Původní sdělení | Original research article

Pilot Evaluation of Endothelin-1 and TG/HDL-C Ratio for Early Cardiovascular Risk Stratification in Adiposity-Based and Cardiovascular-Kidney-Metabolic Syndromes

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SOUHRN

Chronické onemocnění vyvolané zmnožením tukové tkáně a kardio-reno-metabolický syndrom (cardiovascular-kidney-metabolic, CKM) významně přispívají k zátěži nepřenosnými onemocněními (non-communicable disease, NCD), zvláště v zemích s nízkým a středně vysokým příjmem na hlavu (low- and middle-income countries, LMICs), kde je časná stratifikace rizika stále ještě nedostatečná. V této studii se hodnotila spolehlivost použití hodnot endotelinu-1 (ET-1) a poměru triglyceridy-cholesterol v lipoproteinech o vysoké hustotě (triglyceride-to-high-density lipoprotein cholesterol, TG/HDL-C) jako časných, nákladově účinných biomarkerů při stanovování kardiovaskulárního rizika u osob s chronickým onemocněním vyvolaným zmnožením tukové tkáně (adiposity-based chronic disease, ABCD) a v časném stadiu CKM syndromu.

U osob ve věku 30 až 65 let s ABCD (index tělesné hmotnosti > 25 kg/m²) nebo v 1. stadiu syndromu CKM bylo provedeno analytické experimentální vyšetření. Zařazovací kritéria splnilo 97 účastníků studie. Byly stanoveny koncentrace ET-1 v plazmě a lipidové profily a jedinci byli klasifikováni podle závažnosti obezity. Statistické analýzy se prováděly s použitím jednosměrné analýzy rozptylu (analysis of variance, ANOVA), *post hoc* testování a multivariační regrese.

Jednosměrná ANOVA prokázala rozdíly v hodnotách ET-1 a poměrech TG/HDL-C v závislosti na stupni obezity, s hodnotami < 0,001 u obou parametrů. Nejméně statisticky významný rozdíl (least significant difference, LSD) v neobézní subpopulaci ve srovnání s obézní subpopulací (p = 0,051) se významně lišil od populace s obezitou 2. stupně (p < 0,001). Hodnoty LSD u poměru TG/HDL-C proto vykazovaly statisticky významné rozdíly mezi neobézní populací a populací s obezitou 1. stupně (p = 0,002) a mezi neobézní populací a populací s obezitou 2. stupně (p < 0,001). Multivariační analýza odhalila statisticky významné rozdíly v průměrných hodnotách proměnné ET-1 mezi subpopulací s obezitou 2. stupně a neobézní subpopulací, s poměrem šancí 216,29 (95% interval spolehlivosti [CI] 91,25–341,33; p = 0.000), i mezi subpopulacemi s obezitou 2. stupně vs. obezitou 1. stupně, s poměrem šancí 119,49 (95% CI 60,68–178,29; p = 0.000). Poměr TG/HDL-C vykazoval statisticky významný vliv na neobézní populaci i populace s obezitou 1. i 2. stupně, s poměrem šancí 3,16 (95% CI 0,71–5,52; p < 0,001).

Naše výsledky prokázaly endotelovou dysfunkci u všech účastníků studie. Vzhledem k poměru TG/HDL-C byla u všech přítomna inzulinová rezistence. Hodnocená populace byla zařazována do skupin se středně vysokým rizikem (n = 10) a s vysokým rizikem (n = 87) rozvoje aterosklerotické kardiovaskulární nemoci podle aterogenního indexu plazmy (AIP).

Na základě AIP bylo u většiny jedinců rozpoznáno vysoké riziko iniciální aterosklerotické kardiovaskulární příhody. Začlenění hodnot ET-1 a poměru TG/HDL-C do algoritmu stanovování kardiovaskulárního rizika může usnadnit časné vyhledávání a léčbu jedinců s ABCD a syndromem CKM a zvýšit účinnost prevence nepřenosných onemocnění usilující o dosažení udržitelného rozvoje.

Keywords:
Adiposity-based chronic disease
Atherogenic index of plasma
Cardiovascular risk assessment
Cardiovascular-kidney-metabolic syndrome
Endothelin-1
Triglyceride-to-HDL cholesterol ratio

ABSTRACT

Adiposity-related chronic diseases and cardiovascular-kidney-metabolic (CKM) syndrome significantly contribute to the burden of non-communicable diseases (NCDs), especially in low- and middle-income countries (LMICs), where early risk stratification is still inadequate. This study evaluated the efficacy of endothelin-1 (ET-1) and the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio as early, cost-efficient biomarkers for cardiovascular risk assessment in persons with adiposity-based chronic disease (ABCD) and early-stage CKM syndrome.

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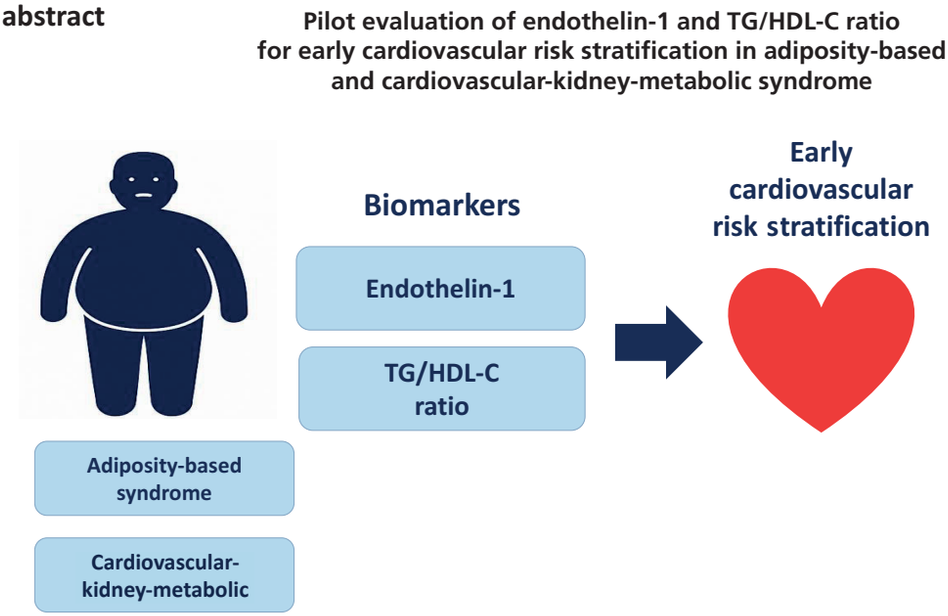
An analytical experimental investigation was performed on persons aged 30 to 65 years with ABCD (body mass index >25 kg/m²) or stage 1 CKM syndrome. 97 participants met the inclusion criteria. Plasma ET-1 concentrations and lipid profiles were assessed, and individuals were classified based on the severity of obesity. Statistical analyses comprised one-way analysis of variance, post hoc testing, and multivariate regression.

The one-way ANOVA test revealed significant differences in ET-1 levels and TG/HDL-C ratios relative to the degree of obesity, with *p*-values <0.001 for both measurements. The least significant difference (LSD) in the non-obesity sub-population compared to obesity (*p*-value = 0.051) was significantly distinct from the obesity II population (*p*-value <0.001). Consequently, the LSD test of the TG/HDL-C ratio revealed significant differences in the non-obesity population compared to obesity I (*p*-value = 0.002) and non-obesity versus obesity II (*p*-value <0.001). The multivariate analysis revealed statistically significant differences in the mean values of the ET-1 variable between the obesity II sub-population and the non-obesity sub-population, with an odds ratio of 216.29 (95% CI: 91.25–341.33; *p*-value = 0.000), as well as between obesity II and obesity I, with an odds ratio of 119.49 (95% CI: 60.68–178.29; *p*-value = 0.000). The TG/HDL-C ratio exhibited a statistically significant impact on the non-obesity, obesity I, and obesity II populations, with an odds ratio of 3.16 (95% CI: 0.71–5.52; *p*-value <0.001).

The findings demonstrated that all participants displayed endothelial dysfunction. All participants were characterized as exhibiting insulin resistance based on the TG/HDL-C ratio. The study population was classified into moderate risk (n = 10) and high risk (n = 87) for the initial incidence of atherosclerotic cardiovascular disease using the atherogenic index of plasma (AIP) method.

The atherogenic index of plasma indicated that most individuals were classified as having a high risk for an initial atherosclerotic cardiovascular event. Incorporating ET-1 and TG/HDL-C ratio into cardiovascular risk assessment models may improve the early identification and management of ABCD and CKM syndrome, facilitating effective non-communicable disease prevention aligned with sustainable development goals.

Graphical abstract



Introduction

The worldwide prevalence of non-communicable diseases (NCDs), especially adiposity-based chronic disease (ABCD) and cardiovascular-kidney-metabolic (CKM) syndrome, is increasing, presenting substantial difficulties to healthcare systems globally, particularly in low- and middle-income countries (LMICs). ABCD, defined by excessive adiposity and its metabolic ramifications, is closely associated with CKM syndrome, a constellation of interconnected disorders that significantly elevate the risk of cardiovascular disease (CVD) and chronic kidney disease (CKD).[1] NCDs are widely acknowledged as the primary cause of worldwide mortality, responsible for about 73% of annual fatalities.

In 2010, almost 80% of these fatalities transpired in LMICs, areas experiencing swift demographic transformations, such as population aging, urbanization, heightened tobacco use, and changing dietary and obesity trends. Nonetheless, the PHC systems in LMICs, historically concentrated on infectious diseases and maternal-child health, are not prepared to address the increasing prevalence of NCDs.[2,3] The PHC systems of LMICs, traditionally focused on infectious diseases and maternity and child

health, are inadequately structured to incorporate NCD treatment.

For notwithstanding progress in comprehending the pathophysiology of ABCD and CKM, prevailing PHC policies sometimes lack efficient instruments for early risk classification, hence constraining prompt management. Recent evidence underscores the potential of incorporating biomarkers like ET-1, a powerful vasoconstrictor associated with endothelial dysfunction and renal damage, alongside the TG/HDL-C ratio, a recognized surrogate marker of atherogenic dyslipidaemia, as complementary indicators of subclinical cardiovascular risk.[4,5]

ET-1 levels connect with diminishing glomerular filtration rate and cardiovascular incidents, whereas the TG/HDL-C ratio forecasts insulin resistance and coronary artery disease, even in individuals with normal cholesterol levels. Nonetheless, the utilization of these biomarkers in primary healthcare settings, especially in resource-constrained areas, remains insufficiently investigated. A significant deficiency exists in existing clinical guidelines concerning their application for early identification and risk stratification in ABCD and CKM populations.[6,7]

Addressing this deficiency corresponds with global health priorities, such as the SDGs and national health security frameworks, by advancing precision medicine strategies that are both economically viable and scalable. This study aims to present a transformative primary healthcare model that incorporates ET-1 and TG/HDL-C ratio measures to improve subclinical cardiovascular risk assessment in persons with ABCD and CKM syndromes.[6,7]

This method aims to enable earlier diagnosis, direct customized therapies, and ultimately enhance cardiovascular and renal outcomes in high-risk groups. Integrating these indicators into a predictive, preventive, and personalized medicine (3PM) framework presents a significant potential to transition from reactive to proactive treatment. The predictive elements provide the identification of patients at increased risk prior to clinical symptoms, while preventative measures can be customized according to biomarker profiles to reduce disease development.[8–10]

Tailored therapies, guided by ET-1 and the TG/HDL-C ratio, enhance therapeutic decision-making, increasing effectiveness and reducing side effects. The utilization of these biomarkers in PHC settings, especially in resource-constrained areas, remains insufficiently investigated. Concerning their application for early identification and risk assessment in ABCD and CKM cohorts. Addressing this deficiency corresponds with global health priorities, such as the SDGs and national health security (NHS) frameworks, by advancing precision medicine strategies that are both economically viable and scalable. The primary objective of this study is to propose a transformative primary healthcare model that incorporates ET-1 and TG/HDL-C ratio measures within a three-phase model to improve subclinical cardiovascular risk assessment in persons with ABCD and CKM syndrome.[11–15]

NHS activities prioritize fortifying health systems for the effective management of non-communicable diseases, guaranteeing fair access to diagnostics and care, and augmenting population resilience against chronic ailments. Simultaneously, the Sustainable Development Goals, especially Goal 3, which seeks to guarantee healthy lives and enhance well-being for all individuals across all age groups, emphasize the reduction of premature mortality from non-communicable diseases through prevention and treatment. The World Health Organization and national programs promote the incorporation of cost-effective, scalable interventions into primary healthcare to meet these objectives, emphasizing the significance of new biomarker-driven solutions in resource-constrained environments.[11–15]

This study aims to assess the efficacy of incorporating plasma ET-1 levels and the TG/HDL-C ratio within a predictive, preventive, personalized, and participatory medicine (4PM) framework to improve subclinical cardiovascular risk stratification in individuals with ABCD and CKM syndrome in primary healthcare environments.

The primary objectives are to:

1) assess the relationship between ET-1 levels and the TG/HDL-C ratio with markers of subclinical cardiovascular and renal dysfunction in the ABCD and CKM cohorts;
2) evaluate the predictive effectiveness of combined ET-1 and TG/HDL-C assays for the early detection of those at heightened risk of cardiovascular events and renal progression;
3) examine the feasibility and therapeutic relevance of integrating ET-1 and TG/HDL-C ratio evaluations in resource-limited primary healthcare environments, and;
4) align the biomarker-based risk stratification technique with national health security (NHS) goals and Sustainable Development Goals (SDGs) to improve the management and outcomes of non-communicable illnesses.

Methodology study framework

This study utilized an analytical cross-sectional design grounded in the principles of 4PM. Objective is to assess the efficacy of ET-1 and the TG/HDL-C ratio in stratifying subclinical cardiovascular risk in persons with ABCD and CKM syndrome. Individuals aged 30–65 years diagnosed with ABCD or CKM syndrome will be recruited in a LMIC context, representing actual clinical practice limitations and demographic diversity.

Data collection and measurements: at baseline, participants will receive a thorough clinical evaluation, encompassing anthropometric measurements and the acquisition of blood samples for ET-1 quantification (by ELISA) and lipid profiling to determine the TG/HDL-C ratio. Further information regarding demographics, medical history, lifestyle factors, and medication usage will be gathered. The study will evaluate the predictive ability of ET-1 and the TG/HDL-C ratio both separately and in conjunction. The study incorporates 4PM by emphasizing early prediction, focused prevention interventions, and individualized risk profile.

The study procedure will comply with international ethical standards and obtain approval from pertinent institutional review boards. Informed consent will be secured from all participants, guaranteeing confidentiality and data protection.

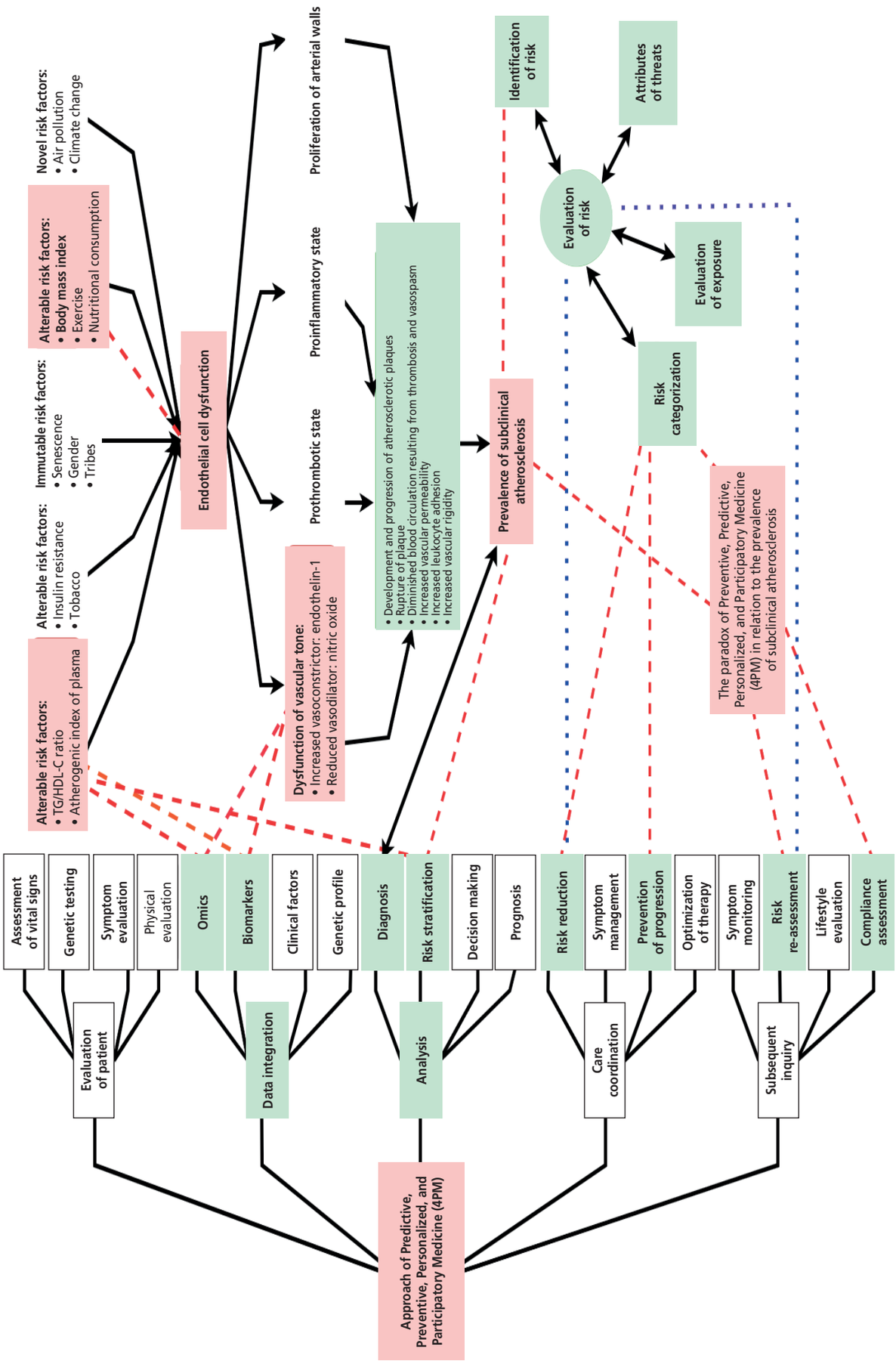


Fig. 1 – The conceptual framework of Predictive, Preventive, Precision, and Personalized Medicine (4PM) concerning paradoxical adiposity-based chronic disease (ABCD) and cardiovascular-kidney-metabolic (CKM) syndrome, amid an increasing prevalence of non-communicable diseases (NCDs).

Setting

This study takes place in primary healthcare centre and tertiary hospitals situated in urban regions of a LMIC, illustrating the healthcare delivery environment where ABCD and CKM syndrome are prevalent yet frequently underdiagnosed. The chosen locations exemplify typical resource-limited settings marked by restricted access to sophisticated diagnostic instruments, workforce deficiencies, and heterogeneous patient demographics with differing socioeconomic statuses. This includes standard management of cardiovascular and metabolic diseases, facilitating the incorporation of biomarker evaluations such as ET-1 and TG/HDL-C ratio into current clinical practices.

Laboratory analysis will utilize established, cost-efficient assays that align with local infrastructure to guarantee practicality and sustainability. This setting facilitates the assessment of the 4PM approach under real-world conditions that correspond with national health security priorities and SDGs, with the objective of enhancing early detection and management of subclinical cardiovascular risk in ABCD and CKM patients within primary health care frameworks.

Conseptual framework

The conceptual framework of this study examines the paradoxical role of obesity in CKM syndrome, integrating key biomarkers – ET-1 and the TG/HDL-C ratio – to improve subclinical cardiovascular risk assessment within the 4PM paradigm. (as illustrated in **Figure 1**).[16] Incorporating essential elements in which paradoxical obesity in cardiovascular risk management syndrome, while obesity is a recognized risk factor for CVD and CKD, paradoxical obesity denotes instances where heightened adiposity is correlated with unforeseen beneficial cardiovascular outcomes or inconsistent risk profiles.[17]

This paradox hampers risk evaluation and therapeutic decision-making in ABCD and CKM syndrome.[18,19] ET-1, a pathophysiological mediator, is a powerful vasoconstrictor and pro-inflammatory peptide that is raised in cases of endothelial failure and renal damage. Elevated ET-1 levels correlate with deteriorating renal function and facilitate vascular remodelling and hypertension, hence associating obesity with cardiovascular and renal diseases.

The TG/HDL-C ratio indicates atherogenic dyslipidaemia and insulin resistance, acting as a proxy marker for lipid-associated cardiovascular risk.[19] Increased TG/HDL-C ratios are associated with heightened plaque susceptibility and worse cardiovascular outcomes.[5,17,20]

The interaction of biomarkers and the resolution of paradoxes involving ET-1 and the TG/HDL-C ratio may clarify the mechanisms of paradoxical obesity by distinguishing between metabolically healthy and unhealthy adiposity phenotypes, as well as revealing subclinical vascular damage not detectable by traditional metrics like BMI alone.[18]

The integration of 4PM facilitates early detection of elevated ET-1 and TG/HDL-C ratios, allowing for the identification of individuals at increased risk despite atypical obesity presentations. This preventive approach enables targeted interventions to modulate ET-1 pathways and lipid abnormalities, thereby averting the progression to overt CVD and CKD. Personalized medicine for risk stratification utilizing integrated biomarker profiles facilitates individualized therapy approaches adapted to the distinct pathophysiology of patients. In the context of health systems, integrating this biomarker-driven 3PM model into primary healthcare aligns with national health security objectives and SDGs, fostering equitable and cost-effective strategies for managing ABCD and CKM syndromes in low- and middle-income countries.[16]

Results

A total of 97 participants were diagnosed with ABCD and CKM syndrome. The baseline characteristics are presented in **Tables 1–4**.[17]

This study involved 97 patients, categorized by inclusion criteria as follows: non-obesity (n = 5), obesity I (n = 27), and obesity II (n = 65).

The ET-1 difference test between individuals with and without obesity was conducted using one-way ANOVA, as the data distribution conformed to normality as determined by the Kolmogorov–Smirnov test. The results of the ET-1 difference test and the TG/HDL ratio regarding the degree of obesity, assessed using one-way ANOVA, produced a *p*-value <0.001. The ET-1 level variable demonstrated a significant difference (*p*-value <0.005) concerning the degree of obesity, as did the TG/HDL-C ratio variable (*p*-value <0.005) in regard to the degree of obesity. The LSD test was performed to determine the significance within each population group.

The post hoc test revealed that the ET-1 level in the non-obesity population group was significantly different from obesity group I (*p*-value ≤0.001) and significantly different from obesity group II (*p*-value ≤0.001). However, the ET-1 level in obesity group I was not significantly different from obesity group II (*p*-value = 0.051). The TG/HDL-C ratio, as determined by the post hoc test, revealed a significant difference between the non-obesity population group and obesity group I (*p*-value ≤0.001), as well as between the non-obesity group and obesity group II (*p*-value ≤0.001). However, obesity group I did not significantly differ from obesity group II (*p*-value = 0.051). The results are presented in **Table 4**, as indicated by the multivariate analysis.

The multivariate analysis indicated that the ET-1 variable significantly influenced the non-obesity population (OR = 216.29; 95% CI: 91.25–341.33; *p*-value = 0.000) and the obesity I population (OR = 119.49; 95% CI: 60.68–178.29; *p*-value = 0.000). The TG/HDL ratio in the obesity II population significantly influenced the obesity I population (OR = 2.94; 95% CI: 1.75–4.12; *p*-value <0.001), indicating that an elevated TG/HDL-C ratio serves as a marker for heightened metabolic risk corresponding to the severity of obesity.

ET-1, a powerful vasoconstrictor and pro-inflammatory agent, may contribute to endothelial dysfunction and insulin resistance, worsening obesity and metabolic dysre-

Table 1 – Characteristics of this study[17]

Characteristics	Non-obesity (n = 5) Mean ± SD	Obesity I (n = 27) Mean ± SD	Obesity II (n = 65) Mean ± SD	*p*-value
Age (years)	43.4 ± 5.89	37.89 ± 8.38	39.96 ± 8.05	0.642
BMI (kg/m^2)	24.06 ± 0.61	34.43 ± 2.73	27.62 ± 1.08	0.533
ET-1	289.40 ± 100.83	386.21 ± 104.69	505.70 ± 107.66	<0.001
Triglycerides	172.47 ± 71.55	295.07 ± 98.54	307.2 ± 130.37	<0.001
Total cholesterol	193.15 ± 61.34	280.55 ± 39.0	292.6 ± 31.18	0.103
LDL-cholesterol	136.3 ± 16.81	157.67 ± 9.39	161.5 ± 9.45	0.091
HDL-cholesterol	50.15 ± 5.40	48.4 ± 6.02	46.81 ± 5.51	0.303
TG/HDL-C ratio	3.56 ± 1.94	6.50 ± 2.45	6.67 ± 3.48	<0.001

* Significant if *p*-value <0.005

Table 2 – Research difference test[17]

Variables	n (%)	Non-obesity Mean ± SD	Obesity I Mean ± SD	Obesity II Mean ± SD	*p*-value
ET-1	97 (100%)	289.40 ± 100.83	386.21 ± 104.69	505.70 ± 107.66	**<0.001**
TG/HDL-C ratio	97 (100%)	3.56 ± 1.94	6.50 ± 2.45	6.67 ± 3.48	**<0.001**

* One-way ANOVA significant if *p*-value <0.005

Table 3 – Post hoc test in this study[17]

Variables	Sub-population study		*p*-value
ET-1	Non-obesity	Obesity I	<0.001
		Obesity II	<0.001
	Obesity I	Obesity II	0.051
TG/HDL-C ratio	Non-obesity	Obesity I	<0.001
		Obesity II	<0.001
	Obesity I	Obesity II	0.002

* Significant if *p*-value <0.005.

Table 4 – Multivariate analysis of ET-1 and TG/HDL-C ratio against obesity degree[17]

Variables	BMI category	Sub-categories BMI	*p*-value	Odds ratio (OR) (95% CI)
ET-1	Non-obesity	Obesity I	0.152	–96.80 (–215.99 to 22.39)
		Obesity II	**0.000***	–216.29 (–341.33 to –91.25)
	Obesity I	Non-obesity	0.152	96.80 (–22.39 to 215.99)
		Obesity II	**0.000**	–119.49 (–2.42 to 6.58)
	Obesity II	Non-obesity	**0.000**	216.29 (91.25 to 341.33)
		Obesity I	**0.000**	119.49 (60.87 to 178.29)
TG/HDL-C ratio	Non-obesity	Obesity I	0.006	3.11 (0.71 to 5.15)
		Obesity II	1.000	0.17 (–2.34 to 2.69)
	Obesity I	Non-obesity	0.006	–3.11 (–5.51 to –0.71)
		Obesity II	**0.000**	–2.94 (–4.12 to –1.75)
	Obesity II	Non-obesity	1.000	–0.17 (–2.69 to 2.34)
		Obesity I	**0.000**	2.94 (1.75 to 4.12)

* Significant if *p*-value <0.005.

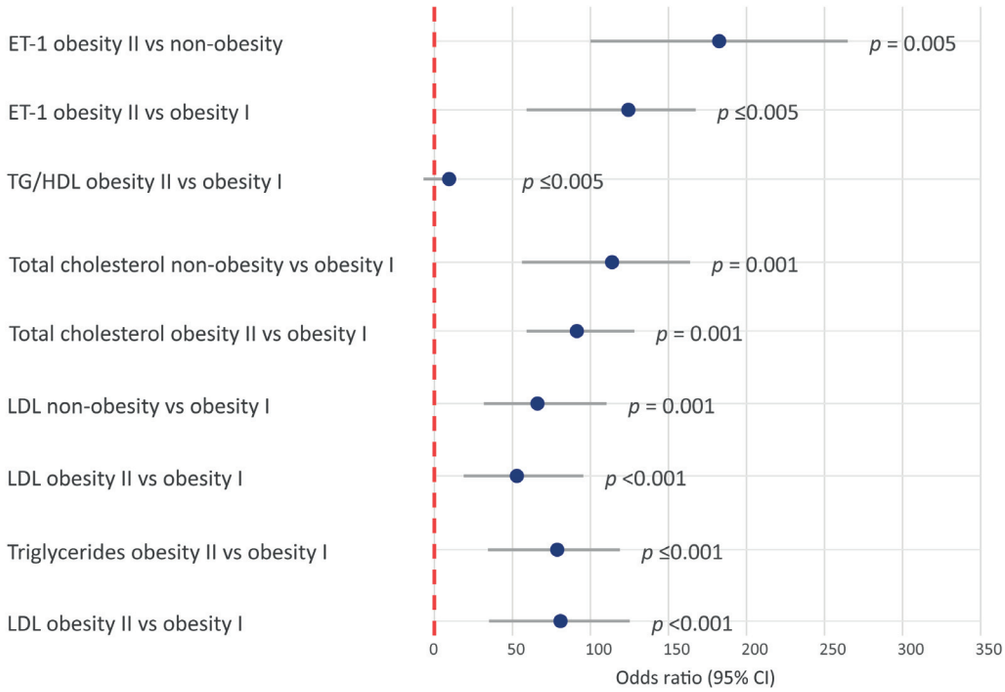


Fig. 2 – Forest plot for ET-1, TG/HDL-C ratio, total cholesterol, LDL-C, and triglycerides across obesity categories.

gulation. In which from non-obesity versus obesity I with OR = 119.49 (95% CI: 60.68–178.29; *p*-value = 0.000) ET-1 levels exhibit a robust, dose-dependent correlation with moderate obesity (obesity I), albeit with a lesser impact size compared to obesity II. This gradient facilitates ET-1's contribution to the advancement of obesity.

The TG/HDL-C ratio and the severity of obesity which class I obesity versus class II obesity, the OR = 2.94 (95% CI: 1.75–4.12; *p*-value = 0.000) mean the TG/HDL-C ratio is markedly elevated in obesity II relative to obesity I, exhibiting an almost threefold increase in odds per unit increment in the ratio. This ratio, indicative of atherogenic dyslipidaemia and insulin resistance, intensifies with the progression of obesity, underscoring its relevance in assessing metabolic risk.

ET-1 as a significant indicator of obesity severity with the remarkably elevated odds ratio for ET-1 indicates it is a primary biomarker for differentiating obesity classifications, likely signifying its involvement in vascular and metabolic impairment. Nonetheless, the substantial impact sizes necessitate caution; potential explanations include collinearity. ET-1 may exhibit a high correlation with unmeasured variables, such as visceral obesity or renal impairment. ET-1 levels may have a non-linear correlation, with only concentrations over a crucial threshold influencing the course of obesity. The TG/HDL-C ratio serves as a graded metabolic risk indicator, with its incremental rise across obesity classifications corresponding to its recognized function in forecasting cardiovascular risk.

The moderate odds ratio (2.94) highlights its significance in clinical practice for early metabolic risk evaluation. Biological synergy: the concurrent increase of ET-1 and TG/HDL-C ratio may synergistically enhance oxidative stress, inflammation, and endothelial injury, hence expediting ABCD/CKM progression. The observational approach prevents causal inferences; long-term studies are required to validate ET-1's involvement in obesity development. Generalizability: excessive odds ratios for ET-1 may indicate cohort-specific attributes (e.g., genetic or environmental variables). Although these biomarkers exhibit potential, the cost-effectiveness and practicality of routine ET-1 testing in primary care necessitate assessment with a definitive conclusion: ET-1 and the TG/HDL-C ratio are reliable, complementary biomarkers for the classification of metabolic risk associated with obesity.

The forest plot and multivariate analysis results elucidate significant insights into the correlation between endothelin-1 (ET-1) and the TG/HDL-C ratio with obesity severity, underscoring their functions as metabolic risk indicators in adiposity-based chronic disease (ABCD) and cardiovascular-kidney-metabolic (CKM) syndrome (Fig. 2).

ET-1 and obesity II compared to non-obesity: OR = 216.29 (95% CI: 91.25–341.33; *p*-value = 0.000) The exceptionally high odds ratio (OR) indicates that increased ET-1 levels are highly predictive of severe obesity (obesity II) in comparison to non-obese persons. The broad confidence interval (CI) signifies considerable heterogeneity in the effect magnitude, although the statistically significant *p*--value underscores the strength of this link.

The TG/HDL-C ratio and the severity of obesity: obesity I compared to obesity II: OR = 2.94 (95% CI: 1.75–4.12; *p*-value = 0.000). The TG/HDL-C ratio is markedly elevated in obesity II relative to obesity I, exhibiting an almost threefold increase in odds per unit increase in the ratio. This ratio, indicative of atherogenic dyslipidemia and insulin resistance, intensifies with the progression of obesi-

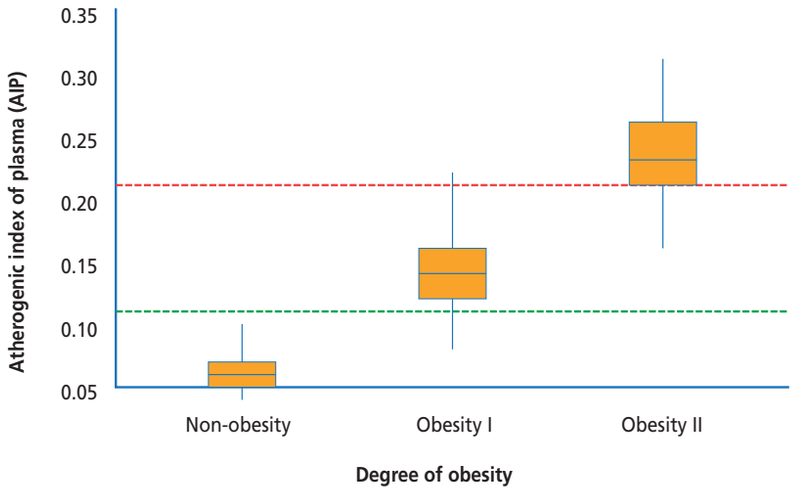


Fig. 3 – Risk stratification in the present study

ty, underscoring its relevance in assessing metabolic risk. The remarkably elevated odds ratio for ET-1 indicates it is a primary biomarker for differentiating obesity groups, likely signifying its involvement in vascular and metabolic dysfunction.

Nonetheless, the substantial effect sizes necessitate prudence; potential explanations encompass collinearity: ET-1 may exhibit a strong correlation with unmeasured variables (e.g., visceral obesity or renal impairment). ET-1 levels may demonstrate a non-linear correlation, wherein only amounts over a crucial threshold facilitate the evolution of obesity. The TG/HDL-C ratio serves as a graded metabolic risk indicator, with its incremental rise across obesity classifications corresponding to its recognized function in forecasting cardiovascular risk.

The moderate odds ratio (2.94) highlights its significance in clinical practice for early metabolic risk evaluation. The concurrent increase of ET-1 and TG/HDL-C ratio may synergistically enhance oxidative stress, inflammation, and endothelial injury, hence expediting ABCD/CKM progression. The observational approach prevents causal inferences; longitudinal studies are required to validate ET-1's involvement in obesity development.

The elevated odds ratios for ET-1 may indicate traits particular to the group, such as genetic or environmental influences. Although these biomarkers exhibit potential, the cost-effectiveness and practicality of frequent ET-1 testing in primary care necessitate assessment, leading to the conclusion that ET-1 and the TG/HDL-C ratio are reliable, complimentary biomarkers for stratifying metabolic risk associated with obesity.

Integrating them into fundamental healthcare processes should enhance the early detection of high-risk ABCD/CKM patients, enabling customized therapy to mitigate cardiovascular and renal repercussions. Further molecular studies are necessary to clarify ET-1's conflicting role in obesity and metabolic dysfunction. The predictive value of the atherogenic index of plasma (AIP) is noted to be significant for the occurrence of atherosclerosis, with evidence-based medicine (EBM) specifying the AIP cut-off classifications: 0.3–0.11 as low risk, 0.11–0.21 as moderate risk, and >0.21 as high risk for the development of initial atherosclerotic heart disease.

The EBM cut-off indicates that the risk stratification for atherosclerotic cardiovascular disease incidence, as illustrated in **Figure 3**, categorizes the study population into moderate and high risk for first-time heart disease based on the AIP, necessitating increased focus from the standpoint of 4PM.

Discussion

The multivariate analysis demonstrates that endothelin-1 (ET-1) and the triglyceride-to-HDL cholesterol (TG/HDL-C) ratio are significant and independent predictors of obesity severity and metabolic risk in relation to adiposity-based chronic disease (ABCD) and cardiovascular-kidney-metabolic (CKM) syndrome.[5,21,22] The significantly increased odds ratios (ORs) for ET-1 in both obesity II (OR = 216.29; 95% CI: 91.25–341.33) and obesity I (OR = 119.49; 95% CI: 60.68–178.29) populations, in comparison to non-obese individuals, highlight ET-1's strong correlation with the advancement of adiposity and its prospective function as a biomarker for vascular and metabolic dysfunction.

These findings corroborate previous research indicating ET-1's role in endothelial dysfunction, vasoconstriction, and pro-inflammatory pathways that contribute to the development of cardiovascular and renal problems associated with obesity.[20,23] The dose-dependent augmentation of ET-1's effect size from obesity I to obesity II indicates a gradual pathophysiological influence, potentially signifying heightened endothelial damage and metabolic dysfunction as adiposity intensifies. Nevertheless, the notably elevated odds ratios necessitate careful interpretation, as they may indicate residual confounding or threshold effects in ET-1 expression that disproportionately increase risk in cases of severe obesity.[24,25] The TG/HDL-C ratio had a statistically significant correlation with the severity of obesity, presenting an odds ratio of 2.94 (95% CI: 1.75–4.12) for obesity ii in comparison to obesity I. This discovery supports a substantial body of evidence

that recognizes the TG/HDL-C ratio as a dependable surrogate marker for atherogenic dyslipidaemia and insulin resistance.[26–28]

A moderate but notable increase in chances indicates that lipid problems worsen with increasing obesity, hence elevating cardiometabolic risk. Utility in primary healthcare contexts, especially in resource-constrained areas.[29–31] The integrated assessment of ET-1 and the TG/HDL-C ratio provides a sophisticated insight into the contradictory influence of obesity on cardiovascular and metabolic health.[28,32] Traditional measurements like BMI offer a rudimentary assessment of body fat, but new biomarkers elucidate underlying pathophysiological mechanisms, vascular impairment, and lipid metabolism, thereby more properly representing individual risk profiles. This biomarker synergy facilitates a predictive, preventive, and personalized medicine (3PM) strategy, allowing for the early identification of high-risk people and customized therapeutic options.[33–36]

Strengths and limitations

A multitude of restrictions requires consideration. The observational approach precludes causal inferences, and the potential for residual confounding remains even multivariate adjustment. The significant odds ratios for ET-1 may indicate population-specific effects or measurement variability. The measurement of ET-1 via ELISA may hinder scalability for primary care due to its reliance on laboratory infrastructure, trained personnel, extended turnaround times, and elevated operational costs per test, which diminishes feasibility in resource-limited environments; thus, the development of a validated point-of-care lateral flow assay (LFA) is essential to facilitate broader screening, expedite decision-making, and promote a preventive, early-detection service model.

Future direction

The forthcoming research initiative aims to convert the ET-1 assay from an ELISA platform into a rapid, straightforward, and scalable point-of-care lateral flow assay (LFA) for primary care in LMICs. This transition will facilitate earlier and broader screening for subclinical endothelial dysfunction in ABCD/CKM, aligning with primary healthcare reforms that advocate a shift from the "sick" paradigm (curative-reactive, concentrating on complications) to the "health" paradigm (promotive-preventive, emphasizing early detection and management of risk factors prior to organ damage).

Subsequent actions must encompass the validation of the analytical and clinical efficacy of the ET-1 LFA in comparison to ELISA (including accuracy, precision, stability in tropical climates, and sample interference), the determination of operational cut-offs for risk stratification, and the incorporation of ET-1 (LFA) with other cost-effective indicators such as the TG/HDL-C ratio and AIP into a risk score that autonomously initiates a standardized suite of preventive measures (structured lifestyle counselling, early targeted risk factor therapy, and selective referral).

Consequently, biomarkers serve not merely as diagnostic instruments but as "health-guided care" mechanisms that transform the care paradigm: shifting from a reactive approach of waiting for patients to become ill to a proactive strategy aimed at maintaining the health of at-risk populations through consistent monitoring, comprehensible risk feedback, and anticipatory follow-up at the community health centre level.

Conclusions

This study underscores the need of incorporating ET-1 and TG/HDL-C ratio into cardiovascular risk assessment models for individuals with ABCD and CKM syndrome. Their strong correlations with obesity severity and metabolic risk underscore their capacity to revolutionize primary healthcare through the facilitation of early, tailored therapies in accordance with national health security and SDGs. Biomarker-driven methods are expected to improve clinical outcomes and alleviate the worldwide burden of non-communicable illnesses.

Contributions of the authors

AAP conceived and drafted the manuscript, AI and SPW revise the study. AAP participated in the study's design and data acquisition, conducted the statistical analysis and interpreted the data, also conducted a critical revision of the manuscript for significant intellectual substance. All authors examined and sanctioned the final version of the text.

Ethical considerations

Ethical approval for this study was secured by the Ethics Committee – Dr. Saiful Anwar Regional Hospital, Malang, Indonesia, under approval number: 553/EP/Date: October 20th 2024. Informed permission was acquired from all eligible participants before enrolment, after the provision of information regarding research aims, methods, potential risks and benefits, voluntary participation, and the possibility to withdraw at any time without compromising care.

Conflict of interest

The authors assert that they possess no conflicting interests.

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