Prevalence of Metabolic Syndrome and Associated Factors in Type 2 Diabetes Mellitus: A Descriptive Cross-Sectional Study at a Follow-up Clinic in Asmara, Eritrea

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Research

Keywords: Metabolic syndrome, Cardiovascular diseases, Type 2 diabetes mellitus, Body Mass Index, Anthropomorphic measures, Cardiometabolic risk, Atherogenic dyslipidemia, Eritrea

DOI: https://doi.org/10.21203/rs.3.rs-139642/v1

Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is an escalating problem worldwide and is frequently associated with Metabolic Syndrome (MetSyn) which, in turn, is causally associated with heightened cardiometabolic risk. Therefore, investigating the magnitude of MetSyn in T2DM patients is critical for cardiovascular disease prevention or management of specific comorbidities.

Methods: This cross-sectional study was conducted among 309 previously diagnosed T2DM patients. Data on specific clinical chemistry and anthropomorphic parameters was collected. MetSyn was defined according to the IDF harmonized criteria. Pearson Chi-Square test (χ^2)/or Fisher's exact test in the CROSSTAB procedure was used to evaluate the relationship between specific variables. Logistic regression models were constructed to assess risk factors associated with MetSyn.

Results: According to the data, 58.1% of the patients had MetSyn. The frequency of MetSyn in females was significantly higher compared to that of males (67.8 vs 49.7%). Among individuals with MetSyn, 54.4% had hypertension; 57.9% had abnormal waist circumference; 75.4% had elevated LDL-C (≥100 mg/dL), 72.8% had raised TG (>150 mg/dl) and 61.0% had reduced HDL-C (males: ≤40 mg/dL and females: ≤50 mg/dL in females). Separately, our study demonstrates that number of MetSyn components is associated with higher averages in multiple traditional (BMI, TG, TC, WHtR, WHR, WC, HC) and non-traditional (TG/HDL-C, TC/HDL-C and LDL/HDL) CVD risk indicators. In the fitted multivariable logistic regression model, the following factors were associated with the presence of MetSyn: age (aOR=1.02, 95%CI=1.00–1.05, p=0.040); LDL-C>100 mg/dL (aOR=3.56, 95%CI=1.52–8.54, p=0.003); Non-HDL-C (aOR=1.02, 95%CI=1.02–1.03, p=0.001); BMI (aOR=1.23, 95%CI = 1.13–1.32, p=0.001). Absence of insulin injection was associated with reduced presence of MetSyn (aOR=0.37,95% CI=0.19–0.70, p=0.002).

Conclusion: A comparatively high prevalence of the MetSyn was found. Therefore, there is an urgent need for improvements in the management and prevention of multiple CVD risk indicators. This will require evidence-based optimization of pharmacological and non-pharmacological interventions.

Background

The incidence and prevalence of Type 2 Diabetes mellitus (T2DM) is increasing substantially worldwide. In their latest report, International Diabetes Federation (IDF) estimated that, globally, there were 463 (uncertainty interval: 368–600.6) million people living with T2DM [1]. The figure is projected to rise to 700.2 (uncertainty interval: 540.7-904.6) million people by 2045. In terms of absolute numbers, demographic models indicate that the largest burden of DM will occur in low- and medium-income countries (LMIC), particularly in Sub-Saharan Africa (SSA) [2]. These settings have limited resources and, often, the dual public health burden of non-communicable (NCDs) and communicable diseases [3]. The said burden can also be appreciated from the fact that DM affects multiple organ systems and is characterized by periods of acute exacerbations, requiring wide-ranging, multidisciplinary care, and often high-cost approach to successfully manage [4]. Furthermore, DM can enhance susceptibility to infectious diseases such as pneumonia, Tuberclosis (TB), to mention a few. Importantly, the observed increase in the prevalence of DM suggests that micro and macroangiopathic complications/comorbidities are likely to emerge as leading causes of morbidity and mortality in the years to come [5].

Needless to say, the connection between micro and macroangiopathic complications and/or comorbidities and T2DM is better appreciated by laying emphasis on the fact that the disease rarely occurs in isolation and has increasing importance in the presence of other systemic metabolic abnormalities/comorbidities. A case in point is the disproportionate co-presence of T2DM and metabolic syndrome (MetSyn). A constellation of interrelated diseases with complex interaction with cardiovascular disease (CVD) make up the MetSyn. These include: abdominal obesity, atherogenic dyslipidemia (high triglyceride (TG) and/or low-high density lipoprotein cholesterol (HDL-C)), elevated BP, dysglycemia (DM and prediabetes). Other features of the syndrome include hypofibrinolysis/or hypercoagulability, low-grade inflammation, insulin resistance (IR), microalbuminuria, among others [6]. Disparate permutations and combinations of these risk factors are emphasized in existing MetSyn definitional criteria and/or statements. Overall, some studies appear to suggest that the joint presence of these markers in the

same individual have a CVD risk magnitude which goes beyond the summative impact of traditional risk factors [5, 6, 7]. This heightened risk is not apparent when attention is directed exclusively at individual risk factors. Importantly, several large-scale clinical trials and meta-analyses have invariably demonstrated that MetSyn can increase the incidence of T2DM; increase arteriosclerotic cardiovascular disease (ASCVD) all-cause morbidity and mortality with reversal of these abnormalities being associated with attenuation in risk [5, 6, 7, 8].

Interestingly, MetSyn concept remains controversial in some quarters [9] and its utility in DM patients has also been questioned [8, 10, 11]. For instance, the question of whether coalescence of risk factors incorporated in the various definitions of MetSyn augment risk beyond the summation of risk attributable to the individual components remain unsettled. Others view it as a premorbid condition with limited practical utility in clinical practice [11]. Indeed, some relatively influential investigators have concluded that the MetSyn concept has questionable prognostic utility when compared to established algorithms such as the Framingham Risk Framingham Risk Assessment Tool (FRAT), QRISK2, Reynold Risk Score (RRS), or the European Systematic Coronary Risk Evaluation (EUROSCORE), among others. Similarly, controversy regarding insulin resistance (IR) as a unifying pathophysiologic pathway that accounts for all the features of MetSyn endures [9, 11].

Despite the debates surrounding the existence and/or relative prognostic utility of MetSyn; there is a consensus that the concept has auxiliary value in clinical practice, particularly in the context of a patient-centered treatment strategy to prevent cardiovascular disease (CVD) or other adverse events/outcomes. It can provide an integrated approach for screening, diagnostic testing, prevention, and treatment of disorders associated with MetSyn [13, 14]. In addition to its potential role as a marker of factor clustering, the concept can serve as an important educational tool. For example, it reinforces the need for health care professionals to take a more comprehensive approach to their patients and to address all relevant CVD risk factors. This point is important, particularly in SSA, where DM is largely regarded by the populace as a '*sugar disease*' and management is predominantly glucocentric. Finally, data on MetSyn may provide a useful window on the health of DM patients in a population.

A present, emerging evidence appears to suggest that diseases/disorders associated with MetSyn have increased worldwide irrespective of cultural, sex, ethnic, genetic, geographical differences or definitional criteria [15]. Multiple point prevalence studies have demonstrated that the current trends are largely influenced by the rapidly evolving socio-economic and cultural milieu (e.g. rapid urbanization accompanied by rapid quantitative and qualitative changes in nutritional intake), among others [16, 17]. This trend is matched by a corresponding increase in MetSyn awareness among physicians in some parts of the world [18] However, data on the clinical epidemiology of MetSyn in T2DM patients or MetSyn awareness among physicians in SSA is largely unavailable [19]. The lack of data is part of a prominent pattern typified by increasing awareness of the growing burden of T2DM or related comorbidities and expressed commitment by countries in the region to address the problem (all countries in SSA adopted the WHO Global Action Plan for the Prevention and Control of NCDs 2013 – 2020); but limited research focus or investments in actions commensurate with the rapidly escalating burden. For instance, there is little or no data on MetSyn from several countries from SSA [20].

In Eritrea, sustained follow-up of T2DM patients is undermined by multiple problems (patients and healthcare system related problems) and data collected during these visits is incomprehensive. For example, specific markers used in MetSyn or CVD risk profiling are not collected – waist circumference (WC), hip circumference (HC), waist/height ratio (WHtR), among others. Although existing data from Eritrea indicates that age-standardized mortality/ death rate (per 100 000 population) due to DM or CVDs is disproportionately high [21]; published research on NCDs like DM is severely limited. The severe lack of reliable epidemiological and clinical information on MetSyn in any sub-group in the country has a negative impact on prevention and management/treatment strategies. Therefore, we conducted a cross sectional study in the largest DM follow-up clinic in Asmara. It's our belief that elucidation of the magnitude of MetSyn and associated factors may permit a more effective and proactive approach to its prevention and treatment.

Materials And Design

Study design

We conducted a single centre cross-sectional study at the outpatient clinic (OPC) of the Halibet Regional Referral Hospital in Eritrea. All data were collected using multiple approaches – patients' charts, standardised questionnaire and samples. Data from patients' charts included DM status, anthropometric data (including height, weight, waist circumference (WC), body mass index (BMI)), age, DM, hypertension status, other DM-related comorbidities and medication. Further, a questionnaire, translated to Tigrigna (a common local dialect) and incorporating queries on a range of well-established DM risk factors was employed to collect a wide array of information including demographic data, lifestyle habits and family history of DM. Blood sample was also collected for the analysis of specific clinical chemistry analytes.

Study setting and period

This study was conducted at Halibet Regional Referral Hospital Zoba Maekel, Asmara, Eritrea, from February 2017 – June 2017. The hospital is one of the tertiary level facilities in Asmara, Eritrea and provides care to the approximately 560 000 residents of Asmara and adjoining catchment areas. The facility has the largest DM follow-up and care clinic in Asmara. Enrolled patients are covered under the Eritrean government universal health insurance. Patients are attended by a multidisciplinary team of internists, medical residents, pharmacists, general nurses during scheduled follow-up visits.

Sample size calculation, Participant Recruitment and Selection

The sample size was estimated using Cochran formula [22]. The DM clinic record book was used as a sampling frame for random selection of eligible study participants. A systematic sampling procedure, involving the selection of every 2nd person aged ≥ 35 years who visited the DM clinic during the study period was employed. Inclusion criteria included DM patients who are currently enrolled at the facility. Exclusion criteria were based on the following considerations: hospitalized and/or individuals with cognitive impairment (dementia or other psychiatric disorders), patients with overt thyroid dysfunction and individual who were unwilling to grant consent.

Questionnaire Administration and Data Collection

All data were collected by suitably trained, competent, and qualified, clinical, and laboratory workers. A researcher administered questionnaire included items on socioeconomic status, medical history, lifestyle medical history (self-reported history of HTN or other comorbidity (coronary, structural or heart failure), among others. Duration of DM was established by subtracting present age from age at diagnosis (a value obtained from hospital record). Additional information was collected from patient records.

Lifestyle/behavioral factors. Lifestyle factors including dieting, alcohol consumption and cigarette/tobacco smoking were defined as per Fiseha *et al* [23].

Clinical Biochemistry measurements: The samples obtained were analyzed at Sembel Hospital laboratory. Five ml of blood was obtained from the femoral vein, after 8 hours of fasting. The samples were subsequently aliquoted into appropriate biochemistry tubes. Fasting plasma glucose (FPG), lipid panel (Triacylglycerol (TG), Total Cholesterol (TC), and High-density cholesterol (HDL-C)) and hemoglobin A1c (HbA1c) were analysed, as per manufactures instructions, using Beckman Coulter: AU480 Chemistry System. LDL-C was estimated using Friedewald formula [LDL = Non-HDL-C − TG/5 (mg/dL]. Non-HDL-C = (LDL-C) + (VLDL) was evaluated using the following equation: (TC) − (HDL-C). The C reactive protein (CRP) Latex test (Cortes Diagnostic, Inc.) was used to evaluate CRP.

Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) formula: eGFR = 186 x [Serum Creatinine (mg/dl)]-1.154 x (Age) − 0.203 × (0.742 if female). An eGFR ≥ 60 ml/min/1.73 m^2 was characterized as reduced eGFR.

Anthropometric Measurement: Anthropometric data (including height, weight and body mass index (BMI)), waist circumference (WC) and hip circumference (HC) were recorded for each participant. BMI categories were defined as per WHO guidelines [24]. According to this scheme, BMI ≤ 18.5 kg/m^2 is considered as underweight; 18.6–24.9 kg/m^2: normal weight; 25–29.9 kg/m^2: overweight; ≥30 kg/m^2: obese. WC was measured with a tape at the point between iliac crest and costal margin in the mid-

axillary line while the patient was standing and breathing normally. WC > 94 (males)/80 (females) cm was considered as abnormal as per the International Diabetes Federation (IDF) harmonized criteria. Abnormal Waist/hip ratio (WHR) was defined according to the WHO criteria (> 0.90 men, > 0.85 women). Body Adiposity Index (BAI) was calculated as follows: BAI = (Hip Circumference (HC) (cm)/ [Height (m)]1.5) – 18 [25].

Hypertension status; Blood Pressure (BP) and Control: We measured blood pressure using an automated oscillometer (MDF® Lenus Digital Blood Pressure Monitor) and appropriately sized arm cuff on subjects after 5 min seated rest. Triplicate readings were taken per subject. Hypertension was defined as per the Joint National Committee on The Prevention, Detection, Evaluation and Treatment of Hypertension (JNC-8) guidelines [26]. The machine was calibrated weekly using a mercury containing sphygmomanometer during data collection. Hypertension status and treatment were also established by participants responding affirmatively to the question, “Have you ever been diagnosed with hypertension?” and “Because of your hypertension/high BP are you now taking prescribed medicine?”

Determination of Metabolic Syndrome (MetSyn): MetSyn was defined according to The International Diabetes Federation, National Heart, Lung, Blood Institute, American Heart Association, and others (IDF/NHLBI/AHA-2009) consensus statement criteria (IDF harmonized criteria) [13]. The approach was chosen to assess MetSyn prevalence because the indicators used are easily and readily measurable. The classification schema requires at least 3 of the following abnormalities: WC (≥ 94/80 (males and females); hyperglycemia defined as current use of antidiabetic medication (insulin or oral agents) or increased FPG ≥ 100 mg/dL (5.6 mmol/l); SBP/DBP ≥ 130/85 mmHg or current antihypertensive medication; TG ≥ 150 mg/dL (1.7 mmol/l) or anti TG medication; Hypo-HDL-C ≤ 40 mg/dl (1.03 mmol/dl) in men and ≤ 50 mg/dl (1.29 mmol/dl) in women.

Data analysis

Analyses were performed using IBM SPSS Statistics (SPSS Inc., Version 21.0, Chicago, IL, USA). Where applicable, the results were expressed as mean ± SD or median ± inter quantile range (IQR). Kolmogorov-Smirnov test, Shapiro-Wilk test and visual inspection of normality plots were used to evaluate gaussian distribution of data. Levene test was used to evaluate homogeneity of variances. Where appropriate, independent sample t-test, Mann Whitney U or One Way-ANOVA (with LSD Post Hoc) were subsequently used to compare mean or median values of continuous variables. A primary aim of this study was also to explore associations between MetSyn and potential risk factors. In these analyses, the Pearson Chi-Square test (χ^2) or Fisher’s exact test in the CROSSTAB procedure were used. The Cochran-Armitage trend test was used in categorical data analysis to evaluate trends. Multivariable logistic regression models were subsequently fitted to identify factors associated with the presence of MetSyn. Two-sided p-values < 0.05 and, where applicable, < 0.01, were accepted as statistically significant.

Ethical Consideration

Ethical approval for the study and experimental protocols used was obtained from Eritrean Ministry of Health (MOH) Research Ethical Committee and Orotta College of Medicine and Health Sciences Scientific and Ethical Committee. Informed consent was obtained from all participants after extensive explanation of the study objective/or purpose, study procedures and possible adverse effects. All participants were duly informed of their rights to refuse or terminate their participation in the study. Information on the maintenance of data confidentiality and integrity was also provided. Strict adherence to approved laboratory protocols was observed during specimen collection.

Result

Characteristics of the study population

Table 1
Clinical characteristics of the study population stratified by sex (n = 309)

Variables	Totals	Female	Male	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	
FPG (mg/dL)	174.64 ± 76.38	179.08 ± 75.31	170.7 ± 77.36	0.337
HbA1c (%)	8.72 ± 0.07	8.93 ± 1.38	8.54 ± 1.06	0.005*
SBP mmHg	128.42 ± 19.85	126.6 ± 19.4	130.0 ± 20.18	0.136
DBP mmHg	79.44 ± 7.70	78.4 ± 7.92	80.38 ± 7.39	0.023*
LDL-C (mg/dL)	133.84 ± 40.56	144.4 ± 43.79	123.68 ± 34.38	< 0.001*
HDL-C (mg/dL)	47.89 ± 11.23	52.54 ± 11.50	43.72 ± 9.18	< 0.001*
TG (mg/dL)	198.42 ± 148.34	174.63 ± 108.2	219.7 ± 174.3	0.007*
TC (mg/dL)	217.48 ± 49.78	230.38 ± 54.65	205.9 **±** 41.88	< 0.001*
Non-HDL (mg/dL)	169.59 ± 45.69	177.84 ± 51.07	162.19 ± 38.95	0.003*
CRP (%)	35 (11.3)	22 (62.9)	13 (37.1)	0.037*
eGFR (MDRD) mL/min/1.73 m^2	81.60 ± 54.45	66.69 ± 31.93	98.74 ± 27.94	< 0.001*
Insulin therapy (%)	104 (33.7)	62 (59.6)	42 (40.4)	0.003*
Hypertension (%)	132 (42.7)	63 (47.7%)	69 (52.3%)	0.488

*Data are presented as mean ± SD: FPG: Fasting plasma glucose; HbA1c: Hemoglobin a1c; SBP: systolic blood pressure; DBP: Diastolic Blood pressure; eGFR: estimated glomerular filtration rate; LDL-C; Low density lipoprotein; HDL-C: High density lipoprotein; TG: Triacylglycerol' TC: Total Cholesterol; CRP: C-reactive protein. $p < 0.01$, *.*

Three hundred and nine patients comprising 146 (47.2%) females and 163 (52.8%) males were studied. The mean HbA1c (%) and FPG in the study subjects were 8.72 ± 0.07 and 174.64 ± 76.38 mg/dL. These concentrations are above the upper limit for all DM management guidelines. On average, males had significantly higher DBP mmHg (80.38 ± 7.39 mmHg) compared to women (78.4 ± 7.92 mmHg). The mean ± SD for eGFR was 81.60 ± 54.45 mL/min/1.73 m^2. Interestingly, females had significantly lower eGFR compared to males – 66.69 ± 31.93 98.74 ± 27.94 mL/min/1.73 m^2, $p < 0.001$. This indicates that a significant number of the female participants had reduced kidney function. Additional sex stratified baseline characteristics of the study population are shown in Table 1.

Table 2
Demographic and Anthropometric characteristic of the study population stratified by Sex (n = 309)

Variables	Totals (n = 309)	Female (n = 146)	Male (n = 163)	P-value
Age (years)	57.80 ± 11.41	55.58 ± 12.11	59.8 ± 10.52	< 0.001*
Duration of Diabetes (years)	12.14 ± 7.42	11.38 ± 6.96	12.82 ± 7.77	0.088
Age at DM onset	45.66 ± 12.24	44.20 ± 13.2	47.70 ± 11.29	0.014*
BMI (kg/m^2)	24.69 ± 0.25	25.58 ± 5.37	23.90 ± 3.04	< 0.001*
WC (cm)	94.39 ± 10.36	94.57 ± 11.81	94.23 ± 8.90	0.777
WHR	0.93 ± 0.06	0.91 ± 0.058	0.95 ± 0.048	< 0.001*
WHtR (IQR)	56.85 ± 0.82	0.59 ± 0.09	0.55 ± 0.07	< 0.001*
BAI	12.71 ± 4.02	14.7 ± 4.58	10.91 ± 2.26	< 0.001*
Diet (%)	261(84.5)	129 (49.4)	132(50.6)	0.051
Alcohol (%)	66 (21.4)	8 (12.1)	58 (87.9)	< 0.001*
Exercising (%)	167 (54.0)	72 (43.1)	95 (56.9)	0.071

BMI: Body mass index; WHR: Waist/hip Ratio; WHtR: Height ratio; BAI: Body Adiposity Index; WC: Waist Circumference; BP blood pressure, p < 0.01.

The mean ± SD age of the studied population was 57.80 ± 11.41 years. In general, the male participants had a higher mean age (59.8 vs. 55.58 years, p < 0.001); lower BMI (23.90 vs. 25.58 kg/m^3 p < 0.001); higher WHR (0.95 vs 0.91 p < 0.001) and higher rates of alcohol consumption (87.9% vs 12.1% p < 0.001). Table 2 provides additional information of anthropometric characteristic of the study population.

Frequency of specific components of metabolic syndrome (IDF harmonized criteria) in the study population

The proportion of patients with specific abnomalities associated with MetSyn are shown in Fig. 1. In this analysis, the proportion of males presenting with abdominal obesity was lower (14.7 vs 69.2% p < 0.001). In contrast, the proportion of males presenting with raised TG was higher (62.6 vs 49.2% p value 0.013). Among individuals with MetSyn, 54.4% had HTN; 57.9% had abnormal WC; 72.8% had raised TG and 61.0% had abnormal HDL.

*Frequency of metabolic syndrome and Component Number (*IDF harmonized criteria*)*

Various organizations have proposed different criteria to describe the relationship between cardiovascular and metabolic diseases. In this analysis, the IDF harmonized criteria was employed. According to the data, 58.1% of the patients had MetSyn. The frequency of MetSyn in females was significantly higher compared to that of men (67.8 vs 49.7%). Patients presenting with ≥ 3 and 4 abnormalities associated with MetSyn were 30.7% (female vs males = 32.2 vs 30.7%) and 24.6% (Female vs males = 34.6 vs 15.3%), respectively. Figure 2.

Relationship between Number of MetSyn Components and mean values of specific variables

Table 5
Mean values of specific variables stratified by the number of MetSyn components (n = 309)

Variables	Number of MetSyn Components					P value
	DM Only	Plus 1 trait	Plus 2 traits	Plus 3 traits	Plus 4 traits	
Mean & Standard Deviation (± SD)						
BMI (Kg/m^2)	21.0(± 2.98)	23.7(± 3.1)	25.1(± 4.43)	27.0(± 3.6)	29.8(± 7.2)	< 0.001$^{\beta}$
eGFR ml/min/1.73 m^2	76.3(± 32)	72.5(± 29)	67(32.51)	66.1(37.5)	53.0(29.0)	0.024
Non-HDL-C	146(± 40)	161(± 37.0)	171(± 41.7)	176.0(± 41)	180 (± 24)	0.012
LDL-C mg/dL	128.0(± 41)	133(± 33.0)	137.5(± 45.0)	134.2(39.2)	135.7(27.3)	0.650
TC mg/dL	199.4(± 43)	212(± 42.0)	222.9(± 56.0)	220(± 45.0)	220.3(± 27)	0.426
TG mg/dL	105(± 31)	143(± 65)	193.3(± 84)	209(± 73.0)	221.8(± 51)	< 0.001$^{\beta}$
HDL-C mg/dL	54(± 9.7)	50.5(11.4)	47.6(± 12.5)	44.0(± 7.7)	40.2(± 4.5)	< 0.001$^{\beta}$
SBP mmHg	123.5(± 13.3)	127.0(± 21)	131.0(± 21)	130.0(± 20)	136(± 15.0)	0.040
DBP mmHg	78.0(± 6.1)	79.0(6.7)	80.2(± 8.6)	80.1(± 6.3)	82.0(± 6.9)	0.027
WHtR	0.51(± 4.7)	0.55(± 5.4)	0.58(± 8.3)	0.62(± 6.5)	0.64(± 5.1)	< 0.001$^{\beta}$
WHR	0.90(± 0.06)	0.92(± 0.05)	0.94(± 0.06)	0.95(± 0.05)	0.93(± 0.07)	0.001$^{\beta}$
WC	85.5(± 9.1)	91.4(± 7.9)	96.2(± 8.4)	112.0(± 10)	102.4±(7.5)	< 0.001 $^{\beta}$
HC	94.5 (± 7.5)	99.4 (± 8.1)	102.9(± 9.9)	107.0(± 8.4)	111.0(± 8.1)	< 0.001$^{\beta}$

Abbreviation: BMI: Body mass Index; eGFR: estimated Glomerular Filtration Rate; Non-HDL-C: Non-High Density Cholesterol; LDL-C: Low Density Cholesterol; TC: Total Choleterol: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CRP: C-Reactive Protein; DM: Diabetes Mellitus. P < 0.001; β: P value < 0.001 for Linearity test.

In an alternative analysis, we evaluated the relationship between number of MetSyn components and several CVD risk markers. Accordingly, a positive dose-response gradient between increasing number of MetSyn components and mean values of BMI, TG, TC, WHtR, WHR, WC, HC was observed (Table 5). That is to say, the higher the component number, the higher the mean values of these risk factors. A similar relationship was observed with TG/HDL, TC/HDL and LDL/HDL ratio (Fig. 3). See Appendix 1 for post hoc data and additional descriptive statistics.

Relationship between BMI and MetSyn

The relationship between BMI, Insulin use and MetSyn was evaluated. In this analysis, increasing BMI was associated with increasing frequency of MetSyn. The linear-by-linear association, p value < 0.001. The data also appears to suggest that women were disproportionally impacted at lower (< 25 kg/M^2) BMI. Overall, 3(18.8%) of the underweight patients had MetS, the proportion of MetSyn in the normal, Overweight and Obese categories were 83 (53.2%); 83 (76.9%) and 26 (89.7%), respectively (p value = 0.001). Figure 4.

Bivariate and multivariate analysis of the factors associated with the presence of MetSyn in patients with T2DM

In a separate analysis, the following factors were significantly associated with the presence of MetSyn: Sex, TC, eGFR, Non – HDL – C, BMI and Insulin injection. All the factors with p value < 0.200 were entered into a multivariable logistic regression model; the results are presented in Table 4. In this analysis, the following factors were associated with enhanced odds of having

MetSyn: Elevated LDL-C (aOR, 3.56, 95% CI, 1.52–8.34, p = 0.003); increasing concentration of Non-HDL-C (aOR, 1.02, 95% CI, 1.01–1.03, p = 0.001) and increasing BMI (aOR, 1.23, 95% CI, 1.13–1.32, p = 0.001). On the other hand, patients who not on insulin injection had reduced likelihood of having MetSyn (aOR, 0.37, 95% CI, 0.19–0.70, p = 0.002).

Table 4

Multivariate analysis of the factors associated with the presence of Metabolic syndrome in patients with type 2 diabetes at a specialized diabetes clinic in Asmara, Eritrea (n = 309).

Variables Categories		MetSyn		Unadjusted OR	P-value	Adjusted OR	P-value
		No	Yes	(95% CI)		(95% CI)	-
Sex	Male	**82 (50.3)**	**81(49.7)**	(Ref)		(Ref)	0.016
	Female	**47(32.2)**	**99(67.8)**	2.0(0.96–4.36)		2.1(1.15–3.82)	
Age				1.02(0.98–1.054)			
	< 40 years	**13(81.3)**	**3(18.8)**			0.08(0.013–0.44)	0.004
	41–60 years	**68(40.0)**	**102(60.0)**			0.63(0.35–1.15)	0.132
	> 60 years	**48(39.0)**	**75(61.0)**			1(Ref)	
Diet	No	22(45.8)	26(54.2)	1(Ref)			
	Yes	107(41.0)	154(59.0)	1.62(0.72–3.61)			
Alcohol	Yes	29(43.9)	37(56.1)	1(Ref)	0.711		
	No	100(41.2)	143(58.8)	1.15(0.54–2.45)			
TC (mg/dl)	< 200	**57(48.7)**	**60(51.3)**	1(Ref)	0.196		
	> 200	**72(37.5)**	**120(62.5)**	1.91(0.72–5.08)			
LDL (mg/dl)	< 100	22(38.6)	35(61.4)	1(Ref)	0.002	1(Ref)	0.001
	> 100	101(43.3)	132(56.7)	4.52(1.71–11.94)		5.2(2.04–13.1)	
eGFR (MDRD) (ml/min/1.73 m^2)				1.0(0.99–1.01)	0.978		
	< 60	**38(33.3)**	**76(66.7)**				
	> 60	**91(46.7)**	**104(53.3)**				
Non-HDL-C (mg/dl)				1.03(1.01–1.04)	**<** 0.001	1.02(1.01–1.03)	< 0.001
	< 130	**38(56.7)**	**29(43.3)**				
	> 130	**91(37.6)**	**151(62.4)**				
BMI (kg/m^2)				1.20(1.10–1.30)	< 0.001	1.19(1.10–1.29)	**<** 0.001
	< 25	**99(57.6)**	**73(42.4)**				
	> 25	**28(21.1)**	**105(78.9)**				
Insulin injection	Yes	38(36.5)	66(63.5)	1(Ref)	0.012	1(Ref)	0.026
	No	91(44.4)	114(55.6)	0.39(0.19–0.813)		0.47(0.24–0.913)	
HsCRP	Positive	16(45.7)	19(54.3)	1(Ref)	0.998		

TC: Total cholesterol; **LDL**: low density cholesterol; **eGFR**: estimated glomerular filtration rate – Modification of Diet in Renal Disease (**MDRD)**; **HDL**- high density lipoprotein; **BMI**: Body Mass index.

Variables Categories	MetSyn		Unadjusted OR	P-value	Adjusted OR	P-value
	Negative	113(38.9)	161(58.8)	1.001(0.39–2.58)		

TC: Total cholesterol; **LDL**: low density cholesterol; **eGFR**: estimated glomerular filtration rate – Modification of Diet in Renal Disease (**MDRD)**; **HDL**- high density lipoprotein; **BMI**: Body Mass index.

Discussion

Detection of individuals at risk of future complication/comorbidity is a fundamental objective of DM treatment and management. As previously discussed, MetSyn represents an important risk stratification strategy that can be used as guide for patient-centered treatment. In this study, the first of its kind in Eritrea, we evaluated the frequency of MetSyn in the largest T2DM follow-up facility in Asmara. In sum, MetSyn was documented in 58.1% of the patients. Available data suggests variable prevalence of MetSyn in different parts of SSA [27]. Hospital-based data applying Adult Treatment Panel III [ATP III]) criteria (NCEP: ATP III) or the closely allied IDF harmonized criteria [13] are available for specific sites in Nigeria 60% [28]; Ethiopia (51.1%) [30]; Ghana (24–78.8%) [31]; Cameroon (60.4%) [32]; Nigeria (62.5%) and [33]. Higher percentages are generally reported if the IDF harmonized definition was applied [31, 32]. The highlighted comparisons should be read with several caveats in mind. Foremost is the fact that the available reports from SSA have mostly provided non-standardised prevalence rates (e.g. disparate definitional criteria). Accuracy of medical examinations, differences in access to clinical care, diagnostic criteria may also undermine direct comparison between studies. Therefore, it is important to seek out the similarities and differences in the study design and patient population in these studies.

Among individual permuted phenotypes, the triplet of hypertriglyceridemia, abnormal HDL-C and HTN were the most frequent. *Vice versa*, a large number of studies from the region have noted that the most predominant component of MetSyn in patients with T2DM is HTN [30, 31, 33, 34, 35, 36, 37] and central obesity [30, 38, 39]. Regardless, the current data is supported by the fact overt DM, especially T2DM, frequently elevates plasma TG and reduces HDL-C. Indeed, multiple studies, have established that T2DM patients almost invariably manifest serious breakdown in lipid dynamics, reflected by increased flux of non-esterified fatty acids (NEFAs), TG, low-HDL-C and increased amount of apolipoprotein (ApoB) particles with preponderance of smaller, cholesteryl ester depleted LDL-C [40, 41]. Although the pathophysiological mechanisms are complex, and not entirely understood; the preponderance of diabetogenic dyslipidemia components in this setting maybe an indicator of IR and suboptimal control of the disease. Unfortunately, management of diabetic dyslipidemia has been overlooked in most countries in SSA. Beyond that, our data demonstrates that caloric restriction/or dieting and increased physical activity/exercising are under-emphasized in this setting. Unfortunately, and as is often the case in SSA, medications for lipid management are largely inaccessible to most patients due to cost and availability.

Further, analysis of the difference between males and females in multiple profiles appears to suggest that women are disproportionately affected in this setting. Significantly higher mean (SD)/or median (IQR) were observed in women for multiple analytes including HbA1c; LDL-C; TC; Non-HDL-C; BMI, among others. A higher percentage of women were also on insulin injection and had positive CRP result. The age at DM onset was also lower in females. In contrast, men had higher average DBP; TG; alcohol consumption and lower HDL-C, among others. The observed pattern of abnormalities in lipid and anthropometric markers has been documented in multiple investigations [31, 34, 38, 34] and might explain disease risk or differential impact between the sexes. Unlike other studies [37], there was no significant sex difference in the prevalence of HTN. The fact that women are disproportionately impacted (e.g. disease incidence, morbidity and mortality) in the NCD landscape in SSA has been reported in the region [32, 34, 37, 38]. The aggravated impact of MetSyn in women was also evidenced by the fact that a large proportion of women had more than 4 abnormal MetSyn components. Taken together, and cardioprotective effects of estrogens in pre-menopausal women notwithstanding; our data reinforces the well-evidenced assertion that women with DM are at a greater risk of CVD than men with DM.

A separate stepwise multivariate analysis demonstrated that the frequency of MetSyn was associated with age, LDL-C, Non-HDL-C, BMI and IR. The link between age and enhanced MetSyn risk is well documented [19]. Several studies have also demonstrated a clear relationship between age, obesity, T2DM and CVD risk. The observed relationship between LDL-C, Non-

HDL-C and MetSyn is equally important. Trial level evidence from a previous study in Mexico indicated that LDL-C levels > 100 mg/dL are observed in 74.8% (95% CI 72.5–76.9%) of previously diagnosed DM patients [42]. In this study, the proportion of patients presenting with elevated LDL-C was 75.4%. Non-HDL-C, a surrogate marker of plasma concentrations of atherogenic Apo B-100 containing lipoprotein particles (VLDL, IDL, LDL, lipoprotein A), was also elevated in most patients (73.3%). Taken as a whole, it's our position that although elevation in LDL-C, Non-HDL-C, age and insulin injection are not part of the MetSyn diagnostic algorithms, they are important surrogate markers of CVD risk. In this respect, the observed associations may further modify absolute risk in this population.

An interesting peculiarity in the clinical expression of MetSyn in SSA is the disproportional contribution of abdominal obesity (WC > 94/80 cm Male/Females) in MetSyn diagnosis in women from the region [34, 35, 38]. A substantial amount of epidemiological and *post hoc* analyses of clinical trial data on intra-abdominal fat, including those involving imaging technologies, have demonstrated that WC is a better predictor of T2DM and MetSyn incidence [35]. In particular, Evans and coworkers [43] found that WC, WHtR and a Computer Tomography (CT) - derived measure of visceral adipose tissue (VAT) performed similarly in predicting MetSyn in pre-menopausal women from disparate racial groups in South Africa (SA). Multiple propositions have been advanced to explain the link between visceral adipose tissue and the other components of MetSyn (elevated BP, dysglycemia, inflammation) – portal visceral hypothesis; endocrine paradigm and the ectopic fat storage hypothesis. Briefly, it's been hypothesized that dysfunctional visceral adipose tissue or/ visceral adipocyte hypertrophy is associated with IR and hypersecretion of bioactive adipokines and proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), angiotensin II (AII), interleukin − 6 (IL-6), interleukin-1β (IL-1β), (RBP-4), plasminogen activator inhibitor-1 (PAI-1), heparin binding epidermal growth factor, leptin, resistin and a decrease in adiponectin, to mention a few [44, 45, 46] – a dynamic which has been implicated in MetSyn etiology and pathogenesis [45].

At present, the use of WC measurements, independently or in conjunction with other risk factors, to predict cardiometabolic disease is not well established in SSA [13, 35]. Unfortunately, it has been recognized for many years that the default WC value (94 cm males/80 cm females) used in the region may underestimate the prevalence of MetSyn among men and overestimate its prevalence among women [47]. For this reason, the prominence of WC as a marker of MetSyn, particularly in women in SSA, remains controversial due to the absence of specific cut points for local populations. Therefore, the possibility that this study may have underestimated the prevalence of MetSyn in men is considerable.

The relationship between BMI and MetSyn was also explored in this study. Like WC, BMI is not a refined research or clinical tool particularly for patients presenting with DM. A major limitation of BMI is the inability to discriminate between visceral adipose tissue (VAT) and other forms of adipose tissue distribution [48]. As a matter of fact, the exclusion of BMI in some MetSyn diagnostic specifications is partly based on the fact that visceral distribution of body fat is, as we noted previously; a stronger risk factor for CVD than general obesity [5, 35]. The relationship between BMI and MetSyn, hence CVD risk is demonstrated in Fig. 3. One thing is clear: the greater the weight, the greater the frequency of MetSyn and *vice versa*. Another important finding was the fact that a large number of patients with MetSyn had low BMI. Interestingly, some authors have argued that MetSyn occurs less frequently in those who are overweight (BMI 25–29.9 kg/m^2) and is relatively rare in normal weight individuals [49]. Clearly, the latter assertion is not evident in our study. Concordant with other studies in SSA [50], a sizable proportion of patients with MetSyn had BMI < 25 Kg/m^2. One additional observation was the finding that the relationship between BMI and MetSyn was a lot more consistent at BMI > 25 kg/m^2. Whilst obesity is evidently important and the lower the BMI, the better; other factors appear to influence susceptibility to MetSyn at lower BMI (< 25 kg/m^2). First and foremost, investigators have noted that compared to the Western world, a sizable proportion of T2DM patients in Africa have (< 25 kg/m^2) [16, 51].

Possible explanations of this phenomenon are multiple and debatable. For instance, some imaging studies have shown that important and physiologically significant visceral fat accumulations can be observed in some ethnic/racial groups even in the normal BMI range [52]. Consistent with this, it has been noted that non-obese individuals with MetSyn may have susceptibility factors, particularly ethnic, and genetic/or epigenetic characteristics [53]. Misclassification of patients with latent autoimmune diabetes in adults (LADA) and other atypical DM phenotypes as T2DM is another possible explanation. The plausibility of this proposition is augmented by the fact that measurement of glutamic acid decarboxylase antibodies (GADab) in adults

diagnosed with T2DM is not a prerequisite to identify subjects with LADA in Eritrea. In all, detailed studies are needed especially among newly-diagnosed DM patients to fully characterize the disease in the region. Understanding the genetic profile of T2DM in the region is another onerous challenge.

In a separate analysis, we evaluated the relationship between specific non-traditional markers (Non-HDL-C, TG/HDL-C, TC/HDL-C and LDL-C/HDL-C) and MetSyn. Broadly speaking, the relationship between number of MetSyn components and mean values of specific traditional and non-traditional cardiometabolic biomarkers is a rare consideration in publications from the region [19, 29–32]. Regardless, it's our belief that the use of multiple break-points in risk stratification (e.g. component number) may provide supplementary information which maybe masked by the usual MetSyn/No MetSyn dichotomy.

In this analysis, a positive dose-response gradient between increasing number of MetSyn components and mean values of BMI, TG, TC, WHtR, WHR, WC, HC was established - the higher the component number, the higher the mean values of these risk markers. Reducing eGFR was also associated with increasing component number. A similar parallel increase in Non-HDL-C, TG/HDL-C, TC/HDL-C and LDL-C/HDL-C with increasing number of components was also demonstrated. Altogether, our study demonstrates that increasing number of MetSyn components is associated with higher averages in multiple traditional and non-traditional CVD risk indicators in this population. The latter associations are interesting given the link between these non-traditional markers and CVD risk. For example, compelling evidence indicates that TC/HDL-C is a fairly good index of the relative contribution of atherogenic vs. antiatherogenic lipoproteins to accelerated atherosclerosis [54]. Some investigators consider it to be superior even to the measurements of the ratio of apo B to apo A-I. The utilization of the TG/HDL-C ratio as a marker of IR and a means to estimate the presence of the more atherogenic small dense LDL-C subfractions has also been proposed [55, 56]. More importantly, NCEP ATP III identifies non-HDL-C as a secondary target of therapy in patients with TG > 200 mg/dL. Regardless, no rigorous outcome data are available to place into clinical context the relationship between these non-traditional markers and MetSyn-associated CVD risk in populations from SSA.

Finally, it is worth mentioning that although all components of MetSyn appear to promote CVD, the relationship between component number and CVD risk or outcome are not completely understood. According to a persistent view, quartets and quintets have no higher CVD risk than triplets of MetSyn components [57, 58]. Conversely, there exists overwhelming evidence that disparate MetSyn phenotypes (component mix) bear dissimilar CVD risk burden. Phenotypes containing elevated BP tended to confer higher risk. This is predictable given the fact that epidemiologic, experimental, and randomized controlled clinical study trial-level evidence have consistently indicated that elevated BP is a robust, consistent, independent and etiologpathologically relevant risk marker for CVD and chronic kidney disease (CKD). In particular, a past study utilizing NCEP-ATP III criteria for MetSyn stratification established a connection between the number of MetSyn components and several CVD risk indicators including severity of subclinical atherosclerosis as reflected by thicker carotid plaques, increased common carotid intima-media thickness (IMT) and increased pulse wave velocity [58]. Clearly, more research is required in order to examine, and possibly confirm, phenotype/component mix and adverse event relationships for this setting.

Strength And Limitation

The main strength of our study is its novelty the first of its kind in Eritrea. Additional strengths include the number of participants which was adequate to make gender-specific comparisons on a wide range of variables. The study was also undertaken in one of the biggest follow-up clinics in Asmara and may thus give a fairly good account of the quality of patient care. Moreover, measurements undertaken during the study followed standardized procedures thus limiting the likelihood of misclassification. Nonetheless, the study has some limitations. The cross-sectional nature of the study imposes certain limitations – it precludes the examination of ephemerality and inference of causality. Unverifiable responses, particularly on issues such as dieting and physical activity, among others; may also be limiting.

Conclusion

In summary, this study demonstrates that the frequency of MetSyn, hence CVD risk, is relatively high and women are disproportionately impacted. This is clearly reflected in the observed clinical and metabolic differences. Although

hypertriglyceridemia and subnormal HDL-C were the most frequent components of MetSyn; the frequency of HTN and abdominal obesity (elevated WC) is substantial. The findings therefore support opportunistic screening for CVD risk factors whenever outpatients visit the follow-up clinic. This may provide an opportunity for early identification and management of CVD risks. In this regard, increasing the capacity to diagnose, manage and prevent obesity, dyslipidemia, hyperglycemia, and other complications/co-morbidities is paramount. Stepwise multivariate modelling demonstrated that the frequency of MetSyn was associated with known correlates of CVD risk such as age, LDL-C, Non-HDL-C, BMI and insulin injection. Sustained focus on non-pharmacological measures such as weight loss, behavioral management, dietary modification as a key component of good care for patients is therefore critical. In many respects, the proposition that number of MetSyn components is associated with increasing magnitude of specific CVD risk markers (TG/HDL-C, TC/HDL-C and Non-HDL-C) add to the evidence on the utility of these markers and MetSyn in this setting. Quite consistently, the current data support a continued focus MetSyn and non-traditional risks factors such as Non-HDL-C as markers of global cardiometabolic risk in T2DM patients in this setting. This finding has implication for clinical practice and public health intervention. In view of all that has been mentioned, the need for large-scale epidemiological studies or clinical studies that can shed more light on the magnitude of MetSyn in this setting is imperative.

Declarations

Conflict of Interest

The authors have no conflict of interest to declare on this study.

Acknowledgment

The authors are grateful to the Eritrea Higher Education Council through Asmara College of Health Sciences for funding this project. The Authors are also grateful for the technical assistance provided by the Staff of Halibet and Sembel hospital.

Authors' contributions

MG, AK, MS, SM, YR, EGY, OAI conceived of the study, participated in the design, performed laboratory experiments. OOA performed the statistical analysis, participated in the design and reviewed/edited the manuscript. All authors read and approved the final manuscript.

Financial support

Material support was obtained from Asmara College of Health Sciences and Eritrean Ministry of Health.

Supporting Documents

The dataset supporting the conclusions of this article are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethical approval for the study and experimental protocols used was obtained from Eritrean Ministry of Health (MOH) research ethical committee. Informed consent was obtained from all participants. During the study, strict adherence to approved laboratory protocols was observed.

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Figures

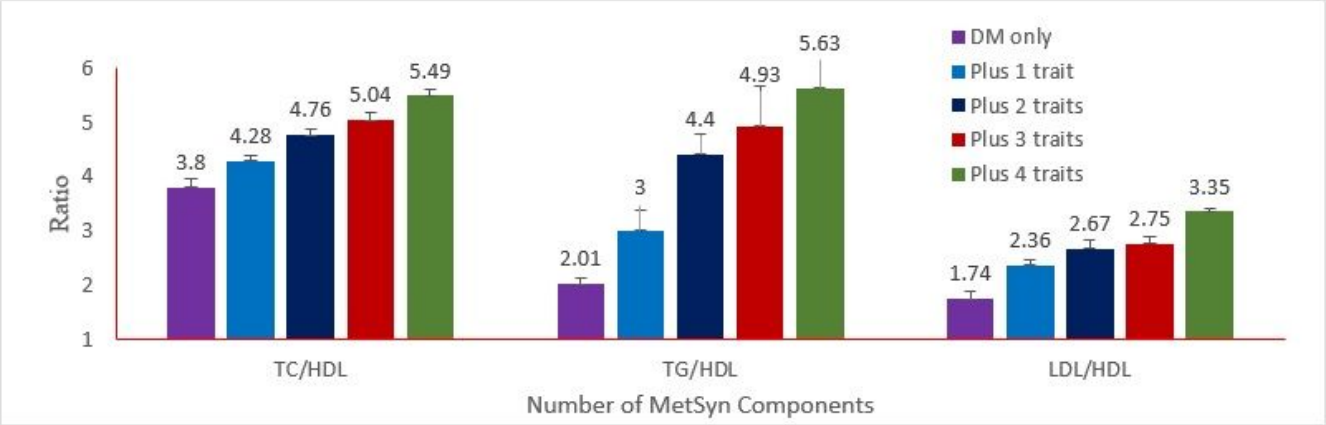

Figure 3

Relationship between the averages of Lipids and Lipoprotein ratios and number of MetSyn components