

Serum neprilysin levels in acromegalic patients with and without diabetes mellitus

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ABSTRACT

Neprilysin is a zinc-dependent membrane metallopeptidase that degrades various bioactive peptides which have been linked to disorders such as obesity and type 2 diabetes mellitus. Acromegaly is characterized by excess growth hormone and insulin resistance; however, neprilysin's involvement in acromegaly, especially in relation to diabetes, remains unclear. The study aimed to evaluate serum neprilysin levels in acromegalic patients with and without diabetes mellitus and to investigate their associations with glycemic and lipid metabolic markers in a cross-sectional study recruited from the National Diabetes Center (Baghdad, Iraq) between November 2024 and March 2025. Serum neprilysin was measured by ELISA, and standard biochemical tests (GH, IGF-1, glycemic indices, and lipid profile parameters) were performed to assess relevant hormones and metabolic parameters. Acromegalic patients had significantly higher GH and IGF-1 levels and worse glycemic and lipid profiles than controls ($p < 0.001$). However, NEP levels (~110–130 pg/mL) did not differ significantly between the groups ($p = 0.316$). Acromegalic group without diabetes showed a numerically higher NEP level than controls and acromegalic group with diabetes but this difference was not statistically significant. NEP showed significant weak inverse correlations with total cholesterol ($r = -0.146$, $p = 0.029$), triglycerides ($r = -0.199$, $p = 0.008$), and VLDL ($r = -0.163$, $p = 0.030$), but no significant correlation with fasting glucose, HbA1c, GH, or IGF-1. In

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conclusion, these findings suggest that NEP is not a useful biomarker of diabetes risk or disease activity in acromegaly.

Keywords: neprilysin, acromegaly, diabetes mellitus, growth hormone, IGF-1

INTRODUCTION

Neprilysin (NEP), also known as CD or neutral endopeptidase, is a zinc-dependent, membrane-associated metallopeptidase characterized by a diverse substrate specificity. It degrades peptides roughly to amino acids in length, encompassing significant hormonal and neurological peptides such as natriuretic peptides, bradykinin, adrenomedullin, substance P, angiotensin I/II, and endothelin. In the central nervous system, diminished NEP activity correlates with the deposition of amyloid β , a characteristic of Alzheimer's disease, likely resulting from impaired amyloid clearance. In contrast, elevated NEP expression in peripheral metabolic organs has been related to obesity and insulin resistance¹.

Patients with acromegaly commonly develop insulin resistance and glucose intolerance, and up to 20–40% develop type 2 diabetes mellitus due to growth hormone-induced post-receptor insulin signaling defects. Given NEP's involvement in cardiovascular and metabolic regulation (for instance, degrading natriuretic peptides that influence blood pressure and lipid metabolism)^{2,3}, it is pertinent to investigate whether NEP levels are altered in acromegaly and whether they relate to the metabolic perturbations in these patients.

This study was therefore designed to measure serum NEP in acromegaly patients (with and without type 2 diabetes mellitus) compared with healthy controls, and to explore associations of NEP with glycemic control and lipid profile.

METHODOLOGY

Study design and sample selection

This study was an observational, cross-sectional study conducted at endocrinology department. A total of participants was enrolled and stratified into three study groups: Group A (acromegaly patients with T2DM), Group B (acromegaly patients without T2DM), and Group C (healthy control subjects). Each of the patient groups (Group A and Group B) included 44 participants, whereas the control group, Group C, consisted of 88 participants.

The sample size for the patient groups was in each (Groups A and B), with participants in the control group (Group C). The groups were not matched on age, sex, or BMI; therefore, all between-group comparisons and correlation analyses were adjusted for age and BMI (and for sex when applicable) using ANCOVA/linear regression (two-tailed $\alpha = 0.05$).

The study took place at National Diabetes Center (NDC), Mustansiriyah University, Baghdad, Iraq, from November 2024 to March 2025 and was approved by the research Ethical Committee of Mustansiriyah College of medicine. (IRB approval No. 8322; approval date: 7/11/2024; registry: not applicable). All procedures were performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants; data confidentiality was maintained. All participants were provided with printed consent forms that included pertinent information.

For all acromegaly participants, the diagnosis had been established before enrollment by the responsible endocrinologist and verified from the medical records as follows: Elevated age-/sex-adjusted IGF-1 above the assay's upper limit of normal on ≥ 2 occasions; Lack of GH suppression during a 75gm OGTT (nadir GH ≥ 0.4 ng/mL with ultrasensitive assay); and Pituitary adenoma on sellar MRI. At study visit, we re-measured GH and IGF-1 (same laboratory platform) to evaluate their associations with serum copeptin. Type 2 diabetes and prediabetes were defined according to ADA criteria (FPG ≥ 126 mg/dL, 2-h OGTT ≥ 200 mg/dL, or HbA1c $\geq 6.5\%$ for diabetes; IFG 100–125 mg/dL, IGT 140–199 mg/dL, or HbA1c 5.7–6.4% for prediabetes). Diagnoses were confirmed from files and, when needed, verified at enrollment with fasting sampling (8–12 h fast) using standardized laboratory methods.

Inclusion criteria

Acromegalic patients aged between 21 and 80 years.

Exclusion criteria

Included smoking, history of renal impairment, presence of cardio metabolic disorder and pregnant women.

Outcome measurements

The primary outcome was the difference in mean serum copeptin across Groups A, B, and C. Secondary outcomes included: (i) correlations between neprilysin and GH/IGF-1; (ii) associations with glycemic indices (FPG and HbA1c); and (iii) associations with lipid profile parameters (total cholesterol, LDL-C, HDL-C, TG, VLDL-C).

Biochemical analyses

Serum NEP concentrations were measured using a commercial Human Nephrylin (NEP) ELISA kit (YL Biont / YL Biotech Co., Ltd., China; Catalog No. YLA2053HU, 96 tests). Growth hormone and IGF-1 concentrations were measured utilizing chemiluminescent immunoassays. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c) and fasting lipid profile were assessed.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean \pm standard deviation (SD) for normally distributed variables or median (IQR) for non-normal data, while categorical data were presented as frequency and percentage. Normality of distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances using Levene’s test. Comparisons among the three study groups (A, B, and C) were conducted using one-way ANOVA. Associations between continuous variables were evaluated using Pearson’s or Spearman’s correlation coefficients depending on data distribution^{4,5}.

RESULTS and DISCUSSION

Results illustrated in Table 1 showed that the age of participants ranged from 21 to 80 years (overall mean 50.2 ± 13.3 years) and the mean ages of Groups A, B, and C were 52.8 ± 12.1 , 48.7 ± 14.0 , and 49.1 ± 13.6 years, respectively which indicated that there was no statistically significant age difference among groups, $p=0.20$. The majority of patients in all groups were middle-aged: the largest age subgroup was 40–years (comprising 63.6% of Group A, 61.4% of Group B, and 45.5% of Group C) as shown in Table 1.

Table 1. General characteristics of study groups

Characteristic	Group A (n=44)	Group B (n=44)	Group C (n=88)	Total (N=176)	p-value
Age (years)	52.8 ± 12.1	48.7 ± 14.0	49.1 ± 13.6	50.2 ± 13.3	0.055
Age group 21–39	5 (11.4%)	11 (25.0%)	29 (33.0%)	45 (25.6%)	
Age group 40–59	28 (63.6%)	27 (61.4%)	40 (45.5%)	95 (54.0%)	
Age ≥ 60	11 (25.0%)	6 (13.6%)	19 (21.6%)	36 (20.5%)	
Sex – male	15 (34.1%)	34 (77.3%)	57 (64.8%)	106 (60.2%)	<0.001
Sex – female	29 (65.9%)	10 (22.7%)	31 (35.2%)	70 (39.8%)	
BMI category					
– Normal weight (BMI 18.5–24.9)	2 (4.6%)	7 (15.9%)	41 (46.6%)	(20.5%)	<0.001
– Overweight (BMI 25.0–29.9)	21 (47.7%)	13 (29.5%)	20 (22.7%)	(44.9%)	
– Obese (BMI ≥ 30.0)	21 (47.7%)	24 (54.5%)	27 (30.7%)	61 (34.7%)	

Gender distributions differed significantly among the groups; there was a slight male predominance overall (60.2% of all participants were male). In Group A, however, females were more frequent (65.9% female vs 34.1% male), whereas Group B had a higher proportion of males (77.3% male vs 22.7% female). Group C was 64.8% male and 35.2% female.

Body mass index (BMI) categorization differed by group: in Group A and Group C, the most common BMI category was overweight (47.7% of Group A and 51.1% of Group C were overweight, with BMIs 25–29.9 kg/m²), whereas in Group B the majority (54.5%) were obese (BMI ≥ 30). Only a small fraction of participants in any group had a normal BMI (4.6% of Group A, 15.9% of Group B, 30.7% of Group C were of normal weight). These data indicate that both acromegaly groups had a high prevalence of overweight/obesity, with the non-diabetic acromegaly Group B having the highest obesity rate.

Biochemical parameters across the three groups are compared in Table 2. As expected, acromegaly was associated with raised levels of GH and IGF-1. Group A and Group B had IGF-1 concentrations of 527.3 ± 250.1 ng/mL and 414.4 ± 197.8 ng/mL, respectively, which were markedly higher than in controls (143.1 ± 28.7

ng/mL, $p < 0.001$ for both comparisons). Mean GH levels were also significantly higher in both acromegalic groups (4.47 ± 4.70 ng/mL in Group A and 4.29 ± 4.90 ng/mL in Group B) relative to the healthy group (0.45 ± 0.53 ng/mL, $p < 0.001$).

Table 2. Comparison of biochemical parameters among study groups

Parameter	Group A (n=44)	Group B (n=44)	Group C (n=88)	p-value
IGF-1 (ng/mL)	527.27 ± 250.1	414.38 ± 197.8	143.38 ± 28.7	0.001
GH (ng/mL)	4.47 ± 4.70	4.29 ± 4.90	0.45 ± 0.53	0.001
Fasting glucose (mg/dL)	177.84 ± 76.9	110.00 ± 41.1	98.29 ± 12.0	0.001
HbA1c (%)	7.53 ± 1.80	5.52 ± 0.81	5.33 ± 0.58	0.001
Total cholesterol (mg/dL)	232.45 ± 40.9	224.54 ± 49.1	176.60 ± 16.5	0.001
Triglycerides (mg/dL)	199.29 ± 53.1	193.20 ± 60.6	183.51 ± 7.4	0.091
HDL cholesterol (mg/dL)	38.87 ± 12.3	38.23 ± 7.7	51.10 ± 9.1	0.001
LDL cholesterol (mg/dL)	153.70 ± 42.1	143.70 ± 52.6	86.47 ± 23.9	0.001
VLDL (mg/dL)	39.86 ± 10.6	38.64 ± 12.12	36.70 ± 1.48	0.091

Regarding glucose metabolism, by definition Group A had diabetes: their mean fasting blood glucose (177.8 ± 76.9 mg/dL) and HbA1c ($7.53\% \pm 1.80$) were significantly elevated relative to both Group B (110.00 ± 41.1 mg/dL FBS, $5.52\% \pm 0.81$ HbA1c) and Group C (98.3 ± 12.0 mg/dL FBS, $5.33\% \pm 0.58$ HbA1c) (both $p < 0.001$). Even Group B had slightly higher mean FBS and HbA1c than controls ($p < 0.001$ for HbA1c), reflecting a degree of insulin resistance in acromegaly despite not meeting diabetes criteria.

Lipid profiles showed that acromegalic patients, particularly those with diabetes, had an adverse lipid profile compared to controls. Group A had the highest mean total cholesterol (232.5 ± 40.9 mg/dL) and LDL-C (153.7 ± 42.1 mg/dL) levels, followed by Group B (224.5 ± 49.1 mg/dL cholesterol, 143.7 ± 52.6 mg/dL LDL). Both were significantly greater than the control group's cholesterol (176.6 ± 16.5 mg/dL) and LDL (86.5 ± 23.9 mg/dL) ($p < 0.001$ for both parameters).

Triglyceride levels were slightly higher on average in Group A (199.3 ± 53.1 mg/dL) and Group B (193.2 ± 60.6 mg/dL) compared to controls (183.5 ± 7.4 mg/dL), but this variation did not attain statistical importance ($p=0.091$).

Mean HDL-C was lower in acromegalic patients ($38.87-38.23$ mg/dL in Groups A and B) than in controls (51.10 ± 9.1 mg/dL, $p<0.001$), indicating reduced “good” cholesterol in patient groups. VLDL levels (calculated) were slightly higher in Group B (mean 38.64 mg/dL) versus Group A (39.9 mg/dL) and controls (36.70 mg/dL), with a marginal overall group difference ($p=0.029$, driven mostly by a modest increase in Group B).

The primary outcome, serum neprilysin concentration, didn’t show major variations among the three groups as shown in Table 3. Mean NEP levels were 110.24 ± 53.2 pg/mL in Group A, 128.72 ± 83.0 pg/mL in Group B, and 117.03 ± 36.5 pg/mL in Group C.

Table 3. Mean serum neprilysin levels in each group

Group	Neprilysin Level (mean \pm SD, pg/mL)
Group A (n=44)	110. \pm 53.2
Group B (n=44)	128. \pm 83.0
Group C (n=88)	117. \pm 36.5
p-value	0.316

Although the mean NEP was highest in Group B and lowest in Group A, one-way ANOVA indicated no statistically significant group effect ($p=0.316$). The finding that NEP levels in acromegaly patients were essentially similar to controls (and that acromegalic patients without diabetes had, if anything, slightly higher NEP than those with diabetes) is noteworthy.

Correlation of Neprilysin with Metabolic Parameters, we investigated if serum neprilysin was linked to important metabolic markers in the overall study population (all groups combined). The correlation analysis results are presented in Table 4. There were important inverse links between neprilysin and various lipid measures. Notably, higher NEP levels were associated with lower total cholesterol ($r = -0.146$, $p=0.029$), lower triglycerides ($r = -0.199$, $p=0.008$), and lower VLDL ($r = -0.163$, $p=0.030$). These correlations, although statistically significant, were weak in magnitude ($|r|<0.2$), suggesting that NEP constitutes merely a minor fraction of the variance in these lipid measurements. There was no significant correlation between NEP and LDL ($r = -0.134$, $p=0.077$) or HDL ($r = +0.092$, $p=0.225$).

Table 4. Correlation between serum neprilysin and biochemical parameters (all subjects, N=176)

Parameter	Pearson r	p-value
Fasting blood glucose	-0.065	0.394
HbA1c	-0.117	0.121
Total cholesterol	-0.146	0.029
Triglycerides	-0.199	0.008
HDL cholesterol	+0.092	0.225
LDL cholesterol	-0.134	0.077
VLDL	-0.163	0.030
IGF-1	+0.043	0.569
GH	+0.142	0.060

Importantly, no significant correlations were found between neprilysin and indices of glycemic control: NEP was not significantly related to fasting glucose ($r = -0.065$, $p=0.394$) or HbA1c ($r = -0.117$, $p=0.121$). In addition, NEP showed no meaningful correlation with GH ($r = +0.142$, $p=0.060$) or IGF-1 ($r = +0.043$, $p=0.569$) levels in the combined cohort. These results indicate that in our sample, circulating neprilysin did not reflect the degree of growth hormone excess or the presence of diabetes.

Our primary finding is that circulating neprilysin concentrations were not rising in acromegalic patients in comparison with healthy controls, and in fact showed insignificant variations among acromegaly patients with diabetes, those without diabetes, and non-acromegalic controls. This result was somewhat unexpected, given prior associations of NEP with metabolic dysfunction in other contexts (e.g., obesity and T2DM in the general population)^{6,7}. Although acromegaly is commonly associated with insulin resistance and cardiovascular alterations—factors that could theoretically influence NEP levels—our data indicate that the condition itself does not substantially affect systemic NEP concentrations. Notably, Group B exhibited the highest mean NEP levels, slightly exceeding those of healthy controls, but this difference did not reach statistical significance.

Nonetheless, the trend raised the question of why acromegalic patients without diabetes might have equal or higher NEP than those with diabetes. If anything, one might expect diabetic patients to have higher NEP (since NEP has been linked to hyperglycemia and diabetic complications in other studies)^{8,9}, but that pattern was not observed here.

The lack of a significant increase in neprilysin in acromegaly (even among those with diabetes) suggests that NEP regulation in acromegaly might be influenced by unique factors related to GH/IGF-1 excess, rather than by glycemic status alone. Several mechanisms could be postulated to explain the NEP levels observed in our study, particularly the relatively higher NEP in non-diabetic acromegalic patients (Group B) compared to those with diabetes.

Acromegaly is known to cause cardiovascular changes such as left ventricular hypertrophy, increased cardiac output, and hypertension. Chronic GH excess leads to hypervolemia and myocardial remodeling, which often triggers increased production of cardiac natriuretic peptides (e.g., B-type natriuretic peptide, BNP) as a compensatory response. Neprilysin is a key enzyme that degrades natriuretic peptides; thus, a state of elevated BNP (as reported in acromegalic patients, especially those with comorbid conditions like obstructive sleep apnea) may induce upregulation of NEP as a counter-regulatory mechanism^{8,9}. In other words, acromegalic patients might have heightened NEP activity to balance the increased natriuretic peptide signaling resulting from GH-induced cardiac strain¹. This upregulation would occur independently of diabetes and could explain why even non-diabetic acromegalics show high NEP levels.

Indeed, a recent study documented significantly elevated BNP levels in acromegaly patients (with and without diabetes) compared to controls, correlating with disease activity and cardiac dysfunction¹.

GH excess in acromegaly has profound effects on the kidneys and vasculature. It increases renal blood flow and glomerular filtration rate (GFR) and can possibly lead to endothelial dysfunction and altered vascular tone. Neprilysin is expressed in renal tubular epithelium and vascular endothelium; changes in renal function and fluid balance provoked by acromegaly might influence NEP expression. For example, increased GFR and renal flow could stimulate renal neprilysin production or release. Additionally, to maintain vascular homeostasis, NEP might be upregulated to degrade vasoactive peptides (like angiotensin II, endothelin, bradykinin) whose levels are affected by GH excess. These effects would again be largely independent of glycemic status¹⁰.

Some hemodynamic studies in acromegaly have noted that parameters like blood volume and cardiac index do not differ substantially between acromegalic patients with vs. without diabetes (i.e., the cardiovascular impact of acromegaly is mostly driven by GH itself rather than the presence of diabetes)¹¹. This supports the notion that NEP elevation in acromegaly could be driven by GH-related cardiovascular changes rather than by diabetes. Many acromegalic patients, even those without frank T2DM, exhibit insulin resistance due to GH's anti-insulin actions¹².

Hyperinsulinemia and insulin resistance have been linked to higher NEP expression in adipose tissue and the circulation in non-acromegaly populations (since NEP degrades insulin-regulatory peptides and is involved in adipose tissue remodeling)⁸. In our cohort, Group B patients (nondiabetic acromegaly) still had evidence of insulin resistance (elevated IGF-1 and mildly high HbA1c).

It is plausible that insulin resistance per se (even without overt diabetes) could drive NEP upregulation in acromegaly. The metabolic milieu of acromegaly (high GH, high IGF-1, high insulin levels) might stimulate NEP expression in tissues such as liver or fat. Thus, by the time acromegalic patients progress to overt diabetes (Group A), NEP might already have plateaued, or other factors (like β -cell failure or use of somatostatin analog medications) could counteract further NEP increases. In summary, NEP may be elevated in acromegaly largely as a response to GH-induced insulin resistance and metabolic changes that precede diabetes¹².

An alternative consideration is that the treatment and chronicity of acromegaly might modulate NEP levels, potentially obscuring differences by diabetes status. Many patients in both Groups A and B had surgery or were on medical therapy (e.g., somatostatin analogs, dopamine agonists). Somatostatin analog (SSA) therapy, commonly used in acromegaly, could influence NEP indirectly; SSAs reduce GH and IGF-1 levels and also have systemic effects on peptide secretion¹³. It has been suggested that SSA treatment may suppress neprilysin activity/expression in certain contexts (for instance, by reducing substrate availability or altering tumor cell secretory profiles)^{13,14}.

If more patients in Group A were on medical therapy for acromegaly (which is plausible if they had longer-standing disease or uncontrolled diabetes prompting adjunct therapy), this could potentially lower their NEP levels relative to untreated patients. Despite the elevated risk of insulin resistance among acromegaly patients, our findings show that neprilysin levels did not differ between those with diabetes and those without, which challenges the concept of NEP as a universal biomarker of metabolic risk. This contrasts with observations in non-acromegalic populations, where higher NEP activity has been linked to obesity, metabolic syndrome, and incident T2DM^{2,15,16}. Supporting evidence from the literature similarly indicates that greater baseline NEP levels may predict the future development of T2DM in the general population^{3,17}.

In our cohort, NEP did not correlate positively with glucose or HbA1c; if anything, NEP showed a modest negative trend with glycemic measures. This suggests that the relationship between NEP and metabolic dysfunction may differ in acromegaly, where chronic GH elevation may overshadow NEP's influence on glucose regulation⁶. GH-induced insulin resistance is a dominant driver of

hyperglycemia, and it may therefore mask subtler contributions of NEP to glucose homeostasis.

Furthermore, acromegaly patients often have reduced hepatic and visceral fat relative to their degree of insulin resistance^{9,10}. Recent imaging findings confirm that successful treatment of acromegaly can increase fat mass and ectopic lipid accumulation as GH levels normalize¹¹. Thus, the absence of elevated NEP in our cohort—despite clear insulin resistance—may reflect the unique metabolic phenotype of GH excess, which affects body composition and related regulatory pathways.

The association between neprilysin and lipid Metabolism revealed a small but significant inverse correlation between neprilysin and cholesterol/triglyceride levels in our population. Although minor, these results demonstrate that elevated NEP may be linked to a marginally improved lipid profile (reduced total cholesterol, triglycerides, and VLDL). A potential mechanism involves natriuretic peptides (NPs), which are substrates of NEP. NPs have been shown to promote lipolysis and enhance adipose tissue browning, thereby improving lipid metabolism. Inhibition of NEP (which increases NP levels) has been reported to cause reductions in plasma cholesterol and triglycerides in some studies¹⁸⁻²⁰. Conversely, if NEP is high, it would degrade NPs more, potentially leading to less NP-driven lipid catabolism and thus higher lipid levels. However, our finding was the opposite (high NEP associated with lower lipids). This might indicate reverse causality or confounding – for instance, patients with worse lipid profiles could have other factors (like obesity or inflammation) that simultaneously elevate NEP, obscuring direct effects. Another explanation is that NEP could be upregulated as a response to elevated lipids, acting to counter-regulate by breaking down vasoactive peptides that might be harmful in dyslipidemia²¹. Despite being weak, the correlations were still statistically significant, indicating that the relationship though modest may still be meaningful. It aligns with some prior observations: Hwang et al. (2021) reported that in hemodialysis patients, higher NEP predicted fewer cardiovascular events, speculating that NEP might reflect a protective counter-regulatory response. Additionally, GH's effect on lipids (increasing HDL, decreasing fat mass) could be interacting with NEP's pathways. Given GH's strong lipolytic action, acromegaly patients often have an improved lipid oxidation state; this might coincide with conditions that keep NEP in check⁷.

Comparison with literatures

The absence of significantly elevated NEP in acromegaly contrasts with conditions like obesity and metabolic syndrome, where NEP is often high and

correlates with adiposity and insulin resistance^{6,9}. Kjeldsen et al. (2023) found that NEP activity is increased in fatty liver disease associated with metabolic syndrome and normalizes after weight-loss interventions, underscoring NEP's link to obesity-related insulin resistance. In our acromegaly patients, GH excess tends to reduce liver fat and body fat despite insulin resistance^{2,8}. This unique metabolic state of acromegaly might result in normal NEP levels, supporting the idea that NEP elevation is not a universal feature of insulin resistance but depends on the context and underlying cause²².

Furthermore, medications used in acromegaly (such as SSAs, as mentioned, and GH receptor antagonists) could modulate enzyme levels. It has been documented that successful treatment of acromegaly (surgery or medical therapy) leads to alterations in body composition—for example, an increase in fat mass once GH is controlled⁸. It would be interesting to see in future studies whether NEP levels rise after acromegaly is treated and patients gain fat mass (which might then make acromegaly patients more similar to typical obese individuals in terms of NEP). Recent evidence also shows that asprosin levels are reduced in acromegaly despite insulin resistance, unlike in obesity where they are elevated, highlighting the unique metabolic profile of GH excess²⁰.

Limitations

This study has several limitations. First, the duration and activity status of acromegaly were not systematically recorded, limiting our ability to assess chronicity effects on NEP levels. Second, treatment modalities—including surgery, SSA therapy, and dopamine agonists—were unevenly distributed and may have influenced NEP independently of diabetes. Finally, data on lipid-lowering medications were incomplete, preventing evaluation of their potential impact on NEP–lipid associations.

Clinical implications

From a clinical standpoint, our findings suggest that measuring serum neprilysin is unlikely to provide additional insight into an acromegaly patient's risk of diabetes or dyslipidemia beyond what traditional risk factors and GH/IGF-1 levels already indicate. In other words, NEP did not emerge as a useful biomarker for stratifying metabolic risk in acromegaly. While NEP inhibitors are being explored as therapies (especially in heart failure), our results do not support a role for NEP as a therapeutic target specifically for improving metabolic outcomes in acromegaly. Future research might focus on whether NEP has prognostic value for cardiovascular complications in acromegaly or whether it changes after long-term disease control.

In conclusion, Serum neprilysin levels did not show significant elevation in acromegaly patients, including those with concurrent type 2 diabetes mellitus. Despite the metabolic and hormonal disturbances characteristic of acromegaly, NEP concentrations remained comparable to healthy controls. A slight inverse correlation was observed between NEP and lipid parameters (cholesterol, triglycerides, and VLDL), while no associations emerged with glycemic indices or GH/IGF-1 levels. These findings indicate that neprilysin is unlikely to serve as a reliable circulating biomarker for glycemic control or disease activity in acromegaly. Notably, this study is among the first in the region to evaluate NEP in acromegaly and provides a foundation for future research exploring mechanistic pathways and potential clinical applications.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of the College of Medicine, Mustansiriyah University, Baghdad, Iraq (Approval No. 8322, Date: 7.11.2024).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

MEG: Conceptualization, methodology, data collection, laboratory work, formal analysis, writing – original draft, writing – review & editing.

SAWAS: Methodology support, data interpretation, writing – review & editing.

AMR: Conceptualization, supervision, data interpretation, critical review of the manuscript.

All authors read and approved the final version of the manuscript.

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