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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.

Poor inhaler technique in patients with bronchial asthma treated in King Hussein Medical Center (KHMC): Rates and effects

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ABSTRACT

Objective: **To 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 was assessed as well.**

Method: **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 rate of poor inhaler technique in patients using inhalers regularly for more than 3 months was assessed during their regular visit to the pulmonary clinic. The effects of poor inhaler technique on asthma control was assessed in these patients as well, using the Global Initiative for Asthma (GINA) control guidelines.**

Results: **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.**

Conclusion: **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.**

Key words: **Bronchial asthma, inhalers, poor technique**

Introduction

Bronchial asthma is one of the most common respiratory diseases worldwide, with an estimated prevalence of 5-10% globally (1,2). Inhaled medications play an important and integral role in the management of bronchial asthma and inhalers are considered to be the cornerstone in bronchial asthma treatment (3). Proper use of the inhalers ensures better deposition of the drug to the lungs, and decreases the systemic side effects (4). Poor inhaler technique in bronchial asthma patients is a significant problem, as it may decrease the therapeutic effect of the delivered medication, causing poor control of the disease (5,6).

The inhaler devices have improved significantly over time in order to ensure easy and proper use of inhalers, and thus to make sure that the medication is delivered properly as intended. However, poor inhaler technique still poses a huge obstacle and might decrease the effectiveness of these inhalers in delivering the drug properly to the lungs (7).

In our study, our aim was to assess the rates of poor inhaler technique in patients with bronchial asthma, treated in the pulmonary clinic in King Hussein Medical Center (KHMC). The cause of the poor inhaler technique was assessed in those patients. The effects of poor inhaler technique on asthma control was evaluated as well.

Methods

In our study, 150 patients who were diagnosed to have bronchial asthma, and who were treated and followed up in the pulmonary clinic in King Hussein Medical Center (KHMC) were enrolled in our study between January 2016 and January 2018. Before being enrolled in the study, the patients were informed properly about the study and its aims, after which written consent was signed by all the patients who agreed to be part of this study. The ethical committee approval was obtained before starting the study. Inclusion criteria were the following: age more than 14 years, an established diagnosis of bronchial asthma, regular follow up in our clinic for at least 2 years, and patients who were given inhaled corticosteroids as pressurized metered dose inhalers (MDI's). Exclusion criteria were the following: patients who were non compliant to their medications, patients who were not given controller inhalers as part of their asthma treatment, and patients with Asthma COPD Overlap (ACO).

After the patients were enrolled in the study, information regarding their age and gender was gathered by the treating pulmonologist. After that, the patients were asked to demonstrate how they used their inhalers in the clinic. The treating pulmonologist evaluated the technique used by the patients. The steps that were checked during the evaluation of the technique of using the pressurized metered-dose inhaler were the following: shaking the canister, holding the canister in an upright position at the mouth, begin with slow breath then actuate the inhaler once while continuing the slow breath, inhaling to total lung capacity, and finally holding the breath for at least 10 seconds. Patients who failed to do any step correctly were considered to have poor inhaler technique.

All the patients were asked whether or not they were educated regarding the importance of using their inhalers properly in order to control their disease, and the proper technique to use their inhaled medications, and their answers were documented in their files. After that, control of their disease was assessed using the Global Initiative for Asthma (GINA) control guidelines.

The number and percentage of the patients who had poor inhaler technique was calculated, and those who were not educated regarding importance of using their inhalers properly in order to control their disease, and the proper technique to use their inhaled medications were calculated as well. The number of patients with poor inhaler technique who had uncontrolled asthma was calculated.

Results

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 proper technique to use their inhaled medications, 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. Out of the 78 patients who demonstrated poor inhaler technique, 57 (73%) patients had uncontrolled asthma, 18 patients (23%) had partially controlled asthma, and only 3 patients (4%) had controlled asthma. While out of the 72 patients who demonstrated proper inhaler technique, 64 patients (89%) had controlled asthma, 6 patients (8%) had partially controlled asthma, and only 2 patients (3%) had uncontrolled asthma.

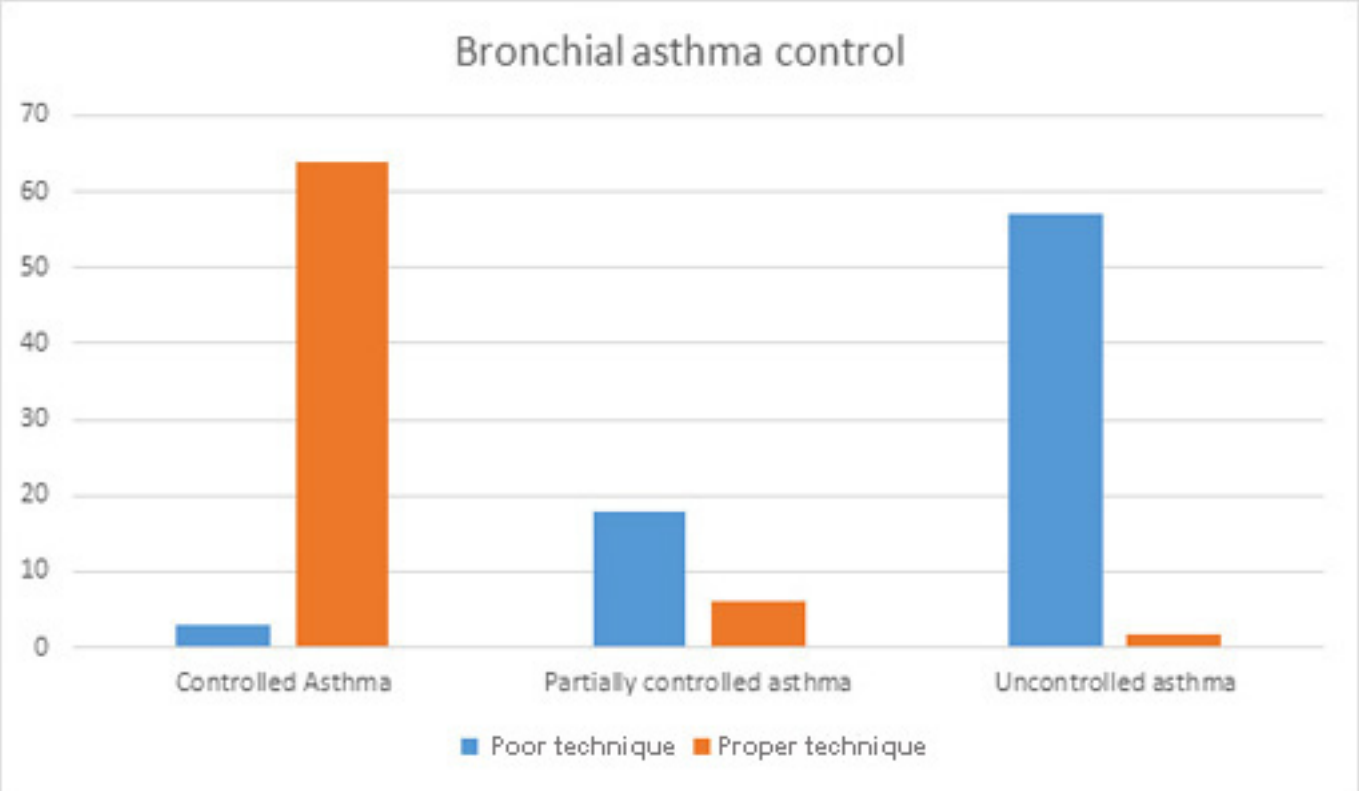
Chart 1 shows a comparison between the control of asthma in patients who demonstrated poor inhaler technique and those who demonstrated proper inhaler technique.

Discussion

Using inhalers in the proper technique is very important in patients with bronchial asthma. Improper inhaler use was shown by many studies to decrease drug delivery to the lungs, which will in turn lead to poor asthma control, and increases ER visits and hospitalization (8-11).

In our study, we evaluated the technique of using the MDI's in patients with bronchial asthma. The rates of poor inhaler technique were found to be significant, with 52% of the patients showing improper inhaler technique. The most common cause for the observed poor technique in our study was the fact that the patients didn't have proper education regarding how to use their device correctly. It is very important, according to the asthma management guidelines, to properly educate asthma patients regarding the handling and technique of their

Chart 1: Comparison between the control of asthma in patients who demonstrated poor inhaler technique and those who demonstrated proper inhaler technique



inhalers, and to assess the technique during each visit to the clinic (12,13). This emphasizes the importance of having inhaler training once the inhaler is prescribed to the patient. This training can be provided either by the pulmonologist or by the respiratory nurse. It was shown that simple verbal description on how to use the inhaler was not sufficient to ensure proper technique in patients with bronchial asthma (14). It is advised that the proper technique should be demonstrated by the healthcare provider in the clinic, and to ask the patients after that to demonstrate their technique (12). A lesser, yet significant factor causing poor inhaler technique was the lack of education about the importance of regular and correct inhaler use on the control of asthma. This emphasizes the importance of the physician-patient relationship, and the importance of explaining the details of the disease to the patient once they are diagnosed in the clinic. Ronmark E et al showed in their study that only 50% of the patients with bronchial asthma showed proper technique when using their inhalers (15). However, the percentage increased to 80% after educating the patients regarding their disease.

An important effect of poor inhaler use in our study was its detrimental effect on the control of bronchial asthma. About 73% had uncontrolled asthma symptoms, compared to only 3% in those who used their inhalers properly. This result is consistent with what was found by other studies, which showed a strong relation between poor inhaler technique and the high rates of uncontrolled asthma (16-20).

Further studies should be done to establish the various factors that can be involved in causing poor inhaler technique in patients with bronchial asthma such as age, gender, level of education and the presence of other comorbidities. Analyzing these factors can help us target the cause, which will in turn increase the rates of proper inhaler use.

In conclusion, the rates of bronchial asthma patients demonstrating poor inhaler technique were significant. Failure to educate the patients regarding the proper technique to use their inhalers was the main cause for this observation. In our study, patients demonstrating poor inhaler technique were found to have higher rates of uncontrolled disease compared to those who used their inhalers properly.

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Is There a Relation between Left Ventricular Ejection Fraction by conventional Simpson's method and Systolic Myocardial Velocity by Tissue Doppler in Heart Failure Patients?

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ABSTRACT

Background: Heart failure is a condition of high morbidity and mortality and its incidence is increasing with the aging of the population. Echocardiography parameters have been shown that correlate well with left ventricular (LV) systolic function.

Aim: This study 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.

Method: This study involved 85 patients with heart failure whose LVEF < 50% (mean age 58 (11) years), LVEF 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.

Results: 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.

Conclusion: 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 maintains high accuracy in prediction of LV systolic dysfunction.

Key words: Systolic function, myocardial velocities, ejection, fraction

Background

Heart failure is a condition of high morbidity and mortality and its incidence is increasing with the aging of the population (1). Left ventricular ejection fraction (LVEF) is the most widely used index to assess cardiac function in clinical studies (2). This is especially due to the lack of an ideal measure of cardiac contractility; as its measurement and understanding are relatively easy, LVEF has remained the most commonly used index. Although LVEF measurement has some prognostic value in certain situations, it is influenced by preload, post load, heart rate, myocardial contractility and dyssynchrony (2).

The distribution of myocardial fibers is not uniform throughout the LV wall. The bundles of subendocardial and subepicardial muscles are arranged longitudinally, while the fibers located in the middle of the wall are aligned circumferentially. This group of muscle fibers is primarily responsible for LV radial axis contraction (3). On the other hand, the longitudinal contraction of the cardiac muscles plays an important role in the pump function of the ventricles (4,5). As the fibers of the longitudinal axis at the heart base correspond to the atrioventricular ring, changes in the longitudinal axis can be measured by the movement of the atrioventricular ring (3).

Longitudinal systolic function of the myocardium can now be evaluated by tissue Doppler imaging (TDI). TDI is a new echocardiography technique that enables the evaluation of the global and regional LV longitudinal functions by the analysis of systolic and diastolic myocardial velocities obtained from mitral annuli and is not affected by the quality of the images or the geometric shapes of the left ventricle (6,7). In recent years, systolic myocardial velocity (Sm) obtained by TDI has been suggested to be an alternative method in the assessment of systolic myocardial functions of various cardiac diseases (8-15) and a cutoff value of (S') greater than 7.5 cm/s had a sensitivity of 79% and a specificity of 88% in predicting normal global function of LV (13).

The objective of this study was to seek whether the assessment of myocardial systolic velocity Sm (average) can be used as an alternative to ejection fraction obtained by Simpson's method. The advantage of this approach is that Sm is not dependent on image quality and therefore could apply to subjects with poor image quality.

Patients and Methods

The study enrolled 85 patients with heart failure who presented to Algamhouria Teaching Hospital and private clinic between January 2016 and July 2017 with signs and symptoms matching the European Society of Cardiology Clinical Practice Guidelines for Heart Failure (16). The study was approved by the local ethics committee of the Faculty of medicine and health sciences, University of Aden (REC-31-2018).

Resting ECGs of the patients were obtained and echocardiographic examinations were performed on all patients. Exclusion criteria included inadequate visualization, severe renal failure, congenital heart disease, cor pulmonale, atrial fibrillation pacemaker and valvular diseases, LVEF ≥ 50%.

Echocardiography Evaluation

All echocardiography examinations were performed by an experienced cardiologist using standard protocol, using ALPINUN medical system E-CUPE 9 echocardiography machine with a 3.5 MHz transducer. Echocardiographic parameters were measured according to the American Society of Echocardiography (17). Values for each parameter were obtained by one examiner averaging measurements from three successive cardiac cycles. Left ventricular ejection fraction was measured by 2D echocardiography obtained by modified Simpson's method from apical four- chambers view. Pulsed-wave TDI was performed by activating the TDI function in the same echocardiographic system. A 3.5mm sample volume was used. In the apical four-chamber view, the TDI cursor was placed at the septal and lateral side of the mitral annulus in such a way that the annulus moved along the sample volume line. In the apical two-chamber view, the TDI cursor was placed at the anterior and inferior side of the mitral annulus in the same manner. Sm was measured at each segment and final LV mean Sm value was represented as the average of four sites (Figure 1).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 20 for Windows statistical software program (SPSS, Chicago, USA). Numeric variables were expressed as mean (±SD), Category variables were expressed as percentage. The Pearson correlation coefficient was used for analysis of linear correlation between variables. A P-value < 0.05 was considered statistically significant.

Results

The mean age of the 85 patients in the study was 58.48 (11) years, 11 (12.9 %) female; 74 (87.1%) male. Of these patients, 56 (65.9%) were hypertensive, 37 (43.6%) were diabetic, 70 (82.4%) had a history of CAD and 61 (71.8%) had dyslipidemia. The mean LVEF was 33.53 (9.94).

Demographic characteristics, 2D echocardiography and TDI parameters for the patients with HF are given in Table 1.

LVEF and Sm values were found to be lower in patients with HF; a stronger correlation was detected between LVEF and Sm ($R = 0.609$, $P < 0.0001$) (Figure 2). The time required to obtain LV average Sm was shorter than the time required calculating LVEF by Simpson's method.

Discussion

This study is the first of its kind in Yemen that evaluates the relation between EF and Sm or the prediction of EF by Sm in patients with heart failure. Spectral TDI could be used as an alternative examination when EF is difficult to assess due to poor image. The study demonstrated a simple quantitative approach to predicting EF using Sm (average) from spectral TDI.

This study found a strong correlation between the two parameters EF and Sm in patients with HF. In daily clinical practice, LV systolic function is mostly evaluated by ejection fraction, which is calculated according to modified Simpson's method, but this method is largely dependent on the quality of images and

Figure 1: Recording of myocardial velocities by TDI from mitral annuli

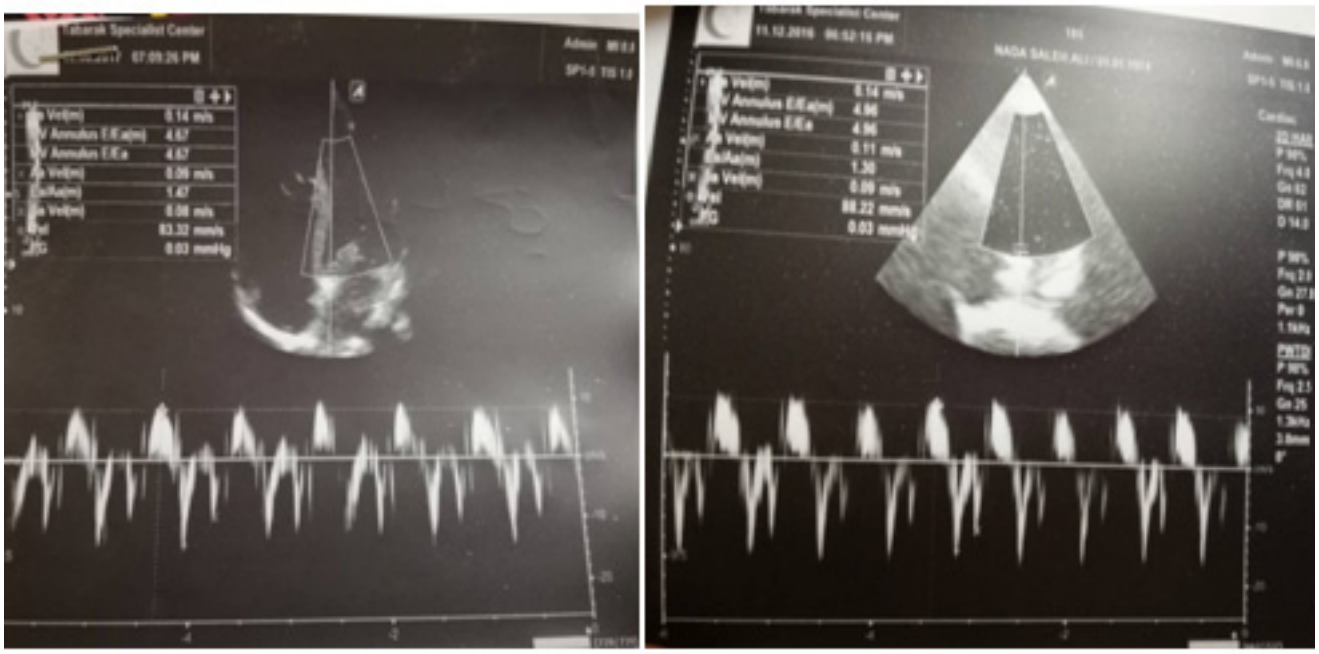
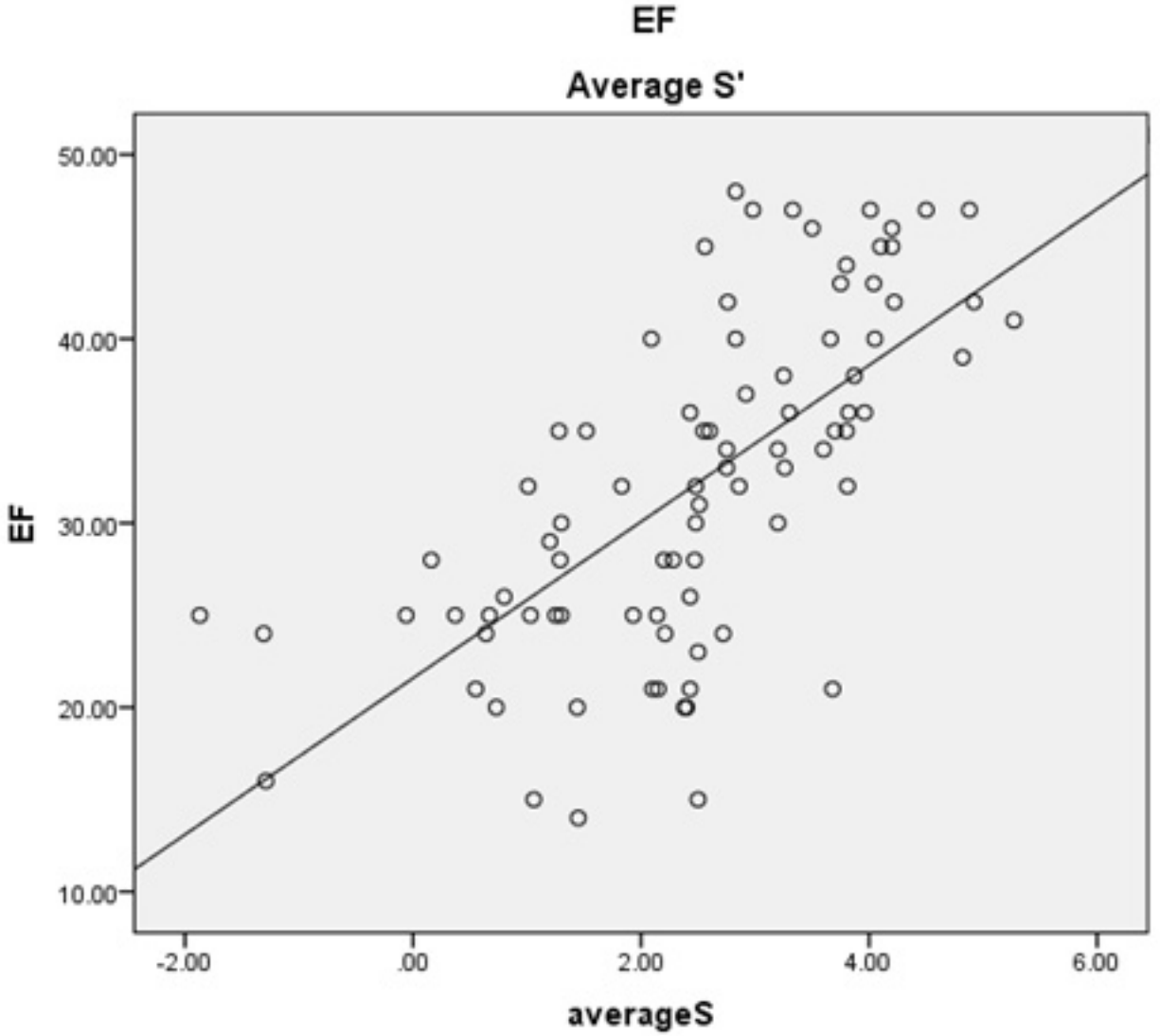


Table 1

TABLE I Demographics and Echocardiography Data	
Variables	Study sample (n =85)
Age (years)	58.48 (11)
Males	74 (87%)
Females	11 (12.9%)
Cause of heart failure	
Ischemic	70 (82.4 %)
Non-ischemic	15 (17.6 %)
HT	56 (65.9%)
DM	37 (43.6%)
Dyslipidaemia	61 (71.8%)
LV ejection fraction	33.53 (9.94)
LV average Sm (cm/s)	2.67 (1.43)

HT = hypertension; DM = diabetes mellitus; LVEF = left ventricular ejection fraction.

Figure 2: Correlation between LV average Sm and LVEF in patients with heart failure. LVEF= left ventricular ejection fraction; Sm= systolic myocardial velocity



LV geometric shapes and is therefore technically difficult in patients with poor image quality. TDI method is clinically useful due to the minimal dependency of Sm on the image quality. In contrast, EF demonstrates strong dependency on the visibility of the endocardial contour when using Simpson's method and is reported to be impossible in an about half of the patients with acute myocardial infarction due to poor image quality (18). Moreover, the calculation of LVEF by this method is time consuming and has a high inter and intra-observer variability (19)

The longitudinal contraction of the cardiac muscles plays an important role in the pump function of the ventricles (4, 5). Longitudinal systolic function of myocardium can now be evaluated by TDI. TDI is a recent technique that allows better assessment of regional and global LV functions by the quantification of myocardial velocities, thereby providing a new way of assessing LV function (20). Assessment of cardiac function by TDI may be more sensitive than traditional methods (6,7). Thus, Sm obtained by TDI has been suggested to be an alternative method in recent years in the assessment of systolic myocardial functions of various cardiac diseases (8-15). In the studies so far, it has been demonstrated that in mixed groups, there has been an agreement between Sm derived from PWD-TDI or color Mmode TDI and LVEF obtained by radionuclide or echocardiographic Simpson's method (8,15).

In the studies conducted in patients with HF, a strong correlation was found between Sm and LVEF (21, 22). The study done by Duzenli et al, including a large number of patients, evaluated the correlation between LVEF derived by modified Simpson's method and Sm obtained by TDI, and found a strong correlation in patients with HF (23).

It was reported that in patients with HF, it has been shown that Sm is decreased in parallel to LVEF (24,25). In HF circumferential dysfunction, as well as longitudinal myocardial dysfunction, can account for the strong correlation between Sm and LVEF in these patients.

The result of this study suggests that in patients with HF in whom the measurement of LVEF is suboptimal because of poor acoustic windows and distorted LV geometry, Sm may be a valuable parameter to select an optimal therapy (pharmacological therapy, cardioverter-defibrillator implantation, etc).

The findings from this study suggest that since Sm is not affected by the quality of the images or geometric shape and is more practical, it can be an alternative parameter to EF in identifying patients with abnormal LV systolic function in patients with HF.

Limitation:

One important limitation of this study was that the results were not valid for patients with preserved EF and normal subjects. Another limitation was the lack of subgroups with atrial fibrillation, conduction abnormalities, pacemakers and prosthetic valves therefore; we could not make any inferences about these specific conditions.

Conclusion

LV myocardial systolic velocities Sm (average) obtained by TDI, a parameter that is easily obtained and practical, can be used to evaluate LV systolic function in patients with HF. The prediction of EF by Sm (average) is a simple method and not time consuming.

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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).

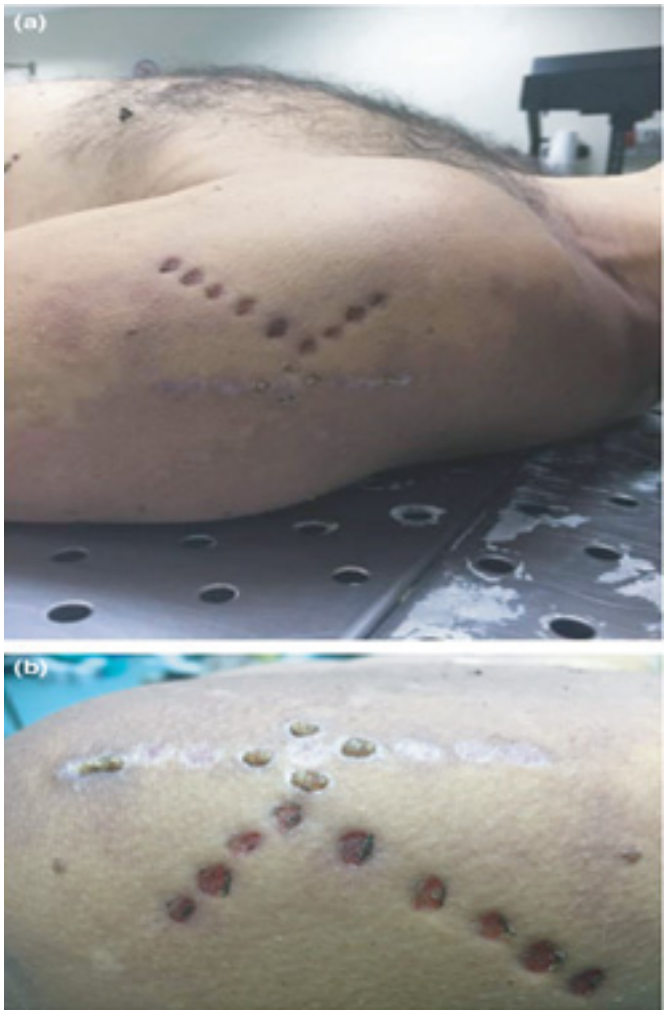

Figure 2: Aligned skin marks

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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