



Original Research

A Novel Marker in Hypogonadal Hypogonadism: Apelin

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Abstract

Objectives: Apelin is a recently identified adipokine with pleiotropic actions in cardiovascular regulation, metabolic homeostasis, bone remodeling, and reproductive physiology. Through binding to the apelin receptor (APJ), apelin has been shown to influence gonadotropin-releasing hormone (GnRH) secretion, which is essential for the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Given its potential role in the hypothalamic–pituitary–gonadal (HPG) axis, alterations in circulating apelin may contribute to hypogonadotropic hypogonadism (HH). This study aimed to investigate whether serum apelin concentrations are altered in patients with HH and to evaluate its potential relevance as a complementary biomarker in the diagnostic approach to HH.

Methods: A total of 60 participants were enrolled: 30 newly diagnosed HH patients (untreated for at least one year, with no comorbid chronic diseases) and 30 age- and body mass index (BMI)-matched healthy controls. Individuals with BMI<20 or BMI>30 were excluded to minimize confounding metabolic influences on apelin secretion. Following overnight fasting, venous blood samples were obtained for complete biochemical and hormonal profiles. Serum apelin levels were measured using a validated human ELISA kit (SunRed Biotechnology, China; intra- and inter-assay coefficients of variation<10%). Statistical analysis was performed using SPSS 17.0.

Results: Apelin concentrations were significantly lower in HH patients compared with healthy controls (median 35.2ng/L vs. 63.3ng/L, p=0.046). ROC analysis yielded an area under the curve (AUC) of 0.65, with a sensitivity of 76% and a specificity of 64%.

Conclusion: These findings demonstrate reduced circulating apelin concentrations in HH, supporting the hypothesis of its involvement in GnRH regulation and the pathogenesis of hypogonadism. Although its diagnostic accuracy is modest, apelin may complement traditional hormonal markers. Further multicenter studies and mechanistic research are required to validate these observations.

Keywords: Apelin, gonadotropin releasing hormone, hypogonadotropic hypogonadism

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Adipose tissue plays an essential role in human physiology by secreting a broad spectrum of bioactive peptides known as adipokines. Among these, apelin has attracted increasing attention since it was first isolated from bovine gastric extracts in 1998 and later identified in adipose tis-

sue in 2005.^[1] Although the precise physiological functions of this adipokine remain to be fully clarified, apelin is considered to exert diverse effects across multiple organ systems. Through interaction with its specific receptor, APJ, a G protein-coupled receptor, apelin has been implicated in

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cardiovascular regulation, metabolic control, and reproductive functions.

Initial investigations focused largely on the cardiovascular system, where apelin was shown to regulate cardiac contractility and vascular tone. Subsequent studies expanded its role to multiple domains: the regulation of food intake,^[2] water and fluid balance,^[3] experimental nociception models,^[4] bone metabolism,^[5] oxidative stress responses in adipocytes,^[6] and modulation of the HPG axis.^[7] The presence of apelin and APJ receptors in the hypothalamus and pituitary supports a potential regulatory role in reproductive endocrinology.^[8–10]

Experimental studies have demonstrated that apelin may influence gonadotropin secretion. In rodent models, central administration of apelin suppressed luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone secretion.^[7] Conversely, clinical and translational studies have suggested associations between circulating apelin concentrations and metabolic states such as obesity and diabetes mellitus.^[11,12] In healthy individuals, serum apelin levels have been reported within the range of 208–466ng/L (0.208–0.466ng/mL).^[13] Taken together, these findings indicate that apelin can act both centrally and peripherally, with possible context-dependent and dose-dependent effects.

Hypogonadotropic hypogonadism (HH) is characterized by impaired gonadotropin-releasing hormone (GnRH) secretion or pituitary responsiveness, resulting in reduced LH and FSH levels and low circulating testosterone. While hormone assays remain essential for diagnosis, additional biomarkers may provide insights into disease mechanisms and facilitate earlier recognition.

Based on experimental and clinical observations, we hypothesized that serum apelin concentrations would be significantly reduced in patients with HH compared with healthy controls. Accordingly, this study was designed as a prospective case–control investigation to evaluate circulating apelin levels and explore the potential contribution of apelin to the pathogenesis and diagnosis of HH.

Methods

Study Design and Ethics

This prospective case–control study was conducted in accordance with the Declaration of Helsinki and approved by the local institutional ethics committee on January 21, 2019 (approval number 37732058-514.10). Written informed consent was obtained from all participants. The study was not registered in a clinical trial registry, as it was an observational, cross-sectional study and registration was not deemed mandatory at the time of study design.

Study Population

A total of 60 subjects were enrolled: 30 newly diagnosed male patients with HH and 30 healthy controls matched for age and BMI. Patients had not received hormonal therapy for at least one year prior to inclusion and had no chronic disease other than HH. Exclusion criteria for both groups were chronic systemic disorders, BMI < 20 or BMI > 30 kg/m², and current endocrine or hormonal treatment.

Clinical Assessment

All participants underwent a detailed clinical evaluation, including assessment of age, age at diagnosis, secondary sexual characteristics, sexual function, and comorbidities. Anthropometric measurements were obtained, including height, weight, waist circumference, and testicular volume.

Biochemical and Hormonal Measurements

After at least eight hours of overnight fasting, venous blood samples were drawn between 08:00 and 10:00 a.m. Laboratory investigations included a haemogram, biochemical profile, and a hormonal panel consisting of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), free thyroxine (FT4), prolactin, cortisol, adrenocorticotropic hormone (ACTH), growth hormone (GH), insulin-like growth factor 1 (IGF-1), haemoglobin A1C (HbA1C), fasting glucose, creatinine, and albumin.

Diagnosis of Hypogonadotropic Hypogonadism

The diagnosis of hypogonadotropic hypogonadism (HH) was established based on a combination of clinical, biochemical, and, where necessary, imaging findings. All male patients presented with clinical signs of hypogonadism, including delayed or arrested puberty, reduced testicular volume (< 4 mL), and/or symptoms such as decreased libido and erectile dysfunction. Anthropometric measurements and testicular volumes were assessed by a physician in the outpatient clinic. Testicular volumes were measured using both a Prader orchidometer and ultrasonography.

Biochemically, HH was confirmed by persistently low serum testosterone levels (< 10 nmol/L or < 300 ng/dL) in conjunction with inappropriately low or normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Secondary causes of hypogonadism, including hyperprolactinemia, thyroid dysfunction, and chronic systemic illnesses, were excluded through comprehensive biochemical screening. Pituitary imaging (MRI) was performed in all patients to rule out structural abnormalities or tumors affecting the hypothalamic–pituitary axis. Constitutional delay of growth and puberty was excluded based on bone age assessment and follow-up observations. Among the

30 HH patients, 18 had idiopathic HH, 7 had Kallmann syndrome, and 5 had other defined etiologies (e.g., pituitary/hypothalamic lesions).

Measurement of Apelin

For apelin analysis, blood samples were collected into anticoagulant-free tubes, allowed to clot for 20 minutes at room temperature, and centrifuged at 3000rpm for 20 minutes. Serum aliquots were stored at -80°C until testing. Apelin concentrations were measured in duplicate using a commercial human apelin enzyme-linked immunosorbent assay (ELISA) kit (SunRed Biotechnology, Shanghai, China; Cat. No. 201 12 2015). According to the manufacturer, the analytical sensitivity of the kit is 1ng/L, with intra- and inter-assay coefficients of variation $<10\%$. A standard calibration curve was generated for each assay run using the manufacturer-provided calibration standards, and all procedures were performed strictly according to the manufacturer's instructions. The mean of the duplicate measurements was used for statistical analyses.

Sample Size and Power Considerations

An a priori power analysis using a two-tailed independent-samples t-test with an anticipated effect size of $d=0.8$, $\alpha=0.05$, and 95% power ($1-\beta=0.95$) indicated that 42 participants per group would be required. Due to the limited number of eligible HH patients presenting to our clinic during the two-year recruitment period, 30 patients with HH and 30 controls were ultimately included.

Statistical Analysis

Statistical analyses were performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables are presented as mean \pm standard deviation (SD) and were compared between groups using the independent-samples t-test. Non-normally distributed variables, including apelin, are presented as median (interquartile range, IQR) or median (range), and group comparisons were performed using the Mann-Whitney U test. Correlations between apelin and clinical or biochemical parameters were evaluated using Spearman's rank correlation coefficient (ρ); both correlation coefficients and p-values are reported. Due to the limited sample size within each etiological subgroup of HH, no separate subgroup analyses were performed. Diagnostic performance was assessed by receiver operating characteristic (ROC) curve analysis. A p value <0.05 was considered statistically significant.

In addition, sensitivity analyses were performed after excluding extreme outliers in apelin values, and the direction

and statistical significance of the difference between the HH and control groups remained unchanged.

Results

As shown in the patient selection flow chart, a total of 30 patients with HH and 30 healthy controls were included in the analysis (Fig. 1). The demographic and anthropometric characteristics of patients with HH and healthy controls were comparable. No significant differences were observed in age (27 ± 9 vs 28 ± 6 years, $p=0.846$), height (179 ± 6 vs 178 ± 5 cm, $p=0.602$), weight (76 ± 6 vs 77 ± 6 kg, $p=0.402$), or BMI (23.8 ± 1.8 vs 24.6 ± 1.9 kg/m², $p=0.159$) (Table 1).

Serum apelin concentrations were significantly lower in HH patients than in controls. In the HH group, apelin levels were 59.9 ± 70.3 ng/L (mean \pm SD) with a median of 35.2ng/L (range 14.3–260.0), whereas in the control group they were 206.9 ± 263.2 ng/L with a median of 63.3ng/L (range 17.3–880.1) ($p=0.046$) (Table 2). These results highlight both the statistically significant reduction of apelin in HH and the wide interindividual variability observed, particularly in the control group. These distributions and extreme values are

Table 1. Comparison of patient characteristics between groups

Variable	HH group (n=30) mean \pm SD	Control group (n=30) mean \pm SD	p^1
Age (years)	27 \pm 9	28 \pm 6	0.846
Height (cm)	179 \pm 6	178 \pm 5	0.602
Weight (kg)	76 \pm 6	77 \pm 6	0.402
BMI (kg/m ²)	23.8 \pm 1.8	24.6 \pm 1.9	0.159
Fasting glucose (mg/dl)	85.8 \pm 10.5	90.0 \pm 13.3	0.190
Total cholesterol (mg/dl)	181.6 \pm 62.1	182.2 \pm 32.5	0.311
LDL-cholesterol (mg/dl)	104.8 \pm 53.2	110.0 \pm 31.9	0.085
HDL-cholesterol (mg/dl)	42.8 \pm 9.9	43.1 \pm 8.0	0.784
Triglycerides (mg/dl)	109.0 \pm 42.1	143.2 \pm 82.2	0.093
TSH (mIU/L)	2.4 \pm 1.4	2.1 \pm 0.7	0.12
Free T4 (ng/dL)	0.99 \pm 0.15	1.22 \pm 0.18	0.06
Albumin (g/dL)	4.5 \pm 0.3	4.7 \pm 0.2	0.32
Creatinine (mg/dL)	0.77 \pm 0.11	0.88 \pm 0.12	0.071

¹Independent-samples t-test p values. Data are presented as mean \pm standard deviation (SD). BMI: Body mass index; HH: Hypogonadotropic hypogonadism; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; mg/dL: Milligrams per deciliter; TSH: Thyroid-stimulating hormone; T4: Thyroxine; ng/dL: Nanograms per deciliter; mIU/L: milli-international units per liter; g/dL: grams per deciliter.

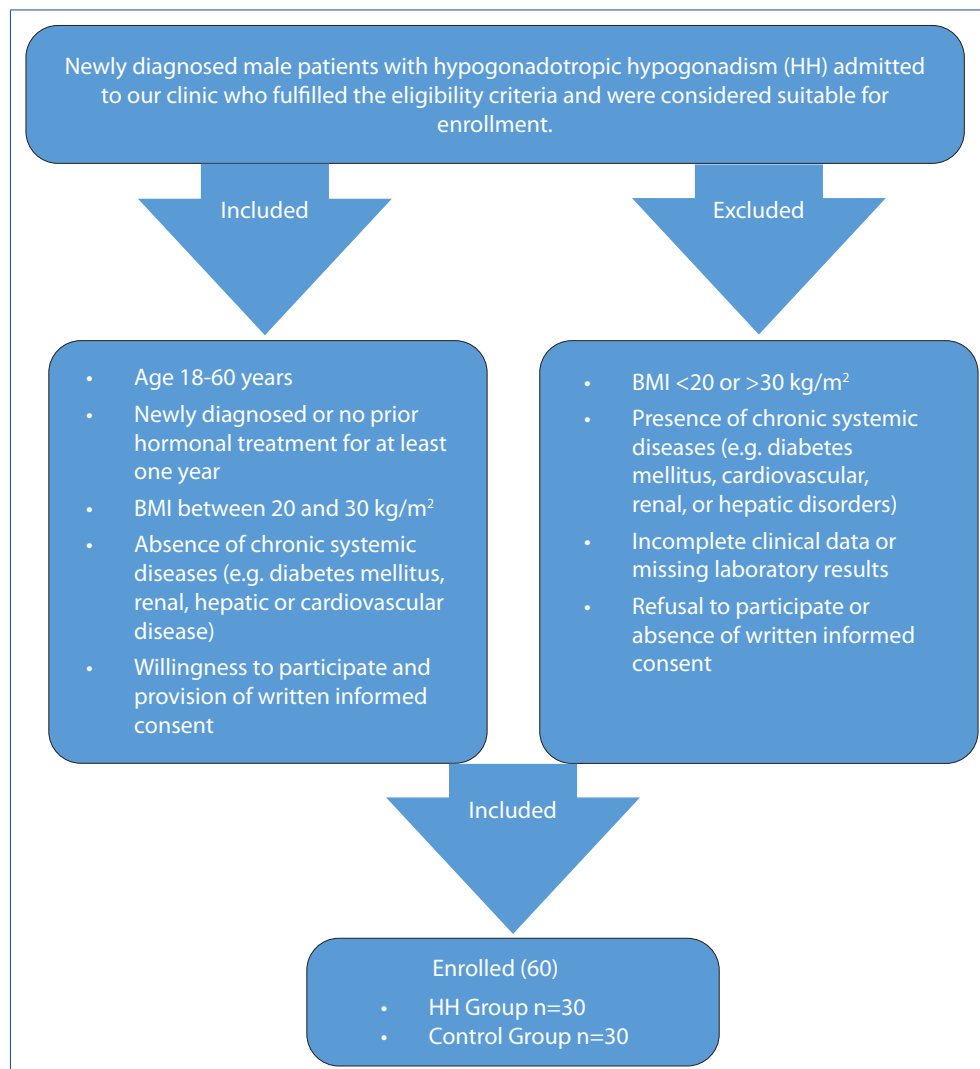


Figure 1. Patient selection flowchart.

HH: Hypogonadotropic hypogonadism; BMI: Body mass index

illustrated in the boxplot of serum apelin levels (Fig. 2).

Receiver operating characteristic (ROC) curve analysis demonstrated modest diagnostic performance of apelin, with an area under the curve (AUC) of 0.65 (95%CI:0.51–0.80, $p=0.046$) (Fig. 3). Although statistically significant, this AUC indicates only limited diagnostic accuracy. The optimal cut-off value of 59ng/L, determined using the Youden index, yielded a sensitivity of 0.76 and a specificity of 0.64, with a positive predictive value (PPV) of 58.8% and a negative predictive value (NPV) of 72.7%. At this cut-off, the positive likelihood ratio (LR+) was 2.11 and the negative likelihood ratio (LR–) was 0.38, indicating only a modest change in post-test probability and thus limited diagnostic utility. At a higher cut-off of 65ng/L, sensitivity increased to 0.84 while specificity decreased to 0.50; PPV and NPV were 59.5% and 78.9%, respectively. Overall, these findings indicate that apelin alone provides only

modest discriminative ability between HH patients and healthy controls.

Serum apelin levels were not significantly correlated with any of the evaluated clinical or biochemical parameters. In Spearman's rank correlation analysis, there was no statistically significant association between apelin and BMI, glucose, albumin, total cholesterol, TSH, WBC count, hemoglo-

Table 2. Comparison of apelin levels between groups

Group	Apelin levels (ng/L)		<i>p</i>
	Mean±SD	Median (IQR)	
HH group (n=30)	59.9±70.3	35.2 (14.3 – 260.0)	0.046*
Control group (n=30)	206.9±263.2	63.3 (17.3 – 880.1)	

* Mann-Whitney U test p value <0.05. HH: Hypogonadotropic hypogonadism; SD: Standard deviation; IQR: Interquartile range

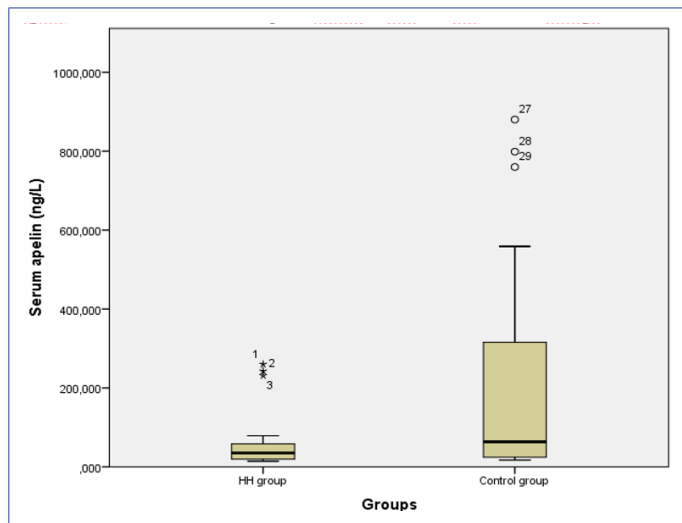


Figure 2. Distribution of serum apelin levels in the HH and control groups.

HH: Hypogonadotropic hypogonadism; ng/L: Nanograms per liter

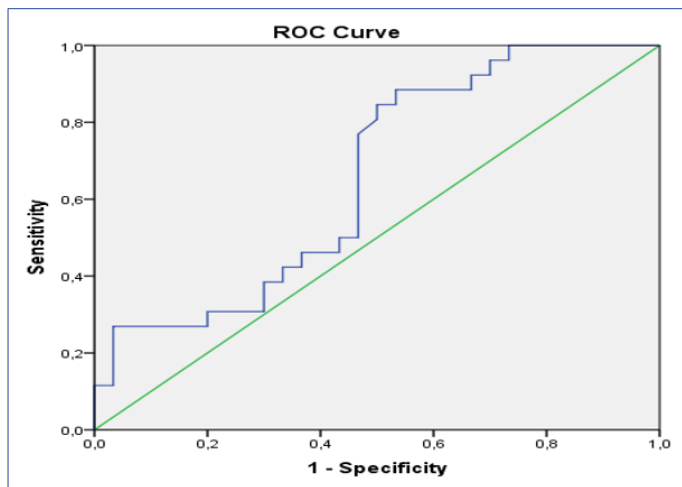


Figure 3. Receiver operating characteristic (ROC) curve of serum apelin levels for discriminating patients with hypogonadotropic hypogonadism (HH) from healthy controls.

*The blue line represents the ROC curve for apelin and the green diagonal line represents the reference line indicating no discrimination (AUC=0.5).

glucose, albumin, total cholesterol, TSH, WBC count, hemoglobin, HbA1c, FSH, LH, prolactin, total testosterone, GH, IGF-1, cortisol, or ACTH (all $p \geq 0.05$) (Table 3).

Taken together, these findings confirm that apelin levels are significantly reduced in patients with HH compared with healthy individuals. However, the modest AUC and variability in sensitivity and specificity across different cut-offs indicate that apelin alone provides limited diagnostic discrimination.

Table 3. Correlations between serum apelin level and clinical/biochemical parameters

Parameter	p
BMI	0.944
Glucose	0.506
Albumin	0.531
Cholesterol	0.845
TSH	0.433
WBC	0.809
HGB	0.482
HbA1c	0.272
FSH	0.645
LH	0.704
Prolactin	0.417
Total T	0.222
GH	0.893
IGF-1	0.108
Cortisol	0.254
ACTH	0.326

*Spearman's rank correlation analysis. No statistically significant correlations at $p < 0.05$ (two-tailed). BMI: Body mass index; TSH: Thyroidstimulating hormone; WBC: White blood cell count; HGB: Hemoglobin; HbA1c: Glycated hemoglobin; FSH: Folliclestimulating hormone; LH: Luteinizing hormone; Total T: Total testosterone; GH: Growth hormone; IGF1: Insulinlike growth factor1; ACTH: Adrenocorticotrop hormone.

Discussion

In this study, apelin concentrations were significantly lower in patients with hypogonadotropic hypogonadism (HH) compared with healthy controls. To our knowledge, this is the first clinical investigation to demonstrate reduced circulating apelin in HH, suggesting a possible role of this adipokine in the pathogenesis of gonadotropin deficiency.

In the correlation analysis, circulating apelin levels were not found to show any significant correlation with metabolic, hematological, or endocrine markers. In particular, the absence of a significant association between apelin and key metabolic parameters such as BMI and glucose suggests that apelin may be considered a marker that is relatively independent of classical metabolic status.

Apelin and its receptor APJ are expressed in GnRH-secreting regions of the hypothalamus and pituitary.^[8-10] Experimental studies have shown that high-dose intracerebroventricular apelin suppresses LH, FSH, and testosterone secretion in rodents.^[3,7] These findings support an inhibitory central action of apelin. In contrast, our results revealed reduced peripheral apelin concentrations in HH patients whose gonadotropin

and testosterone levels were already low. This discrepancy may reflect differences in experimental design, route of apelin administration, species variation, and central versus peripheral mechanisms. It is plausible that adequate circulating apelin is required to maintain physiological GnRH release and that deficiency may disturb hypothalamic–pituitary signaling.

Human data directly linking apelin to HH are virtually absent. Most previous human studies have evaluated apelin in cardiometabolic and cardiovascular settings rather than in the context of gonadotropin deficiency. Thus, our work represents, to the best of our knowledge, one of the first clinical studies to assess circulating apelin levels in HH patients. These findings should therefore be regarded as exploratory and interpreted in light of the differences between high-dose central apelin administration in animal models and peripheral apelin measurements in humans.

Beyond reproduction, apelin is a pleiotropic peptide with important cardiovascular effects. It increases cardiac contractility,^[13,14] induces vasodilatation and lowers blood pressure,^[15–17] and has protective roles in heart failure and hypertension.^[18,19] Apelin deficiency has been associated with increased cardiovascular risk. Patients with HH are known to have a higher prevalence of cardiometabolic disorders and mortality compared with the general population. Thus, low apelin concentrations in HH may contribute not only to hypogonadism itself but also to the increased burden of cardiovascular disease in these patients.

Previous human studies have evaluated circulating apelin levels in various metabolic conditions, including obesity, metabolic syndrome, and PCOS. In obese women, serum apelin concentrations are significantly higher than in non-obese controls and correlate positively with adverse metabolic markers such as insulin resistance and dyslipidemia.^[20] In metabolic syndrome, apelin has been associated with indices of adiposity, blood pressure, and inflammatory cytokines, although weight loss interventions do not consistently normalize apelin levels.^[21] In PCOS, apelin dysregulation has been linked to insulin resistance and hyperandrogenism, but the direction of change in apelin levels is heterogeneous across studies.^[22] In contrast to these predominantly metabolic and often hyperandrogenic settings, our cohort consisted of relatively lean male patients with hypogonadotropic, rather than hypergonadotropic, hypogonadism and without overt chronic systemic diseases. Therefore, the reduced apelin concentrations observed in our HH patients are less likely to be driven primarily by obesity-related metabolic derangements and may instead reflect mechanisms more directly related to GnRH and gonadotropin deficiency, although subtle metabolic contributions cannot be fully excluded.

Our findings demonstrate reduced apelin levels in HH patients. However, the diagnostic utility of apelin alone appears limited, with an AUC of 0.65 (95%CI:0.51–0.80) indicating only modest discriminative ability. Alterations in apelin levels may be related to HH pathophysiology, and apelin has neuroprotective properties, but direct evidence that apelin therapy can correct HH is lacking. Given its known inhibitory effects on GnRH neurons, suggesting a direct stimulatory effect remains speculative. Thus, apelin should currently be considered a complementary biomarker candidate rather than a stand-alone diagnostic tool for HH or its early detection, and there is insufficient evidence to recommend any apelin-based therapeutic intervention.

The strengths of this study include its prospective design, the use of newly diagnosed and untreated HH patients, and validated biochemical methods. However, some limitations must be acknowledged. The small sample size, inherent to the rarity of HH, limits generalizability. Although etiological subgroups of HH (e.g., Kallmann syndrome vs. idiopathic HH) were classified, the number of patients in each subgroup was insufficient to allow meaningful subgroup analyses based on specific causes of hypogonadism. No mechanistic assays or longitudinal follow-up were conducted; therefore, causality between apelin deficiency and HH cannot be confirmed.

Conclusion

This study demonstrates significantly reduced serum apelin concentrations in HH patients, providing evidence for its potential involvement in disease pathogenesis. Given the established cardiovascular effects of apelin, its deficiency in HH may also contribute to the increased cardiovascular risk observed in this population. While its diagnostic accuracy alone is modest, apelin may be considered a promising complementary biomarker candidate and only a hypothetical therapeutic target whose clinical utility remains to be established in future studies. Larger multicenter studies and interventional trials are warranted to confirm these findings and to explore whether apelin supplementation might benefit both reproductive and cardiovascular outcomes in HH. Bottom of Form

Disclosures

Ethics Committee Approval: This study was approved by the Health Sciences University Erzurum Regional Training and Research Hospital Ethics Committee (Date: 21.01.2019, Decision no: 37732058-514.10).

Informed Consent: Written informed consent was obtained from all participants included in the study.

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