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Table of Content: Volume 10 Number 7 July 2018

ARTICLES

- Polycystic ovary syndrome: Impact of obesity and aging on the profile of gonadotrophin and adrenal hormones** 79
Dere K. A. L., Koffi K. G., Niamke A. G., Bitu D. V., Manhan K. E. and Tiahou G. G.
- Factors associated with atherogenic dyslipidemia among hypertensive patients at southern Ethiopia** 86
Agete Tadewos Hirigo and Eshetu Nigussie Geleta

Full Length Research Paper

Polycystic ovary syndrome: Impact of obesity and aging on the profile of gonadotrophin and adrenal hormones

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Many studies have been conducted to understand thoroughly the mechanism of polycystic ovaries syndrome (PCOS), but very few of them came from Africa. The aim of this study, was firstly to make a diagnostic of this syndrome, according to Rotterdam criteria, and secondly to assess the correlation of obesity and age on this pathology. The study was conducted at Bouaké, within the medical School and Hospital, during the period, September 2014 to January 2016. All participants have been diagnosed with PCOS on the basis of the Rotterdam criteria. The mean age was 25.37 ± 5.47 and the mean body mass index (BMI) was 28.82 ± 8.51 kg/m². There were either significant or no significant statistical differences about parameters value concerning age or BMI into the population. There was no significant statistical difference between age and BMI. Otherwise the overweight and obese patients were both present in the group under 25 years old and in the group having above 25 years old. The differences related to the mean value of hormonal parameters were observed in the two populations according to the BMI range. The mean value of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) has increased according to the augmentation of BMI and age. Contrary to this trend, the mean value of estradiol and sex hormone binding globulin (SHBG) has decreased in the same conditions. The data suggest that in everyday practice, the collaboration between clinician and biologist must be built up in order to make early the diagnosis of PCOS among infertile women.

Key words: Polycystic ovaries syndrome, obesity, age, gonadotrophin, adrenal hormones.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders among adolescent girls and women of reproductive age. PCOS is the leading cause of female infertility (Ehrmann, 2005).

Menstrual irregularity, chronic anovulation, hyperandrogenism, and multiple small sub-capsular cystic follicles in the ovary on ultrasonography characterize the syndrome. Obesity, mainly central obesity, is present in

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varying degrees (30-70%) in women with PCOS. An ethnic variation of the metabolic and endocrine pattern in PCOS was also reported (Ramanand et al., 2012). All features of this syndrome may not be present in an individual patient. Depending on the interactions of different hormones in PCOS patients, the pathogenesis, clinical presentation, and biochemical profile varies in an individual. Hence biochemical parameters and the hormone profile become important in understanding the pathogenesis of PCOS.

Obese women with PCOS are more prone to dyslipidaemia, particularly elevated triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) (Bickerton et al., 2005). However, in other investigations, no difference was observed in lipid profile between PCOS women and control participants. A study (Ehrmann et al., 2006) showed that metabolic syndrome and its components are common in PCOS, especially among women with the highest BMI and insulin levels. Obesity is regarded one of the putative factors leading to metabolic syndrome (MetS); it seems to contribute mainly to the link between PCOS and MetS (Grundy et al., 2007).

During aging in normal subjects of either sex, a gradual increase in body weight is observed, which is associated with an unfavorable impact on metabolic profile and insulin resistance (IR) has been considered as the main pathophysiological link between obesity and metabolic disturbances (Karakelides et al., 2010).

Many other studies have been conducted in order to understand thoroughly its mechanism, but very few of them coming from Africa in general and particularly in the undeveloped countries.

The main goal of this study, realized in Cote d'Ivoire (West Africa), was on the one hand to make a diagnostic of this syndrome, according to Rotterdam criteria, and on the other hand to assess the correlation of obesity and age on the disturbances of the value of hormonal parameters.

MATERIALS AND METHODS

This study was conducted at Bouaké, within the medical school and hospital (Côte d'Ivoire), during the period of September 2014 to January 2016. The study comprised 71 newly diagnosed PCOS women. All participants were in the age group of 15 to 41 years. Patients have been diagnosed with PCOS on the basis of the Rotterdam criteria (Fr and Tarlatzis, 2004); which state that, two out of three of the following are required for diagnosis: Oligo- and/or anovulation (defined by the presence of oligomenorrhea or amenorrhea); clinical and/or biochemical signs of hyperandrogenism [defined by presence of hirsutism (Ferriman-Gallwey score ≥ 6), acne or alopecia, and/or elevated androgen levels]; and polycystic ovaries by gynecological ultrasound. During investigation, patients with congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, and those who were under any medication that affected endocrinal parameters were excluded.

Height and weight were obtained from each subject. The BMI was calculated as the weight in kilograms divided by the square of height in meters.

Laboratory measurements

After a 12-h overnight fasting, 5 mL blood was obtained in the follicular phase of the menstrual cycle (that is, serum progesterone level lower than 2.5 ng/mL). Fasting blood samples were collected in plain and then centrifuged at 3500 rpm for 10 min to separate the serum. The study analyzed either immediately or during the same week after conservation at +4°C.

Hormones, such as, free Testosterone (fT), free estradiol (fE2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), $\Delta 4$ androstene-dione ($\Delta 4$), dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA) and sex hormone binding globulin (SHBG) were measured by the chemiluminescence immunoassay (CLIA) method using a Beckman Coulter Access fully automated analyzer. The hormone kits used in the Beckman Coulter Access analyzer (USA) were from Beckman Coulter, Ireland.

Hyperandrogenaemia was considered at either serum testosterone level above 2.08 nmol/L and/or serum DHEAS level above 7.80 nmol/L (Noorbala 2010). Increased serum 17-OHP was defined in levels above 4.8 nmol/L to exclude congenital adrenal hyperplasia (Tziomalos et al., 2013).

Statistical analysis

All the results were tabulated as mean and standard deviation. The SPSS 20.0 version for statistical analysis was used. The unpaired student t test was used to determine the statistical significance between the study groups. Pearson correlation was used for correlating different parameters. A P value of <0.05 was considered to be statistically significant.

Ethical considerations

The study was approved by the Institutional Ethics Committee, Medical and Scientific Direction, Medical School, Bouaké, Côte d'Ivoire. Written and informed consent was obtained from the individuals who participated in the study.

RESULTS

There were 71 clinically proved, confirmed PCOS patients in the age range 15n to 41 years chosen for the study (Rotterdam criteria). 34 patients were obese against 37 patients hence 47.88% (Table 1), on the another hand 54.93% patients had above 25 years old. The mean age was 25.37 ± 5.47 and the mean BMI was $28.82 \pm 8.51 \text{ kg/m}^2$. There were either significant or no significant statistical differences about parameters value concerning age or BMI in the study population. There was no significant statistical difference between age and BMI. Otherwise the overweight and obese patients were both present in the group under 25 years old and in the group having above 25 years old. The differences related to the mean value of hormonal parameters were observed in the two populations according to the BMI range.

The mean value of testosterone, $\Delta 4$ progesterone, FSH, LH and DHEA were more important in the group of overweight/obese patients than in the normal BMI range.

Table 1. General characteristics of PCOS women in the study.

Parameter	Minimum	Mean	S.D	Median	Mode	Maximum
Age (an)	15	25.37	5.47	25	23	41
Weight (Kg)	40.0	77.82	22.24	71.0	60.0	123.0
size (m)	1.26	1.64	0.08	1.65	1.66	1.80
BMI	15.0	28.82	8.51	26.0	25.0	46.68
T (nmol/L)	0.12	0.58	0.26	0.57	0.60	1.50
D4 (nmol/L)	1.70	3.44	1.18	3.30	2.50	5.80
LH (mIU/L)	0.56	8.27	5.07	7.50	12.0	25.0
FSH (mIU/L)	1.30	5.12	1.60	5.20	7.00	8.50
E2 (pg/ml)	12.0	49.90	47.37	35.0	35.0	227.0
DHEAS (nmol/L)	142.0	2272.82	1079.54	2221.0	892.0	5836.0
DHEA (nmol/L)	2.10	9.68	4.61	8.90	12.0	22.0
SHBG (nmol/L)	2.80	37.96	32.27	31.0	33.0	215.0

T, Testosterone; E2, Estradiol; LH, Luteinizing hormone; $\Delta 4$, $\Delta 4$ androstene-dione; FSH, Follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

Amongst all abnormalities observed, SHBG concentration was the only one which had a significant statistical difference; this value was more important for the patients in the normal BMI group than those in overweight and obese group. The mean value of estradiol was more important in the normal-weight PCOS patients group contrary to all others parameters where the concentration were more elevated into the otherwise and obese group (Table 2).

The mean concentration of estradiol, DHEAS, DHEA and SHBG were statistically significant according to the age. The value of estradiol and SHBG increased with age while the DHEAS and the DHEA concentration decreased in the same time. However, overweight and obese proportion was more important amongst the range under 25 years old and then the mean value of testosterone; LH and FSH were more increased into the group above 25 years old (Table 3).

In total, the mean value of testosterone, LH and FSH has increased according to the augmentation of BMI and age. Contrary to this trend, the mean value of estradiol and SHBG has decreased in the same conditions.

DISCUSSION

Results showed that there is a real difference within hormonal profile within the population. Most of hormonal values were more increasing for overweight and obese PCOS women in contrast to those who had a normal BMI. Amongst the PCOS patients, there were more normal women according to the body mass index than overweight or obese women. This trend could be explained away by the length of the study population and moreover by the bias in the recruitment. Many studies proved that (Moran et al., 2012) obesity is associated mainly to abdominal adiposity in PCOS patients. It is

important to recognize the presence of obesity and its upper body distribution or abdominal adiposity, which changes in accordance to race and geographical distribution (Saxena et al., 2012). They reported that obese PCOS patients have a greater prevalence of some clinical manifestations, such as hirsutism and menstrual disorders; however, other studies have not found differences (Saxena et al., 2012). The main pathophysiological components of PCOS are gonadotropic dysfunction and insulin resistance (Dale et al., 1992). It has been found that both of these components are related to BMI.

In this study, only the difference of SHBG between PCOS patients are statistical significant. The mean value is more elevated to normal PCOS than overweight and obese patients. Out of this parameter and estradiol, the value of testosterone, LH, FSH, $\Delta 4$ androstenedione, DHEA and DHEA-S were more elevated for overweight and obese patients than the lean. Controversy exists about the effect of obesity on serum androgen concentrations in PCOS. Some investigators have reported that testosterone and androstenedione levels are similar in obese and non obese PCOS patients (Dale et al. 1992). However, it is well known that obesity generates a decrease in the sexual hormone-binding globulin (SHBG), and therefore an increase in the free androgens (Holte et al. 1994). Other studies have found that obesity generates an increase in testosterone levels in PCOS patients (Moran et al., 2008). These findings corroborated the explanations of Bhathena (2011), and Mathur et al., (2008) who stated that hyperinsulinemia probably acts at the level of hypothalamic-pituitary axis and stimulates LH secretion which leads to anovulation with irregular cycles. This hypothesis was, in fact, provided by the Escobar-Morreale group, who reported a significantly higher prevalence of PCOS in overweight and obese women compared with their lean peers (28.3

Table 2. Correlation between body mass index (BMI) and the mean value of hormonal parameters.

Parameter		BMI	
		< 25	≥ 25
T	Number	37	34
	Mean	0.56	0.61
	Variance	0.06	0.07
	P value	0.406	
D4	Number	37	34
	Mean	3.36	3.53
	Variance	1.56	1.23
	P value	0.541	
LH	Number	37	34
	Mean	7.60	9.0
	Variance	30.19	2.,62
	P value	0.249	
FSH	Number	37	34
	Mean	4.87	5.40
	Variance	3.04	1.96
	P value	0.167	
E2	Number	37	34
	Mean	50.05	49.73
	Variance	2595.83	1927.35
	P value	0.977	
DHEAS	Number	37	34
	Mean	2309.09	2233.16
	Variance	1065000	1310000
	P value	0.776	
DHEA	Number	37	34
	Mean	9.81	9.53
	Variance	21.54	21.56
	P value	0.813	
SHBG	Number	37	34
	Mean	51.44	22.99
	Variance	1475.34	155.42
	P value	0.000	

T, Testosterone; E2, Estradiol; LH, Luteinizing hormone; $\Delta 4$, $\Delta 4$ androstene-dione; FSH, Follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

vs 5.5% respectively) (Alvarez-Blasco et al., 2006), and this finding has been confirmed by other researchers groups (Liang et al., 2012, Stovall et al., 2011). In the liver, it decreases production of sex hormone-binding protein and IGF-1-binding protein which results in an increase in free androgen in the blood and an increase in free IGF-1 in the ovary.

It is known that androstenedione and testosterone are

produced mainly in the ovaries, while dehydroepiandrosterone and dehydroepiandrosterone sulfate are secreted predominantly in the adrenals (Azziz et al., 2009). However, the disturbance of secretion triggers a high production by the ovaries approximated 50% of testosterone and androstenedione while the adrenals 70% of dehydroepiandrosterone and almost all dehydroepiandrosterone sulfate (Miller et al., 2006).

Table 3. Correlation between age and the mean value of hormonal parameters.

Parameter		Age (years)	
		< 25	≥ 25
BMI	Number	32	39
	Mean	30.43	27.49
	Variance	84.62	60.27
	P value		0.150
T	Number	32	39
	Mean	0.55	0.61
	Variance	0.08	0.06
	P value		0.296
D4	Number	32	39
	Mean	3.59	3.32
	Variance	1.63	1.20
	P value		0.331
LH	Number	32	39
	Mean	7.71	8.73
	Variance	27.79	24.28
	P value		0.406
FSH	Number	32	39
	Mean	4.99	5.27
	Variance	2.71	2.45
	P value		0.404
E2	Number	32	39
	Mean	41.63	56.69
	Variance	1849.60	2519.15
	P value		0.008
DHEAS	Number	32	39
	Mean	2606.93	2001.92
	Variance	1681000	613775
	P value		0.021
DHEA	Number	32	39
	Mean	11.83	7.79
	Variance	19153	15.78
	P value		0.000
SHBG	Number	32	39
	Mean	32.62	42.78
	Variance	1565.66	557.10
	P value		0.016

T, Testosterone; E2, Estradiol; LH, Luteinizing hormone; $\Delta 4$, $\Delta 4$ androstene-dione; FSH, Follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

According to age, it was found that the PCOS was more present among patients in the range above 25 years old. This trend may be justified through the occurrence of disturbance in the regulation of hormonal

secretion related to age. Aging arouses alterations of many functions and make several diseases such as PCOS appear. Although, there were more overweight/obese PCOS patients in the range under 25

years old and amongst them, the level of E₂, DHEA-S and DHEA were statistical significant contrary to SHBG. These results are in accordance with evidence given by previous studies (Herter et al., 2002; Carmina et al., 2010). Additionally, it has been demonstrated that in patients younger than 24 years of age, age is negatively correlated with homeostasis model assessment of insulin resistance (HOMA-IR) and only in patients older than 28 years of age there was a weak-positive association between age and HOMA-IR (Livadas et al., 2014). Accordingly, in this age group, HOMA-IR is strongly correlated with BMI and this positive association should be attributed mainly to BMI increment. There are data suggesting that women with PCOS display a higher degree of intrinsic insulin resistance compared with age and BMI-matched peers (Moran et al., 2010; Palmert, 2002). Additionally, in their study, women with PCOS displayed higher HOMA-IR values compared with their control peers, even in those older than 30 years of age, irrespective of the BMI. Nevertheless, these authors for the first time provided ample evidence that in women with PCOS through time IR is not increased, but rather ameliorated, in non-obese women with PCOS.

The mean value of testosterone, LH, FSH and estradiol are more elevated in the range of PCOS patients above 25 years old in this study. This trend may be due to the number of patients in this proportion; because, age has an adverse impact on this augmentation up to pre- or postmenopausal normal women. In their report, Corbould (2008), notified that androgen action declining with aging. In their report for women with PCOS, but also in controls, androgen levels gradually decrease through time, as has been shown in several studies (Spencer et al., 2007; Panidis et al., 2012). However, it should be emphasized that androgens decreased irrespective of the BMI, implying that the association of androgens with age is direct and not through obesity. Tsikouras et al. (2015) reported that over the past few decades, there has been a striking increase in the prevalence of obesity among adolescents. This obesity is the *primum movens* of this pathology and predisposes to the development of insulin resistance, hyperinsulinemia and PCOS. Due to an increasingly unhealthy lifestyle, growing numbers of adolescent girls are at risk of becoming obese and thus develop a metabolic syndrome. Obesity is found in 50% of the patients with PCOS and is linked to insulin resistance, the metabolic syndrome and cardiovascular complications. It is notable that a large number of young girls with PCOS have a normal body weight and will not develop clinical symptoms of the syndrome until they become overweight. According to Leibel et al. (2006), the frequency of the metabolic syndrome in PCOS patients is approximately 25%.

Conclusion

Based on the results, it can be concluded that PCOS is

independent of age and BMI. Many over hormonal disturbances could arise according to IR resulted from central obesity. The recommendations match what previous authors said about this pathology. Whether this trend should be attributed to the resolution of ovulation, as has been recently suggested, to decrease in androgens, to prevention of obesity, or to a combination of these interrelated factors remains to be further elucidated. However, the data suggest that in everyday practice, the collaboration between clinician and biologist must be built up in order to make early the diagnosis of PCOS among infertile women. The clinician should encourage lean women to maintain their body weight and insist on obese women to reduce their body weight.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Factors associated with atherogenic dyslipidemia among hypertensive patients at southern Ethiopia

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Atherogenic dyslipidemia worsens cardiovascular functions and supporting data concerning dyslipidemia among hypertensive patients in Ethiopian situation is very limited. The objective of this study was to assess factors associated with atherogenic dyslipidemia among hypertensive patients at Southern Ethiopia. A cross-sectional study was conducted on 238 hypertensive participants at Hawassa University comprehensive specialized hospital from September 2015 to June 2016. Systematic random sampling technique was used and written informed consent was obtained from each participant. Socio-demographic and other relevant data were collected by pre-structured questionnaires. In addition overnight fasting blood sample was collected from each study subjects for serum biochemicals determination. About 90.8% of patients had least one dyslipidemia, with the most frequent being hypertriglyceridemia (62.2%) and low high-density lipoprotein cholesterol (HDL-c, 60.9%). Being a female was significantly associated with dyslipidemia. The adjusted odds ratio (95% CI) was 2.1 (1.2-3.9; P=0.01) for hypercholesterolemia (TC), 2.4 (1.1-4.9; P=0.02) for raised low-density cholesterol (LDL-c) and 2.9 (1.6-5.4; P<0.0001) for low HDL-c. In addition, patients with hyperuricemia were more likely to develop hypercholesterolemia, hypertriglyceridemia, low HDL-c and raised TC/HDL-c when compared to patients with normouricemia. The adjusted odds ratio (95% CI) was 1.8 (1.1-3.1; P=0.047), 2.6 (1.4-4.8; P= 0.001), 2.7 (1.5-4.8; P=0.001) and 3.1 (1.7-5.4, P<0.0001), respectively. The prevalence of raised TC, LDL-c, triglycerides and low HDL-c were higher in hypertensive patients and these are an established atherogenic lipid profiles. Therefore, lipid profiles should be performed at the baseline of hypertension diagnosis prior to starting any anti-hypertensive agents and then periodically through treatment follow-up to manage any increasing trends.

Key words: Atherogenic dyslipidemia, hypertension, cardiovascular risks, Southern-Ethiopia.

INTRODUCTION

Hypertension (HTN) is a disease that is characterized by raised blood pressure; and HTN is one of the main indicators of the cluster of clinical anomalies that characterize metabolic syndrome (MetS). About 30 to

40% of the hypertensive subjects develop MetS (Marchi-Alves et al., 2012). Dyslipidemia is the one, which causes atherosclerosis, and the atherosclerosis is linked with pathophysiologic as well as structural alteration in

arteries, and it contributes to the progress of arterial hypertension and other risks (Oparil et al., 2003). In addition, atherogenic dyslipidemia consists of raised blood triglycerides (TGs) and apolipoprotein B (apoB), raised level of small low-density lipoprotein cholesterol (LDL-c) particles, and a reduced level of high-density lipoprotein cholesterol (HDL-c) (NCEP III, 2002). Besides, it is well known that cardiovascular disease (CVD) is associated with HTN and altered level of blood lipids (increased levels of LDL-c, total cholesterol (TC), and TGs) and low level of HDL-c (NCEP III, 2002; Jacobson et al., 2014; Mora et al., 2013). The frequent bunching of hypertension with atherosclerotic dyslipidemia, and other metabolic derangements in patients has been obviously proven to be synergistic and accelerating the development of atherosclerosis and CVD related morbidity and mortality (NCEP III, 2002). Moreover, several studies suggested that serum LDL-c, TGs, TC, apolipoprotein-B levels, TG/HDL-c, were strongly associated with serum hyperuricemia, while the HDL-c level was significantly and inversely associated with hyperuricemia (Peng et al., 2015, Lu et al., 2012, and Conen et al., 2004). This signifies that serum uric acid is a strong risk factor of coronary heart diseases (CHD) (Choi and Ford, 2007). Besides, older age and female gender was also risk factors of dyslipidemia except for low HDL-c (Yu et al., 2015).

Furthermore, urbanization, increased life expectancy, the effect of non-healthy diet and individuals' lifestyle have a great impact on rising trend of CVD in developing as well as developed countries (Joshi et al., 2007). Nowadays, the increasing incidence of hypertension situation and atherogenic dyslipidemia in patients may worsen the health condition and predisposes to other non-communicable diseases. In addition, CVD related illnesses and diabetes are 21st century great temptations in most developing countries. However, data concerning dyslipidemia among hypertensive patients in Africa situation including Ethiopia is limited. Therefore, the present study aimed to assess factors associated with atherogenic dyslipidemia among hypertensive populations.

MATERIALS AND METHOD

Study setting and study population

This institution based cross sectional study was conducted at Hawassa University comprehensive specialized Hospital, Southern Nations Nationalities and Peoples Region (SNNPR) from

September 2015 to June 2016. The Hospital was established in November 2006 and it provides teaching and health services for more than 15 million people of the south region and neighboring regions. Currently, the hospital has over 400 beds and gives different health services including students' practical training. All hypertensive subjects age greater than or equal to 18 years old who had a regular follow-up were eligible in the study. However, patients using lipid-altering drugs, pregnant women, and patients with confirmed diabetes, cardiac and renal failure were excluded from the study.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Hawassa University, College of Medicine and Health Sciences. All the study subjects were well informed about the procedures of the study, the involvement was voluntary and written informed consent was obtained from each study participant prior to data collection.

Sample size and technique

The sample size was calculated based on single population proportion formula and the prevalence of 17.8% of combined dyslipidemia in hypertensive patients (Akintunde et al., 2010).

Based on the above-mentioned, formula, including with 10% non-response rate, the final sample size was calculated to be 248. To select participants from the study population, direct patients flow was checked for one week in the chronic diseases clinic including with patients' logbook assessment. Thus, the trend showed that the average weekly hypertensive patients flow was about 80. Lastly, every fourth hypertensive patients were selected using systematic random sampling approach.

Data collection and measurements

Socio-demographic data and other important clinical information of the study participants were collected by trained nurses using pre-tested structured questionnaires. Hydrodynamic data (Systolic blood pressure and diastolic blood pressure) was measured from each subjects using automatic electronic sphygmomanometer (Omron). The accuracy of the measurement was sustained by measuring a minimum of two readings within 3-5 min differences after patients rested about 10-15 min in the clinic and finally the average blood pressure (BP) was taken and recorded. Regarding anthropometric data, weight, height and waist circumference were measured based on WHO steps. By using weight and height, body mass index (BMI) was calculated for each individual as the weight (Kg) divided by the height square (m²) and classified based on international conventions (WHO, 2016). In addition, waist circumference (WC) of the individuals was measured at the navel using a non-stretched tape (to the nearest 0.1 cm) with standing position.

Overnight fasting 4-5 ml of venous blood sample was collected from each study subjects and then serum was obtained and analyzed for determination of lipid profile and uric acid using A25TM BioSystem Random Access chemistry analyzer in the Hawassa

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University Comprehensive specialized hospital laboratory. While, TC/HDL-c ratio was calculated from TC and HDL-c.

Definition of dyslipidemia

According to National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III,) Guideline, individuals should have at least one of the following lipid parameters abnormal to be categorized under the presence of dyslipidemia: TC ≥ 200 mg/dl, HDL-c (< 40 mg/dl in men and < 50 mg/dl in women), LDL-c ≥ 130 mg/dl, TG ≥ 150 mg/dl and TC/HDL-c ratio ≥ 5 (NCEP III, 2002) whereas hyperuricemia was assessed based on uric acid levels ≥ 7.2 mg/dl in males and ≥ 6.0 mg/dl in females (Sui et al., 2008).

Statistical analysis

All questionnaires were checked and entered into epidata version 3.1 Statistical Package for Social Sciences (SPSS version 20) was used for statistical analysis. Categorical variables were summarized as frequencies and percentages, while mean values and standard deviations were tabulated for normally distributed quantitative continuous variables. In addition, median values and interquartile range (IQR) were tabulated for skewed variables. Chi-square was used for categorical variables. Furthermore, bivariate and multivariate binary logistic regression analysis was used to evaluate study groups variations in the distribution of categorical variables. Finally, in all cases, alpha level was set at 0.05 at 95% confidence interval (CI) for statistical significance.

RESULTS

Socio-demographic and other features of the study participants

From 248 study subjects, about 238 participated in this study with 96% (238/248) response rate. Of whom, 44.1% (105/238) were men and 55.9% (133/238) were women with a mean age of 53.2 (± 14.5) years. Majority, 226 (95%) of the patients had been using at least one anti-hypertensive agents. About 26.1, 7.6, and 24.4% of the study participants were rural residents, non-married and educationally unable to read and write, respectively. In addition, 17.2% of the study participants had BMI ≥ 30 Kg/m² (obese). The prevalence of lipid derangements (TC ≥ 200 mg/dl, TGs ≥ 150 mg/dl, LDL-c ≥ 130 mg/dl and low HDL-c) was 38.7, 62.2, 21 and 60.9%, respectively. Further, 73.1% of the participants had no trends of doing regular physical exercises and 39.9% of the study subjects had hyperuricemia (Table 1).

Pattern of dyslipidemia in relation to different variables

The prevalence of low HDL-c and TC ≥ 200 mg/dl were significantly higher in females when compared to males, (45.1% vs. 30.5%, $P=0.02$) and low HDL-c (70.7% vs.

48.6%, $P=0.001$), respectively. The raised TC was significantly higher among patients older than >45 years when compared to ≤ 45 years (43.3% vs. 24.8%; $p=0.03$), respectively. As well, raised TC, TGs and TC/HDL-c were significantly higher among patients with BMI ≥ 25 Kg/m² (overweight to obese) when compared to patients with BMI < 25 Kg/m² (45.3% vs. 30.9%, $p=0.02$; 67.7% vs. 53.1%, $p=0.01$ and 44.5% vs. 26.4%, $P=0.004$), respectively. Moreover, patients who have no current history of performing of regular exercise had significantly raised TC and raised LDL-c (44.3% vs. 23.4%, $P=0.003$; and 26.4% vs. 6.2%, $P=0.001$) when compared to those patients having experiences of performing regular physical exercise. Furthermore, the prevalence of hyperuricemia was 95 (39.9%) and abnormal levels of TC, TGs, HDL-c and TC/HDL-c were higher among patients with hyperuricemia (Table 2). About 90.8% of the study population had at least one lipid profile abnormal that is compatible with the diagnosis of dyslipidemia and 61.8% of the study participants had greater than or equal to two lipid profiles abnormal (dyslipidemia) (Figure 1).

Patients with a single profile derangement: reduced HDL-c was 37 (15.5%), two-profile derangement: raised TG-HDL-c was 23 (11.8%), three-profile derangement: raised TG-HDL-TC/HDL was 28 (11.8%) and four profile derangement: raised TC-TG-HDL-TC/HDL-c was 16 (6.7%).

Factors associated with lipid derangements

Bivariate analysis, model was applied to assess the independent risk factors for each lipid profile derangements. Being a female, the crude odds ratio [COR (95% CI): 1.9(1.1-3.2), $P=0.02$ for TC; 2.1(1.1-4.2), $P=0.02$ for LDL-c and 2.5(1.5-4.3), $p=0.001$ for HDL-c]. Hyperuricemia [COR (95% CI): 2.0(1.2-3.4), $P=0.001$ for TC; 2.8(1.5-4.9), $P=0.001$ for TGs; 2.5(1.4-4.4), $P=0.001$ for HDL-c; and 3.3(1.9-5.7), $P<0.0001$ for TC/HDL-c]. In addition, BMI and physical activity were significantly associated with TC, while the duration of HTN since its diagnosis and physical activity were significantly associated with LDL-c. However, multivariate analysis, was adjusted for independent factors and being a female, the adjusted odds ratio [AOR (95% CI): 2.1(1.2-3.9), $P=0.01$ for TC; 2.4(1.1-4.9), $P=0.02$ for LDL-c; and 2.9(1.6-5.4), $P<0.0001$ for HDL-c]. Hyperuricemia [AOR (95% CI): 1.8(1.1-3.1), $P=0.047$; for TC; 2.6(1.4-4.8), $P=0.001$ for HDL-c; and 3.1(1.7-5.4), $P<0.0001$ for TC/HDL-c].

In addition, experiences of performing physical exercise and the duration of HTN were significantly associated with LDL-c (Table 3).

Table 1. Socio-demographic and other characteristics of hypertensive patients.

Variables		N=238	Variable	N=238
Gender :	Female	133(55.9%)	WC, cm (mean \pm SD)	89.7(12)
	Male	105(44.1%)	SBP, mmHg (mean \pm SD)	134(18.1)
Age in years (mean \pmSD)		53.2(14.5)	DBP, mmHg (mean \pm SD)	84.9(12.1)
	\leq 45 years	74(31.1%)	HDL-c, mg/dl (median, IQR)	41.0(34-51)
	46-60 years	88(37.0%)	TGs, mg/dl (median, IQR)	175(129-256)
	>60 years	76(31.9%)	TC, mg/dl (median, IQR)	188(153-216)
Residence:	Rural	62(26.1%)	LDL-c, mg/dl (median, IQR)	103.7(76.8-125)
	Urban	176(73.9%)	TC/HDL-c (median, IQR)	4.4(3.5-5.7)
Marital status:	Single	18(7.6%)	TG/HDL(Log ¹⁰) (mean \pm SD)	0.64(0.28)
	Married	214(89.9%)	BMI, kg/m ² (mean \pm SD)	25.4(5)
	Divorced/widow	6(2.5%)	<18.5 kg/m ²	15(6.3%)
Occupation	Employed	75(31.5%)	18.5-24.9 kg/m ²	99(41.6%)
	Unemployed	163(68.5%)	25-29.9 kg/m ²	83(34.9%)
Educational status:	Illiterate	58(24.3%)	\geq 30 kg/m ²	41(17.2%)
	Primary	87(36.6%)	MetS (by IDF)	145(60.9%)
	Secondary and above	93(39.1%)	Low HDL-c	145(60.9%)
Ways of transportation:	Foot/bicycle	185(77.7%)	TC (\geq 200 mg/dl)	92(38.7%)
	Motorized vehicles	53(22.3%)	LDL-c (\geq 130 mg/dl)	50(21.0%)
Doing regular physical exercise:	Yes	64(26.9%)	TC/HDL-c (\geq 5)	86(36.1%)
	No	174(73.1%)	TGs (\geq 150 mg/dl)	148(62.2%)
Ever drink alcohol	Yes	3(1.3%)	Uric acid, mg/dl (mean \pm SD)	6.1(1.9)
	No	235(98.7%)	Hyperuricemia	95(39.9%)

IQR, interquartile range; BMI, body mass index; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; SD, standard deviation; WC, waist circumference; SBP, systolic blood pressure; TGs, triglycerides; TC, total cholesterol; MetS, metabolic syndrome; IDF, international diabetes federation.

DISCUSSION

We found that the prevalence of raised TC and low HDL-c were significantly higher in women when compared to men, and thus indicating the influence of gender in lipid derangement. In addition, we found that the prevalence of dyslipidemia (TC \geq 200 mg/dl, TGs \geq 150 mg/dl, LDL-c \geq 130 mg/dl and low HDL-c) was 38.7, 62.2, 21 and 60.9%, respectively. Besides, the majority of hypertensive patients (90.8%) had at least one dyslipidemia and the mixed type of dyslipidemia (greater than or equal to two lipid profile derangements) was 61.8%. Moreover, female gender was associated with raised levels of TC, LDL-c and reduced HDL-c, while hyperuricemia was associated with abnormal level of TC, TGs, HDL-c and TC/HDL-c. Studies reported that the prevalence of dyslipidemia was 52.7% and 68.7% (Luo et al., 2014; Yu et al., 2015), respectively. In addition, Framingham Heart Study indicated that more than 80% of hypertensive patients had at least one additional cardiovascular disease risk factor and mainly these risk

factors were atherogenic in nature. Also, frequently co-existence of hypertension and altered lipids cause a dyslipidemic hypertension (Kannel et al., 2000). This indicates the described lipid derangements (TC, LDL-c, HDL-c and TG) are atherogenic (NCEP 2002; Sudano et al., 2006), and suggest a possible risk for the increasing of cardiovascular diseases in a significant proportion among hypertensive patients in the near future.

In the present study, majority of hypertensive patients (90.8%) had at least one laboratory abnormality that is compatible with the diagnosis of dyslipidemia. Similarly, Pramiladevi et al. (2011) reported that the incidence of the overall forms of dyslipidemia was 90%. However, other two studies reported that low rate of dyslipidemia, was 50.8% (Osuji et al., 2012) and 41.2% (Iloh et al., 2012). Moreover, the altered levels of serum cholesterol are known to increase the risk of developing macrovascular complications such as coronary heart disease (CHD) and stroke (Albucher et al., 2000; Rader, 2002).

Our study indicated that the prevalence of raised TC

Table 2. Patterns of lipid derangements in relation to different variables.

Variable	Outcome variables					
	TC \geq 200 mg/dl: 92(%)	LDL-c \geq 130 mg/dl: 50(%)	TGs \geq 150 mg/dl: 148(%)	Low HDL-c : 145(%)	TC/HDL-c \geq 5: 86(%)	
Gender	Male	32(30.5)	15(63.8)	67(63.8)	51(48.6)	38(36.2)
	Female	60(45.1)	35(60.9)	81(60.9)	94(70.7)	48(36.1)
	P-value	0.02	0.02	0.64	0.001	0.99
Age in years	\leq 45	21(24.8)	14(18.9)	43(58.1)	48(64.9)	26(35.1)
	$>$ 45	71(43.3)	36(22.0)	105(64.0)	97(59.1)	60(36.6)
	p-value	0.03	0.59	0.38	0.40	0.83
Hyperuricemia	No	46(32.2)	31(21.7)	76(53.1)	75(52.4)	36(25.2)
	Yes	46(48.4)	19(20.0)	72(75.8)	70(73.7)	50(52.6)
	p-value	0.01	0.75	<0.0001	0.001	<0.0001
Occupation	Unemployed	64(39.3)	34(20.9)	95(58.3)	96(58.9)	59(36.2)
	Employed	28(37.3)	16(21.3)	53(70.7)	49(65.3)	27(36.0)
	p-value	0.77	0.93	0.07	0.34	0.98
BMI (kg/m ²)	$<$ 25	34(30.9)	18(16.4)	59(53.6)	63(57.3)	29(26.4)
	\geq 25	58(45.3)	32(25.0)	89(69.5)	82(64.1)	57(44.5)
	p-value	0.02	0.10	0.01	0.28	0.004
HTN duration (years)	\leq 5	56(36.8)	24(15.8)	97(63.8)	96(63.2)	57(37.5)
	$>$ 5	36(41.9)	26(30.2)	51(59.3)	49(57.0)	29(33.7)
	p-value	0.44	0.009	0.49	0.35	0.56
Doing regular exercise	Yes	15(23.4)	4(6.2)	36(56.2)	44(68.8)	18(28.1)
	No	77(44.3)	46(26.4)	112(64.4)	101(58.0)	68(39.1)
	p-value	0.003	0.001	0.13	0.13	0.12
FHCD	No	72(38.3)	42(22.3)	115(61.2)	112(59.6)	68(36.2)
	Yes	20(40.0)	8(16.0)	33(66.0)	33(66.0)	18(36.0)
	p-value	0.82	0.33	0.53	0.41	0.98
MetS (IDF)	No	31(33.3)	17(18.3)	31(33.3)	32(34.4)	14(15.1)
	Yes	61(42.1)	33(22.8)	117(80.7)	113(77.9)	72(49.7)
	p-value	0.18	0.41	<0.0001	<0.0001	<0.0001

BMI, body mass index; HDL-c, high density lipoprotein cholesterol; TGs, triglycerides; TC, total cholesterol; MetS, metabolic syndrome; IDF, international diabetes federation.

was 38.7%. The finding is comparable with the rate reported by Osuji et al. (2012), which was 35.6%.

However, low prevalence was reported from a resource poor West-African setting (Iloh et al., 2012) and the rate in this study was 17.2%. The possible explanations for the variation could be genetic disparities between populations, ethnicity, and lifestyle, duration of hypertension and experiences of antihypertensive agents. Based on HDL-c cut off value, we found that the prevalence of reduced HDL-c was 60.9%. However, the low rate was reported from Nigeria (Osuji et al., 2012), and India (Akintunde et al., 2010), which was 21.6% and 47.9%, respectively. The differences may be attributed to the reality that only newly identified hypertensive participants were included in these two studies. The

prevalence of raised LDL-c in our study was 21%. This rate is lower than the studies reported by Iloh et al. (2012) and Unniachan et al. (2014). The prevalence rate in these two studies was 23.8% and 86.2%, respectively. However, these studies used the cutoff $>$ 100 mg/dl; and this cutoff is lower than that of NCEP criteria (\geq 130) as used in our study.

The prevalence of raised TG in the present study was 62.2%. This is not in line with the prevalence reports of two Nigerian studies of (Osuji et al., 2012; Iloh et al., 2012) and North-west Ethiopia (Tachebele et al., 2014). The prevalence rate in these three studies was 6.4%, 14.8%, and 27.3%, respectively. However, there are suggestions that evidenced the magnitude of lipid derangements could show variation with the duration of

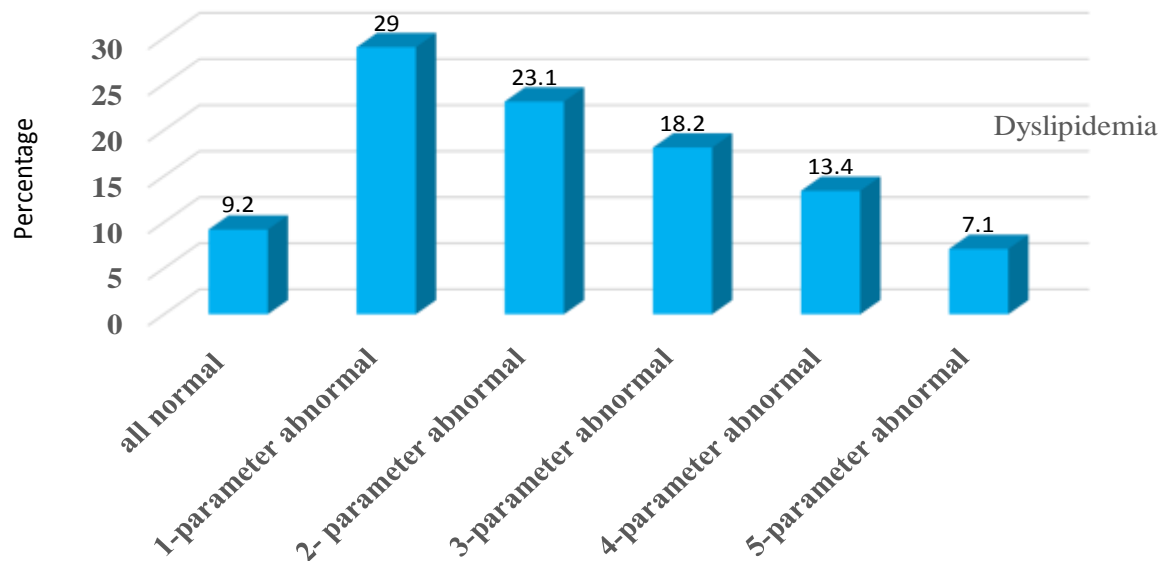


Figure 1. Trends of lipid profiles derangement within a single individual of hypertensive patients.

treatment, across populations and settings.

We found that the prevalence of raised TC/HDL-c was 36.1%. This rate is lower and not in line with the prevalence reported by Pramiladevi et al. (2011), which was 50%. In addition, the variation possibly could be the small number of the study participants and the TC/HDL-c cutoff (>4.5) was used in this study; and the cutoff is lower than that of NCEP (≥ 5), as used in our study. Further, the increasing pattern of TC and decrement in HDL-c level in relation to age in both sex may have an impact to increase TC/HDL-c ratio.

According to O'Meara et al (2004) report, the prevalence of dyslipidemia was significantly higher among men when compared to women in both black and whites ethnic groups. Conversely, our study indicated that female sex was significantly associated with dyslipidemia and this in line with the other report of studies (Yu et al., 2015; Choudhury et al., 2014). Furthermore, menopause age in women predisposes them to develop dyslipidemia as well as MetS, because HDL-c (good lipid) starts to decline following menopause and this consequences other lipid profiles derangement.

Several studies reported that BMI has a positive correlation with dyslipidemia (Iloh et al., 2012), and it is an independent risk factor of dyslipidemia (Yu et al., 2015); however, except TC/HDL-c our study indicates no association in between BMI and dyslipidemia after adjusting for confounding factors.

Hyperuricemia is significantly associated with raised TC, TGs, TC/HDL-c and low HDL-c in the current study. Similarly, studies reported that hyperuricemia was a

significant predictor of dyslipidemia (Vekic et al., 2009; Peg et al., 2014). Besides, one study revealed that a significant correlation of uric acid with all components of MetS, as well as other risk factors in hypertensive patients (Papavasileiou et al., 2016). Furthermore, these depicted abnormal lipids highlight the complex interaction between serum uric acid and lipids, and this might have an impact on CVDs.

Furthermore, this study showed that physical activity was significantly associated with dyslipidemia. In consistent, several studies pointed out that the relation of increased physical activity with improved (lowered) the rate of cardiovascular risks, including with arterial blood pressure levels (Carnethon et al., 2003 and Hambrecht et al., 2000). However, one study forwarded that an acute physical exercise encourages the oxidative stress in untreated and mild hypertensive patients who have raised atherogenic lipids (Čaparević et al., 2009). In addition, the study highlights the requirement of pharmacological correction for those patients with atherogenic lipid profiles in order to prevent high peroxidation of lipids through severe exercise (Čaparević et al., 2009).

Limitation of the study

The study design was a cross-sectional that only approximates a single point in time. In addition, our study included only hypertensive patients and no control group, and this made the study not comprehensive. Regardless

Table 3. Factors associated with dyslipidemia among hypertensive patients.

Descriptive variables		Outcome variables (at 95% CI)				
		TC≥200 mg/dl	LDL-c≥130 mg/dl	TG≥150 mg/dl	HDL-c<40mg/dl	TC/HDL-c ratio≥ 5
Gender: Female	COR	1.9(1.1-3.2)	2.1(1.1-4.2)	0.9(0.52-1.5)	2.5(1.5-4.3)	1.0(0.6-1.7)
	AOR	2.1(1.2-3.9)	2.4(1.1-4.9)	0.91(0.50-1.6)	2.9(1.6-5.4)	0.83(0.45-1.5)
	P-value	0.02* ; 0.01†	0.02* ; 0.02†	0.64*; 0.74†	0.001* ; <0.0001†	0.99*; 0.54†
Hyperuricemia: Yes	COR	2(1.2-3.4)	0.9(0.5-1.7)	2.8(1.5-4.9)	2.5(1.4-4.4)	3.3(1.9-5.7)
	AOR	1.8(1.1-3.1)	0.82(0.41-1.6)	2.6(1.4-4.8)	2.7(1.5-4.8)	3.1(1.7-5.4)
	P-value	0.01* ; 0.047†	0.76*; 0.58†	0.001* ; 0.001†	0.001* ; 0.001†	<0.0001* ; <0.0001†
Age: >45 years	COR	1.9(1.1-3.5)	1.2(0.6-2.4)	1.3(0.73-2.2)	0.78(0.44-1.4)	1.1(0.6-1.9)
	AOR	2.2(1.2-4.5)	1.3(0.60-2.8)	1.3(0.71-2.5)	0.98(0.51-1.9)	0.84(0.44-1.6)
	P-value	0.03* ; 0.01†	0.59*; 0.49†	0.38*; 0.37†	0.4*; 0.95†	0.83*; 0.62†
Occupation: Employed	COR	0.92(0.52-1.6)	1.0(0.53-2.0)	1.7(0.96-3.1)	1.3(0.74-2.3)	0.99(0.56-1.7)
	AOR	1.3(0.7-2.5)	1.4(0.62-3.0)	1.8(0.92-3.6)	1.7(0.85-3.3)	0.87(0.44-1.7)
	P-value	0.77*; 0.46†	0.93*; 0.44†	0.07*; 0.08†	0.34*; 0.13†	0.98*; 0.69†
BMI: ≥25 kg/m ²	COR	1.8(1.1-3.1)	1.7(0.9-3.2)	1.9(1.2-3.3)	1.3(0.8-2.2)	2.2(1.3-3.9)
	AOR	1.5(0.83-2.3)	1.6(0.77-3.2)	1.5(0.85-2.6)	1.0(0.57-1.9)	2.2(1.2-4.0)
	P-value	0.02* ; 0.17†	0.1*; 0.21†	0.01* ; 0.15†	0.28*; 0.91†	0.004* ; 0.01†
HTN duration: >5 years	COR	1.2(0.72-2.1)	2.3(1.2-4.3)	0.83(0.5-1.4)	0.77(0.45-1.3)	0.85(0.49-1.5)
	AOR	1.1(0.63-2.0)	2.3(1.1-4.5)	0.77(0.43-1.4)	0.84(0.47-1.5)	0.85(0.47-1.5)
	P-value	0.44*; 0.67†	0.01* ; 0.02†	0.49*; 0.39†	0.35*; 0.57†	0.56*; 0.60†
Doing regular physical exercise: No	COR	2.6(1.3-4.9)	5.4(1.8-15.7)	1.4(0.78-2.5)	0.63(0.34-1.1)	1.6(0.88-3.1)
	AOR	2.6(1.3-5.1)	5.2(1.7-15.4)	1.5(0.81-2.8)	0.54(0.28-1.05)	1.6(0.83-3.2)
	P-value	0.004* ; 0.07†	0.002* ; 0.003†	0.25*; 0.19†	0.13*; 0.07†	0.12*; 0.15†
FHCD: Yes	COR	1.1(0.57-2.0)	0.67(0.29-1.5)	1.2(0.64-2.4)	1.3(0.68-2.5)	0.99(0.52-1.9)
	AOR	0.98(0.49-1.9)	0.59(0.24-1.44)	1.1(0.52-2.1)	1.0(0.49-2.0)	0.82(0.4-1.7)
	P-value	0.83*; 0.95†	0.33*; 0.25†	0.53*; 0.87†	0.41*; 0.98†	0.98*; 0.59†

AOR, adjusted odds ratio; BMI, Body Mass Index; CI, Confidence Interval; COR, crude odds ratio; FHCD, family history of chronic diseases; *P-value of crude odds ratio; †, P-value of Adjusted odds ratio. Reference category: male, normouricemia, age≤45 years, unemployed, BMI<25 kg/m², HTN duration ≤5 years, doing regular physical exercise, no FHCD.

of these limitations, the study eventually increases evidence to the limited data situations.

Conclusion

Our study showed a high prevalence of dyslipidemia in hypertensive patients. Some of the non-modifiable risk factors like age, gender, and duration of hypertension were associated with dyslipidemia. In addition, some of the modifiable risk factors like BMI and experiences of physical exercise were significant with lipid derangements. This may indicate that a significant proportion of hypertensive patients are at risk of developing atherosclerosis and CVDs related morbidity and mortality.

Therefore, lipid profiles should be performed at baseline prior to receiving any anti-hypertensive agents and then periodically through treatment follow-up to

manage any increasing trends.

In addition, National level of policies are required regarding awareness creation, life style modification and physical exercises. Furthermore, controlled cohort studies are also required to assess other risk factors of atherogenic dyslipidemia as well as cardiovascular risks including genetic variation.

ABBREVIATIONS

AOR, adjusted odds ratio; **BMI**, body mass index; **BP**, blood pressure; **CI**, confidence interval; **CVD**, cardiovascular diseases; **CHD**, coronary heart disease; **COR**, crude odds ratio; **HDL-c**, high density lipoprotein-cholesterol; **TC**, total cholesterol; **LDL-c**, low density lipoprotein-cholesterol; **HTN**, hypertension; **WHO**, World Health Organization; **TG**, Triglycerides; **SPSS**, Statistical package for Social Sciences; **NCEP-ATP**, National

Cholesterol Education Program-Adult Treatment Panel; **MetS**, metabolic syndrome.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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