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Original Article

Plasma level of nerve growth factor in patients with metabolic syndrome and its relation to atherosclerotic cardiovascular disease

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Abstract

Nerve growth factor (NGF) regulates neuro-cardiovascular interactions, promotes postnatal angiogenesis/vasculogenesis, and its altered levels are linked to metabolic and inflammatory disorders. This study aimed to detect links between NGF and MetS and its relation to atherosclerotic cardiovascular disease (ASCVD) in those subjects. This study was executed on 60 adult participants, who fulfill the International Diabetes Federation consensus definition of MetS (MetS group) along with 30 healthy individuals suited by age and sex possessing MetS group. NGF were significantly reduced in MetS group than control group (P<0.05) and in MetS group with 4 and 5 criteria than those with 3 criteria. There was a significant inverse relation among NGF with each of weight and BMI, LDL, HBA1C, HOMA.IR and ASCVD risk %. In the multivariate analysis, BMI together with HBA1C and NGF showed a significant independent predictor of MetS in our study. NGF at cut-off value of 7.76 ng/ml was found to be a marker of ASCVD in MetS with high sensitivity (87.5%) and specificity (90%). The reduction of NGF in MetS which increased with increase number of criteria of metabolic syndrome suggest its protective value in MetS. NGF in addition to BMI and HbA1C are independent predictor of the metabolic syndrome and NGF could be a good marker of ASCVD risk in MetS with very high sensitivity and specificity which may suggest now therapeutic option by using NGF analogue to reduce ASCVD risk associated with metabolic syndrome.

Keywords: plasma, nerve growth factor, metabolic syndrome, cardiovascular disease

Introduction

Metabolic syndrome (MetS) constitutes a complex, multifactorial condition of modern life that has gained increasing socio-medical significance, affecting approximately 38.3% of the global population [1].

The hypertrophic adipose tissue releases more free fatty acids as MetS progresses, which has the potential to cause peripheral insulin resistance and decreased pancreatic beta cell production of insulin [2].

The macrophages that have infiltrated adipose tissue encourage the liberation of pro-inflammatory cytokines, which results in the emergence of a low-grade systemic inflammation, progression of insulin resistance and other cardio-metabolic shifts [3].

In MetS, insulin resistance represents the central pathophysiological abnormality. Expanded adipose tissue becomes metabolically active and releases a wide range of pro-inflammatory cytokines and adipokines, encompassing TNF-α, IL-6, MCP-1, resistin, as well as leptin, which promote systemic inflammation alongside impair insulin signalling [4].

Neurotrophins (NTs) additionally been proposed as potential adipokines, with possible associations with MetS and other inflammation-related disorders. The most well-characterized NT, nerve growth

factor (NGF), is a pleiotropic growth factor liberated via various cell types within the neuro-immuno-endocrine system as well as is pivotal regarding regulating whole-body metabolic homeostasis [5].

NTs were originally recognized as critical regulators of nervous system function, playing essential roles in the enhancement, maintenance, and survival of neuronal cells [6]. Neurotrophins, especially NGF, exert effects not just upon cells of the central and peripheral nervous systems but additionally on components of the immunological and endocrine systems [7].

One of the most serious complications of MetS is cardio vascular disease (CVD) [8]. Growing evidence proves that NGF serves a pivotal perform in communication between the nervous and cardiovascular systems. It served as the initial neurotrophin demonstrated to take part in postnatal angiogenesis alongside vasculogenesis through both autocrine and paracrine mechanisms [9].

Some studies showed that NGF and BDNF decrease in metabolic syndrome patient [10]. while Other studies revealed that in women with metabolic syndrome, waist circumference, body mass index, HOMA index, glucose, total cholesterol, as well as triglyceride levels were substantially elevated accompanied by overexpressed plasma leptin alongside NGF levels, as well as lowered adiponectin [11].

The goal of this study was to measure the level of NGF in MetS subjects in comparison to healthy group, to investigate association of circulating NGF to MetS components, explore relation between level of NGF and number of criteria of MetS, to find out if NGF is independent parameter of MetS and to investigate association of circulating NGF and atherosclerotic cardiovascular disease (ASCVD) risk.

Material and methods

This case control study encompassed 90 participants. They were divided into two groups: MetS group (n=60): diagnosed based on IDF criteria (2006) for MetS [12] which requires central obesity (waist circumference) in conjunction with any two of the subsequent four parameters: elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L] or undergoing specific therapy for this lipid abnormality); decreased HDL cholesterol (<40 mg/dL [1.03 mmol/L] in men and <50 mg/dL [1.29 mmol/L] in women, or receiving targeted treatment for this condition); elevated blood pressure (≥130/85 mm Hg or receiving antihypertensive therapy for a prior diagnosis of hypertension); and elevated fasting plasma glucose (≥100 mg/dL [5.6 mmol/L] or a preceding diagnosis of type 2 diabetes mellitus).

The age of this group was ranged from 18 to 74 years old, 22 male and 38 females, BMI ranged from 27.8–34.5 kg/m^2 and their waist circumference ranged from 88 –107 cm.

Control group (n=30): apparently healthy subjects and their age and sex were matched with MetS group with normal BMI without any comorbidity.

All subjects had adequate hepatic, renal, cardiac and respiratory functions.

Exclusion criteria were patients with BMI ≥40 kg/m^2, presence of infectious or chronic inflammatory disorder, or a record of psychiatric disorders thyroid disorders, endocrine diseases, and irregular menstrual periods, having anti-obesity, anti-inflammatory, corticosteroid, or estrogen therapies, as well as medications known to influence serum NGF levels, including corticosteroids and NSAIDs.

The study was executed subsequent authorization from the Ethical Committee Zagazig University Hospitals, Zagazig, Egypt (approval code: ZU-IRB #10901-20-06-2023). This study was done in accordance with Declaration of Helsinki (as revised in Brazil 2013), a documented consent was gathered from the participants or relatives of the participants.

All participants of this study underwent: A comprehensive history taking, clinical examination, routine laboratory tests encompassing [complete blood count (CBC), C-reactive protein (CRP), Lipid profile (serum total cholesterol (TC), triglycerides (TG), LDL, HDL), fasting plasma glucose, 2-hour post prandial plasma glucose, HbA1c, fasting insulin level, homeostatic model assessment for insulin resistance (HOMA-IR), liver function tests and kidney function tests], and other routine investigations including [electrocardiogram (ECG) and pelviabdominal ultrasound] in addition to anthropometric measurement including:

Calculation of the BMI

BMI, also called Quetelet's index, was determined by dividing the individual's weight by the square of their height [13].

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} = \text{kg/m}^2$$

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Calculation of waist circumference: using a tape measure

Waist circumference was determined at the end of a normal expiration, at a horizontal plane positioned midway between the inferior margin of the ribs and the superior border of the iliac crest [13]. Abdominal obesity was known as a waist circumference of ≥102 cm in men and ≥88 cm in women [14].

Calculation of hip circumference: using a tape measure

Hip circumference (HC) was determined to the nearest 0.1 cm at the level of maximal buttock protrusion at the end of normal expiration, with participants standing upright, feet together, and arms relaxed. Each measurement was performed three times, and the average of the two closest values was recorded. Waist-to-hip ratio (WHR) was subsequently calculated as the waist circumference divided by HC [15].

WHR was calculated by dividing the waist circumference by the hip circumference.

Calculation of 10-year risk of cardiovascular disease using the ACC/AHA ASCVD risk calculator (2013)

The ASCVD risk calculator applies the Pooled Cohort Equations to estimate a 10-year risk of atherosclerotic cardiovascular disease—encompassing coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke estimated according to age, sex, race, total cholesterol, HDL-C, systolic blood pressure, ongoing antihypertensive therapy, presence of diabetes, and smoking status. Risk categories are defined as <5% (low), 5–7.5% (borderline), 7.5–20% (intermediate), and ≥20% (high), in line with the 2013 ACC/AHA guidelines [16].

Measurement of plasma NGF levels using ELISA technique

For the ELISA, prepare seven wells for standards, one well for the blank, and the remaining wells for samples, adding 100 µL per well. Seal the plate and incubate for 2 hours at 37°C. After incubation, remove the liquid without washing and add 100 µL of Detection Reagent A to each well, followed by a 1-hour incubation at 37°C. Wash the plate three times with 300 µL of 1× Wash Buffer (1–2 minutes per wash) and blot dry. Add 100 µL of Detection Reagent B, incubate for 1 hour at 37°C, and then perform five washes. Add 90 µL of Substrate Solution and incubate for 15–25 minutes at 37°C, protected from light, until a blue color develops. Terminate the reaction upon adding 50 µL of Stop Solution, producing a yellow color, mix gently, and immediately read the absorbance at 450 nm, ensuring that there are no bubbles or residue on the bottom of the wells.

Statistical analysis

It was done via SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were shown as mean and standard deviation (SD) and related among the two groups utilizing unpaired Student's t-test. Qualitative variables were shown as frequency and percentage and analyzed via the Chi-square or Fisher's exact test when appropriate. Correlation between various variables was done via Pearson moment correlation equation. Univariate regression was applied to determine the relationship among a response variable and one standalone variable. Multivariate regression was also utilized to determine the relationship among a response variable and more standalone variables. A two-tailed P-value<0.05 was considered statistically significant. A ROC curve was constructed to determine the ability of plasma NGF to identify elevated ASCVD risk (defined as ASCVD ≥7.5%).

Result

Age, sex, WBCs, HB, MCV, PLT, CRP and creatinine were insignificantly different between both groups. Associated comorbidities, weight, BMI, WC, HC, W/H ratio, ALT, AST, fatty liver, cholesterol, triglycerides, LDL, FBS, PP BS, HBA1C, HOMA.IR and ASCVD risk % were significantly elevated in metabolic group than control group (P<0.05). Height, albumin, HDL, Fast. insulin and NGF were significantly reduced in metabolic group than control group (P<0.05) (Table 1).

There was no significant link of NGF with demographic data and comorbidities among metabolic group (Table 2).

The mean value of NGF among studied MetS patients (n=60) classifying them according the numbers of items fulfilled from the classification criteria. Patients who fulfilled all the 5 items of criteria had significantly lower NGF levels (5.62±1.93) in comparison to patients who fulfilled 4 items (7.42±2.1) and 3 items (9.35±2.54). This difference in mean NGF levels between the groups was statistically significant (t=−9.25, P=0.04) (Table 3).

Table 1: Comparison of demographic data, clinical, laboratory investigations and ASCVD risk % among studied groups.

		Metabolic group (n=60)	Control group (n=30)	t/X²	P
Age (Years)		45.5±13	41.1±15.6	1.42	0.16
Sex	Male	22 (36.7%)	17 (56.7%)	3.26	0.07
	Female	38 (63.3%)	13 (43.3%)		
Associated comorbidities	DM	18 (30%)	0 (0.0%)	85.7	**<0.001***
	HTN	13 (21.7%)	0 (0.0%)		
	DM+HTN	29 (48.3%)	0 (0.0%)		
Anthropometric measures	Height (cm)	166.8±10.1	171.8±11.5	-2.12	**0.037***
	Weight (kg)	86.4±11.6	67.8±11.1	7.29	**<0.001***
	BMI (kg/m²)	30.5±4.1	22.8±1.9	9.76	**<0.001***
	WC (cm)	91.3±6.8	71.1±9.5	12.7	**<0.001***
	HC (cm)	98.3±6.5	86.2±6.2	8.5	**<0.001***
	W/H ratio	0.92±0.03	0.82±0.04	13.6	**<0.001***
US findings					
Fatty liver		12 (20%)	2 (6.7%)	6.92	**0.009***
Laboratory investigations					
WBCs (10³/cm)		7.1±2.1	6.3±1.5	1.8	0.07
HB (g/dl)		12.9±1.6	13.2±1.7	-0.8	0.42
MCV (fl)		81.4±8.4	82.1±8.4	-0.38	0.70
PLT (10³/cm)		298.3±104.4	294.3±84.8	0.18	0.86
CRP (mg/l)		5.65±3.24	5.95±3.6	-0.40	0.69
Creatinine (md/dl)		0.81±0.3	0.84±0.26	-0.4	0.66
ALT (u/L)		30.7±11.1	21.3±10.5	3.86	**<0.001***
AST (U/L)		35.2±10.4	28.7±25	2.67	**0.009***
Albumin (g/dl)		3.7±0.5	4.1±0.5	-3.16	**0.002***
Lipid profile					
Cholesterol (mg/dl)		222.2±42.9	158.6±20.7	7.68	**<0.001***
Triglycerides (mg/dl)		183.2±43.7	130.6±13.6	6.42	**<0.001***
LDL (mg/dl)		135.5±34.8	83±17.2	7.8	**<0.001***
HDL (mg/dl)		50.5±9.3	57±5.9	-3.5	**<0.001***
Glycemic measurements					
FBS (mg/dl)		130.6±30.1	87.4±16.3	7.32	**<0.001***
PP BS (mg/dl)		242.2±72.7	131.3±28.9	8.02	**<0.001***
HBA1C (%)		8.2±2	5.14±1.1	7.72	**<0.001***
Fast. Insulin (u/ml)		10.6±4.9	13.6±4.8	-2.78	**0.007***
HOMA.IR		5.4±3.5	1.02±0.4	6.82	**<0.001***
NGF (pg/mL)		8.98±2.83	55.44±21.92	-11.2	**<0.001***
ASCVD risk %		11.9±4.9	1.4±0.9	5.2	**<0.001***

Note: Data are shown as mean±SD or frequency (%). * – Significant P-value<0.05; DM – Diabetes mellitus; HTN – Hypertension; WC – Waist circumference; HC – Head circumference; W/H – Waist-to-Hip Ratio; USL – Ultrasound; WBCs – White blood cell; HB – Hemoglobin; MCV – Mean corpuscular volume; PLT – Platelet count; CRP – C-reactive protein; ALT – Alanine transaminase; AST – Aspartate aminotransferase; FBS – Fasting blood sugar; PP BS – Postprandial Blood Sugar; HBA1C – Glycated hemoglobin.

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Table 2: Association of plasma NGF with demographic data and comorbidities among metabolic group.

		Metabolic group (n=60)	t/F	P
Age (years)	<50 years	9.12±1.24	2.12	0.09
	>50 years	8.22±2.4		
Sex	Male	9.7±2.6	1.53	0.13
	Female	8.6±2.9		
Comorbidities	DM	8.31±2.2	2.07	0.15
	HTN	8.25±3.4		
	DM+HTN	7.72±2.8		

Note: Data is shown as mean±SD. DM – Diabetes mellitus; HTN – Hypertension.

There was a significant inverse relation among NGF with weight (r=-0.311, P=0.025) and BMI (r=-0.0314, P=0.023), LDL (r=−0.261, P=0.044), HBA1C (r=-0.420, P=0.021) and HOMA.IR (r=-0.389, P=0.032) and ASCVD risk % (r=-0.429, P=0.002). Additionally, while not statistically significant, total cholesterol (r=−0.230, P=0.077) showed a borderline inverse relation (Table 4).

In univariate and multivariate regression. BMI (p<0.001, OR=1.8) and HbA1c (p<0.001, OR=3.3) showed strong positive associations in univariate analysis, while NGF (p=0.001, OR=0.59) exhibited a significant inverse relationship. Age and gender were not significant. In the multivariate analysis, BMI persisted as a significant standalone positive predictor. (p=0.02, OR=1.2), HBA1C (p=0.03, OR=1.5) and NGF continued to show a significant inverse association (p=0.04, OR=0.65) (Table 5).

The ROC curve analysis demonstrates excellent discriminatory ability of plasma NGF for predicting ASCVD in MetS participants (AUC=0.949). The optimal cut-off of 7.76 ng/ml provides high sensitivity (87.50%) and specificity (90.00%), with strong positive predictive value (94.59%) and overall accuracy (88.33%), supporting NGF as a reliable biomarker for ASCVD risk assessment (Table 6 and Figure 1).

Discussion

The increasing global prevalence of Metabolic Syndrome (MetS) emphasizes the critical need to elucidate its underlying pathophysiological mechanisms and identify novel biomarkers for risk stratification. Our case-control study provides compelling evidence

Table 3: Comparison of the mean value±SD of NGF according to number of criteria in MetS patients.

	NGF	f	P
Met.s Fulfilling 3 items of criteria	9.35±2.54		
Met.s Fulfilling 4 items of criteria	7.42±2.1[a]	**-9.25**	**0.04***
Met.s Fulfilling 5 items of criteria	5.62±1.93[a, b]		

Note: [a] – significant in relation to Mets with 3 criteria; [b] – significant in comparison to Mets with 4 criteria.

Table 4: Correlation coefficient among plasma level of NGF with anthropometric measurement, lipid profile, metabolic parameters and ASCVD risk among metabolic group.

	NGF	
	r	P
Height (cm)	0.024	0.854
Weight (kg)	-0.311	**0.025***
BMI (kg/m²)	-0.314	**0.023***
WC (cm)	-0.012	0.929

Table 4: Continued.

	NGF	
	r	**P**
HC (cm)	0.002	0.987
W/H ratio	-0.031	0.812
Lipid profile		
Cholesterol (mg/dl)	-0.230	0.077
Triglycerides (mg/dl)	-0.064	0.626
LDL (mg/dl)	-0.261	**0.044***
HDL (mg/dl)	-0.039	0.768
CRP (mg/L)	-0.204	0.119
Metabolic measurement		
FBS (mg/dl)	0.079	0.550
PP BS (mg/dl)	0.195	0.136
HBA1C (%)	-0.420	**0.021***
Fast. insulin (u/ml)	-0.037	0.781
HOMA.IR	-0.389	**0.032***
ASCVD risk %	-0.429	**0.002***

Note: r – Pearson Coefficients; * – Significant P-value<0.05; HC – Head circumference; FBS – Fasting blood sugar; PP BS – Postprandial Blood Sugar; HBA1C – Glycated hemoglobin; HOMA.IR – Homeostasis Model Assessment of Insulin Resistance.

for a significant association between circulating Nerve Growth Factor (NGF) and MetS. The principal findings reveal that serum NGF levels are markedly reduced among individuals with MetS in contrast to healthy controls, and this reduction is progressively more pronounced with an increasing number of MetS diagnostic criteria fulfilled (Table 3). Furthermore, lower NGF levels demonstrated a significant inverse correlation with key metabolic parameters—involving BMI, HbA1c, HOMA-IR, and LDL cholesterol—and emerged as a strong, independent predictor of both MetS presence and elevated 10-year ASCVD risk (Tables 4).

The reduction in NGF levels observed in our MetS cohort presents a compelling, if seemingly paradoxical, finding. While NGF is classically understood as a neurotrophin, it is now recognized as a pleiotropic signaling molecule with integral roles in immune modulation, endocrine function, and metabolic homeostasis [17].

Table 5: Multivariate regression analysis for predictors of MetS.

		MetS			
		Univariate		Multivariate	
		P	**OR (95% CI)**	**P**	**OR (95% CI)**
Age (years)		0.16	0.9 (0.95–1.01)	-	-
Sex	Female	-0.07	(ref.) 0.4 (0.18–1.08)	-	-
	Male				
BMI (kg/m²)		**<0.001***	1.8 (1.44–2.18)	**0.02***	1.2 (1.02–1.39)
HBA1C		**<0.001***	3.3 (1.90–5.65)	**0.03***	1.5 (1.29–2.89)
NGF (pg/ml)		**0.001***	1.9 (1.22–2.65)	**0.04***	1.4 (1.11–2.23)

Note: * – Significant P-value<0.05; OR – odds ratio; CI – Confident interval; HBA1C – Glycated hemoglobin.

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Table 6: ROC Curve Analysis of NGF Levels for detection of ASCVD in Patients with Metabolic Syndrome.

AUC (95%CI)	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy	P
0.949	7.76	87.5%	90%	94.59%	78.26%	88.33	0.001*

Note: * – Significant P-value<0.05; AUC – Area under curve; CI – Confident interval; PPV – Positive predictive value; NPV – Negative predictive value.

The prevailing literature often describes elevated NGF in acute inflammatory states, where it acts as a mediator of pain and inflammation [18]. However, our results suggest that in the context of chronic, low-grade inflammation characteristic of established MetS, the regulatory dynamics of NGF are fundamentally different. We hypothesize that the significantly lower NGF level in our patients does not contradict its inflammatory role but may instead reflect a state of "neurotrophic exhaustion" or a maladaptive downregulation following persistent inflammatory and metabolic stress. This hypothesis aligns with the observed stepwise decline in NGF corresponding to the increasing severity of MetS, indicating that the neurotrophic deficit parallels the progression of metabolic dysregulation.

Our results align with an expanding body of research suggesting that NGF deficiency is a feature of advanced cardiometabolic dysfunction. The findings by Kolesnikova *et al.* [19], which demonstrated lower serum NGF in metabolically unhealthy obesity, support this concept. The strong inverse correlations we observed between NGF and HbA1c/HOMA-IR (Table 4) highlight a potential link to pancreatic β-cell function as well as systemic insulin resistance. Experimental models have shown that NGF supports β-cell survival alongside enhances glucose-stimulated insulin secretion [20]. Thus, the depletion of NGF could contribute to the deterioration of β-cell function and aggravate insulin resistance, creating a vicious cycle that stimulates the progression of MetS and type 2 diabetes.

The highly significant negative correlation between NGF and ASCVD risk (Table 4), coupled with the excellent discriminatory power of NGF for identifying high-risk individuals (AUC=0.949) (Table 6),

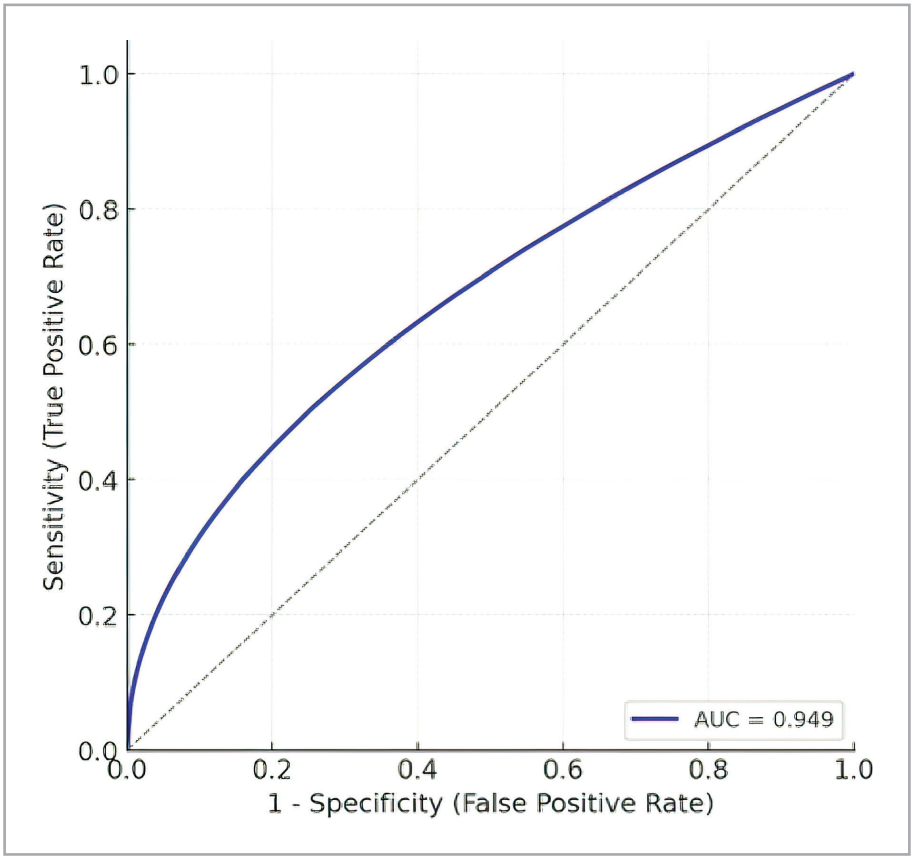

Figure 1: ROC Curve Analysis of plasma NGF levels for detection of High ASCVD Risk.

underscores the clinical relevance of our findings. NGF is known to exert protective effects on vascular endothelium and cardiomyocytes [9]. Therefore, a decline in NGF bioavailability may contribute to endothelial dysfunction, a key precursor to atherosclerosis. This positions NGF not merely as a bystander but as a potential participant in the pathogenesis of cardiovascular complications in MetS.

It is crucial to address the apparent discrepancy with studies, such as that by Bulló *et al*. [21], which reported elevated NGF levels in obesity. This divergence may be attributed to key methodological and population differences. The study by Bulló *et al*. [21] focused on overweight and obese subjects, not all of whom had the full cluster of MetS components, potentially capturing an earlier, compensatory phase of metabolic dysfunction where NGF is upregulated. In contrast, our study population had confirmed MetS, often with multiple comorbidities, likely representing a more advanced and chronic disease stage where compensatory mechanisms have been depleted. Furthermore, differences in assay specificity and the molecular forms of NGF detected (*e.g.*, pro-NGF *vs*. mature NGF) could also contribute to these contrasting results.

The multivariate regression analysis (Table 5) solidifies the role of NGF by identifying it as an independent predictor of MetS, nonetheless after considering recognized variables like BMI and HbA1c. This suggests that NGF provides unique pathophysiological information beyond traditional metrics, potentially reflecting the integrated burden of metabolic and neuro-inflammatory dysfunction [22].

The ROC curve analysis (Table 6) demonstrated that the cut-off value of serum level of NGF of 7.76 ng/ml can be used as a reliable diagnostic biomarker for ASCVD risk in MetS subjects with AUC (=0.949), sensitivity (87.50%) and specificity (90.00%), with strong positive predictive value (94.59%), negative predictive value (78.26%) and overall accuracy (88.33%).

Our interpretations must be interpreted in accordance with the study's limitations. The cross-sectional design precludes any inference of causality; we cannot determine whether low NGF is a driver or a consequence of MetS. The single-center nature and modest sample size may affect the generalizability of our findings. Furthermore, we measured total circulating NGF, which does not distinguish between its pro- and mature forms, each with distinct biological activities and receptor affinities [23]. Future research should aim to speciate NGF isoforms to gain a more precise understanding. Despite these limitations, the strengths of our study include the well-phenotyped patient groups, the use of standardized IDF and ASCVD risk criteria, and the robust statistical associations uncovered.

Based on our findings, we propose the following recommendations for future research and clinical practice:

1. Longitudinal Studies: Large-scale, prospective cohort studies are essential to establish the temporal relationship between NGF levels and the development or progression of MetS and its complications. This will help determine if low NGF is a predictive risk factor;
2. Mechanistic Research: Further investigation is needed to unravel the precise mechanisms behind NGF depletion in MetS. Studies should explore the expression of NGF and its receptors (TrkA and p75NTR) in key metabolic tissues (adipose, liver, pancreas, and vasculature) in relation to the syndrome;
3. Molecular Speciation: Future work should employ assays capable of distinguishing between pro-NGF and mature NGF to clarify which specific isoform is implicated in MetS pathophysiology, as their biological roles can be antagonistic;
4. Exploration of Therapeutic Potential: While highly speculative, our findings open a conceptual avenue for exploring whether strategies to modulate NGF signaling could have therapeutic benefits in mitigating metabolic dysfunction or its cardiovascular sequelae. This requires extensive pre-clinical investigation;
5. Multi-Center Validation: The diagnostic and prognostic performance of the proposed NGF cut-off value for ASCVD risk should be validated in larger, multi-center, and ethnically diverse populations to assess its generalizability and potential for clinical translation.

Conclusions

Our study demonstrates that serum NGF is significantly depleted in patients with Metabolic Syndrome. The degree of this reduction is associated with the severity of the syndrome, the degree of insulin resistance, and the estimated risk of atherosclerotic cardiovascular disease. The independence of this association from traditional risk factors suggests that NGF may play a distinct role in the pathophysiology of MetS, potentially as a marker of neuro-immuno-endocrine

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dysfunction. The measurement of NGF, particularly at a cut-off value of ≤7.76 ng/mL, shows promising utility as a biomarker for identifying MetS patients at the highest risk for cardiovascular events.

Conflict of interest

The authors declare no conflict of interest.

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