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From the Editor

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This is the first issue this year with papers from Jordan, Yemen, Lebanon , Turkey and Australia.

Haddad R.M et al; did a prospective observational study of 150 patients, diagnosed to have bronchial asthma, and who were followed up in pulmonary clinic in King Hussein Medical Center (KHMC), between January 2016 and January 2018. The aim is find out the rates of poor inhaler technique in patients diagnosed to have bronchial asthma visiting the pulmonary clinic in King Hussein Medical Center (KHMC). The effect of poor inhaler technique on asthma control will be assessed as well. Of the 150 patients enrolled in our study, 95 patients (63.3%) were males. The mean(±SD) age was 46.0±6.8 years. The ages ranged between (21-64) years. Poor inhaler technique was observed in 78 patients (52%). The most common cause of poor inhaler technique in these patients was the lack of education about asthma medication use, which was seen in 64 patients (82%), followed by lack of education about the importance of regular and correct inhaler use on the control of asthma, which was seen in 14 patients (18%). Patients with poor inhaler technique were found to have poor asthma control, with 57 (73%) patients having uncontrolled asthma, 18 patients (23%) having partially controlled asthma, and only 3 patients (4%) having controlled asthma. The authors concluded poor inhaler use in patients with bronchial asthma was found to be significant in our study, with more than half the patients showing improper technique. Proper education about the use of asthma medications should be done to ensure the proper use of inhalers. Patients with poor inhaler technique were found to have poor asthma control; a fact that emphasizes the importance of proper inhaler use in asthma patients.

A paper from Yemen sought the correlation between systolic myocardial velocity (Sm) obtained by Tissue Doppler imaging (TDI) and left ventricular ejection fraction (LVEF) measured by conventional Simpson's method in patients with heart failure. This study involved 85 patients with heart failure whose LVEF < 50% (mean age 58 (11) years), LV EF measured by conventional Simpson's method correlating with average Sm measured at septal, lateral, anterior and inferior side of mitral annulus by tissue Doppler echocardiography.

The mean age of the 85 patients in the study was 58.48(11) years, 11(12.9 %) female; 74(87.1%) male. The mean LVEF was 33.53 (9.94). A significant correlation was detected between systolic mitral annulus velocity Sm and LV ejection fraction EF (R: 0.609, p: 0.000). LV mean Sm obtained by TDI is a parameter that is easily obtained and practical, can be used to evaluate LV systolic function in patients with HF. The authors concluded that the assessment of average systolic myocardial velocity (Sm) could be used as an alternative to LVEF. This approach may be useful especially when the image quality is poor and maintain high accuracy in prediction LV systolic dysfunction.

Helvaci M.R et al; tried to understand significance of high density lipoproteins (HDL) in metabolic syndrome. Patients with plasma HDL values lower than 50 mg/dL were collected into the first and 50 mg/dL and higher into the second groups. There were 183 patients in the first and 73 patients in the second groups. Although the male ratio (49.7 versus 16.4%, p<0.001), smoking (32.7 versus 17.8%, p<0.01), plasma triglycerides values (162.7 versus 134.5 mg/dL, p= 0.005), and chronic obstructive pulmonary disease (COPD) (16.9 versus 10.9%, p<0.05) decreased, the mean age (45.6 versus 51.8 years, p= 0.002), body mass index (BMI) (26.8 versus 29.3 kg/m2, p= 0.013), fasting plasma glucose (FPG) (110.8 versus 134.1 mg/dL, p= 0.02), low density lipoproteins (LDL) (119.6 versus 135.3 mg/dL, p<0.001), white coat hypertension (WCH) (26.2 versus 36.9%, p<0.05), hypertension (HT) (13.6 versus 28.7%, p<0.001), and diabetes mellitus (DM) (15.3 versus 23.2%, p<0.05) increased by the increased plasma HDL values (40.4 versus 58.2 mg/dL, p<0.000), significantly. Whereas coronary heart disease did not change, probably due to effects of smoking on the first and aging and excess weight on the second groups. The authors concluded that the decreased male ratio, smoking, plasma triglycerides values, and COPD, the mean age, BMI, FPG, LDL, WCH, HT, and DM increased by the increased plasma HDL values. So HDL may act in similar direction with LDL in the metabolic syndrome.

Helvaci M.R et al; tried to understand whether or not low density lipoproteins (LDL) may actually be some negative acute phase proteins (APP) in the plasma. Patients with plasma triglycerides values lower than 100 mg/dL were collected into the first, lower than 150 mg/dL into the second, lower than 200 mg/dL into the third, and 200 mg/dL and higher into the fourth groups, respectively. They studied 457 cases (266 females and 191 males), totally. The male ratio, mean age, body mass index (BMI), fasting plasma glucose (FPG) and prevalences of smoking, white coat hypertension (WCH), hypertension (HT), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) increased parallel to the increased plasma triglycerides values from the first towards the fourth groups, continuously (p<0.05 nearly in all steps). Whereas the mean LDL values increased just up to the plasma triglycerides value of 200 mg/dL and then decreased, significantly (140.9 versus 128.2 mg/dL, p= 0.009). The authors concluded increased plasma triglycerides values may be one of the most significant parameters of the metabolic syndrome that is characterized with disseminated endothelial damage, inflammation, fibrosis, accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Although the continuously increased male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD, parallel to the increased plasma triglycerides values, the mean LDL values increased just up to the plasma triglycerides values of 200 mg/dL and then decreased, significantly. The significant decrease can be explained by the hypothesis that LDL may actually be some negative APP in the plasma.

Ebtisam, E from Libya, looked at the Kambo Ritual. Those who practice it claim it is a source of vitality and health but is it an addictive substance with a short term euphoria.

A Comparative Retrospective Study of Lipid Profile in Obese Type 2 Diabetics and Obese Non Diabetics in Aseer Region, K.S.A.

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ABSTRACT

Background: There is an increase in the prevalence of obesity all over the world. It has become a serious problem as it leads to several other metabolic chronic disorders including Diabetes mellitus (DM), one of the major global pandemics nowadays. Obesity and DM are currently threatening health, well-being and welfare of humans. They have a close relationship, and type 2 diabetes mellitus (T2DM) is strongly associated with obesity. T2DM is a common disorder known to everybody, with a prevalence that usually rises with increasing degrees of obesity. Dyslipidemia is found high in patients with diabetes mellitus and obesity. There is increasing evidence that abnormal changes in the metabolism of lipids are amazingly very important risk factors of diabetes leading to many complications. The most important complications are lipid profile abnormalities which are a good indicator for risk (risk factor). Abnormalities in the serum lipid levels are most likely to participate to the increased risk of coronary artery diseases in patients with diabetes. The Aim of this study is to assess the correlation between serum lipid profile as a risk factor for cardiovascular disease with other biochemical/hormonal variables, anthropometric and clinical variables among obese diabetes mellitus and obese non-diabetic patients.

Methods: A comparative retrospective cross sectional study of obese type 2DM and obese non-diabetic patients was conducted at the Family Medicine Department, College of Medicine, King Khalid University, Abha, Saudi Arabia through data provided by the Medical Specialist Center in Abha city and Diabetes and endocrine Centre which belong to Khamis Mushait Military Hospital from March 2020 to May 2020. A total of 500 Saudi participants (200 obese Type 2 diabetic patients (T2DM) [Group I], 200 obese non-diabetic patients [Group II] and 100 healthy controls [Group III]) were randomly selected using systematic random sampling technique to assess the association of dyslipidemia and other biochemical/hormonal variables as risk factors in obese T2DM and obese non-diabetic patients. Fasting venous blood sample was collected. Patients were subjected to investigations of fasting blood sugar, glycosylated hemoglobin (HbA1c), fasting serum lipids profile, kidney function tests, liver enzymes, thyroid function tests and vitamin D level. Anthropometric and clinical variables among obese diabetes mellitus and obese non-diabetic patients were evaluated. Statistical analysis was carried out using standard deviation and chi-square from which 'p' value is derived. Independent sample t-test was used to compare means. P-value < 0.05 was considered statistically significant.

Results: **In the obese diabetic patient group (GI) and obese non-diabetic patient group (GII), the mean total cholesterol levels, triglycerides levels, LDL-C levels were found to be [TC =210.45±43.12 mg/dl, 224.32±63.47], TG [192.48±85.46 mg/dl, 205.41±120.81] and LDL-C[115.46±40.13 mg/dl, 135.27±45.87] and this was significantly higher than in the controls (GIII) (P<0.01). However, the mean HDL-c value for GI & GII was found to be 58.79±18.93 mg/dl and 53.27±18.59 mg/dl. The HDL-c /LDL-c ratio was calculated in GI and GII and it was found to be (0.26 +0.05 & 0.53 + 0.47 vs 0.56 + 0.28) which was higher than those reported in the control group. A significant difference (P<0.0001) was found between patients and control population when the serum TC, TG, HDLc values, LDLc values, HDLc /LDLc ratio were compared to them. No significant differences were observed between different age categories and gender along with both patient groups and controls. Evident correlation was observed between anthropometric measurements and the lipid profile in GI and GII.**

Conclusion: **The study has documented several lipid abnormalities in obese type 2 diabetes mellitus and obese non-diabetic patients and has pointed to the significance of diabetic management in the control of lipid abnormalities where the control of overweight and obesity is of utmost importance. That is why in the upcoming studies we will try to detect the pattern of eating in Saudi people in Aseer Region and its relation to obesity with its subsequent. DM patients as well as obese patients are more prone to dyslipidemia which is an important risk factor for atherosclerosis and coronary heart disease so they require special attention to proper eating, and hypolipidaemic drugs to avoid associated co-morbidity of diabetes mellitus. This can be done through health education at the primary care level and the diabetic clinics.**

Key words: **Type 2 Diabetes Mellitus; Obesity; Dyslipidemia; Lipid Profile; BMI (Body Mass Index)**

Introduction

Overweight and obesity are the main risk factor for diabetes that can be modified. Adults with obesity are many times more likely to develop diabetes mellitus than adults of a healthy weight. Currently 90% of adults with type 2 diabetes are overweight or obese (1). People with severe obesity are exposed to a high risk of developing type 2 diabetes than obese people with a lower BMI (2). There is a marked association between obesity and type 2 diabetes. The likelihood and severity of type 2 diabetes are linked with increased weight and body mass index (BMI). There is more than five times greater risk of diabetes in obese people compared to those of a healthy weight, with a threefold increase in risk for overweight people (3). It is well known that the body fat distribution is usually an important determinant of increased risk of diabetes; the precise mechanism of association remains unclear. It is really unclear why not everybody who is obese develops type 2 diabetes and why not all people with type 2 diabetes are obese (4,5). Everybody with overweight or obesity is more vulnerable to have type 2 diabetes. When BMI increases, the risk of developing type 2 diabetes increases (6).

The most important environmental risk factors in T2DM patients were high caloric intake, family history, decreased physical activity and stronger multiple genetic predisposition. Obese patients have an induced insulin resistance and the mechanism of this resistance is not well known. Inflammation may be the common mediator linking obesity to the pathogenesis of diabetes (7).

Once there is obesity, the first and foremost observable changes are impaired glucose tolerance and increased insulin resistance, which result in hyperinsulinemia. This may be resulting from a combination of multiple genetic predispositions and environmental factors, that causes deranged insulin secretion (8).

Dyslipidemia is usually associated with obesity and diabetes. An increased level of plasma free fatty acids, cholesterol and triglycerides leads to deceased levels of high-density lipoprotein (HDL), and altered low-density lipoprotein (LDL) which are associated with a higher risk of cardiovascular disease (9).

The metabolic effects of subcutaneous and intra-abdominal fat are different which may be due to differences in adipose tissue distribution. It is known that abdominal fat is considered to be most likely lipolytic than subcutaneous fat. It has an unusual role in producing insulin resistance leading to diabetes mellitus. The body fatty acid release is higher in obese subjects as compared to lean subjects because of their greater fat mass (10). One of the studies found that the association between enlargement of visceral adipocytes and dyslipidemia are independent of the body composition and the fat distribution in obese subjects (11). The data collected were similar to those seen in patients suffering from type 2 diabetes. Inflammatory molecules that are produce by a lot of adipose tissue including TNF-α, IL-6, IL-1, serum amyloid A (SAA) and adiponectin, also play an important role in the development of dyslipidemia (12).

The association of hyperglycemia with dyslipidemia affects the progression of coronary heart disease and thus increases the rate of mortality in diabetes mellitus patients. Aggressive management and control of increased lipid levels along with antidiabetic treatment not only reduces the complications of type 2 diabetes mellitus but also reduces the mortality rate (13).

Obesity is a disorder of the body regulatory system characterized by accumulation of excess body fat. It is an abnormal growth of fat cell size (hypertrophic obesity) or an increase in fat cell number (hyperplastic obesity) or a combination of both. Obese people are more likely to have high cholesterol levels; so this increases the risk of atherosclerosis (14). Obesity is important in the development of insulin resistance in metabolic

syndrome that links with coronary heart disease. T2DM patients with dyslipidemia and obesity have markedly increased risk of coronary heart disease than dyslipidemic non diabetic obese patients (15).

Vitamin D has its unique roles other than calcium homoeostasis and bone metabolism as it has emerged linking the fat-soluble vitamin to obesity and T2DM. It appears to enhance insulin sensitivity through different mechanisms (16). The studies have found a strong link between vitamin D deficiency, obesity and metabolic syndrome. Many cross sectional and some prospective epidemiological studies have found that low serum 25(OH)D concentrations are associated with T2DM (17).

Vitamin D plays a major role in the pathogenesis and prevention of diabetes, as some evidence suggests (17). In addition, vitamin D deficiency is an independent predictor of the development of coronary artery disease in individuals with diabetes. Furthermore, another study has shown that vitamin D deficiency in diabetes may predict all causes of mortality (18).

The aim of this study was to assess the correlation between serum lipid profile as a risk factor for cardiovascular disease with other biochemical/hormonal variables, anthropometric and clinical variables among obese Type 2 diabetes mellitus and obese non-diabetic patients compared to healthy controls.

Methods

A comparative retrospective cross sectional study of obese type 2DM and obese non-diabetic patients was conducted at the Family Medicine Department, College of Medicine, King Khalid University, Abha, Saudi Arabia through data provided by Medical Specialist Center in Abha city which is allocated for chronic disease in Abha city and receives patients looking for the management of their chronic and endocrine disorders, and Diabetes Centre of Khamis Mushait Military Hospital from March 2020 to May 2020. Abha and Khamis cities constitute the central capital of Aseer region and all the citizens from all Aseer districts are pooled to these two cities for specialized medical and non-medical issues.

A total of 500 Saudi participants were categorized as follows: (200 obese Type 2 diabetic patients (T2DM) [Group I], 200 obese non-diabetic patients [Group II] and 100 healthy controls [Group III]) were randomly selected using systematic random sampling technique from March 2020 to May 2020. The demographic clinical data and medical history were recorded. The Body mass index (BMI) was considered normal if it was below 25kg/m2 and 30 kg/m2 or greater was obese (19).

Fasting blood glucose, Glycosylated hemoglobin (HbA1c), and lipid profile were tested as well as other Biochemical findings such as: liver enzymes [Aspartate transaminase (AST), Alanine transaminase (ALT), alkaline phosphatase (ALP)], and kidney function tests. These biochemical findings were estimated with commercially available kits and run on AU480 Chemistry Analyzer, Beckman Coulter. Thyroid function test (Free T3, Free T4 and TSH) and vitamin D were also estimated through Access 2 immunoassay system, Beckman Coulter. Serum lipids profile were done on a sample of blood after fasting for 14-16 hours. LDL-Cholesterol was estimated by using Friedewald formula (20) LDL-Cholesterol = Total Cholesterol – (HDL cholesterol + Triglycerides/5).

The method used for determining the cholesterol and triglycerides levels in the laboratory was the enzymatic color method. Dyslipidemia was defined according to the American Association of Clinical Endocrinologists' guidelines (21). The study was approved by the ethical board of King Khalid University in March 2020. Inclusion and exclusion criteria were involved in this study and that included (22):

Inclusion Criteria: The obese patients have been diagnosed with diabetes mellitus (GI). Obese non-diabetic group (GII), All had BMI more than 30 kg/m2.

Exclusion Criteria:

1. Diabetic patients with overt complications including neuropathy, nephropathy, retinopathy, and ischemic heart disease.

2. Patients with acute complications like diabetic keto-acidosis, non-ketosis hyperosmolar coma and hypoglycemia.

3. Patients with coexisting illness like chronic liver disease or hypothyroidism.

4. Patients on drug therapy like diuretics, steroids, oral contraceptives and beta blockers etc.

Preformat was filled in for each patient and a full history was also taken from them. The basic anthropometric measures including: height (mts), weight (kg) and BMI were obtained in all subjects.

Statistical analysis:

Data entry and data analysis were done using SPSS version 24 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation. Chi-square test and Fisher Exact test were used to compare between qualitative variables. Independent sample t-test was used to compare quantitative variables between groups. P-value was considered statistically significant when $P < 0.05$. Paired-T was used to compare between variables in the same group. ANOVA analysis was done to compare the mean of each parameter.

Results

This study was conducted on 200 obese type 2 diabetes mellitus patients (T2DM, GI), 200 obese non-diabetic patients (GII) and 100 age matched controls (GIII). The demographic distribution of our study population was gathered including age, sex, systolic and diastolic blood pressure (BP) and Anthropometric measures including : height (cm) ,weight (Kgm) and Body Mass Index(BMI) of the study groups as shown in (Table I & II), (Figure 1).

Lipid Profile evaluation revealed that the cholesterol levels were increased (n=154, 77.0 %) in obese T2DM patients (GI) and were increased also (n=122 , 61.0%) in obese non-diabetics (GII). The triglycerides were increased in (n=142, 71.0%)

obese T2DM patients and (n=108 ,54.0%) of the obese non diabetics showed increased values. The LDL-C levels were increased in (n=140, 70.0 %) of obese patients with T2DM, where (n=122 , 61.0 %) of the obese non diabetics had increased values. The HDL-C levels were decreased in (n=144, 72.0%) of obese T2DM; whereas only (n=92, 46.0 %) of the obese non diabetics had decreased values as shown in Figure 2.

Overall, obese T2DM patients (GI) had significantly higher total cholesterol (224.32 ± 63.47 vs. 165.42 ± 43.12 mg/dl), triglycerides levels (205.41±12.81 vs. 110.49±52.43 mg/dl), low density lipoprotein (135.27±45.87 vs. 102.15±34.21mg/dl) and significant decline of high density lipoprotein cholesterol (35.27±2.59 vs 62.71±14.89 mg/dl) as compared to healthy controls, respectively. Along with the obese non-diabetic patients (GII), a significant difference was found between patients and control population when the serum total cholesterol, triglycerides, LDLc values and HDLc values were compared to them (210.45±43.12 vs. 165.42 ± 43.12 mg/dl, 192.48±85.46 vs. 110.49±52.43 mg/dl, 115.46±40.13 vs. 102.15±34.21mg/dl and (58.79±18.93 vs 62.71±14.89 mg/dl).

However, the HDLc /LDLc ratio was found to be lower in GI and GII than those reported in the controls (0.26 +0.05 & 0.53 + 0.47 vs 0.56 + 0.28).

The detailed anthropometric parameters: height in meters, weight in kilograms and body mass index (BMI) are shown in Table 2. Evident correlation was observed between anthropometric measures with lipid profile (Figures 3 & 4) (obese T2DM (GI) : P value was <0.05 [P= 0.048*,0.025*, 0.003**,0.026*] regarding correlation of BMI to total cholesterol, Triglycerides, HDL-C and LDL-C respectively while in obese non-diabetic patients(II), P value was<0.05 [P= 0.002**,0.019*, 0.042*] regarding correlation of BMI to total cholesterol, Triglycerides and HDL-C respectively, while it was non-significant regarding LDL-C, P value was >0.05(P=0.108).

The estimated levels of lipid profile in obese type 2 diabetes (GI) and obese non diabetic patients (GII) along with fasting blood sugars and HBA1c compared to the control group (GIII) are shown in Table 3. Regarding the fasting blood sugars, it was significantly higher in GI compared to GII and III (P<0.001**, P<0.000*** respectively). In both groups (II and III), the fasting blood sugar was within normal limits (P>0.05).

Hemoglobin A1c (HBA1c) level showed highly significant increase in GI compared to GII and the control group (GIII); although it is noticed to be increased in GII to the upper border of normality it is still within normal.

There is no significant difference all over the three groups regarding the other biochemical variables including: serum creatinine level, liver enzymes: Aspartate transaminase (AST), Alanine transaminase (ALT), alkaline phosphatase (ALP) and Thyroid function tests (free T3, Free T4 and TSH) 9P>0.05). Regarding vitamin D estimation, it was found that there was negative significant correlation (highly significant decline) in vitamin D levels in GI and GII compared to the healthy control group (GIII) [P=0.002**,0.031*] .

Table 1: Descriptive clinical characteristic status of the study groups

Variable \ Group		Obese T2DM group (GI)	Obese non-DM group (GII)	Control group (GIII)	*P* value
Age (Mean ± SD)		55.03±16.21	39.53±14.46	40.80±6.89	*P > 0.05 NS*
Sex (N, %)	Male	81(40.5%)	75(37.5%)	39(39.0%)	*P > 0.05 NS*
	Female	119(59.5%)	125(62.5%)	61(61.0%)	
Systolic BP (Mean ± SD)		138.22±19.12**	132.73±13.50**	119.80±7.70	*P*<0.001
Diastolic BP (Mean ± SD)		78.96±12.88*	73.61±9.13*	71.80±2.43	*P*<0.05

*SD = Standard deviation, T2DM= type 2 diabetes mellitus, BP=Blood pressure. P < 0.05 = Significant. N.S.=Non-significant.

Table 2: Anthropometric Parameters of the study groups

Parameter \ Group	Obese T2DM group (GI)	Obese non-DM group (GII)	Control group (GIII)	P value
Height(m) (Mean ± SD)	159.83±9.81	165.59±10.04	160.32±8.66	*P>0.05*
Weight (Kg) (Mean ± SD)	79.96±16.21	98.47±18.94	78.76±12.89	*P<0.01*
BMI (Mean ± SD)	31.07±6.38	37.33±7.12	28.70±3.58	*P<0.01*

SD-Standard deviation, BMI – Body mass Index, T2DM – Type2 Diabetes Mellitus, P < 0.05 = Significant.

Table 3: Lipid Profile, FBS and HBA1c in the Study Group

Parameter \ Group	Obese T2DM group (GI)	Obese non-diabetic group (GII)	Healthy control group (GIII)	P value
Cholesterol(mg/dl) (Mean ± SD)	224.32 ±63.47	210.45±43.12	165.42 ±43.12	*P<0.000****
Triglycerides(mg/dl) (Mean ± SD)	205.41±12.81	192.48±85.46	110.49±52.43	*P<0.000****
HDL-C(mg/dl) Mean ± SD	35.27±2.59	58.79±18.93	62.71±14.89	*P<0.02**
LDL-C(mg/dl) (Mean ± SD)	135.27±45.87	115.46±40.13	102.15±34.21	*P<0.001***
FBS (mg/dl) (Mean ± SD)	170.45±12.79	135.29±15.43	81.31±8.45	*P<0.000****
HBA1c (%) (Mean ± SD)	12.88±56.91	5.63 ± 0.85	4.94± 0.68	*P<0.05**

Obese T2DM= obese type 2 diabetes mellitus, SD= standard deviation, HDL-C=high density lipoprotein, LDL-C=low density lipoprotein, FBS=fasting blood sugar, HBA1c = Hemoglobin A1c, P<0.05= significant, NS=Non Significant, S = significant.

Figure 1: Distribution of study population based upon gender

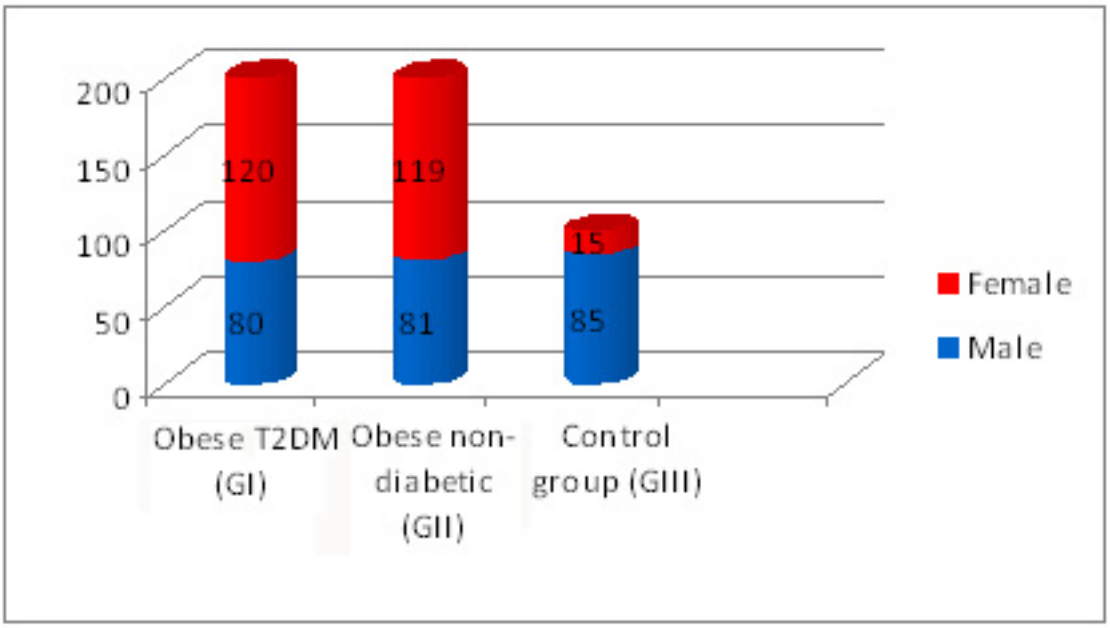
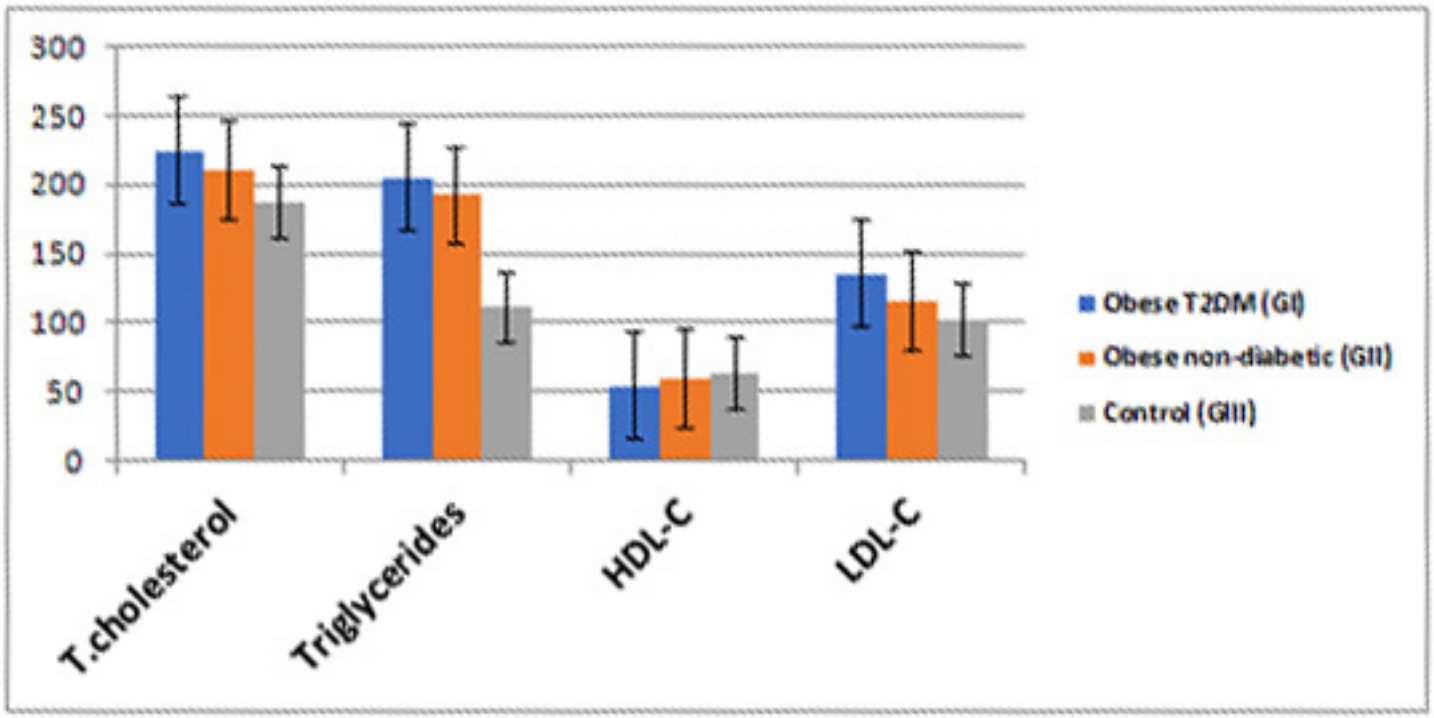


Figure 2: Distribution of study population: (Obese T2DM (GI), Obese non-diabetics (GII) and Control Group (GIII) based upon Serum Lipid Profiles level



DM= Diabetes Mellitus HDL-C=high density lipoprotein, LDL-C=low density lipoprotein

Figure 3: Correlation between BMI and Cholesterol (A), Triglyceride (B), HDL-C (C) and LDL-C (D) in obese-T2DM group (Group I).

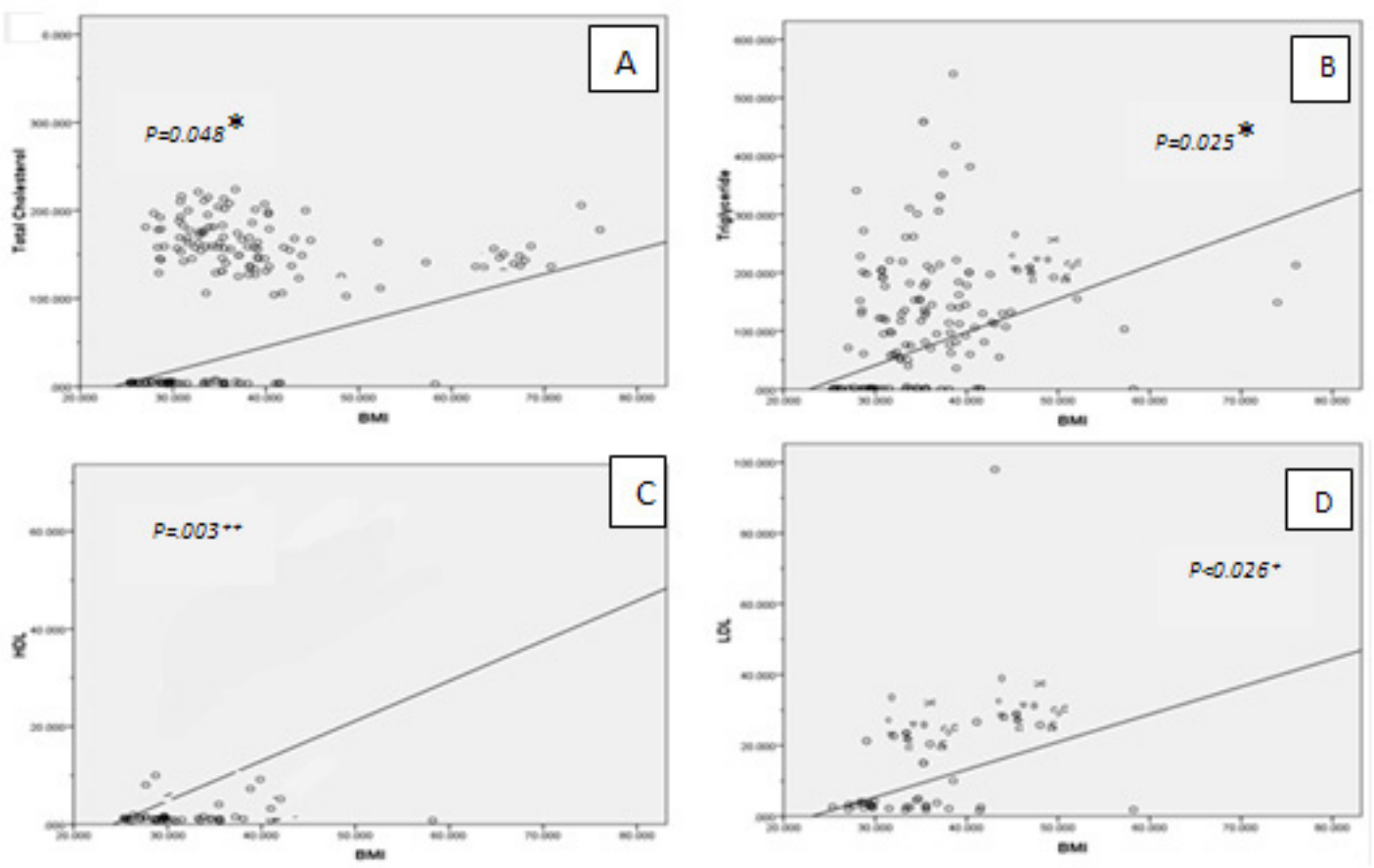
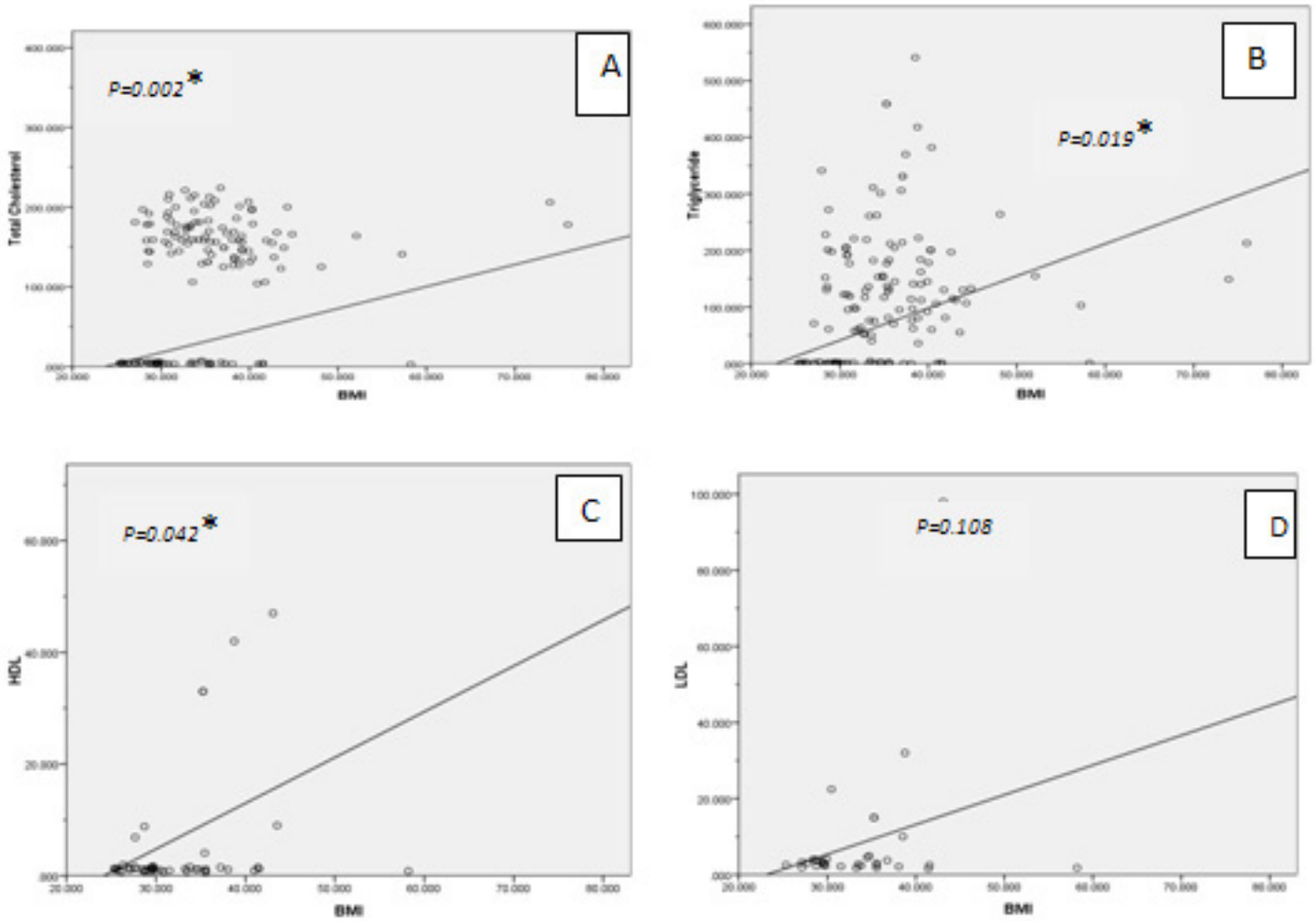


Figure 4: Correlation between BMI and Cholesterol (A), Triglyceride (B), HDL-C (C) and LDL-C (D) in obese non- diabetic patient group (Group II)



Discussion

Diabetes and obesity are chronic metabolic disorders, which are greatly increasing all over the world. They are usually accompanied by many complications which mostly lead to morbidity. Body mass index has a strong relationship to diabetes and obesity.

In our study we were trying to figure out the link between overweight and obesity condition in obese diabetic patients and obese non-diabetic patients based on the serum lipids profile in the Saudi population in Aseer Region, KSA and we were planning to discover the best ways to deal with these serious conditions through controlling the events happening in the body of these patients.

In dyslipidemia in patients with diabetes there are hypertriglyceridemia and low levels of HDL-C (23). Hypertriglyceridemia increases the risk of developing life threatening complications like diabetic ketoacidosis, coronary artery disease and lipaemia retinalis (24). It is more common in diabetics as compared to non-diabetics due to a four fold increase in VLDL triglyceride (25).

Usually type 2 diabetes mellitus and obesity are accompanied by and increased in the deposition of triglycerides in non-adipose tissue, such as skeletal muscle, liver, heart and pancreas. To define obesity, it is fat accumulation in the subcutaneous abdominal and visceral depots, and is most strongly associated with the risk of metabolic and cardiovascular complications (26). Similar to our study, some studies conducted by Santen et al. and Peret et al. observed mean serum triglyceride levels much higher in obese diabetics in comparison to obese control subject (27&28). The relationship between obesity and T2DM is affecting anthropometric indices so that is supplying us with an effective screening and follow up for T2DM. However, the best index (BMI) for indicating the relationship between obesity and T2DM is unknown and the conclusions are not uniform (29).

Evident correlation was observed between anthropometric measures with lipid profile (obese T2DM (GI)) : P value was <0.05 [P= 0.048*,0.025*, 0.003**,0.026*] regarding correlation of BMI to total cholesterol, Triglycerides , HDL-C and LDL-C respectively while in obese non-diabetic patients (GII), P value was<0.05 [P= 0.002**,0.019*, 0.042*] regarding correlation of BMI to total cholesterol, Triglycerides and HDL-C respectively, while it was non-significant regarding LDL-C; P value was >0.05(P=0.108). We observed that females in both GI and GII had much increased serum total cholesterol, triglycerides and LDL-c when compared to males participating in the same study. There was an increase in the level of HDL-c among females compared to males in our study and this is good evidence of the positive effect of estrogen in increasing HDL level, as was previously studied (30).

Cardiovascular disease associated with atherogenic dyslipidemia is the more increasing risk to be developed in patients with type 2 diabetes. This signifies individuals having diabetes and those with obesity are more susceptible to develop cardiovascular disease than control individuals. It has been well documented that high levels of cholesterol and LDL play an important role in the development of arteriosclerosis and hence coronary artery disease (22). Dyslipidemia is one of the common associations in T2DM as well as in obese non diabetics and the reported prevalence of dyslipidaemia varied from 25 to 60% (31). Hypercholesterolemia and hypertriglyceridemia, High LDL-C, Low HDL-C and low HDL-C/LDL-C ratio were highly significant in this study in both obese diabetic and obese non-diabetic groups compared to the control group [P<0.001, P<0.01, P<0.05,P<0.001). These values did not differ significantly from the obese non diabetic patient group (GII)[P>0.05).

This is consistent with the study of Jain Darshna, et al who showed that hypertriglyceridemia predisposes the patients to life threatening complications like diabetic ketoacidosis, coronary artery disease and lipaemia retinalis (26). In the study of Gambhir et al, there was low HDL-C which was considered as an independent risk factor for occurrence of premature coronary artery disease (28). Many studies have strongly suggested an inverse correlation of HDL-cholesterol level with the development of ischemic heart disease (29).

Similar studies of D Sharma and A Jain observed increase in the levels of serum total lipids, total cholesterol, serum triglycerides and serum phospholipids in diabetic subjects as compared to normal controls (32). While Yadav NK et al observed Serum HDL – cholesterol levels did not differ significantly (P >0.05) in the two study groups but levels were low in obese diabetics compare to obese controls (33).

Genetic or acquired hypercholesterolemia is considered as an independent CHD risk factor. It is estimated that of most of the total heart diseases, about 56% may be caused by hypercholesterolemia (> 200 mg/dl) alone (34).

Our study showed that there was no apparent sex variation in the prevalence of increased lipid profile regarding obese T2DM as well as obese non-diabetic patients group; with only a slight increase in the female group A study by Nalchjavani and other authors found that all types of dyslipidemia were significantly more prevalent in females (35).

Modern therapy of patients with diabetes demands that the physician aggressively treats lipids to reduce the high risk of cardiovascular disease in this susceptible population and in those with very high triglycerides to reduce the risk of pancreatitis (36&37).

In the current study, increased TG concentrations are consisten tly accompanied by low HDL concentrations that often coexist with the elevated plasma glucose levels. This is in agreement with Shabana et al, who found that a high amount of sugar in plasma (hyperglycemia) results in the transfer of cholesterol esters from HDL-C to VLDL particles (38).

Apparently healthy individuals should get their lipid profiling done once or twice a year and go for appropriate lifestyle changes so as to prevent the onset of metabolic aberrations (39).

Conclusion

In this study we reported that obese type 2 diabetes mellitus patients and obese non-diabetic patients have almost similar serum lipid profile levels. The prevalence of both obesity and type 2 diabetes continues to rise in Aseer region, KSA, along with associated direct patient care costs and wider costs to society. The purpose of this study is to describe the relationship between obesity and type 2 diabetes based on lipid profile and BMI and not to review treatment options and setting plans for further studies. Those groups of patients have well established risk factors for cardiovascular diseases. Realizing that most of the diabetics and obese have a high probability of developing cardiovascular and cerebrovascular disease, it is essential that in an individual who is obese and diabetic (two strong risk factors for coronary artery disease) their dyslipidemia should be properly taken care of, to reduce morbidity and mortality in diabetics.

Despite the small number of studies included, this study provided crucial insights into intervention strategies to address the emerging pandemic of obesity and T2DM among Saudi adults though more elaborate studies with increased sample size may provide more insights.

Other clinical studies worked at reducing the bad effects of these conditions; have been conducted or are undergoing trials. Detailed exploration of the metabolic and molecular basis of the disease may guide new approaches to prevent and treat these conditions since genetic predisposition plays an important role in the pathogenesis of insulin resistance.

Declaration of conflicting interests:

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author declare no conflicts of interest.

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High density lipoproteins may act in a similar direction with low density lipoproteins in the metabolic syndrome

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ABSTRACT

Background: We tried to understand the significance of high density lipoproteins (HDL) in metabolic syndrome.

Methods: Patients with plasma HDL values lower than 50 mg/dL were collected into the first and 50 mg/dL and higher into the second groups.

Results: There were 183 patients in the first and 73 patients in the second groups. Although the male ratio (49.7 versus 16.4%, p<0.001), smoking (32.7 versus 17.8%, p<0.01), plasma triglycerides values (162.7 versus 134.5 mg/dL, p= 0.005), and chronic obstructive pulmonary disease (COPD) (16.9 versus 10.9%, p<0.05) decreased, the mean age (45.6 versus 51.8 years, p= 0.002), body mass index (BMI) (26.8 versus 29.3 kg/m2, p= 0.013), fasting plasma glucose (FPG) (110.8 versus 134.1 mg/dL, p= 0.02), low density lipoproteins (LDL) (119.6 versus 135.3 mg/dL, p<0.001), white coat hypertension (WCH) (26.2 versus 36.9%, p<0.05), hypertension (HT) (13.6 versus 28.7%, p<0.001), and diabetes mellitus (DM) (15.3 versus 23.2%, p<0.05) increased by the increased plasma HDL values (40.4 versus 58.2 mg/dL, p<0.000), significantly. Whereas coronary heart disease did not change, probably due to the effects of smoking on the first, and aging and excess weight on the second groups.

Conclusions: Though the decreased male ratio, smoking, plasma triglycerides values, and COPD, the mean age, BMI, FPG, LDL, WCH, HT, and DM increased by the increased plasma HDL values, HDL may act in a similar direction with LDL in the metabolic syndrome.

Key words: High density lipoproteins, low density lipoproteins, triglycerides, male gender, smoking, excess weight, accelerated atherosclerosis, metabolic syndrome

Introduction

Chronic low-grade endothelial inflammation may be the most common type of vasculitis, and the leading cause of aging in human beings (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by triggering recurrent injuries on endothelium. Probably whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic low-grade endothelial injury, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, all of which reduces blood supply to the end-organs, and increases systolic BP further. Some of the well-known underlying causes and/or indicators of the inflammatory process are physical inactivity, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), cancers, prolonged infections such as tuberculosis, and chronic inflammations such as rheumatologic disorders (5, 6). Some of the irreversible consequences of the chronic low-grade inflammatory process include obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, stroke, other end-organ insufficiencies, early aging, and premature death (7-9). Although early withdrawal of the underlying causes may delay terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, stroke, or early aging, endothelial destruction cannot be reversed effectively due to their fibrotic nature. The triggering etiologies and terminal consequences of the chronic low-grade inflammatory process are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the literature, extensively (10-13). Although the absolute significance of plasma triglycerides in the metabolic syndrome, role of high density lipoproteins (HDL) is suspicious (19). We tried to understand the prognostic significance of HDL in the metabolic syndrome in the present study. Due to the significant association between high plasma triglycerides and CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II (15, 16). Although ATP II determined the normal upper limit of triglycerides as 200 mg/dL in 1994, World Health Organisation in 1999 (17) and ATP III in 2001 reduced the normal upper limit as 150 mg/dL (16). Despite these cutpoints, there are several reports about the lower and safer limits of the triglycerides in the literature (18-20). Tthough the absolute significance of plasma triglycerides in the metabolic syndrome, role of high density lipoproteins (HDL) is suspicious (19). We tried to understand the prognostic significance of HDL in the metabolic syndrome in the present study.

Materials and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients above the age of 15 years were studied. Their medical histories were learnt, and a routine check up procedure including fasting plasma glucose (FPG), serum creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, triglycerides, low density lipoproteins (LDL), HDL, an electrocardiogram, and an abdominal ultrasonography was performed. A Doppler echocardiogram was performed just in required cases. Current daily smokers with six pack-months and cases with a history of three pack-years were accepted as smokers. Patients with devastating illnesses including type 1 DM, malignancies, hemodialysis, ascites, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Additionally, anti-hyperlipidemic drugs, metformin, and/or acarbose users were excluded to avoid their possible effects on blood lipid profiles and/or body weight (21, 22). Body mass index (BMI) of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (16). Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (16). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater is DM (16). Additionally, office blood pressure (OBP) was checked after a 5 minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous -hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases after a 10-minute education about proper BP measurement techniques (23). An additional 24-hour ambulatory blood pressure monitoring was not required due to its similar effectivity with the HBP measurements (3). Eventually, HT is defined as a mean BP of 135/85 mmHg or higher on HBP measurements, and WCH as an OBP of 140/90 mmHg or higher but a mean HBP measurement of lower than 135/85 mmHg (23). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CHD is diagnosed either angiographically or with the Doppler echocardiographic findings as the already developed movement disorders in the cardiac walls. The spirometric pulmonary function tests were performed in required cases and the criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (24). Eventually, patients with plasma HDL values lower than 50 mg/dL were put into the first and 50 mg/dL and higher into the second groups, respectively. The mean age, male ratio, smoking, BMI, FPG, triglycerides, LDL, HDL, WCH, HT, DM, COPD, and CHD were detected in each group and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

There were 183 patients in the first and 73 patients in the second groups. Although the male ratio (49.7 versus 16.4%, p<0.001), smoking (32.7 versus 17.8%, p<0.01), plasma triglycerides values (162.7 versus 134.5 mg/dL, p= 0.005), and COPD (16.9 versus 10.9%, p<0.05) decreased, the mean age (45.6 versus 51.8 years, p= 0.002), BMI (26.8 versus 29.3 kg/m2, p= 0.013), FPG (110.8 versus 134.1 mg/dL, p= 0.02), LDL (119.6 versus 135.3 mg/dL, p<0.001), WCH (26.2 versus 36.9%, p<0.05), HT (13.6 versus 28.7%, p<0.001), and DM (15.3 versus 23.2%, p<0.05) increased by the increased plasma HDL values (40.4 versus 58.2 mg/dL, p<0.000), significantly. On the other hand, CHD did not change between the study groups probably due to the effects of smoking on the first and excess weight and aging on the second groups (Table 1).

Table 1: Characteristic features of the study cases according to the plasma high density lipoproteins values

Variable	Lower than 50 mg/dL	*p*-value	50 mg/dL and higher
Number of cases	183		73
Mean age (year)	*45.6 ± 14.7 (16-79)*	*0.002*	*51.8 ± 11.6 (21-77)*
Male ratio	*49.7%*	*<0.001*	*16.4%*
Smoking	*32.7%*	*<0.01*	*17.8%*
BMI (kg/m²)*	*26.8 ± 4.5 (18.4-39.9)*	*0.013*	*29.3 ± 6.1 (17.8-48.6)*
FPG† (mg/dL)	*110.8 ± 44.2 (63-386)*	*0.02*	*134.1 ± 77.0 (74-400)*
Triglycerides (mg/dL)	*162.7 ± 92.3 (27-617)*	*0.005*	*134.5 ± 81.5 (37-418)*
LDL‡ (mg/dL)	*119.6 ± 35.8 (10-223)*	*<0.001*	*135.3 ± 32.3 (54-239)*
HDL§ (mg/dL)	*40.4 ± 6.1 (22-49)*	*<0.000*	*58.2 ± 8.0 (50-91)*
WCH?	*26.2%*	*<0.05*	*36.9%*
*HT***	*13.6%*	*<0.001*	*28.7%*
*DM****	*15.3%*	*<0.05*	*23.2%*
*COPD*****	*16.9%*	*<0.05*	*10.9%*
CHD*****	15.3%	Ns******	16.4%

*Body mass index

†Fasting plasma glucose

‡Low density lipoproteins

High density lipoproteins

White coat hypertension

*Hypertension

***Diabetes mellitus

****Chronic obstructive pulmonary disease

*****Coronary heart disease

******Nonsignificant (p>0.05)

Discussion

Excess weight may be the most common cause of vasculitis worldwide, and the leading cause of major health problems in this century, since nearly three-quarters of cases above the age of 30 years have excess weight, nowadays (25). Excess weight causes a chronic low-grade vascular endothelial inflammation, terminating with an accelerated atherosclerotic process all over the body (26). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines; all of those behave as acute phase reactants in the plasma (27). Beside that, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of an increased oxygen need of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy, terminating with a decreased cardiac compliance. Additionally, FPG and total cholesterol (TC) increased, parallel to the increased BMI values (28). A combination of these cardiovascular risk factors will eventually terminate with an increase in left ventricular stroke work and higher risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI values in the other study (29), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (30). The relationships between excess weight, increased BP, and higher plasma triglycerides values are well-known in the metabolic syndrome (14). Similarly, prevalence of smoking (42.2% versus 28.4%, $p<0.01$), excess weight (83.6% versus 70.6%, $p<0.01$), DM (16.3% versus 10.3%, $p<0.05$), and HT (23.2% versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in the other study (31). On the other hand, the prevalence of hyperbetalipoproteinemia was similar both in the hypertriglyceridemia (200 mg/dL and greater) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) (31). Similarly, plasma LDL values increased just up to the plasma triglycerides value of 200 mg/dL in the above study (20). Beside that, the mean BMI values increased just up to the plasma triglycerides value of 150 mg/dL, significantly ($p<0.05$ for each step) (20). In our opinion, although excess weight does not affect each individual with the same severity, overweight, obesity, severe obesity, and morbid obesity histories of years should be added into the calendar age with various degrees during calculation of physiological age of the individuals.

Smoking and alcohol may be the second and third most common causes of vasculitis, respectively. According to our experience, both of them should be included into the major components of the metabolic syndrome since they cause chronic inflammation on the vascular endothelium, terminating with an accelerated atherosclerotic process all over the body. Tobacco's destructive effects are particularly prominent in the respiratory tract and lungs, probably due to the highest concentrations of toxic substances found in the cigarette smoke there. The strong and irreversible atherosclerotic effects of tobacco are most clearly detected in Buerger's disease. It 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 in the literature. Eventually, the atherosclerotic effects terminate with early aging, end-organ insufficiencies, and premature death (32). According to our clinical observations, although tobacco does not affect each individual with the same severity, the smoking history of pack-years should be added into the calendar age during calculation of physiological age of the patients. Probably, alcohol gives harm to vascular endothelium by means of similar ways with smoking but alcohol's main targets are the gastrointestinal tract and liver due to the highest concentrations of alcohol and its products there. Thus the drinking history of drink-years should also be added into the calendar age during calculation of physiological age of the individuals. Due to the very low prevalence of alcoholism in Turkey (33), we did not include regular alcohol intake into the present study. On the other hand, although alcoholic drinks provide extra calories for body, smoking in humans and nicotine administration in animals may be associated with a decreased BMI (34). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (35), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (36). According to an animal study, nicotine may lengthen intermeal time, and simultaneously decrease amount of meal eaten (37). Additionally, BMI seems to be the highest in former and lowest in current smokers (38). Smoking may be associated with a postcessation weight gain (39). Similarly, although CHD was detected with similar prevalence in both genders, prevalence of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females in the previous study (40). Additionally, the incidence of myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (41). In another definition, smoking may be more dangerous for women probably due to the higher BMI and its consequences in them. So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite (42). Smoking-induced appetite loss may be related with the smoking-induced vascular endothelial inflammation in whole body, since loss of appetite is one of the major symptoms of disseminated inflammation in the body. Physicians can even understand healing of patients by means of their normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract and lungs, and cause a vascular endothelial inflammation in whole body until their clearance from the circulation. But due to the repeated smoking habit of the individuals, the clearance never terminates. So the patients become ill with loss of appetite, permanently. In another explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (36-38). After smoking cessation, appetite normalizes with a prominent weight gain but the returned weight is the patients' physiological weight, actually.

The prevalence of excess weight increased by decades, particularly after the third decade, up to the eight decade of life (25). So 30th and 70th years of age may be the breaking points of life for body weight, and aging may be the major determiner factor of excess weight. Probably, partially decreased physical and mental stresses after the age of 30 years, and debility and comorbid disorders-induced restrictions after the age of 70 years may be the major causes of the changes of BMI at these ages. Interestingly, the mean age and BMI increased just up to the plasma triglycerides values of 200 mg/dL and 150 mg/dL in the above study, respectively (20). So smoking remained as

the major causative factor of hypertriglyceridemia above the plasma triglycerides value of 200 mg/dL. Beside that, only cases with plasma triglycerides values lower than 60 mg/dL had a normal mean BMI (20). On the other hand, the triglycerides values increased about 8.1 mg/dL for each year of aging up to 200 mg/dL in the plasma (20) indicating that aging alone may be another risk factor for chronic low-grade inflammation on vascular endothelium in whole body. Although ATP III reduced the normal upper limit of plasma triglycerides as 150 mg/dL in 2001 (16), the above study indicated that lower limits provide additional benefits for human health (20). Similar to the recent study (43), prevalence of smoking was the highest in the highest triglycerides having group in the above study (20) that may also indicate the inflammatory role of smoking in the metabolic syndrome, since triglycerides may behave as acute phase reactants in the plasma. FPG, BMI, HT, DM, and COPD increased parallel to the increased plasma triglycerides in the above study, gradually (20). In our opinion, significantly increased mean age by the increased plasma triglycerides values may be secondary to aging-induced decreased physical and mental stresses, which eventually terminates with excess weight and its consequences. Interestingly, although the mean age increased from the lowest triglycerides having group up to the triglycerides value of 200 mg/dL, it then decreased. The similar trend was also seen with the mean LDL values. These trends may be due to the fact that although the borderline high triglycerides values (150-199 mg/dL) are seen together with physical inactivity and overweight, the high (200-499 mg/dL) and very high triglycerides values (500 mg/dL and greater) may be secondary to smoking, genetic factors, and irreversible consequences of the metabolic syndrome including obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (16). But although the underlying causes of the high and very high plasma triglycerides values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalence of HT, DM, and COPD were the highest in the highest triglycerides having group in the above study (20). Eventually, although some authors reported that lipid assessment can be simplified by measurements of TC (44), the present study and most of the others indicated significant relationships between LDL, HDL, and triglycerides values and irreversible end-points of the metabolic syndrome (19, 20, 45). Similar to the present study, the mean age, FPG, systolic and diastolic BP, TC, and HDL values gradually increased from the normal weight towards the overweight and obesity groups in the previous study (19).

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Low density lipoproteins may actually be some negative acute phase proteins in the plasma

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ABSTRACT

Background: **We tried to understand whether or not low density lipoproteins (LDL) may actually be some negative acute phase proteins (APP) in the plasma.**

Methods: **Patients with plasma triglycerides values lower than 100 mg/dL were collected into the first, lower than 150 mg/dL into the second, lower than 200 mg/dL into the third, and 200 mg/dL and higher into the fourth groups, respectively.**

Results: **We studied 457 cases (266 females and 191 males), totally. The male ratio, mean age, body mass index (BMI), fasting plasma glucose (FPG) and prevalences of smoking, white coat hypertension (WCH), hypertension (HT), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) increased parallel to the increased plasma triglycerides values from the first towards the fourth groups, continuously ($p<0.05$ nearly in all steps). Whereas the mean LDL values increased just up to the plasma triglycerides value of 200 mg/dL and then decreased, significantly (140.9 versus 128.2 mg/dL, $p= 0.009$).**

Conclusions: **Increased plasma triglycerides values may be one of the most significant parameters of the metabolic syndrome that is characterized with disseminated endothelial damage, inflammation, fibrosis, accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Although the continuously increased male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD, parallel to the increased plasma triglycerides values, the mean LDL values increased just up to the plasma triglycerides values of 200 mg/dL and then decreased, significantly. The significant decrease can be explained by the hypothesis that LDL may actually be some negative APP in the plasma.**

Key words: **Low density lipoproteins, triglycerides, acute phase proteins, metabolic syndrome**

Introduction

Chronic endothelial damage may be the most common sort of vasculitis, and the leading cause of early aging and premature death in human beings (1-4). Much higher blood pressure (BP) of the afferent vasculature may be the major underlying mechanism by inducing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are predominantly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Because of the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature that reduces blood flow to terminal organs, and increases systolic BP further. Some of the well-known components of the inflammatory process are physical inactivity, animal-rich diet, overweight, smoking, alcohol, hypertriglyceridemia, hyperbetalipoproteinemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension (WCH), rheumatologic disorders, chronic infections, and prolonged cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), mesenteric ischemia, osteoporosis, stroke, early aging, and premature death (5-10). Although early withdrawal of the predisposing factors may delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, or aging, endothelial changes cannot be reversed completely due to their fibrotic nature. Up to now, the predisposing factors and terminal endpoints have been researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medicine, extensively (11-14). Although its normal limits could not been determined clearly yet, increased plasma triglycerides may be one of the most significant indicators of the metabolic syndrome (15-17). Due to the growing evidence about the strong association between higher plasma triglycerides and prevalence of CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for triglycerides abnormalities than did ATP II (18, 19). Although ATP II determined the normal plasma triglycerides value as lower than 200 mg/dL in 1994 (19), World Health Organisation in 1999 (20) and ATP III in 2001 reduced their normal limit as lower than 150 mg/dL (18). Although these cutpoints are usually used to define limits of the metabolic syndrome, there are still suspicions about the safest value of plasma triglycerides in the medicine (16, 17). Although the absolute significance of plasma triglycerides in the metabolic syndrome, role of low density lipoproteins (LDL) is suspicious (21). We tried to understand whether or not LDL may actually be some negative acute phase proteins (APP) in the plasma.

Material and Methods

The study was performed in the Internal Medicine Polyclinic of the Dumlupinar University between August 2005 and March 2007. Consecutive patients at and above the age of 15 years were included. Their medical histories including HT, DM, COPD, and already used medications were learnt, and a routine check up procedure including fasting plasma glucose (FPG), triglycerides, and LDL was performed. Current daily smokers with six pack-months and cases with a history of three pack-years were accepted as smokers. Patients with devastating illnesses including type 1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Additionally, anti-hyperlipidemic drugs, metformin, and/or acarbose users were excluded to avoid their possible effects on blood lipid profiles and/or body weight (22, 23). Body mass index (BMI) of each case was calculated by the measurements of the same physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (18). Cases with an overnight FPG value of 126 mg/dL or greater on two occasions or already using antidiabetic medications were defined as diabetics (18). An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG value between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose value of 200 mg/dL or greater is DM (18). Additionally, office blood pressure (OBP) was checked after a 5 minute rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2 hours. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in the normotensives in the office due to the risk of masked HT after a 10-minute education about proper BP measurement techniques (24). An additional 24-hour ambulatory blood pressure monitoring was not needed due to its similar effectivity with the HBP measurements (3). Eventually, HT is defined as a mean BP of 135/85 mmHg or greater on HBP measurements, and WCH as an OBP of 140/90 mmHg or greater but a mean HBP measurement of lower than 135/85 mmHg (24). The spirometric pulmonary function tests were performed in required cases after the physical examination, and the criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (25). Eventually, patients with plasma triglycerides values lower than 100 mg/dL were collected into the first, lower than 150 mg/dL into the second, lower than 200 mg/dL into the third, and 200 mg/dL and higher into the fourth groups, respectively. The male ratio, mean age, BMI, FPG, triglycerides, and LDL, and prevalences of smoking, WCH, HT, DM, and COPD were detected in each group and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

Results

We studied 457 cases (266 females and 191 males), totally. The male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD increased parallel to the increased plasma triglycerides values from the first towards the fourth groups, continuously ($p<0.05$ nearly in all steps). Whereas the mean LDL values increased just up to the plasma triglycerides value of 200 mg/dL and then decreased, significantly (140.9 versus 128.2 mg/dL, $p= 0.009$) (Table 1).

Table 1: Characteristics features of the study cases according to plasma triglycerides values

Variable	Lower than 100 mg/dL	p-value	Lower than 150 mg/dL	p-value	Lower than 200 mg/dL	p-value	200 mg/dL or greater
Number	159		133		78		87
Mean age	*40.6 ± 17.6 (16-83)*	*0.001*	*46.9 ± 15.9 (16-82)*	*0.014*	*51.7 ± 11.8 (23-73)*	Ns*	50.5 ±12.3 (21-86)
Male ratio	*35.8%*	Ns	*42.1%*	Ns	*43.5%*	Ns	*50.5%*
Prevalence of smoking	*16.3%*	*0.05>*	*23.3%*	Ns	*28.2%*	*0.01>*	*42.5%*
Mean BMI†	*26.7 ± 5.6 (16.7-49.3)*	*0.000*	*29.5 ± 6.0 (18.4-50.5)*	Ns	30.0 ±4.9 (19.2-49.0)	Ns	29.7 ±4.7 (21.0-42.9)
Mean value of FPG‡	102.7 ±40.3 (59-341)	Ns	*102.7 ± 26.6 (71-244)*	*0.009*	*114.6 ± 43.6 (68-320)*	Ns	*117.1 ± 42.1 (80-287)*
Mean value of triglycerides	*70.3 ± 16.4 (27-99)*	*0.000*	*120.8 ± 14.8 (100-149)*	*0.000*	*174.6 ± 14.9 (150-199)*	*0.000*	*304.8 ± 118.7 (200-1.144)*
Mean value of LDL§	*109.7 ± 33.7 (43-269)*	*0.000*	*132.1 ± 31.8 (64-228)*	*0.048*	*140.9 ± 27.7 (75-210)*	*0.009*	*128.2 ± 39.8 (10-239)*
Prevalence of WCH‖	*23.2%*	*0.05>*	*30.8%*	Ns	*32.0%*	Ns	*34.4%*
*Prevalence of HT***	*11.9%*	*0.001 >*	*23.3%*	Ns	*25.6%*	Ns	25.2%
*Prevalence of DM****	*8.1%*	Ns	*12.7%*	Ns	*16.6%*	Ns	*22.9%*
*Prevalence of COPD*****	*9.4%*	Ns	*11.2%*	Ns	*15.3%*	*0.001 >*	*28.7%*

*Nonsignificant ($p>0.05$) †Body mass index ‡Fasting plasma glucose §Low density lipoproteins ‖White coat hypertension
**Hypertension ***Diabetes mellitus ****Chronic obstructive pulmonary disease

Discussion

Excess weight may lead to both structural and functional abnormalities of many organs of the body. Adipose tissues produce leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines acting as acute phase reactants in the plasma (26, 27). Excess weight-induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathogenesis of accelerated atherosclerosis in the whole body (1, 2). Additionally, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of increased oxygen need of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors will eventually terminate with increased left ventricular stroke work and risks of arrhythmias, cardiac failure, and sudden cardiac death. Similarly, the prevalence of CHD and stroke increased parallel to the increased BMI values in the other studies (28, 29), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (30). The relationship between excess weight, elevated BP, and plasma triglycerides is described in the metabolic syndrome (15), and clinical manifestations of the syndrome include obesity, dyslipidemia, HT, insulin resistance, and proinflammatory and prothrombotic states (13). Similarly, prevalence of smoking (42.2% versus 28.4%, $p<0.01$), excess weight (83.6% versus 70.6%, $p<0.01$), DM (16.3% versus 10.3%, $p<0.05$), and HT (23.2% versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in the other study (31). On the other hand, the prevalence of elevated LDL cases were similar both in the hypertriglyceridemia (200 mg/dL and higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (31). Similarly, plasma LDL values increased up to the plasma triglycerides values of 200 mg/dL, but then decreased in the present study, too ($p<0.05$ for all). Beside that, the mean BMI increased just up to the plasma triglycerides values of 150 mg/dL ($p=0.000$) but it did not change with the higher plasma triglycerides values, significantly ($p>0.05$).

Smoking may be found among the most common causes of vasculitis all over the world. It causes a chronic inflammatory process on the vascular endothelium, probably depending on the concentration of smoke that terminates with an accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Thus smoking has to be included among the major components of the metabolic syndrome. Strong and terminal atherosclerotic effects of smoking are the most obviously seen in Buerger's disease (thromboangiitis obliterans). It is an obliterative disease characterized by inflammatory changes in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the medical literature. Although the well-known strong atherosclerotic effects of smoking, smoking in human beinga and nicotine administration in animals may be associated with decreased BMI values (32). Evidence revealed an increased energy expenditure during smoking both on rest and light physical activity (33), and nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (34). According to an animal study, nicotine may lengthen intermeal time and decrease amount of meal eaten (35). Additionally, the mean BMI seems to be the highest in the former, the lowest in the current and medium in never smokers (36). Smoking may be associated with a postcessation weight gain (37). Similarly, although CHD was detected with similar prevalence in both genders, prevalences of smoking and COPD were higher in males against the higher BMI, LDL, triglycerides, WCH, HT, and DM in females (38). This result may show both the strong atherosclerotic and weight decreasing roles of smoking (39). Similarly, the incidence of a myocardial infarction is increased six-fold in women and three-fold in men who smoke 20 cigarettes per day (40). In another definition, smoking may be more dangerous for women probably due to the associated higher BMI and its consequences in them. Parallel to the above results, the proportion of smokers is consistently higher in men in the literature (23). So smoking is probably a powerful atherosclerotic risk factor with some suppressor effects on appetite. Smoking-induced weight loss may be related with the smoking-induced chronic vascular endothelial inflammation all over the body, since loss of appetite is one of the main symptoms of the disseminated inflammations in the body. Physicians can even understand healing of the patients via their normalizing appetite. Several toxic substances found in cigarette smoke get into the circulation by means of the respiratory tract, and cause a vascular endothelial inflammation until their clearence from the circulation. But due to the repeated smoking habit of the individuals, the clearance process never terminates. So the patients become ill with loss of appetite, permanently. In another explanation, smoking-induced weight loss is an indicator of being ill instead of being healthy (34-36). After smoking cessation, normal appetite comes back with a prominent weight gain but the returned weight is the patients' physiological weights, actually.

Although the several negative effects of excess weight on health, nearly three-quarters of cases above the age of 30 years have excess weight (41). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eight decade of life (41). So 30th and 70th years of age may be the breaking points of life for weight, and aging may be the major determiner factor of excess weight. Probably, partially decreased physical and mental stresses after the age of 30 years and debility and comorbid disorders-induced restrictions after the age of 70 years may be the major causes for the changes of BMI values at these ages. Interestingly, the mean age and BMI increased just up to the plasma triglycerides values of 200 mg/dL in the present study. So smoking remained as the major causative factor for the hypertriglyceridemia after the plasma triglycerides values of 200 mg/dL in the present study.

Although ATP III reduced the normal limit of plasma triglycerides values as lower than 150 mg/dL in 2001 (18), whether or not much lower limits provide additional benefits for health is unknown. In the present study, prevalence of smoking was the highest in the highest triglycerides having group which may also indicate inflammatory roles of smoking in the metabolic syndrome, since triglycerides may actually be some acute phase reactants in the plasma. The FPG, smoking, WCH, HT, DM, and COPD increased parallel to the plasma triglycerides values from the first towards the fourth groups, gradually. As

an opinion of us, significantly increased plasma triglycerides values by aging may be secondary to aging-induced decreased physical and mental stresses, those eventually terminate with onset of excess weight and many associated health problems. Interestingly, although the mean age increased from the lowest triglycerides having group towards the triglycerides values of 200 mg/dL, then it decreased. The similar trend was also seen with the mean LDL and BMI values. These trends may be due to the fact that although the borderline high triglycerides values (150-199 mg/dL) is seen together with physical inactivity and overweight, the high triglycerides (200-499 mg/dL) and very high triglycerides values (500 mg/dL or greater) may be secondary to both genetic factors and terminal consequences of the metabolic syndrome including smoking, obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (18). But although the underlying causes of the high and very high plasma triglycerides values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalences of HT, DM, and COPD were the highest in the highest triglycerides having group in the present study. Eventually, although some authors reported that lipid assessment can be simplified as the measurements of total cholesterol and high density lipoproteins (HDL) values alone (42), the present study and most of the others indicated significant relationships between triglycerides and LDL and terminal consequences of the metabolic syndrome (43).

APP are a class of proteins whose plasma concentrations increase (positive APP) or decrease (negative APP) as a response to inflammation, infection, and tissue damages (44-46). In case of inflammation, infection, and tissue damages, local inflammatory cells (neutrophils and macrophages) secrete several kinds of cytokines into the blood, most notable of which are the interleukins. The liver responds by producing many APP. At the same time, production of many proteins is reduced. Thus these proteins are called as negative APP. Some of the well-known negative APP are albumin, transferrin, retinol-binding protein, antithrombin, and transcortin. The decrease of such proteins is also used as an indicator of inflammation. The physiological role of decreased synthesis of such proteins is generally to save amino acids for producing positive APP more effectively. Due to the decreased production of some proteins in liver during severe inflammatory conditions, production of LDL may also be suppressed. Similarly, although the mean triglycerides, fibrinogen, C-reactive protein, and glucose values were significantly higher in cases with ischemic stroke, the oxidized LDL values did not correlate with age, stroke severity, and outcome in the other study (47). Additionally, significant alterations occur in lipid metabolism and lipoprotein composition during infections, and triglycerides increase whereas HDL and LDL decrease in another study (48). Furthermore, a 10 mg/dL increase of LDL was associated with a 3% lower risk of hemorrhagic stroke in another study (49).

As a conclusion, increased plasma triglycerides values may be one of the most significant parameters of the metabolic syndrome that is characterized with disseminated endothelial damage, inflammation, fibrosis, accelerated atherosclerosis, end-organ insufficiencies, early aging, and premature death. Although the continuously increased male ratio, mean age, BMI, FPG, smoking, WCH, HT, DM, and COPD parallel to the increased plasma triglycerides values, the mean LDL values increased just up to the plasma triglycerides values of 200 mg/dL and then decreased, significantly. The significant decrease can be explained by the hypothesis that LDL may actually be some negative APP in the plasma.

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The Kambo ritual

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ABSTRACT

I am writing about an experience I came across accidentally and thought to shed light on for the purpose of education and a snippet of knowledge, about this practice, in the field of dermatology. A mature white lady was noticed to have some aligned, carefully rounded skin dot marks, extensively laid out on different parts of her extremities, including the right shoulder. I asked myself what might they be? On asking about the nature of the wound, a Kambo was mentioned. I was astonished what that might be. So I decided to do my own research, in the scientific journals by using the major data bases; to find answers to its conceptual understanding, nature, applicability and what benefits it could provide to those people who might seek it.

Key words: **toad toxins, phyllomedusa bicolor, kambô, giant leaf frog toxin, shaman ritual.**

Introduction

Kambo is a traditional medicine that is practiced in the Amazonian territory of South America and was long ago used in Chinese medicine. They believed it conferred luck and health to hunters. Also recently, it has been used for pain relief, to clear negative energies, and detox and body cleansing and depression in the UK. Having said that, many people revert to it for various reasons and some are looking for biologically friendly medicines when medicine has failed to sort their agony and misery.

It is basically about the application of frogs' secretions at specific times as a cleansing ritual.

The lady I came across stated it was a cleanser and a detox agent for her body and that she feels wonderful. She is a strong believer in this habit.

Kambo concept

In my search, I found multiple terms that are used for Kambo descriptions, namely Sapo, shaman healer, toad vaccine, frog medicine and ritual of Kambô. It is a traditional medicine in South America.

Kambo is basically a white-colored substance extracted from the skin secretions of a frog, Phyllomedusa bicolor (giant leaf frog, monkey frog or kambô), which is popular in the Amazon region. It is applied through a freshly created skin wound by a superficial burn, for the purification of chronic body and mind ailments(1, 4, 5). This practice has expanded its application now to include substance misuse, sexual stamina and depression (6). This secretion is naturally used by the frog as a defense mechanism in dangerous situations.

The collected toxins have specific chemicals with extreme pharmaceutical potentials. There are approximately 100 including peptides, steroids, indole alkaloids, bufogargarizanines, organic acids, and others, located in the parotoid gland and skins of toads(1). The excreted peptides are; phyllokinin, phyllocaerulein, phyllomedusin, sauvagine, deltorphins, dermorphins, and adrenoregulin(5).

The mucus secretions of toads contain potent opioids which are far more potent than morphine and endorphin substances used for relief pain; however, it is well known to trigger the central nervous system, provoking respiratory inhibition and evoking heavy dependency(4). Not only that, it can exert profound effects on blood vessels, adrenal cortex and many other body organs failing which is its actual functionality (4).

Figure 1: Different styles of Kambo applications

The proposal of it is application is to induce effects to purge, detox and cleanse the body as is peptides have a vasodilative action and analgesic effect, for a complete 15 minutes, after fasting overnight from food but not water.

There have been a few reported cases in the existing literature about emergency presentation of severe gastroenteritis, facial swelling, urine and stool incontinence, muscle weakness, spasms, seizure, confusion, lethargy, dizziness, memory loss, mental confusion state, heart toxicity along with failure and psychosis. All of which were linked to a preceding Kambo administration, by discovering skin marks of superficial burns on various parts of the body(2, 4).

The actual practice

The practice is said to consist of collecting early morning bright green giant leaf frogs after a rain fall with great delicate care to the captured frog. The frog is said to be tapped on the head for the poison, to be released on it is back, tied to a cross stick in front of an open fire, to scrape the secretion then wrapped dry in front of the fire, in small sticks for storage, then applied on the fresh burnt skin by a stick.

There are nearly four to five regularly spaced and aligned dots on the exposed skin of right shoulder or ankle, applied by a heated stick or vine, spreading the dried kambo excreta, on the freshly inflicted burn in the skin. It is usually on the extremities and can be found on other covered body parts. It can range from one application per month to as many as the patient wants. The frog is never harmed and is released to the forest again to preserve its wellbeing (4, 5).

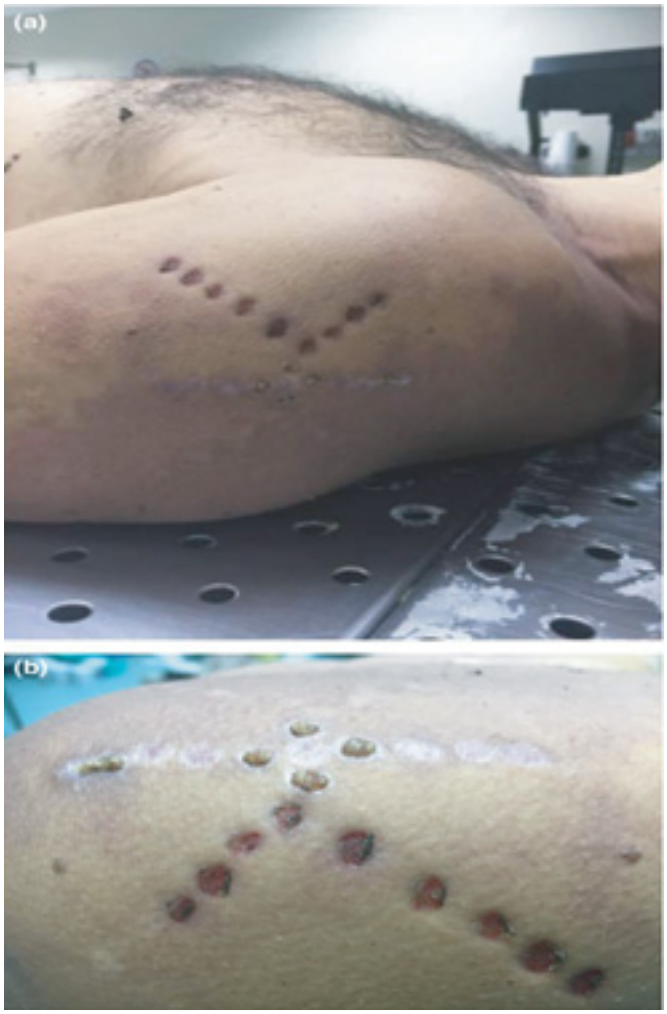

Figure 2: Aligned skin marks

The observed lady had multiple rounded aligned skin marks on multiple rows of three, on her shoulder and the ankle. They were approximately 0.5 cm in diameter with a dried brownish black scab with surrounding skin erythema. After a few days she mentioned she was off work sick and had vitamin deficiency. It is not quite clear how this could link to the Kambo practice. She did not comment much about it on questioning as she strongly believed on the practice and it is alleviating effects. She is however very happy and content. The cost of each session ranges between £UK 60-150.

Those sticks are commercially marketed and sold on the internet as Kambo sticks. They are promoted as voluntary envenomation.

The prevailing belief is that Kambo brings and provides a strong sensation of elevated stamina and strength. Kambo, although controversial, is a growing trend among Britain lately. The process of this cleanse is becoming a common practice in the west including Europe, Australia and USA (3). The question is why someone would like to have a poison in their body when we are already created and programmed to have our own defense and detox mechanism. It is clear the practice is not safe and scientifically not proven from the observed symptoms and clinical trials. There has been so far five reported deaths post Kambo introduction in the literature. It obviously posseses neurochemical effects and it could incur and entail unexpected multiple organ damage and could be fatal and life threatening due to the toxicological effects of the bioactive peptides(5). There should be legislation on it is application and patients should be warned about the possible health impacts and risks.

To conclude, the Kambo is believed in certain tribes of South America to be a purification ceremony. It was first described by Daly et al. Nowadays the practice has expanded extensively and is used by urban people as well. It is said that this practice brings luck to hunters and enhances physical stamina as well as sexual strength. There is no proven scientific evidence in randomized controlled trials, for its effectiveness however those stated healing effects would just reflect the experiences of users and remains merely placebo(7). It seems that some people are turning away from the pharmaceutical industry which is more interested in customers and profitability gained rather than cures, and looking to nature for their ailments and answers.

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