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FASTING GLP-1 LEVELS IN WOMEN WITH PCOS AND CAH

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Abstract. Background: *Polycystic ovarian syndrome (PCOS) is the most prevalent condition associated with increased androgens, but some rare diseases, e.g., congenital adrenal hyperplasia (CAH), should also be considered in the differential diagnosis of hyperandrogenemia. The potential role of incretin hormones has been thoroughly studied in different metabolic conditions, but data about women with PCOS and CAH are insufficient.* ***Aims:*** *Therefore, the present study aims to investigate the fasting GLP-1 levels in women with PCOS and CAH compared to healthy women and to establish the possible associations with the ovarian and adrenal androgens, obesity, and hyperinsulinemia in these conditions.* ***Methods:*** *Fasting GLP-1 levels were measured in 47 women with PCOS, 11 CAH patients, and 26 healthy volunteers. The associations between the GLP-1, metabolic, and hormonal characteristics in the investigated groups have been studied.* ***Results:*** *GLP-1 levels did not differ between healthy women and patients with PCOS but were significantly higher in CAH patients ($p = 0.025$). CAH patients were similarly obese as PCOS women, but they showed increased testosterone ($p = 0.009$), 11-ketotestosterone ($p = 0.046$), 17-OH-progesterone ($p < 0.001$), and insulin levels ($p = 0.043$), and lower luteinizing hormone ($p = 0.002$) and dehydroepiandrosterone-sulfate levels ($p = 0.004$). In the PCOS group, the fasting GLP-1 levels were positively related to BMI ($r = +0.327$; $p = 0.024$) but not to other hormonal or metabolic indices.* ***Conclusions:*** *Our results show increased fasting GLP-1 and insulin levels in CAH individuals compared with PCOS patients but similar fasting GLP-1 levels in PCOS and healthy women. Further studies are necessary to clarify the incretin effects and the role of incretin-based therapy in women with different hyperandrogenic states and increased metabolic risk.*

Key words: *CAH, PCOS, GLP-1, hyperandrogenism, incretin*

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INTRODUCTION

Hyperandrogenic states are common in young women; for instance, polycystic ovarian syndrome (PCOS) might affect between 5% and 15% of them, depending on the criteria used [1]. On the other hand, rare diseases, such as different types of congenital adrenal hyperplasia (CAH), are also associated with increased androgens, and should be considered in the differential diagnosis of PCOS [2, 3]. Hyperandrogenic states are closely associated with obesity and subsequent metabolic abnormalities. The prevalence of obesity in PCOS patients might reach 80%, while about 26% of overweight and obese wom-

en suffer from the syndrome [4, 5]. On the other hand, CAH female patients have shown more than ten times higher risk of obesity and four times higher risk of diabetes mellitus than the general population [6]. From the clinical point of view, the treatment of obesity is much more difficult in these hyperandrogenic groups than in other obese female patients.

In the last 30 years, studies on the essential physiological role of incretins in the metabolism have become a fundament for the development of successful obesity treatment [7]. The most well-known incretin is a glucagon-like peptide 1 (GLP-1) produced in the pancreatic α-cells and the L-cells of the intestinal mucosa [8]. GLP-1 exerts a potent insulinotropic activity, but it also has other pleiotropic effects, including but not limited to suppression of glucagon secretion, gastric emptying delay, increased feeling of satiety, decreased body weight, cardio- and neuroprotection [8, 9]. However, the role of endogenous GLP-1 secretion in women with hyperandrogenic conditions prone to the development of obesity and carbohydrate disorders is poorly investigated. Only a few studies have determined the GLP-1 levels in PCOS with conflicting results [10, 11]. On the other hand, to date, incretin levels have not been studied in women with CAH despite the high percentage of metabolic disturbances in the same group. The accumulation of more scientific data about the potential role of GLP-1 and other satiety hormones in women with hyperandrogenic conditions might help find the most appropriate therapy for obesity in these conditions.

Therefore, the present study aims to investigate the fasting GLP-1 levels in women with PCOS and CAH compared to healthy women and to establish the possible associations with the ovarian and adrenal androgens and hyperinsulinemia in these conditions.

MATERIALS AND METHODS

Participants

A total of 84 individuals of reproductive age (18-41 years) participated in the study. PCOS, according to the ESHRE criteria [2], was diagnosed in 47 women, while 11 female patients had congenital adrenal hyperplasia (classic and non-classic form) [3]. Other causes for the hyperandrogenic symptoms had been excluded in all patients, as suggested in current guidelines [2]. Additionally, 26 healthy women with regular menstruation and no signs of hirsutism volunteered for the study.

The patients and the control group underwent complete anthropometric and biochemical assessment. Height, weight, body mass index (BMI), and the presence of hirsutism and acne were described in all women. All CAH patients were on corticosteroid treatment (2.5 to 10 mg prednisolone equivalent) except two newly diagnosed patients, but most CAH individuals showed poor adherence to treatment and strongly increased 17-OH progesterone levels. No one from the patients with PCOS or the control group received glucocorticoids or other hormonal medication; however, 14 PCOS patients were on long-term metformin treatment. In all women, blood samples for hormonal investigations were collected as previously described [12]. The local ethics committee approved the study, and all participants gave written informed consent.

The study protocol and hormonal investigations

Biochemical investigations, e.g., fasting glucose, high-density lipoprotein cholesterol levels (HDL-ch), low-density lipoprotein cholesterol levels (LDL-ch), triglycerides (TG), total cholesterol (TC), liver enzymes were measured enzymatically by an automatic analyzer (Cobas Mira Plus; Hoffmann La Roche). Hormonal parameters included immunoreactive insulin (IRI), total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone-sulfate (DHEAS), 17-OH progesterone (17OHP), measured through commercially available RIA kits as described previously [12]. The homeostasis model assessment of insulin resistance index (HOMA-IR) was also calculated according to the well-known equation [13].

Blood samples for glucagon-like peptide-1 and 11-ketotestosterone (11KT) were stored at -80º until analyses. GLP-1 levels were determined by the ELISA method (DRG International, Inc). 11KT levels were measured also by ELISA method (MBS7213123). One patient with CAH was on GLP-1-agonist treatment so her GLP-1 level was not measured.

Statistical analysis

Most parameters deviated from the normal distribution by a Kolmogorov–Smirnov test. Therefore, non-parametric tests, e.g., Mann-Whitney and Kruskal-Wallis tests, were used to establish differences between two or three groups. The results were presented as a median ± interquartile range. Associations between variables were estimated through a two-tailed Spearman's correlation analysis. A p-level < 0.05 was considered statistically significant. The data were analyzed using MedCalc® Statistical Software version 20.110 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

RESULTS

Our data showed significant differences in metabolic and androgen indices between healthy women,

patients with PCOS, and those with CAH (Table 1). Patients with PCOS were younger than controls, but they showed worse lipid profiles, higher insulin resistance indices, and increased liver enzymes and androgens compared to controls, as expected. Patients with CAH were significantly shorter than patients with PCOS but with similar BMI. CAH patients also had similar lipid parameters but increased testosterone, 11KT, 17-OHP, and insulin levels compared to PCOS women. Additionally, CAH patients showed lower DHEAS and LH levels than PCOS women, while FSH concentrations were similar.

GLP-1 levels did not differ between healthy women and patients with PCOS, but they were significantly higher in CAH patients (Figure 1).

Table 1. Characteristics of the investigated patients and controls. PCOS – polycystic ovarian syndrome; CAH – congenital adrenal hyperplasia; * – Kruskal-Wallis test. ^^ – Man-Whitney test (PCOS vs. CAH)

	Healthy women (n = 26)	PCOS (n = 47)	CAH (n = 11)	p^^	p*
Age (years)	29.00 (25.00-31.00)	24.00 (21.25-27.00)	31.00 (22.50-36.50)	0.052	< 0.001
Height (cm)	168.50 (163.00-173.00)	168.00 (164.00-170.75)	150.00 149.25-151.75	< 0.001	< 0.001
BMI (kg/m^2)	20.67 (19.00-22.10)	23.90 (19.92-26.87)	24.14 (20.87-32.34)	0.525	0.063
Cholesterol (mmol/l)	3.92 (3.68-4.46)	4.46 (3.85-5.05)	4.75 (4.11-5.43)	0.331	0.086
HDL-cholesterol (mmol/l)	1.58 (1.33-1.76)	1.48 (1.24-1.87)	1.57 (1.20-1.84)	0.847	0.977
LDL-cholesterol (mmol/l)	2.55 (2.08-2.79)	2.68 (2.43-3.17)	2.92 (2.54-3.42)	0.357	0.198
Triglycerides (mmol/l)	0.46 (0.38-0.64)	0.71 (0.53-0.97)	0.97 (0.65-1.29)	0.159	< 0.001
Glucose (mmol/l)	4.95 (4.70-5.15)	4.91 (4.51-5.10)	5.04 (4.75-5.19)	0.297	0.535
Insulin (µmol/l)	4.85 (3.40-6.50)	8.40 (6.15-12.10)	16.50 (10.07-24.51)	0.043	< 0.001
HOMA-IR	1.13 (0.75-1.45)	1.92 (1.25-2.85)	2.93 (2.25-6.22)	0.058	< 0.001
ALAT (IU/l)	9.90 (7.70-11.60)	13.00 (11.00-19.00)	12.00 (10.00-19.25)	0.525	0.005
ASAT (IU/l)	14.35 (13.60-16.30)	16.00 (14.00-18.92)	14.00 (10.75-16.75)	0.073	0.067
GGT (IU/l)	10.30 (8.80-12.00)	13.00 (11.00-16.00)	15.00 (11.00-21.25)	0.528	0.009
Testosterone (nmol/l)	1.00 (0.90-1.52)	2.20 (1.50-3.55)	3.60 (2.92-8.10)	0.009	< 0.001
DHEAS (µmol/l)	7.60 (6.10-10.60)	8.65 (7.10-12.35)	1.37 (1.00-6.92)	0.004	0.006
LH (IU/l)	3.35 (2.30-4.50)	5.30 (3.65-7.90)	2.05 (1.20-3.97)	0.002	< 0.001
FSH (IU/l)	7.05 (5.60-7.80)	6.30 (4.82- 7.85)	5.60 (3.60-7.40)	0.564	0.336
17-OH- progesterone (nmol/l)	2.90 (2.12-3.85)	4.20 (3.22-5.67)	102.50 (12.50-902.60)	< 0.001	< 0.001
11-keto-testosterone (pg/ml)	236.80 (213.20- 257.37)	234.40 (203.40-258.02)	263.50 (229.05-287.67)	0.046	0.089

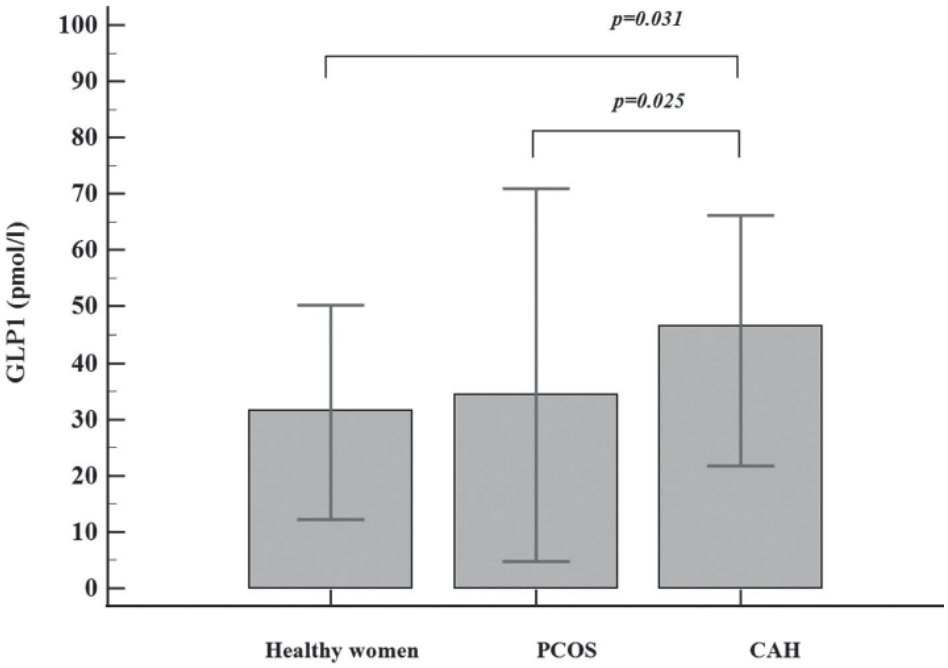

Fig. 1. Different GLP-1 levels in women with PCOS and CAH compared to healthy women

GLP-1 levels were similar in PCOS women with different PCOS phenotypes and did not depend on the presence of hirsutism, acne, anovulation, or metformin treatment ($p > 0.05$ for all). GLP-1 levels were significantly higher in the PCOS women with obesity (BMI ≥ 30) than in the lean and overweight PCOS patients (48.06 vs. 33.05 pmol/l, $p = 0.021$). In the PCOS group, the fasting GLP1 levels were positively related to BMI ($r = +0.327$; $p = 0.024$), while 11KT levels were positively related to 17-OHP ($r = +0.307$; $p = 0.045$), but not with other metabolic or hormonal parameters. Such associations were not found in healthy women. GLP1 levels did not correlate with metabolic characteristics, prednisolone equivalent dose, or androgens in CAH patients, but the small number of women preclude drawing definitive conclusions.

DISCUSSION

Our results show similar fasting GLP-1 levels in patients with PCOS and healthy young women. Thus, they support several other studies that have not observed differences in fasting GLP-1 concentrations between PCOS and healthy individuals [14-17]. Conversely, Lin et al. showed increased fasting and early postprandial GLP-1 levels in Chinese PCOS patients compared to controls, irrespective of weight [10]. However, both fasting and post-meal GLP-1 concentrations were significantly decreased in Turkish PCOS women compared to healthy individuals [11]. GLP-1 levels were also decreased in obese, but not lean Greek PCOS patients [18], and the presence of prediabetes was related to a further decrease in GLP-1 levels of obese PCOS patients [19]. The PCOS heterogeneity, as well as ethnic and methodological differences, could explain the contradictory results.

Our data did not show any changes in GLP-1 fasting levels based on the PCOS phenotype or the presence of hirsutism, acne, and anovulation. Additionally, the GLP-1 levels did not differ between the PCOS patients with and without metformin treatment. Other studies have found a significant increase in fasting GLP-1 levels after metformin treatment, especially in lean PCOS women [17, 20]. However, Glintborg et al. did not find changes in the overall GLP-1 secretion after one year of metformin treatment, suggesting that metformin effects on GLP-1 secretion might depend on the duration of treatment [17].

In our study, GLP-1 levels in obese PCOS women were slightly increased compared to the lean patients and correlated positively with the BMI. Conversely, most authors have not found differences in GLP-1 levels of PCOS women with different body weight [10, 16]. On the other hand, increased GLP-1 levels associated with HOMA-IR have been found in obese children and adolescents compared to healthy peers [21]. However, in obese and lean adults, similar fasting GLP-1 levels have been described in most, though not all, studies [22-24]. The increase of GLP-1 might be a compensatory reaction in young obese individuals targeting appetite suppression and body weight stabilization [25].

On the other hand, the GLP-1 elevation in a subpopulation of obese PCOS patients might result from resistance to GLP-1 effects. Incretin effects in obese patients decrease with the BMI progress, and GLP-1 receptor expression is negatively associated with weight gain and insulin increase [26, 27]. Moreover, pharmacological GLP-1 treatment, which could overcome the possible resistance, exerts multiple beneficial effects in PCOS extending beyond weight loss, e.g., gonadotropin secretion regulation and influence on follicular development [reviewed by 28]. Further studies are needed to clarify the pathophysiological significance of endogenous GLP-1 decrease and/or GLP-1 resistance for the metabolic and reproductive disturbances in PCOS women.

Our data show increased fasting GLP-1 levels in CAH compared to PCOS patients despite the similar age and BMI. To the best of our knowledge, this is the first study comparing the incretin concentrations in both conditions, though the small number of CAH individuals is a serious limitation. Patients with CAH showed increased insulin, testosterone, 11-ketotestosterone, and 17-OH progesterone levels compared to PCOS patients but lower LH and DHEAS concentrations. Other authors have also found increased 17-OH progesterone and lower LH to FSH ratio in patients with CAH compared to PCOS women, while data about DHEAS levels are contradictory [29, 30]. Obesity and insulin resistance are common findings in CAH patients [31], but studies providing a thorough comparison of metabolic parameters between CAH and PCOS individuals are currently lacking. The increased GLP-1 levels in patients with CAH might be associated with corticosteroid use, excessive hyperandrogenemia, or other unknown factors. However, several animal studies have shown a direct inhibitory effect of exogenous glucocorticoids on L-cells, leading to a decreased GLP-1 secretion [32, 33]. Moreover, the adherence of our CAH patients to glucocorticoid treatment was insufficient. Thus, the excessive hyperandrogenia leading to pronounced hyperinsulinemia and insulin resistance seems a more likely cause for GLP-1 secretion changes in CAH. Recently, a new 17-OH progesterone-dependent metabolic pathway in the liver has been described by Lu et al. [34]. The authors showed a selective activation of

the liver glucocorticoid receptor by 17-OH progesterone but not by other steroids, inducing increased hyperglycemia and insulin resistance [34]. Moreover, 17-OH progesterone levels were positively related to hyperinsulinemia and glucose abnormalities in CAH and non-CAH individuals [34]. Further studies are needed to explore the proper interactions between steroids, insulin, and GLP-1 secretion.

The 11-oxygenated C19 steroids are produced in the adrenal gland and peripheral tissues and might exert substantial androgenic effects in women, with 11KT being similarly active androgen as testosterone [35]. 11KT is significantly increased in patients with CAH, while in PCOS patients, it might be average or increased depending on the adrenal involvement in the hyperandrogenemia [36-39]. Usually, the 11-oxygenated C19 steroids are measured by the LC-MS/MS, which limits their use beyond scientific projects [35, 36, 39]. In our study, we found increased 11-ketotestosterone levels measured by ELISA in CAH compared to PCOS patients, but no differences between PCOS and healthy women. Further efforts should be made to provide new methods for 11-oxygenated C19 steroid measurements that could be widely used in the real clinical practice.

In conclusion, our results show increased fasting GLP-1 and insulin levels in CAH individuals compared with PCOS patients but similar fasting GLP-1 levels in PCOS and healthy women. Further studies are necessary to clarify the differences in metabolic regulation and incretin metabolism in different female hyperandrogenic states. Moreover, additional studies on GLP1-based treatment should be carried out in groups of patients with an exceptionally high risk of obesity and metabolic complications, such as individuals with CAH and PCOS.

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