

ORIGINAL RESEARCH

LIPID ACCUMULATION PRODUCT AND WAIST-TO-HEIGHT RATIO ARE PREDICTORS OF THE METABOLIC SYNDROME IN A NIGERIAN MALE GERIATRIC POPULATION

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Abstract

Objective: The metabolic syndrome (MetS) describes a clinical constellation of distinct but interrelated abnormalities that have been linked to many cardio-metabolic diseases which result in increased morbidity and mortality. Several indices have been developed to predict cardio-metabolic diseases. This study evaluated the accuracy of such indices as the lipid accumulation product (LAP), visceral adiposity index (VAI), waist-to-height ratio (WHtR), waist-to-hip ratio (WHpR) and body mass index (BMI) to predict the metabolic syndrome in a male geriatric population. **Methods:** Forty geriatric males (age range 65 to 84 years) were studied. Their fasting blood glucose levels, serum lipid profile, blood pressures and relevant anthropometric indices were determined using standard protocols. Validated and appropriate equations were used to derive the necessary indices. **Results:** Only LAP ($p < 0.001$) and WHtR ($p = 0.022$) were significantly higher in subjects with MetS relative to those without the syndrome. The ROC analyses showed that LAP [Area under the curve (AUC) = 0.937] and WHtR (AUC = 0.905) predicted the MetS, better than the other indices. A LAP threshold of 4.391 had a MetS predictive sensitivity of 100% and specificity of 81%, while a WHtR threshold of 0.61 had a sensitivity of 100% and specificity of 78%. **Conclusion:** LAP and WHtR are associated with, and are sensitive and fairly specific predictors of, the MetS in this geriatric population.

Key Words: Lipid accumulation product; Metabolic syndrome; Visceral adiposity index; Waist-to-height ratio.

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INTRODUCTION

The metabolic syndrome (MetS) is a term used to describe the clinical clustering of distinct but interrelated metabolic abnormalities that are thought to share a common patho-aetiological pathway. MetS is thought to be at the core of diabetes and atherosclerotic diseases (Bhatheja and Bhatt, 2006; Borgman and McErean, 2006). Its features include (but are not limited to) insulin resistance with resulting hyperinsulinaemia (Pagano *et al.*, 2002), impaired glucose tolerance/type 2 diabetes mellitus (Zimmet *et al.*, 1999), hypertension (Marre *et al.*, 2001), lipid triad – increased triacylglycerols, decreased high density lipoprotein cholesterol (HDL-C) and increased low density lipoprotein cholesterol

(LDL-C) (Ginsberg and Huang, 2000), obesity/visceral adiposity (Lemieux, 2001), elevation of inflammatory markers (Ahmad and Miller, 2001), increased prothrombotic and antifibrinolytic factors (Juhan-Vage, 1996), hyperuricemia (Zavaroni *et al.*, 1993), hyperhomocysteinemia (Meigs *et al.*, 2001), microalbuminuria (Savage *et al.*, 1996), benign prostatic hyperplasia (Ejike and Ezeanyika, 2008), non-alcoholic fatty liver disease (Machado and Cortez-Pinto, 2006) and impaired lung function (Lin *et al.*, 2006). Various diagnostic criteria for MetS have been proposed by different organizations in the past. A recent harmonized diagnostic definition requires the presence of any three of the five components listed in Table 1.

Table 1: Harmonized criteria for clinical diagnosis of the metabolic syndrome.

Measure	Categorical Cut Point
Elevated waist circumference	* Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100mg/dL

*It is recommended that the IDF cut-points be used for non-Europeans and either the IDF or AHA/NHLBI cut-points used for people of European origin until more data are available. IDF recommends ≥ 94cm for sub-Saharan African men (adapted from Alberti *et al.*, 2009).

Obesity/visceral adiposity is believed to be a major determinant of MetS (Fan, 2007). Obesity is commonly used to imply excess fat, but is often classified according to excess weight. For obesity [as measured by body mass index (BMI) and other such anthropometric indices] to perform better as a predictor of medical risk, lipid accumulation should be defined and measured in those contexts where accumulation may represent

a physiological danger (Unger, 2003; Bozorgmanesh *et al.*, 2010a). The lipid accumulation product (LAP) is a simple index for estimating lipid over accumulation in adults, that is based on only waist circumference and fasting circulating triacylglycerol concentration (Kahn, 2005 and 2006). The visceral adiposity index (VAI) also expresses visceral fat function, and is based on waist circumference, BMI, triacylglycerols and HDL-C

(Amato *et al.*, 2010). Both LAP and VAI capture the contexts in which lipid over-accumulation presents physiological challenges.

An early diagnosis of the MetS could lead to early initiation of management, and may lower mortality from its components and sequelae. In resource poor settings, the identification, development and validation of simple, accurate and cost effective diagnostic tools for (chronic) diseases would improve clinical outcomes. This study therefore investigated which index of obesity/visceral adiposity – LAP, VAI, BMI, WHtR and WHpR – is associated with, and predicts, the MetS better. The results are expected to be useful in firstly, motivating further studies in this regard, and support early and easy detection of MetS, especially in geriatric populations.

METHODS

Subjects

This one center cross-sectional study recruited forty (40) male subjects aged 65 to 84 years (as reported by the subjects), attending the Urology Clinic at the Federal Medical Center Umuahia, Abia State, Nigeria. Only subjects who were out-patients, who did not have any signs of overt morbidity, who had not been previously diagnosed with any known cardio-metabolic disorder and who were not taking any prescription drugs or herbal formulations were recruited for the study. Each participant gave an informed oral consent before being invited to take part in the study. The study was designed in accordance with the Helsinki declaration. The Ethics committee of the Federal Medical Center Umuahia and the Board of the Department of Biochemistry, Michael Okpara University of Agriculture, Umudike, approved the design and methods for this study.

Anthropometry

Each participant's height was measured with a measuring tape fastened to a vertical rod, and with the subject standing on bare feet, to the nearest 0.1cm. The waist circumference (WC) and the hip circumference (HC) of each participant was measured using a non-elastic measuring tape, to the nearest 0.1cm. WC was measured midway between the lowest rib and the superior border of the iliac crest at the end of normal expiration while HC was measured at the widest circumference over the buttocks. The weight of each subject was measured using an electronic weighing balance, to the nearest 0.1kg, with the subject wearing light clothes and no shoes. The same weighing balance was used throughout the study, and it was appropriately calibrated each morning before use. From these measurements, the waist to hip ratio (WHpR) was calculated as WC/HC; the waist to height ratio (WHtR) was calculated as WC/Height; and body mass index (BMI) was calculated as $\text{Weight (kg)}/[\text{Height (m)}^2]$.

Blood pressure measurements

The blood pressures of the participants were measured between 8am and 10am, using a mercury sphygmomanometer and appropriate cuff sizes, after the subjects had rested for an initial ten minutes in a cool noiseless room. Three separate measurements were taken (while allowing for five minutes intervals between measurements) with the subject seated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken at the 1st and 5th Korotkoff sounds respectively. The first values were discarded and the average of the second and third readings per subject was recorded.

One properly trained nurse took all anthropometric and blood pressures measurements, in triplicates, throughout the duration of the study.

Biochemical analyses

Fasting circulating serum triacylglycerol (TAG), total cholesterol and HDL-C concentrations were measured using the enzymatic colorimetric methods of Lopes-Virella *et al.* (1977), Allain *et al.* (1974) and Tietz (1990), respectively. LDL-C was estimated by difference (Friedwald *et al.*, 1972). Fasting blood glucose levels were determined by the glucose oxidase method (Washako and Rice, 1961).

Definitions and derivations

The metabolic syndrome was defined using the harmonized definition (Alberti *et al.*, 2009) as presented in Table 1.

Lipid Accumulation Product was derived using the equation: $\text{LAP} = (\text{WC}-65) \times \text{TAG}$ (Kahn, 2005).

Visceral Adiposity Index was derived using the equation: $\text{VAI} = [\text{WC}/39.68 + (1.88 \times \text{BMI})] \times (\text{TAG}/1.03) \times (1.31/\text{HDL-C})$ (Amato *et al.*, 2010).

Statistical analyses

Descriptive statistics were carried out on the continuous data generated (and their derivatives), and the results reported as means \pm standard deviations. Independent samples t-tests were conducted to assess the relationship between the MetS and the studied variables. The receiver operating characteristic (ROC) analysis was employed to determine the predictive performance of the studied variables with respect to the MetS. For the areas under the curves (AUCs) (measures of true diagnostic/discriminatory power) of the ROC analyses, threshold values for MetS prediction were determined for each studied variable, and their sensitivities (true positive rates) and specificities (true negative rates), determined. An AUC value of 1 signifies that the test is perfectly accurate, while an AUC value of 0.5 indicates that the test performs equal to chance. An AUC value of ≥ 0.85 is considered an accurate test (Zou *et al.*, 2007). Threshold values whose sensitivities and specificities gave the maximum sums were recorded for each variable. The level of significance for all analyses was fixed at 0.05. All data analyses were done using the statistical software package, SPSS for windows version 17.0 (SPSS Inc, Chicago IL).

RESULTS and DISCUSSION

The mean age of the forty male participants was 75 ± 6 years. A total of 7.5% of the 40 participants had the metabolic syndrome. The mean LAP and VAI of the subjects were 3959.7 ± 730.2 and 3.9 ± 0.7 , respectively. The mean BMI of the subjects was within the over-weight range (28.5 ± 3.7) and their mean WHtR and WHpR were 0.58 ± 0.04 and 1.07 ± 0.04 , respectively. A standard waist circumference dictum is "keep your waist circumference at less than half your height" that is, an ideal WHtR should be <0.5 (Ashwell and Hsieh, 2005) while an ideal WHpR should be <1 (WHO, 2000). The anthropometric indices of the general population therefore fell slightly above the ideal ranges, indicating the presence of mild obesity/visceral adiposity. Independent samples t tests showed that mean LAP ($p < 0.001$) and mean WHtR ($p = 0.022$) measurements were significantly higher in the MetS group, relative to the group without the syndrome (Table 2).

Table 2: Mean values (SD) of the studied variables for subjects with and without the metabolic syndrome.

Characteristic	Yes MetS (n=3)	No MetS (n=37)	p-value
LAP	5339.00 (820.57)	3847.84 (607.36)	<0.001
VAI	4.10 (0.68)	3.85 (0.67)	0.537
BMI	31.11 (0.47)	28.29 (3.73)	0.205
WHtR	0.63 (0.02)	0.58 (0.04)	0.022
WHpR	1.10 (0.06)	1.07 (0.03)	0.163

Though BMI is traditionally used in epidemiological studies as an index of excess weight, it is now known that other indices of fat mass, like the WHpR perform better than BMI in predicting cardiovascular disease (CVD) risk (Huxley *et al.*, 2010). WHtR has also been shown to predict obesity-related cardio-metabolic disorders (Ashwell, 2005; Lee *et al.*, 2008). These are largely because ectopic fat has been shown to be the major culprit in conferring CVD risk. The two factors in LAP – that is enlarged abdominal depots and increased circulating TAG – are each an indication that the body's capacity to buffer and safely store its major form of acquired energy has been exceeded. Genetics and environmental factors however determine whether an individual's excess lipid fuel appears as an enlarged abdomen or as circulating TAG (Kahn, 2005). Like LAP, VAI includes both anthropometric and metabolic parameters, and possibly reflects other non-classical risk

factors for CVD, such as altered production of adipocytokines, increased lipolysis, and plasma free fatty acids – factors that are not signified by BMI, WC, TAG, and HDL-C separately. VAI is therefore a valuable index of both fat distribution and function (Amato *et al.*, 2010). It is however interesting that only WHtR and LAP were associated with the MetS, however, this might be due to the small sample size in the current study. Earlier studies had linked the WHtR and LAP to cardio-metabolic diseases (Kahn, 2005; Hadaegh *et al.*, 2009). This is not entirely surprising since LAP has been shown to be superior to both WHtR and WHpR in predicting CVD (Bozorgmanesh *et al.*, 2010b) and an accurate predictor of the MetS in adult males (Taverna *et al.*, 2011).

Both LAP and WHtR had AUC values that were ≥ 0.85 , signifying both were accurate diagnostic tests for the MetS. Though both had maximum sensitivities at the respective threshold values, LAP had higher specificity for the MetS at its threshold value (Table 3). In resource poor settings, the diagnosis of diseases could be costly and cost-inefficient. The development of cheap, but accurate and reliable indices for the diagnosis of chronic diseases would definitely lower the cost of healthcare delivery, improve the chances of commencing interventions and treatments early, and overall, improve outcomes.

Table 3: Areas under the ROC curves of the studied variables for predicting the MetS; threshold values and their respective sensitivities and specificities

	AUC (SE); (95% C.I.)	p-value	Threshold Value	Sensitivity (%)	Specificity (%)
LAP	0.937 (0.058); (0.00-1.00)	0.013	4391	100	81
VAI	0.640 (0.181); (0.29-0.99)	0.426	4.44	67	84
BMI	0.793 (0.069); (0.66-0.93)	0.095	30.47	100	73
WHtR	0.905 (0.060); (0.00-1.00)	0.021	0.61	100	78
WHpR	0.635 (0.211); (0.13-1.00)	0.441	1.08	67	76

The diagnosis of MetS requires five factors – one anthropometric and four clinical factors. The measurement of blood pressure through the standard auscultation protocol introduces observer bias, could expose the subject and practitioner to mercury (in places where mercury devices are still used) and is difficult to use in large epidemiological studies especially in resource-poor settings (Mengden *et al.*, 2010). Though the use of oscillometric blood pressure monitors does not have these inherent disadvantages of the auscultation protocol, it is still not the gold standard for use in blood pressure studies, and such devices often give values that differ from those obtained with auscultation (Lithell and Berglund, 1998; Part *et al.*, 2001). Measurements of anthropometric indices also have some inherent observer bias though the degree is less than that of the auscultation protocol. The determination of circulating levels of blood glucose, TAG and HDL-C using the standard enzymatic and colorimetric methods are all time consuming and have high cumulative cost implications. Therefore the finding that LAP and WHtR provide sensitive screening/diagnostic tests for MetS is interesting since both indices require far less factors for their derivation. LAP requires only the determination of circulating TAG and the measurement of WC; while WHtR requires only the subject's height and WC. Using the LAP (the superior predictor of the MetS, based on the data presented in this report) would reduce the cost (economic- and time-wise) of the diagnosis of the MetS considerably. The use of the WHtR, though a less specific diagnostic tool for the MetS, would virtually eliminate any economic burden in the diagnosis of MetS. Both indices

would surely be useful in epidemiologic studies on the MetS especially in areas where researchers have limited resources.

The use of LAP as a predictor of the MetS would appear superior to the use of WHtR, not just because of its superior specificity, but because it captures both anthropometric and metabolic dimensions of visceral fat over-accumulation. This implies that regardless of whether excess lipids are stored as visceral fat or as TAG, it is captured by LAP; whereas WHtR would miss the excess lipids stored as TAG. Logically therefore, LAP will increase as more lipids are deposited in non-adipose "ectopic" tissues such as the liver, blood vessels, pancreas, kidneys and skeletal muscles, where they may adversely affect cellular function and interfere with cardiovascular regulation (Unger, 2003; Montani *et al.*, 2004) and/or when they are stored as TAG with its attendant cardio-metabolic implications (Austin *et al.*, 1998). The fact that WHtR does not require venupuncture (which is a problem for many subjects) makes it all the same attractive.

This study is limited by its small sample size and its narrow population of study of males attending an urology clinic. It would be ideal to repeat the study in not just geriatric females, but also in younger populations of both sexes since age and sex specific differences in the predisposition to, and manifestation of, cardio-metabolic diseases are known to exist. Again, a proper diagnosis of hypertension requires that blood pressures should be measured on many occasions, preferably on different days. Blood pressures were however measured

only on a single day for this study, a fairly common short-coming of epidemiological studies resulting in the detection of "point hypertension" not "hypertension". Nevertheless, the blood pressure values obtained and the methods used are valid as the blood pressure component in the diagnosis of the MetS only requires the presence of elevated blood pressure (or treatment for such); and this study was not designed to strictly address hypertension. Furthermore, this study is robust in its design and analysis, and clearly serves as a good starting point in the search for simple, accurate and cheap diagnostic tools for the MetS – a syndrome that is at the heart of cardio-metabolic diseases.

Conclusion

This study investigated which of lipid accumulation product (LAP), visceral adiposity index (VAI), body mass index (BMI), waist-to-height ratio (WHtR) and waist-to-hip ratio (WHpR) predicted the MetS in a geriatric population of Nigerian males best, in an attempt to seek out a cost effective but accurate diagnostic tool for the syndrome. LAP and WHtR were found to be simple, affordable, specific and sensitive diagnostic tools for the MetS in the studied population. LAP however is the preferred index as it captures both possible storage sites of excess lipids, which is central to the development of the MetS.

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