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Research Article

Serum Copeptin in Acromegaly with and Without Diabetes: A Comparative Cross-Sectional Study

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ABSTRACT

Background: Copeptin serves as a stable substitute marker for vasopressin and is emerging as a biomarker in endocrine disorders. Given the complex metabolic interactions in acromegaly and the role of growth hormone in fluid balance, this study examined copeptin levels in patients with acromegaly and diabetes mellitus, non-diabetic acromegaly, and healthy controls.

Objectives: To compare serum copeptin concentrations among acromegalic patients with diabetes, acromegalic patients without diabetes, and healthy controls.

Subjects and Methods: This is a comparative cross-sectional study that included 176 participants: acromegalic patients with diabetes, acromegalic patients without diabetes, and healthy controls. Serum copeptin was measured using a standardized ELISA method. A comprehensive biochemical profile was also assessed, including growth hormone, insulin-like growth factor-1, fasting glucose, glycated hemoglobin, and lipid parameters. One-way ANOVA with post-hoc least significant difference testing was used to analyze group differences. The study was conducted at the National Diabetes Center (Baghdad, Iraq) with fasting samples collected between November 2024 and March 2025.

Results: Mean copeptin concentrations demonstrated a statistically significant variation between the groups ($p = 0.012$). Non-diabetic acromegalic patients exhibited the highest copeptin levels (72.6 ± 59.3 pmol/L), followed by diabetic acromegalic patients (57.3 ± 49.2 pmol/L) and control subjects (48.0 ± 25.7 pmol/L). Post-hoc analysis indicated a substantial elevation in copeptin levels among non-diabetic acromegalic patients compared to controls ($p = 0.003$; Cohen's $d = -0.45$, 95% CI: -0.85 to -0.05), indicating a small-to-medium effect size. Copeptin demonstrated a positive correlation with growth hormone ($r = 0.443$, $p = 0.003$) and insulin-like growth factor-1 ($r = 0.333$, $p = 0.027$), while it correlated negatively with triglycerides ($r = -0.326$, $p = 0.031$) and VLDL ($r = -0.332$, $p = 0.028$).

Conclusions: Serum copeptin levels were significantly higher in non-diabetic acromegalic patients than in controls, while diabetic acromegalic patients were not significantly different from controls.

Introduction

Acromegaly is a rare, lifelong endocrine disorder mainly caused by pituitary adenomas, leading to excess secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). This hormonal imbalance results in characteristic somatic changes and multiple systemic complications, including insulin resistance, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease [1]. Diabetes mellitus develops in about 20–40% of patients, primarily due to GH-induced insulin resistance, and contributes to increased cardiovascular and renal risks [2].

Copeptin is a 39–amino acid glycopeptide derived from the C-terminal part of pre-pro-vasopressin (pre-pro-AVP) and is secreted in equimolar amounts with arginine vasopressin (AVP) and neurophysin II [3]. Its secretion parallels that of AVP in response to osmotic and hemodynamic stimuli, helping regulate water balance, vascular tone, and responses to non-osmotic stressors such as hypoglycemia and cardiovascular stress [4]. Because direct AVP measurement is limited by its instability and low plasma concentration, copeptin is widely used as a reliable surrogate marker for vasopressin activity in disorders of water balance and as a prognostic marker in various diseases [5]. In central diabetes insipidus, for instance, postoperative copeptin <2.5 pmol/L suggests AVP deficiency, while levels >30 pmol/L indicate preserved secretion [5].

Recent evidence suggests that diabetes may influence copeptin levels in acromegaly through interactions between glucose metabolism, vasopressin system activation, and the pathophysiological effects of GH excess. Chronic GH and IGF-1 overproduction induces significant insulin resistance, enhances hepatic gluconeogenesis, and impairs pancreatic β-cell function, leading to glucose dysregulation. The coexistence of diabetes in acromegaly further stimulates the vasopressin system through hyperglycemia-induced osmotic changes, thereby increasing copeptin levels [3]. Elevated copeptin has also been linked to adverse cardiovascular outcomes and improves the rapid rule-out of acute myocardial infarction when combined with cardiac troponin [6].

Beyond water and cardiovascular disorders, copeptin relates to metabolic disease. Type 2 diabetes is strongly associated with insulin resistance and biochemical alterations (GABA, IRAP, GLUT4), which may interact with copeptin regulation in acromegaly [7]. Recent studies demonstrated increased serum Meteorin-like (METRNL) in newly diagnosed type 2 diabetes and correlations with metabolic risk factors, highlighting the role of novel biomarkers in glucose and lipid metabolism [8]. Similarly, bariatric surgery improves BMI, glycemic control, and lipid profile in obese diabetic patients, underscoring the clinical relevance of biomarker research [9].

Clinical studies also suggest a link between GH and copeptin. In GH-deficient patients, copeptin increased significantly after GH replacement therapy [10]. In acromegaly, postoperative copeptin monitoring may help predict fluid balance disturbances and risk of central diabetes insipidus after pituitary surgery [11]. In diabetes, elevated copeptin correlates with albuminuria and renal decline [12], and patients with type 2 diabetes show ~60% higher copeptin levels compared to healthy individuals. In addition, in the context of diabetes and diabetic nephropathy, elevated copeptin correlates with albuminuria and declining renal function [13]. Acromegaly exacerbates insulin resistance and dyslipidemia, which may compound diabetic kidney injury, further elevating copeptin. There is a negative correlation between fasting glucose and copeptin in acromegaly, suggesting hyperglycemia might suppress AVP secretion or reflect altered fluid dynamics. Diabetes can modulate copeptin via osmotic diuresis (e.g., with SGLT2-induced glucosuria) and hyperosmolar states, altering AVP/copeptin dynamics [6]. These findings suggest that in acromegaly, GH excess may elevate copeptin, but hyperglycemia and osmotic diuresis in diabetic patients could counteract this effect, modulating copeptin's diagnostic and prognostic role [14].

The aim of the study is to compare serum copeptin concentrations among acromegalic patients with diabetes, acromegalic patients without diabetes, and healthy controls.

Subjects and Methods

This was a comparative cross-sectional study including 176 participants, divided into three groups: Group A (acromegaly with diabetes; n = 44), Group B (acromegaly without diabetes; n = 44), and Group C (healthy controls; n = 88). 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 was conducted at the National Diabetes Center (NDC), Mustansiriyah University, Baghdad, Iraq, from November 2024 to March 2025, and was approved by the Research Ethics Committee of the Mustansiriyah College of Medicine (IRB approval No. 8322; approval date: 7 Nov 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.

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 ≥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.

Criteria for inclusion for acromegalic patients that have received Octreotide monthly injection for at least one year duration and were aged between 21 and 80 years. Exclusion criteria included, renal impairment defined as eGFR < 60 mL/min/1.73 m² (CKD-EPI 2021) or macroalbuminuria (UACR ≥ 300 mg/g), or acute kidney injury within the prior 3 months; presence of cardiometabolic disorder with major fluid/osmotic impact: decompensated heart failure (NYHA II–IV), recent acute coronary syndrome or stroke (<6 months),

uncontrolled hypertension (≥160/100 mmHg despite therapy), medications that materially alter water/sodium balance: current loop or thiazide diuretics, alcohol abuse, type 1 diabetes, smoking and pregnant women. (Type 2 diabetes and dyslipidemia were not excluded by design).

Concentrations of serum copeptin were detected by a standardized lab technique of enzyme-linked immunosorbent assay (ELISA) kit (Human Copeptin ELISA Kit, YL Biotech Co., Ltd., China; Catalog No. YLA1139HU, 96 tests). A comprehensive biochemical assessment was carried out, including measurements of growth hormone (GH), insulin-like growth factor-1 (IGF-1), fasting blood glucose (FBS), glycated hemoglobin (HbA1c), and a complete lipid profile.

The primary outcome was the difference in mean serum copeptin across Groups A, B, and C. Secondary outcomes included: (i) correlations between copeptin 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). All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation (SD) for normally distributed variables or as median (IQR) for non-normally distributed data, while categorical data were presented as frequencies and percentages. 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 when assumptions were met, and Welch's ANOVA or Kruskal–Wallis's test when violated. Post-hoc analyses were performed using LSD, Games–Howell, or Dunn's test (Bonferroni-adjusted) as appropriate. Associations between continuous variables were evaluated using Pearson's or Spearman's correlation coefficients, depending on data distribution. Effect sizes (Cohen's d, 95% CI) were calculated to assess the magnitude of group differences. All tests were two-tailed, and a P-value of < 0.05 was considered statistically significant.

Results

The general demographic and anthropometric characteristics of the groups are summarized in Table 1. Study participants' age ranged from 21 to 80 years, with a mean of 50.19 years and a standard deviation (SD) of ± 13.26 years. The highest proportions of patients in groups A, B, and C were aged 40-59 years (63.6%, 61.4%, and 45.5%, respectively).

In addition, Table 2 presents selected general characteristics and biochemical profiles for the three groups. The distribution of sex differed among the groups (χ^2 test, $p < 0.01$, $\eta^2 = 0.18$): in group B and in controls C, males were a majority (77% and 65%, respectively), whereas in group A, females comprised a higher fraction (66%). In terms of body mass index (BMI) categories, the highest proportion of group A was overweight (47.7%), while (54.5%) of group B were obese, whereas in the control group, the majority had a normal BMI (46.6%). The overall difference in BMI category distribution between the groups was statistically significant ($p < 0.001$).

As expected, patients with acromegaly (groups A and B) showed marked hormonal and metabolic abnormalities compared to healthy controls. Levels of IGF-1, GH, FBS, HbA1c, Total Cholesterol and LDL were significantly elevated in both group A and group B relative to controls, while HDL levels were significantly higher ($p < 0.05$) in group C compared to groups A and B. No statistically significant difference in the mean of S. TG and VLDL between study groups ($P = 0.091$).

Table 1: Age distribution of study groups (Group A: acromegaly with diabetes, Group B: acromegaly without diabetes, Group C: controls).

Group	Age < 40 (n, %)	Age 40–59 (n, %)	Age ≥ 60 (n, %)
A (Acromegaly + DM)	3 (6.8%)	28 (63.6%)	13 (29.5%)
B (Acromegaly no DM)	14 (31.8%)	27 (61.4%)	3 (6.8%)
C (Healthy controls)	24 (27.3%)	40 (45.5%)	24 (27.3%)

The primary outcome of interest, serum copeptin levels, differed across the groups (Table 3). The mean copeptin concentration in group B was 72.61 ± 59.3 pmol/L, which was the highest among the three groups. One-way ANOVA indicated a significant overall difference in copeptin levels ($p = 0.012$, $\eta^2 = 0.05$).

Post-hoc LSD comparisons (Table 4) showed a significant rise in group B copeptin level when compared to Group C (mean difference ~24.6 pmol/L, 95% CI: 9.0–40.1, $p = 0.003$). The distinction between Group A and Group C was not significant ($p = 0.24$), nor did the distinction between the two acromegaly groups ($p = 0.101$).

Effect sizes (Cohen's d with 95% CI) were calculated and summarized in Table 5, in addition to post-hoc tests to assess the strength of group differences. Most parameters showed large effects, whereas the difference in copeptin between group B and controls was small to moderate.

Correlation analyses were performed to explore associations between copeptin and other biochemical and hormonal parameters across the three study groups (Tables 6-8). In group A, copeptin showed a significant positive correlation with GH ($r = 0.443$, $P = 0.003$) and IGF-1 ($r = 0.333$, $P = 0.027$), and a significant negative correlation was observed with triglycerides ($r = -0.332$, $P = 0.028$) and VLDL ($r = -0.326$, $P = 0.031$). Groups B and C showed no significant correlations between copeptin and any of the biochemical or hormonal parameters studied ($P > 0.05$).

Table 2: Distribution of the study participants by general characteristics.

Characteristic / Parameter	Group A (n=44)	Group B (n=44)	Group C (n=88)	P-value
Gender				
Male	15 (34.1%)	34 (77.3%)	57 (64.8%)	<0.001
Female	29 (65.9%)	10 (22.7%)	31 (35.2%)	
BMI Category (kg/m^2)				
Normal (18.5–24.9)	2 (4.6%)	7 (15.9%)	41 (46.6%)	<0.001
Overweight (25–29.9)	21 (47.7%)	13 (29.5%)	20 (22.7%)	
Obese (≥30)	21 (47.7%)	24 (54.5%)	27 (30.7%)	
IGF-1 (ng/mL)	527.27 ± 250.1	414.38 ± 197.8	143.09 ± 28.7	0.001
GH (ng/mL)	4.47 ± 4.70	4.29 ± 4.90	0.45 ± 0.53	0.001
Fasting Blood Sugar (mg/dL)	177.84 ± 76.9	110.0 ± 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

Table 3: Mean (± SD) serum copeptin levels in the study groups.

Group	Copeptin Level (pmol/L, Mean ± SD)
Group A (Acromegaly + DM)	57.30 ± 49.2
Group B (Acromegaly no DM)	72.61 ± 59.3
Group C (Healthy controls)	48.03 ± 25.7
P-value	0.012

Table 4: Post-hoc LSD test results for pairwise comparisons of copeptin levels between groups.

Comparison	Mean Difference in Copeptin	P-value
Group A vs Group B	–15.31 pmol/L (A < B)	0.101
Group A vs Group C	9.27 pmol/L (A > C)	0.240
Group B vs Group C	24.58 pmol/L (B > C)	0.003

Table 5: Effect size analysis (Cohen's d and 95% CI) of biochemical and hormonal parameters.

Parameter	Comparison	Cohen's d	95% CI	Interpretation
IGF-1	A vs C	1.13	0.53 – 1.94	Large (↑ in A)
	B vs C	0.51	0.14 – 0.87	Medium (↑ in B)
GH	A vs C	1.19	0.81 – 1.58	Large (↑ in A)
	B vs C	1.19	0.80 – 1.58	Large (↑ in B)
FBS	A vs C	2.16	1.71 – 2.61	Very large (↑ in A)
	A vs B	1.19	0.79 – 1.59	Large (↑ in A)
HbA1c	A vs C	2.16	1.71 – 2.61	Very large (↑ in A)
	A vs B	1.26	0.85 – 1.67	Large (↑ in A)
Cholesterol	A vs C	1.83	1.43 – 2.23	Large (↑ in A)
	B vs C	1.36	0.97 – 1.76	Large (↑ in B)
HDL	A vs C	–1.19	–1.58 – –0.80	Large (↓ in A)
	B vs C	–1.49	–1.89 – –1.08	Large (↓ in B)
LDL	A vs C	2.16	1.71 – 2.61	Very large (↑ in A)
	B vs C	1.59	1.18 – 2.00	Large (↑ in B)
Copeptin	B vs C	–0.45	–0.85 – –0.05	Small–medium (↑ in B)

Table 6: Pearson correlation between copeptin levels and selected biochemical parameters across group A.

Biochemical Parameter	Copeptin Correlation R	P- Value
Fasting Blood Sugar (mg/dL)	0.082	0.596
HbA1c (%)	0.196	0.209
Total Cholesterol (mg/dL)	-0.255	0.095
Triglycerides (mg/dL)	-0.332	0.028
HDL cholesterol (mg/dL)	0.238	0.119
LDL cholesterol (mg/dL)	-0.234	0.126
VLDL (mg/dL)	-0.326	0.031
IGF-1 (ng/mL)	0.333	0.027
GH (ng/mL)	0.443	0.003
Age (Year)	-0.133	0.391
BMI (Kg/m^2)	-0.055	0.724

Table 7: Pearson correlation between copeptin levels and selected biochemical parameters across group B.

Biochemical Parameter	Copeptin Correlation R	P- Value
Fasting Blood Sugar (mg/dL)	-0.013	0.933
HbA1c (%)	0.06	0.697
Total Cholesterol (mg/dL)	-0.195	0.204
Triglycerides (mg/dL)	-0.229	0.135
HDL cholesterol (mg/dL)	0.097	0.532
LDL cholesterol (mg/dL)	-0.143	0.355
VLDL (mg/dL)	-0.239	0.119
IGF-1 (ng/mL)	0.036	0.819
GH (ng/mL)	-0.034	0.827
Age (Year)	-0.173	0.262
BMI (Kg/m^2)	-0.153	0.322

Table 8: Pearson correlation between copeptin levels and selected biochemical parameters across group C.

Biochemical Parameter	Copeptin Correlation R	P- Value
Fasting Blood Sugar (mg/dL)	0.009	0.931
HbA1c (%)	-0.154	0.152
Total Cholesterol (mg/dL)	0.004	0.969
Triglycerides (mg/dL)	0.167	0.121
HDL cholesterol (mg/dL)	-0.084	0.437
LDL cholesterol (mg/dL)	0.025	0.817
VLDL (mg/dL)	0.080	0.459
IGF-1 (ng/mL)	-0.043	0.689
GH (ng/mL)	-0.095	0.380
Age (Year)	-0.134	0.214
BMI (Kg/m^2)	-0.162	0.132

Discussion

According to the study groups' ages, the mean age of participants was 50.19 ± 13.26 years. Most individuals were middle-aged, with 63.6% of group A, 61.4% of group B, and 45.5% of group C falling within the 40–59 age range. The prevalence of acromegaly among individuals aged 40 to 59 highlights the disease's gradual progression and common delays in diagnosis, which often span five to ten years after initial symptom onset, which aligns with the typical diagnostic window for acromegaly (15). The slightly older mean age in this cohort compared to studies reporting averages of 40–50 years may indicate regional disparities in healthcare access or awareness. The younger age distribution in group C likely mirrors general population demographics, as acromegaly is rare (16).

Sex distribution differs among groups: group A was 65.9% females whereas groups B and C were predominantly male (77.3% and 64.8%, respectively). The female predominance in group A contrasts with the male majority in group B. This pattern may suggest sex-related differences in metabolic risk among patients with acromegaly. Females with acromegaly may face heightened DM risk due to hormonal interactions, where estrogen attenuates GH signaling, potentially exacerbating insulin resistance (17). Conversely, males' higher IGF-1 levels might protect against DM despite greater obesity prevalence in group B. This agrees with the findings of Lenders et al., who reported that women with acromegaly have higher DM prevalence (30% vs. 24% in men) and longer diagnostic delays, aligning with group A's female majority (18).

According to BMI, this pattern aligns with findings in healthy populations and underscores the closer association between excessive obesity and acromegaly. Importantly, GH excess in acromegaly modifies body composition, promoting visceral adiposity and insulin resistance independently of BMI (19). Despite the presence of diabetes, group A's lower obesity rate compared to Group B may indicate more advanced disease or greater insulin deficiency and some studies reported a positive correlation between BMI and IGF-1, linking obesity to disease severity—consistent with group B's elevated BMI and GH activity (2). In contrast, others argue that obesity is the primary driver of diabetes in acromegaly, a view differing from Group B's profile, implying that GH excess may play a more dominant role than BMI in metabolic dysfunction (20).

In this study, both acromegaly groups showed significantly higher GH and IGF-1 levels compared to healthy controls, in line with evidence that elevated IGF-1 is associated with impaired glucose metabolism via GH/IGF-1–induced insulin resistance and lipolysis (21). The dyslipidemia pattern observed in acromegalic patients is also compatible with mechanistic links between GH excess driven lipolysis, increasing free fatty acids, hepatic VLDL production, and lower HDL (22).

According to copeptin (CPP) levels, the observed increase in CPP levels among acromegaly patients—particularly those without diabetes mellitus (group B: 72.61 ± 59.3 vs. controls: 48.03 ± 25.7, p = 0.003)— supporting emerging evidence of vasopressin system dysregulation in states of GH excess. The markedly elevated CPP

concentrations in group B compared to controls indicate that GH excess may modulate vasopressin regulation through pathways independent of glucose metabolism. Recent studies have also indicated that CPP correlates with GH and may predict fluid-balance changes after pituitary surgery (11). The sodium-retaining effects of GH and its influence on extracellular fluid volume may induce compensatory mechanisms that up-regulate the AVP/copeptin system. In the absence of diabetes-related osmotic diuresis, this activation could occur independently of glycemia, potentially explaining the higher CPP levels observed in group B (12).

Although the difference between acromegalic patients with and without diabetes was not statistically significant in post-hoc testing, CPP was numerically lower in diabetic acromegaly patients (57.3 ± 49.2 vs. 72.61 ± 59.3). This may reflect the competing osmotic effects of hyperglycemia and glycosuria that can blunt AVP/CPP responses; a recent study reported an inverse relationship between fasting glucose and copeptin in acromegaly, supporting the hypothesis that diabetes mellitus may modulate the vasopressin response in this population (14).

Effect-size analyses (Cohen's d) demonstrated large differences versus controls for IGF-1, GH, fasting glucose, HbA1c, total cholesterol, and LDL, with a large negative effect for HDL—consistent with the profound metabolic disturbances of acromegaly. By contrast, CPP showed a small-to-moderate difference between non-diabetic acromegaly and controls, suggesting a less pronounced but potentially relevant clinical role.

CPP correlated positively with GH and IGF-1 and negatively with triglycerides and VLDL. The inverse CPP–triglyceride association could reflect the interplay between GH-driven lipolysis (which lowers circulating TG) and AVP/CPP activation under metabolic stress. Because CPP primarily indexes water–osmoregulatory balance rather than lipid metabolism modulation. Additionally, several confounding factors, including lipid-lowering therapy, diet, physical activity, and hydration, should also be considered as these could have influenced lipid variability and masked potential relationships (23). Moreover, GH/IGF-1 excess induces systemic effects—renal sodium and water retention, endothelial dysfunction, and hypertension—that increase cardiovascular stress (14). In group A, the positive association between CPP and somatotropic activity may therefore mirror greater overall metabolic stress. This might indicate that the presence of diabetes or higher metabolic stress amplifies the link between the somatotropic axis (GH/IGF-1) and vasopressin release (24).

No significant correlations between CPP and biochemical or hormonal indices were found in groups B or C (all $p > 0.05$). In non-diabetic acromegaly (group B), this may indicate that CPP is less tightly coupled to metabolic markers when hyperglycemia is absent, or it may reflect limited power and narrower ranges of exposure, and the metabolic disturbances in group B were milder, so the vasopressin system was not markedly stimulated. This aligns with the idea that copeptin's associations become more evident under greater metabolic stress – for instance, copeptin correlates with glycemia and lipids mainly in populations with metabolic syndrome or diabetes (14). In controls (group C), the lack of associations is expected under normal homeostasis and is consistent with reports showing minimal associations between copeptin and lipid or glycemic measures in metabolically healthy populations (24).

Finally, elevated CPP has been linked to adverse cardiovascular outcomes—including myocardial infarction, heart failure, and vascular dysfunction. Such elevations may reflect metabolic disturbances similar to dyslipidemia in diabetic patients, underscoring CPP's value as an integrated biomarker of cardiometabolic stress. The CPP alterations observed in acromegaly may therefore indicate an increased cardiometabolic burden in this population and warrant further prospective evaluation (6,25).

Study Limitations

This cross-sectional design limits the ability to draw conclusions about causality or longitudinal changes, as copeptin was measured only once. Hydration status and plasma osmolality were not assessed, despite their known influence on copeptin release. Considerable variability in copeptin levels may reflect biological heterogeneity or assay differences. Only patients with established acromegaly were included, and tumor characteristics such as size, disease stage, activity, and prior surgical treatment were not analyzed, which could influence results.

The present study suggests that copeptin may serve as a promising biomarker in acromegaly, reflecting mechanisms beyond glucose metabolism and potentially linking growth hormone excess to vasopressin system dysregulation. Future research should focus on longitudinal assessments to determine its value in monitoring disease activity and treatment outcomes, as well as its possible role in predicting cardiovascular and renal complications. Exploring copeptin in combination with other biochemical markers may further clarify its clinical utility and support its integration into routine management of acromegalic patients.

Conclusion

Serum copeptin levels were markedly elevated in acromegaly patients, especially in those without diabetes. Furthermore, in patients with diabetic acromegaly, Copeptin levels showed positive correlations with GH and IGF-1 and negative correlations with TG and VLDL. These findings suggest that Copeptin could serve as a biomarker reflecting acromegaly's underlying disease processes beyond just glucose regulation. Notably, this was the first study of its kind to be conducted in the local region.

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Conflict of Interest

The authors declare no conflicts of interest related to this work.

Data availability

Data are available upon reasonable request.

Author Contributions

MEG contributed to conceptualization, methodology, data collection, laboratory work, formal analysis, writing—original draft, and writing—review and editing. SAA contributed to methodology support, data interpretation, writing, review, and editing. AMR contributed to conceptualization, supervision, data

interpretation, and critical review of the manuscript. All authors read and approved the final version of the manuscript.

All authors meet the ICMJE criteria for authorship and agree to be accountable for all aspects of the work.

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References

[1] Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. The Lancet Diabetes & Endocrinology. 2022;10(11):804-26. https://doi.org/10.1016/S2213-8587(22)00244-3

[2] Esposito D, Boguszewski CL, Colao A, Fleseriu M, Gatto F, Jørgensen JOL, et al. Diabetes mellitus in patients with acromegaly: pathophysiology, clinical challenges and management. Nature Reviews Endocrinology. 2024;20(9):541-52. https://doi.org/10.1038/s41574-024-00993-x

[3] Christ-Crain M, Refardt J, Winzeler B. Approach to the patient: utility of the copeptin assay. The Journal of Clinical Endocrinology & Metabolism. 2022;107(6):1727-38. https://doi.org/10.1210/clinem/dgac113

[4] Refardt J, Winzeler B, Christ-Crain M. Copeptin and its role in the diagnosis of diabetes insipidus and the syndrome of inappropriate antidiuresis. Clinical endocrinology. 2019;91(1):22-32. https://doi.org/10.1111/cen.13991

[5] Moodley N. Copeptin analysis in endocrine disorders. Frontiers in Endocrinology. 2023;14:1230045. https://doi.org/10.3389/fendo.2023.1230045

[6] Mu D, Cheng J, Qiu L, Cheng X. Copeptin as a diagnostic and prognostic biomarker in cardiovascular diseases. Frontiers in Cardiovascular Medicine. 2022;9:901990. https://doi.org/10.3389/fcvm.2022.901990

[7] Rezazadeh H, Sharifi MR, Soltani N. Insulin resistance and the role of gamma-aminobutyric acid. Journal of Research in Medical Sciences. 2021 Jan 1;26(1):39. https://doi.org/10.4103/jrms.JRMS_374_20

[8] Wang K, Li F, Wang C, Deng Y, Cao Z, Cui Y, Xu K, Lin P, Sun Y. Serum levels of meteorin-like (Metrnl) are increased in patients with newly diagnosed type 2 diabetes mellitus and are associated with insulin resistance. Medical science monitor: international medical journal of experimental and clinical research. 2019 Mar 31;25:2337. https://doi.org/10.12659/MSM.915331

[9] Laibee AR, Akkila SS, Khamees N, Eleiwe SA, Salem YG. Short-Term effects of laparoscopic sleeve gastrectomy on anatomical & biochemical parameters in morbidly obese Iraqi Patients. Bali Medical Journal. 2021;10(3):1045-9. https://doi.org/10.15562/bmj.v10i3.2615

[10] Sjöström A, Chisalita SI, Höybye C. Copeptin in growth hormone-treated patients. Journal of Clinical Medicine. 2022;11(19):5510. https://doi.org/10.3390/jcm11195510

[11] Varaldo E, Prencipe N, Berton AM, Aversa LS, Bioletto F, De Marco R, et al. Utility of copeptin in predicting non-pathological postoperative polyuria in patients affected by acromegaly undergoing pituitary neurosurgery. Pituitary. 2024;27(5):488-96. https://doi.org/10.1007/s11102-024-01407-x

[12] Mustafa HK, Gaballah AM, Fathalla MS. Assessment of serum copeptin in poorly controlled type 1 diabetes. Zagazig University Medical Journal. 2020;26(3):397-404. https://doi.org/10.21608/zumj.2019.145

[13] Rojas-Humpire R, Soriano-Moreno DR, Galindo-Yllu B, Zafra-Tanaka JH. Association between copeptin and metabolic syndrome: a systematic review. Journal of Nutrition and Metabolism. 2022;2022(1):5237903. https://doi.org/10.1155/2022/5237903

[14] Strzelec M, Kubicka E, Kuliczkowska-Płaksej J, Kolačkov K, Janek Ł, Bolanowski M, et al. Copeptin and Mid-Regional Proadrenomedullin Are Not Useful Biomarkers of Cardiometabolic Disease in Patients with Acromegaly—A Preliminary Study. Biomedicines. 2025;13(3):666. https://doi.org/10.3390/biomedicines13030666

[15] Bogusławska A, Gilis-Januszewska A, Godlewska M, Nowak A, Starzyk J, Hubalewska-Dydejczyk A. Sex and age differences among patients with acromegaly. Polish Archives of internal Medicin. 2022;132(6) :16232 https://doi.org/10.20452/pamw.16232

[16] Chanson, P., Salenave, S. 2008. Acromegaly. Orphanet journal of rare diseases, 2008; 3:17. https://doi.org/10.1186/1750-1172-3-17

[17] Găloiu S, Toma ID, Tănasie DI, Bărbulescu A, Baciu I, Niculescu DA, Trifănescu RA, Căpăţînă C, Radian Ş, Poiană C. High mortality risk among women with acromegaly still persists. Frontiers in Endocrinology. 2024 Feb 21;15:1348972. https://doi.org/10.3389/fendo.2024.1348972

[18] Lenders NF, McCormack AI, Ho KK. Management of endocrine disease: does gender matter in the management of acromegaly?. European Journal of Endocrinology. 2020 May;182(5):R67-82. https://doi.org/10.1530/EJE-19-1023

[19] Khiyami A, Mehrotra N, Venugopal S, Mahmud H, Zenonos GA, Gardner PA, Fazeli PK. IGF-1 is positively associated with BMI in patients with acromegaly. Pituitary. 2023 Apr;26(2):221-6. https://doi.org/10.1007/s11102-023-01307-6

[20] Yamamoto M, Takahashi Y. Genetic and epigenetic pathogenesis of acromegaly. Cancers. 2022 Aug 10;14(16):3861. https://doi.org/10.3390/cancers14163861

[21] Gatto F, Arecco A, Amarù J, Arvigo M, Campana C, Milioto A, Esposito D, Johannsson G, Cocchiara F, Maggi DC, Ferone D. Differential Impact of Medical Therapies for Acromegaly on Glucose Metabolism. International Journal of Molecular Sciences. 2025 Jan 8;26(2):465. https://doi.org/10.3390/ijms26020465

[22] Moustaki M, Paschou SA, Xekouki P, Kotsa K, Peppa M, Psaltopoulou T, Kalantaridou S, Vryonidou A. Secondary diabetes mellitus in acromegaly. Endocrine. 2023 Jul;81(1):1-5. https://doi.org/10.1007/s12020-023-03339-1

[23] Chang DC, Basolo A, Piaggi P, Votruba SB, Krakoff J. Hydration biomarkers and copeptin: relationship with ad libitum energy intake, energy expenditure, and metabolic fuel selection. European journal of clinical nutrition. 2020 Jan;74(1):158-66. https://doi.org/10.1038/s41430-019-0445-6

[24] Enhörning S, Wang TJ, Nilsson PM, Almgren P, Hedblad B, Berglund G, Struck J, Morgenthaler NG, Bergmann A, Lindholm E, Groop L. Plasma copeptin and the risk of diabetes mellitus. Circulation. 2010 May 18;121(19):2102-8. https://doi.org/10.1161/CIRCULATIONAHA.109.909663

[25] ALShaban SA, Hashim RK, Bohan AH, Akram RS. Study The Effect of Dyslipidemia in Iraqi Diabetes with both genders. History of Medicine. https://historymedjournal.com/index.php/medicine/article/view/539