ORIGINAL PAPER

Submitted: 28.12.2022
Accepted: 11.03.2023
Early publication date: 26.04.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0026
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 2/2023

Galanin-like peptide and its correlation with androgen levels in patients with polycystic ovary syndrome

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Abstract

Introduction: We aimed to investigate serum galanin-like peptide (GALP) levels and their correlation with hormonal and metabolic parameters in patients with polycystic ovary syndrome (PCOS).

Material and methods: The study included 48 women (age range, 18–44 years) with a diagnosis of PCOS, and a control group that included 40 healthy females (age range, 18–46 years). Waist circumference, body mass index (BMI), and Ferriman-Gallwey score were evaluated and plasma glucose, lipid profile, oestradiol, progesterone, total testosterone, prolactin, insulin, dehydroepiandrosterone sulphate (DHEA-S), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), 25-hydroxyvitamin D (25(OH)D), fibrinogen, d-dimer, C-reactive protein (CRP), and GALP levels were measured in all study subjects.

Results: Waist circumference ($p = 0.044$) and Ferriman-Gallwey score ($p = 0.002$) were significantly higher in patients with PCOS compared to the control group. Among the metabolic and hormonal parameters studied, only total testosterone was significantly higher in patients with PCOS ($p = 0.002$). Also, the serum 25(OH)D level was significantly lower in the PCOS group ($p = 0.001$). CRP, fibrinogen, and D-dimer levels were all similar between the 2 groups. Serum GALP level was significantly higher in PCOS patients ($p = 0.001$). GALP was negatively correlated with 25(OH)D ($r = –0.401$, $p = 0.002$) and positively correlated with total testosterone values ($r = 0.265$, $p = 0.024$). Multiple regression analysis revealed that both total testosterone and 25(OH)D significantly contributed to GALP levels.

Conclusions: Our study is the first in the literature to evaluate serum GALP levels in patients with PCOS. Increased GALP levels in PCOS and its association with total testosterone levels might show that GALP can act as an intermediary in increased GnRH-mediated LH release, which is one of the underlying pathogenetic mechanism of PCOS. **(Endokrynol Pol 2023; 74 (2): 197–202)**

Key words: *galanin-like peptide; polycystic ovary syndrome; androgen levels; vitamin 25(OH)D*

Introduction

Polycystic ovary syndrome (PCOS) is a multifactorial condition, characterized by clinical or biochemical hyperandrogenism, ovarian dysfunction, and/or polycystic ovaries. Insulin resistance and central adiposity are often present, and women with PCOS are at higher risk for metabolic comorbidities such as dyslipidaemia, prediabetes, and type 2 diabetes [1–3]. Also, PCOS is associated with important reproductive comorbidities including infertility, irregular uterine bleeding, and increased pregnancy loss during the reproductive years. Due to the long-term unopposed oestrogen stimulation, these patients are prone to increased risk of endometrial cancer [4].

The exact aetiology of PCOS is not completely understood; it is considered a heterogenous disorder with multifactorial causes. Possible underlying causes of PCOS include the increased pulse frequency of gonadotrophin-releasing hormone (GnRH), leading to increased amplitude and frequency of luteinizing hormone (LH) secretion and stimulation of theca cells to produce androgen; decreased levels of follicle-stimulating hormone (FSH) relative to LH, insulin resistance in adipose tissue and skeletal muscles via a post-receptor defect (abnormal phosphorylation of tyrosine kinase), pancreatic beta-cell dysfunction, and obesity [4–6].

The elevated LH pulse frequency, increased hypothalamic kisspeptin levels, and increased activity of the GnRH neural network are among the aforementioned proposed underlying pathologies in PCOS [7]. This elevated hypothalamic GnRH output is likely to stem in part from a change of the metabolic state of the body. Neuropeptide Y (NPY), ghrelin (GHRL), galanin (GAL), and galanin-like peptide (GALP) have been proposed as candidates conveying metabolic status to the GnRH neuronal network in animals [8]. GALP is a recently identified hypothalamic peptide, localized

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in the arcuate nucleus (ARC), which seems to stimulate hypothalamus and GT1-7 cells (a GnRH neuron cell line) to release GnRH [9]. GALP is a neuropeptide involved in the regulation of food intake behaviour, body weight, and energy metabolism.

Because the pathogenesis of PCOS includes neuroendocrine abnormalities, we aimed to investigate serum GALP levels (with neural and metabolic functions) in patients with PCOS. We also aimed to evaluate the correlation of serum GALP levels with hormonal profile as well as metabolic parameters, vitamin D, and serum biomarkers of cardiovascular disease risk such as CRP, fibrinogen, and D-dimer in patients with and without PCOS. To date, there has been no study in the literature about GALP levels in patients with PCOS.

Material and methods

This cross-sectional, case-control study included 48women (aged 18–44 years) with a diagnosis of PCOS defined in accordance with the Rotterdam criteria [6]. The control group consisted of 40 healthy females (aged 18–49 years). The study was carried out between January 2022 and August 2022 at the Department of Endocrinology and Metabolism Disease at Tepecik Research and Training Hospital, University of Health Sciences. Women with chronic diseases such as overt hypothyroidism or hyperthyroidism, kidney or liver failure, hyperprolactinaemia, late-onset adrenal hyperplasia, diabetes, hypertension, or Cushing's syndrome as well as women taking thyroid hormones or anti-thyroid medication were excluded from the study. Additionally, women who had been receiving hormonal therapy, including oral contraceptive pills or steroids (glucocorticoids), within 6 months were excluded. All participants provided written informed consent to participate, as approved by the Ethics Committee of the Izmir Tepecik Training and Research Hospital, University of Health Sciences, (Date: 15 November 2021; Meeting Number: 11; Decision: 9) and in accordance with the Declaration of Helsinki.

Body mass index (BMI) and waist circumference were measured in all study subjects. Hirsutism was evaluated based on the Ferriman-Gallwey scoring index over 9 body areas [10]. Fasting venous blood was obtained from all study subjects to evaluate biochemical parameters including plasma glucose and lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)] as well as hormones including oestradiol, progesterone, total testosterone, prolactin, insulin, dehydroepiandrosterone sulphate (DHEA-S), FSH, LH, free triiodothyronine (FT3), free thyroxine (FT4), TSH, and anti-thyroid peroxidase (anti-TPO) antibodies. Serum samples were aliquoted, frozen, and stored at –80ºC for GALP analysis. The blood samples were obtained during the third to ninth days of the menstrual cycle or 60 days after the last menstrual period. Pelvic ultrasonography was performed for all participants. Laboratory assessments glucose, TG, TC, and HDL-C levels were measured by enzymatic methods using an AU5800 autoanalyzer (Beckman Coulter Inc., CA, United states). LDL-C was calculated by the Friedewald equation. Insulin, FSH, LH, TC, oestradiol, progesterone, prolactin, and DHEAS levels were analysed by chemiluminescence assay method using a DxI immunoanalyser (Beckman Coulter Inc., CA, United States). FT3, FT4, TSH, and anti-TPO levels were measured by chemiluminescent method using an Immulite 2000 autoanalyzer (Immulite XPi, Siemens, Germany). Glycated haemoglobin (HbA_{1c}) was measured using boronate affinity high-performance liquid chromatography method (Trinity Biotech, Kansas City, MO, United States). Chemiluminescence immunoassay method was used for detection of serum 25-hydroxyvitamin D (25(OH)D) (Siemens Advia Centaur XP, Mannheim, Germany). Fibrinogen and D-dimer levels were analysed with a Sysmex CS-2500-analyzer (Sysmex Corporation, Kobe, Japan). GALP was measured using the enzyme-linked immunosorbent assay (ELISA) method with commercially available kits (sensitivity: 1.4 pg/mL; assay range: 4.69–300 pg/mL).

Homeostasis model assessment (HOMA) was used to measure insulin sensitivity with the equation:

$$\textit{Fasting insulin (mU/L)} \times \textit{glucose (mmol/L)}/22.5$$

Insulin resistance is determined by having a HOMA value > 2.7 [11].

Results

The clinical characteristics of the patient and control groups are shown in Table 1. No significant differences were observed between the 2 groups according to age and BMI. Waist circumference (90.72 ± 15.36 cm *vs*. 84.33 ± 12.21 cm, p = 0.044) and Ferriman-Gallwey score (8.95 ± 2.94 *vs*. 7.10 ± 4.11, p = 0.002) were significantly higher in patients with PCOS compared to the control group.

Fasting blood glucose and HbA_{1c} values, lipid parameters, free T3, free T4, TSH, and anti-TPO were similar between the 2 groups (Tab. 2). Likewise, fasting insulin levels and HOMA values were not significantly different between the 2 groups. Serum 25(OH)D levels (9.62 ± 6.84 ng/mL *vs*. 16.73 ± 9.87 ng/mL, p = 0.001) were significantly lower in patients with PCOS with respect to the control group.

While FSH, LH, oestradiol, progesterone, prolactin, and DHEAS levels were similar, total testosterone was significantly higher in patients with PCOS. The total testosterone level was 67.68 ± 34.68 ng/dL in the patient

Table 1. *Clinical characteristics of the study population*

	Group 1 (patients with PCOS) (n=48)	Group 2 (control group) (n=40)	
Age	29.94 ± 6.18	31.32 ± 11.06	0.088
BMI [kg/m^2]	27.77 ± 6.65	28.27 ± 7.22	0.573
Waist circumference [cm]	90.72 ± 15.36	84.33 ± 12.21	0.044*
Ferriman-Gallway index	8.95 ± 2.94	7.10 ± 4.11	0.002*

*Statistically significant, p-value < 0.05. BMI — body mass index

Table 2. *Laboratory parameters of the study population*

	Group 1 (patients with PCOS) (n = 48)	Group 2 (control group) (n = 40)	p-value
Fasting glucose [mg/dL]	92.78 ± 16.71	99.92 ±17.12	0.321
Insulin [μU/mL]	12.79 ± 11.38	14.62 ± 11.76	0.640
HOMA	3.37 ± 2.01	3..97 ± 2.64	0.638
HbA_{1c} [%]	5.46 ± 0.85	5.71 ± 1.16	0.338
LDL-C [mg/dL]	104.31 ± 27.02	116.55 ± 31.22	0.081
HDL-C [mg/dL]	55.81 ± 12.45	52.36 ± 10.02	0.195
TC [mg/dL]	183.30 ± 33.59	186.07 ± 37.56	0.489
TG [mg/dL]	114.72 ± 72.58	106.33 ± 52.66	0.596
FSH [mIU/mL]	3.17 ± 1.15	4.17 ± 3.46	0.134
LH [mIU/mL]	5.97 ± 2.11	4.53 ± 2.91	0.272
Oestradiol [pg/mL]	52.24 ± 18.07	49.38 ± 19.21	0.617
Total testosterone [ng/dL]	67.68 ± 34.68	47.87 ± 19.32	0.002*
Progesterone [ng/mL]	1.17 ± 1.73	1.36 ± 1.18	0.134
Prolactin [ng/mL]	16.00 ± 9.16	22.47 ± 19.10	0.084
DHEA-S [μg/dL]	287.48 ± 127.82	252.56 ± 111.08	0.150
25[OH]D [ng/mL]	10.94 ± 8.68	16.39 ± 9.95	0.031*
FT3 [pg/mL]	3.41 ± 0.63	3.40 ± 0.35	0.958
FT4 [ng/mL]	0.89 ± 0.14	0.88 ± 0.22	0.960
TSH [uIU/mL]	2.04 ± 1.08	2.20 ± 1.38	0.607
Anti-TPO [IU/mL]	58.92 ± 35.87	49.29 ± 28.54	0.152
CRP [mg/L]	3.57 ± 3.72	3.90 ± 4.92	0.796
Fibrinogen [mg/dL]	332.39 ± 99.08	325.60 ± 66.70	0.738
D-dimer [ng/mL]	320.00 ± 169.09	324.88 ± 197.23	0.918
GALP [ng/mL]	24.84 ± 12.08	1.54 ± 1.21	0.001*

*Statistically significant. p-value < 0.05. HOMA — homeostasis model assessment; HbA_{1c} — glycated haemoglobin; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TC — total cholesterol; TG — triglycerides; FSH — follicle-stimulating hormone; LH — luteinizing hormone; DHEA-S — dehydroepiandrosterone sulphate; 25[OH]D — 25-hydroxyvitamin D; FT3 — free triiodothyronine; FT4 — free thyroxine; TSH — thyroid-stimulating hormone; anti-TPO — anti-thyroperoxidase antibodies; CRP — C-reactive protein; GALP — galanin-like peptide

group and 47.87 ± 19.32 ng/dL in the control group (p = 0.002).

CRP, fibrinogen, and D-dimer levels were all similar between the 2 groups.

Serum GALP level was significantly higher in PCOS patients (24.84 ± 12.08 ng/mL) than in controls (1.54 ± 1.21 ng/mL) (p = 0.001). Also, a receiver operating characteristic (ROC) curve analysis demonstrated that, when taking the cut-off value as > 5.83, the sensitivity of GALP was 69.7% and specificity 100% in identifying PCOS [area under the curve (AUC) 0.892] (p = 0.001) (Fig. 1).

Correlation analyses between GALP and all the other parameters studied were performed. GALP was negatively correlated with 25(OH)D (r = –0.401, p = 0.002) and positively correlated with total testosterone values (r = 0.265, p = 0.024) (Fig. 2). No correlation was observed between GALP and other parameters. Multiple regression analysis revealed that although both total testosterone and 25(OH)D levels significantly contributed to GALP levels, the contribution of 25(OH)D was greater (beta = –0.379, p = 0.003) (Tab. 3).

Discussion

PCOS is the one of the most common endocrinopathies in reproductive-aged women, and it is characterized by hyperandrogenism, menstrual disturbances, and polycystic ovarian morphology on ultrasound. Apart from reproductive morbidities, it is also frequently associated with metabolic dysfunction—including type 2 diabetes—and cardiovascular disease [12]. Although the exact aetiology remains unidentified, several pathogenetic mechanisms are suggested: genetic factors, increased GnRH pulse frequency and LH pulsatility, and relatively decreased FSH levels, hyperinsulinaemia, and insulin resistance [4, 13]. Increased LH pulsatility promotes increased androgen production

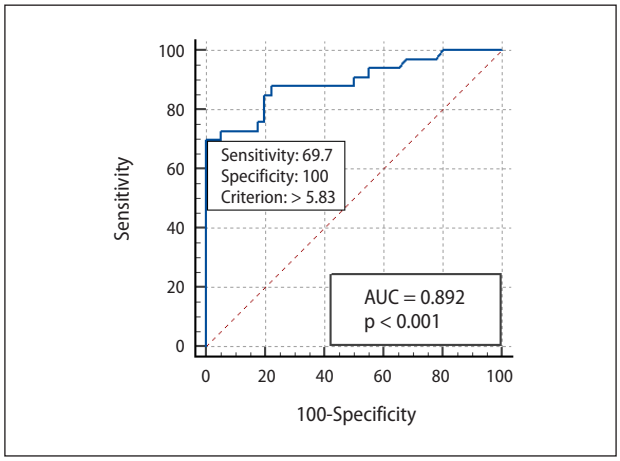

Figure 1. *Receiver operating characteristic (ROC) analysis showed an area under the curve (AUC) of 0.892 in identifying polycystic ovary syndrome (PCOS) patients. GALP — galanin-like peptide*

from theca cells, and decreased FSH levels lead to impaired aromatisation to oestrogens, follicle maturation, and ovulation. Insulin resistance observed in PCOS is caused by abnormal phosphorylation of the insulin receptor by intracellular serine kinases in adipose tissue and skeletal muscle, which contributes to increased 17,20-lyase activity of P450c17 in ovarian theca cells and up-regulation of testosterone formation via increased *HSD17B5* gene expression in adipose tissue [14, 15]. Hyperinsulinaemia enhances LH stimulation of ovarian androgen production by up-regulating LH-binding sites and increasing androgen production at the level of cytochrome P450c17 [14, 16].

In addition to playing a significant role in calcium homeostasis and bone metabolism, vitamin D was suggested to play a role in the pathogenesis of PCOS. Vitamin D deficiency was found to be a contributing factor for obesity, insulin resistance, and metabolic syndrome, which are usually observed in PCOS and are associated with ovulatory dysfunction [17–19]. Also, correction of vitamin D deficiency was reported to increase soluble receptor of advanced glycation end-products (sRAGE) and decrease elevated anti-Mullerian hormone (AMH). sRAGE binds to circulating AGES and inhibits its inflammatory deleterious effects [17, 20]. Because LH is known to increase AMH production in granulosa cells

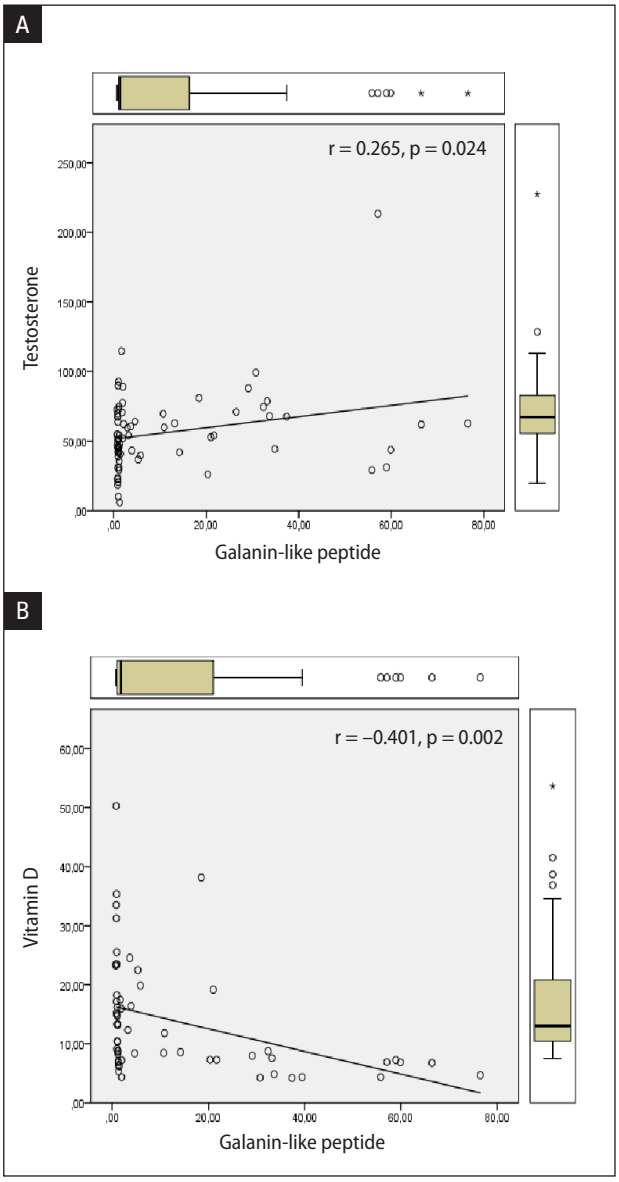

Figure 2. *Correlation between galanin-like peptide (GALP) and total testosterone* (**A**) *and 25-hydroxyvitamin D (25(OH)D)* (**B**)

of PCOS ovaries, a decrease in AMH levels associated with a decrease in LH levels leads to a decrease in intrafollicular androgens and an increase in follicular sensitivity to FSH, which all improve the ovulatory process [21]. There are numerous studies about vitamin D levels in PCOS. While some of them did not reveal

Table 3. ***Evaluation of the effect of total testosterone and 25-hydroxyvitamin D (25(OH)D) on galanin-like peptide (GALP) using multiple regression analysis ($R^2 = 0.577$)***

Variables	β	95% CI (Min — Max)	p
Total testosterone	0.256	0.009 — 0.325	0.038*
25(OH)D	–0.379	–1.287 — –0.284	0.003*

Multiple regression analysis was used. β: Unstandardized regression coefficient. *p-value < 0.05 was considered significant. CI — confidence interval

vitamin D deficiency, the majority of them showed lower vitamin D levels in patients with PCOS [22–25]. In some of the studies, serum 25(OH)D concentrations were negatively correlated with fasting glucose, insulin, triglycerides, CRP, free androgen index, and DHEAS. Consistent with previous findings, in our study we found significantly lower serum 25(OH)D levels in patients with PCOS compared to controls. However, we found no correlation between serum 25(OH)D and metabolic and hormonal parameters.

Cardiovascular disease risk biomarkers such as CRP and coagulation parameters including fibrinogen and D-dimer were evaluated in previous studies [26–28]. While some of the studies found similar levels in both PCOS and control groups [26], others found elevated values in PCOS [27, 28]. In our study, we found similar values in both the PCOS and control groups regarding CRP, fibrinogen, and d-dimer. This can be explained by the fact that in previous studies the hypercoagulable state in PCOS was attributed to increased BMI, insulin resistance, and inflammation and in our study, BMI and insulin values were similar in both groups.

GALP was discovered in 1999 in the porcine hypothalamus, and it shares a sequence homology to galanin. It was found that it could bind and activate all 3 receptor subtypes of galanin (GalR1, GalR2, GalR3). In experimental rat studies, cells producing GALP m-RNA and protein were found in the arcuate nucleus, median eminence, infundibular stalk, and posterior pituitary [26, 27]. After intracerebroventricular (ICV) administration in rats, GALP increased C fos expression in NPY-containing neurons in DMH and stimulated food intake over 2 hours [26, 28]. However, GALP was shown to have a bidirectional effect on feeding, in that after 24 hours of ICV GALP administration, a decrease in food intake and body weight and an increase in body temperature were reported in rats and mice [26, 29]. Subsequently, experimental studies demonstrated that GALP-immunoreactive (GALP-ir) fibres were in close contact with GnRH cell bodies in the diagonal band of Broca and medial preoptic area. In rats, central administration of GALP stimulated GnRH-mediated LH secretion [26, 30–34]. Since GALP was found to be involved in increased GnRH mediated LH secretion, it might function as an intermediary in increased GnRH pulse frequency and LH pulsatility in PCOS. Our study is the first in the literature to investigate serum GALP levels in patients with PCOS. We found significantly higher levels of GALP in PCOS patients.

In our study, we found significant positive correlation between between GALP and total testosterone values. This may be explained by the fact that GALP stimulation of increased GnRH-mediated LH secretion might lead to increased androgen production in theca cells of the ovary. We also found a significant negative correlation between serum 25(OH)D and GALP levels. Because vitamin D receptors were also found in the hypothalamus in experimental studies, and vitamin D supplementation was found to decrease intrafollicular androgens and increase follicular sensitivity to FSH, it can be hypothesized that there might be an interconnection between vitamin D and GALP. However, there is no evidence supporting this hypothesis in the literature.

Conclusions

In conclusion, PCOS is a complex disorder that includes insulin resistance or LH excess. However, the exact pathogenesis is not still revealed. Our study is the first in the literature to evaluate serum GALP levels in patients with PCOS. Increased GALP levels in PCOS and its association with total testosterone levels might show that GALP can act as an intermediary in increased GnRH-mediated LH release, which is one of the underlying pathogenetic mechanism of PCOS. Because we cannot confirm causality due to the cross-sectional design of the study, further studies should be performed about the possible role of GALP in PCOS.

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