400 grams of glycogen stored in the skeletal muscles and liver, respectively [61]. 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 blood glucose homeostasis. For example, smoking was negatively associated with FPG and DM just in Chinese men with normal weight, but not in men with excess weight or in women [62]. Similarly, smokers have a lower likelihood of newly-diagnosed DM in Chinese men with a lower BMI in the other study [63]. 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 the 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 [42].

## CONCLUSION

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

## REFERENCES


1. Myers KA, Farquhar DR. (2001). The rational clinical examination. Does this patient have clubbing? JAMA. 286(3):341-347.
2. Schamroth L. (1976). Personal experience. S Afr Med J. 50(9):297-300.
3. Sridhar KS, Lobo CF, Altman RD. (1998). Digital clubbing and lung cancer. Chest. 114(6):1535-1537.
4. Goodyer MJ, Cronin MC, Ketsitlile DG, O'Reilly SP, Moylan EJ, Maher MM, et al. (2009). Hodgkin's lymphoma with digital clubbing. J Clin Oncol. 27(26):95-96.
5. Dever LL, Matta JS. (2009). Digital clubbing in HIV-infected patients: an observational study. AIDS Patient Care STDS. 23(1):19-22.
6. Mathur SK, Sharma BB, Choudhary D, Rao RS, Shibin TS, Singh V. (2008). Clubbing in a case of hypothyroidism. J Assoc Physicians India. 56:241.
7. 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.
8. 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.
9. 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. (2002). Circulation. 106(25):3143-3421.
10. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. (2013). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 187(4):347-365.
11. Uppal S, Diggle CP, Carr IM, Fishwick CW, Ahmed M, Ibrahim GH, et al. (2008). Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet. 40(6):789-793.
12. Toovey OT, Eisenhauer HJ. (2010). A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses. 75(6):511-513.
13. Fomin VV, Popova EN, Burnevich EZ, Kuznetsova AV. (2007). Hippocratic fingers: clinical importance and differential diagnosis. Klin Med (Mosk). 85(5):64-68.
14. Ferrari R, Tanni SE, Lucheta PA, Faganello MM, do Amaral RA, Godoy I. (2010). Gender differences in predictors of health status in patients with COPD. J Bras Pneumol. 36(1):37-43.
15. Helvaci MR, Kaya H, Borazan A, Ozer C, Seyhanli M, Yalcin A. (2008). Metformin and parameters of physical health. Intern Med. 47(8):697-703.
16. Helvaci MR, Algin MC, Abyad A, Pocock L. (2018). Physical inactivity or an excessive eating habit. Middle East J Nursing. 12(1):14-18.
17. Eckel RH, Grundy SM, Zimmet PZ. (2005). The metabolic syndrome. Lancet. 365(9468):1415-1428.
18. Helvaci MR, Ayyildiz O, Muftuoglu OE, Yaprak M, Abyad A, Pocock L. (2017). Aging syndrome. World Family Med. 15(3):39-42.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. Helvaci MR, Ayyildiz O, Gundogdu M, Aydin Y, Abyad A, Pocock L. (2019). Body mass and blood pressure. World Family Med. 17(1):36-40.
25. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, et al. (1999). Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med. 38(2):202-206.

26. 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.

27. Helvaci MR, Altintas E, Yalcin A, Muftuoglu OE, Abyad A, Pocock L. (2022). Positive and negative acute phase reactants in smokers. Middle East J Nursing. 16(2):42-48.

28. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, Niaura R, 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.

29. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ, Stamford BA. (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.

30. 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.

31. 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.

32. Froom P, Melamed S, Benbassat J. (1998). Smoking cessation and weight gain. J Fam Pract. 46(6):460-464.

33. Helvaci MR, Altintas E, Yalcin A, Muftuoglu OE, Abyad A, Pocock L. (2023). Smoking may not prevent overweight or obesity. World Family Med (in press).

34. Helvaci MR, Kaya H, Gundogdu M. (2012). Gender differences in coronary heart disease in Turkey. Pak J Med Sci. 28(1):40-44.

35. 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.

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

37. 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.

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

39. Rehm J. (2014). Alcohol and mortality. Alcohol Res. 35(2):174-183.

40. 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.

41. Westman J, Wahlbeck K, Laursen TM, Gissler M, Nordentoft M, Hällgren J, 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.

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

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

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

45. 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.

46. 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.

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

48. 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.

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

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

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

52. 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.

53. 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.

54. 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.

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

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

57. 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). (1994). Circulation. 89(3):1333-1445.

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

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

60. 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).

61. Wasserman DH. (2009). Four grams of glucose. Am J Physiol Endocrinol Metab. 296(1):E11-E21.

62. Wang S, Chen J, Wang Y, Yang Y, Zhang D, Liu C, 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. 2019:1853018.

63. Hou X, Qiu J, Chen P, Lu J, Ma X, Lu J, 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.