ALINEA

NUTRITION

FEBRUARY 2022

www.alineanutrition.com

TABLE OF

CONTENTS

Polak AM, Krentowska A, Lebowski A, Buczyńska A, Adamski M, Adamska-Patruno E, Fiedorczuk J, Krętowski AJ, Kowalska I, Adamska A. The Association of Serum Levels of Leptin and Ghrelin with the Dietary Fat Content in Non-Obese Women with Polycystic Ovary Syndrome. Nutrients. 2020 Sep 10;12(9):2753.

What We Know, Think We Know, or Are Starting to Know

We know that Polycystic Ovary Syndrome [PCOS] has several phenotypes*, i.e., different presentations of the condition that vary based on underlying clinical characteristics. However, a common culprit present in most PCOS phenotypes is high by high androgens [male sex hormones, e.g., testosterone] [(1)].

The focus of the research to date has been the high-androgen PCOS phenotype characterised by higher bodyweight, insulin resistance, and central abdominal adiposity [(2)]. However, little to date is known about the "lean PCOS" phenotype [(3)]. This phenotype has been suggested to exhibit lower insulin resistance, although insulin resistance can still be present in lean women with PCOS [(3)].

This phenotype exhibits a higher ratio of luteinizing hormone [LH] and follicle-stimulating hormone [FSH], and also significantly increased levels of the hormone leptin [see ***Figure***, below] [(4,5)]. It is the latter hormone, leptin, that may be particularly interesting for lean women with PCOS. The balance of leptin to oestrogen may have a role in elevating the LH:FSH ratio [(3)].

While leptin may have a role in the hypothalamic-pituitary-adrenal-ovarian axis dysfunction that characterises PCOS, we also know that leptin has a primary role in the regulation of energy balance [(6)]. Leptin is secreted by adipose tissue cells ['adipocytes'], and provides a feedback signal to the hypothalamus in the brain regarding the status of the body' s energy reserves, in the form of stored fat [(6)]. It is known, for example, that dieting and loss of body results in declining leptin levels, while conversely with increasing body fat there is an increase in circulating leptin [(6)].

Ordinarily, low leptin levels would signal to the brain a need for increased energy intake, and is associated with increased hunger, appetite, and food-seeking behaviours, while high leptin levels would downregulate hunger and appetite and drive for food [(6)]. However, "leptin resistance" has been suggested to be present in obesity, i.e., despite elevated leptin levels, the hypothalamus does not respond to decrease hunger and appetite signalling [(6)]. So, what of the lean PCOS phenotype with elevated leptin levels? The present study investigated the associations between leptin, ghrelin, and clinical presentations of PCOS in lean women.

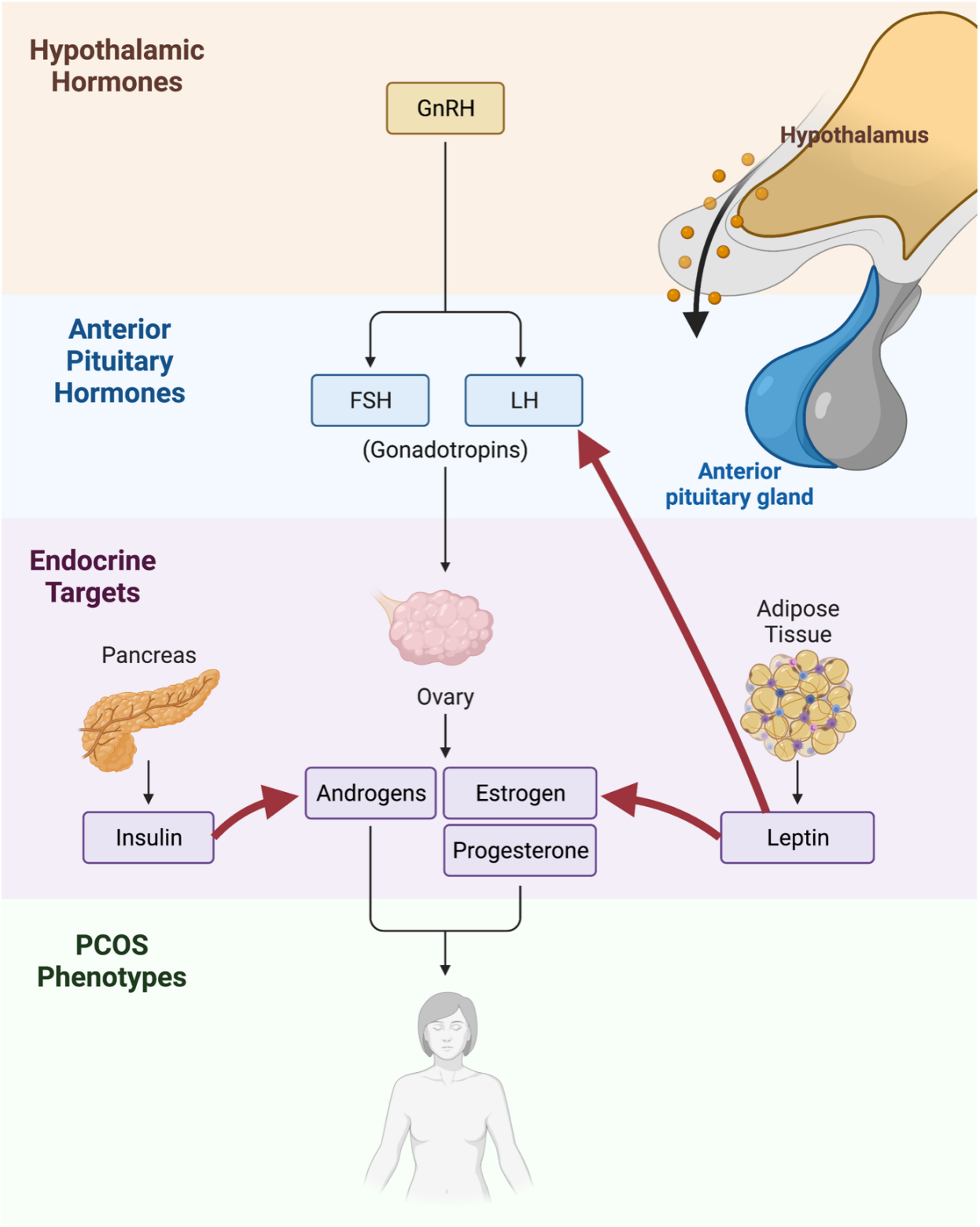

Figure *fillustrating the hypothalamic-pituitary-ovarian axis of hormonal secretion relevant to PCOS. GnRH = gonadotropin-releasing hormone. This is not exhaustive. It is meant to provide a basic overview, without overwhelm. For example, the adrenals have been left of this graph, despite the fact that in women the adrenals are a site of androgen production, and women with PCOS often have elevated physiological stress levels and production of DHEA. The main purpose of this illustration is to highlight the relationships between insulin, androgens, leptin and oestrogen, and the feedback of leptin to LH secretion, which may then have downstream influences on ovarian function.*

*Geek Box: Rotterdam Criteria

The 'Rotterdam criteria' established a consensus in 2003 for the pathophysiological characteristics of PCOS. However, PCOS has multiple clinical manifestations, and the criteria has expanded to emphasize four distinct phenotypes:

1. *High androgens with clinical anovulation;*
2. *High androgens with polycystic ovaries, but with ovulatory cycles;*
3. *Clinical anovulation with polycystic ovaries on ultrasound, but without high androgens*
4. *High androgens, clinical anovulation, and polycystic ovaries*

It is important not to treat these criteria as set in stone; there is constant, ongoing debate in the field. For example, the presence of cysts on ovaries may not be required at all if the wider hormonal milieu is present. Nevertheless, the Rotterdam criteria is a useful heuristic to think about the complex heterogeneity of PCOS, and the differences in pathophysiology between phenotypes.

The Study

The study was an observational study investigating the associations between leptin, ghrelin [a gut-derived hormone which stimulates hunger], and macronutrient intake in lean women with PCOS. PCOS was diagnosed according to the Rotterdam criteria, required the presence of two out of the following three: elevated androgens, oligo/anovulatory cycles, or polycystic ovaries.

39 women with PCOS were included and compared to 34 otherwise healthy women, matched for BMI. Mean BMI in the PCOS group was 23.5 and 22.9 in the control group.

Dietary intake was assessed using three 24hr diet diaries recorded on consecutive days, following which a questionnaire was completed regarding the type and amount of foods consumed on those days.

Blood samples were taken to measure leptin, ghrelin, LH, FSH, glucose and insulin, testosterone and oestrogen [oestradiol]. The study investigated associations between macronutrient intake, leptin and ghrelin, and also associations between glucose/insulin, other hormones, and leptin and ghrelin.

Results: In the baseline characteristics of both groups, there were no significant differences between groups in levels of oestradiol, FH, FSH, glucose or insulin, or circulating leptin levels. In women with PCOS, total testosterone was higher, while sex-hormone binding globulin [SHBG] was significantly lower [the higher the SHBG levels, the lower the circulating free testosterone]. The Free Androgen Index [FAI], a marker for free circulating testosterone levels, was significantly higher in women with PCOS.

- ***Macronutrients, Leptin & Ghrelin*:** In women with PCOS, total fat, saturated fat, and monounsaturated fat all correlated with higher leptin, while each of these and, additionally, polyunsaturated fats and long-chain polyunsaturated fatty acids [omega-3 and omega-6] all correlated with lower ghrelin levels. Protein also correlated with lower ghrelin levels. There were no significant associations between macronutrients and leptin/ghrelin in the control group.
- ***BMI, Leptin & Ghrelin: In women with PCOS*:** BMI was correlated with higher leptin, and correlated with lower ghrelin levels. In the control, BMI also positively correlated with [higher] leptin, but there was no correlation with ghrelin levels.
- ***Insulin Resistance, Leptin & Ghrelin*:** Insulin resistance was correlated with higher leptin levels, and lower ghrelin levels, in women with PCOS. Insulin resistance also correlated with total dietary fat intake.
- ***Androgens, Leptin & Ghrelin*:** In women with PCOS, the FAI correlated with higher leptin levels, and low SHBG correlated with leptin levels.
- ***Macronutrients & Androgens*:** In women with PCOS, saturated fat intake was correlated with higher FAI and lower SHBG, while total fat was also correlated with lower SHBG. There were no associations in the control group.

The Critical Breakdown

Pros: The study addressed an area with limited research, i.e., the lean PCOS phenotype [more under *Key Characteristic*, below]. Participants were screened according to the Rotterdam criteria, while other endocrine and metabolic disorders, including menstrual irregularities for reasons other than PCOS, were excluded. The blood samples were drawn standardised to time of the menstrual cycle in controls, and within three months of anovulatory cycles in women with PCOS. This would be expected to minimise differences in hormonal measures relative to cycle, particularly in the controls. The study analysed both diet and hormonal markers, and the relationship between hormonal markers.

Cons: The dietary assessment will always be crucial in any observational nutrition study, and the assessment in the present study is opaque. The paper states that a three-day diet diary was recorded, following which a questionnaire was completed based on the foods consumed in those three days, but no details on the questionnaire are provided. Consecutive days may also fail to capture within-person variation in dietary intake. Whenever a study uses a novel approach to dietary assessment, it should set out how it attempted to validate the assessment, which this study hasn't done. The study had a small sample size, and given the complex, multifactorial nature of PCOS, it should not be taken to be broadly representative of the lean PCOS phenotype. It would have been very useful to analysed correlations between oestradiol and leptin. And, always important to bear in mind the study was correlational.

Key Characteristic

The focal point of PCOS research tends to be the insulin-resistant, central adiposity phenotype. As a result, our current understanding of "lean PCOS", and the potentially distinct hormonal characteristics and pathways associated with this phenotype, is lacking. Thus, the focus on young, lean women with PCOS that were well matched for baseline characteristics is a strength of the present study, limitations aside.

Several characteristics did, however, separate the women with PCOS in the present study. First, women with PCOS exhibited insulin resistance, corroborating that insulin resistance can be present in lean women with PCOS [3]. Second, elevated androgens were present, particularly the combination of low SHBG and elevated Free Androgen Index [FAI], indicating that the combination of elevated androgens and insulin resistance is not exclusively related to central adiposity in PCOS [3,4]. Finally, there was no difference in LH/FSH levels between PCOS women and controls, while previous research has suggested that the "lean PCOS" phenotype is characterised by higher LH/FSH levels [3,7].

The present study highlights the complex, multifaceted presentations of PCOS, with clinical characteristics that may be similar [i.e., high androgens], but potentially influenced by different pathways, with different presentations.

Interesting Finding

Both insulin resistance and androgens were positively correlated with leptin levels. These may be indirectly related, but these relationships are interesting for the lean PCOS phenotype. We know that elevated insulin is associated with lower SHBG levels, which in turn increases the availability of circulating androgens [evident here in the elevated FAI levels] [3]. Other research in both obese and lean women with PCOS has found associations between insulin resistance and leptin, although the mechanism for this relationship remains unclear [4]. It has been suggested that circulating leptin itself may not necessarily reflect the action of leptin on ovarian function [4].

To what degree is the relationship between insulin and androgens, and leptin, distinct or related? We think of leptin mostly from the perspective of appetite regulation, but elevated leptin may arrest follicular development and may stimulate LH secretion independent of the stimulation of gonadotropin-releasing hormone [GnRH] by oestradiol [3]. These effects are relevant to the pathophysiology of PCOS. So, there is evidence of a relationship between leptin, androgens, oestrogens, and insulin, that appears to be important for PCOS, but whether these hormones exert regulatory effects on leptin is unclear. The complexity of PCOS never gets simpler.

Relevance

We' ve delved more into PCOS pathophysiology in the ***Key Characteristic*** and ***Interesting Finding***, above. Lower ghrelin would typically be considered a 'good thing' from the perspective of appetite regulation, while higher leptin would also, ordinarily, be considered a 'good thing' . However, we know that defective leptin signalling can occur, such that the regulatory effect on energy balance is lost [6].

The BMI associations need consideration because the BMI of the entire study group was ~23. This should probably not be interpreted as related to BMI *per se*, because we know that lean women with PCOS exhibit elevated leptin levels [4,5]. Thus, this finding may more simply be interpreted as consistent with lean women with PCOS also exhibiting higher leptin levels [although there was no statistically significant difference in leptin between groups, the absolute values were higher in the PCOS group].

But let' s come back to diet. There is a potential chain of biological plausibility at play in the relationship between dietary fat, saturated fat, insulin and androgens, that was apparent in the findings of the present study. Associations with dietary saturated fat and insulin resistance are well-established [8,9]. As is the relationship between insulin and androgens in women with PCOS [1]. To what extent is this a chain from saturated fat>insulin resistance>high androgens? This would be helpful to see tested more directly in an intervention. The finding in relation to ghrelin would be more consistent with prior knowledge, given the noted effect of dietary protein on satiety and high-protein diets on lowering ghrelin [10].

But we do have evidence of effects of dietary interventions on insulin and androgens in the "lean PCOS" phenotype. Jakubowicz *et al*. found that frontloading energy intake [980kcal breakfast, 640kcal lunch, 190kcal dinner] in lean women with PCOS led to a 50% decrease in free testosterone 105% increase in SHBG, while lowering postprandial insulin levels by 54% [11].

Application to Practice

The findings in relation to the role of specific macronutrients on leptin/ghrelin in women with PCOS are inconsistent, and it is difficult to make any particular recommendations at this present time. However, there are wider correlates of appetite regulation and evidence from diet which we have evidence for. First, in relation to ghrelin, it appears that high energy, protein and carb intake early in the day suppresses ghrelin and enhances satiety [10]. Second, as highlighted above, temporal distribution of energy could be a factor in lowering insulin responses, thereby having a positive effect on androgens [11]. Finally, it could be energy balance is an important consideration for the "lean PCOS" phenotype, as if there is a relationship between leptin, sex hormones, and ovarian function, restriction of energy may drive menstrual irregularities in lean woman with PCOS, by affecting leptin action and further aggravating the defective signalling in the hypothalamic-pituitary-ovarian axis.

References

1. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocrine Reviews. 2016;37(5):467–520.

2. Baptiste CG, Battista MC, Trottier A, Baillargeon JP. Insulin and hyperandrogenism in women with polycystic ovary syndrome. Journal of Steroid Biochemistry and Molecular Biology. 2010;122:42–52.

3. Rojas J, Chávez M, Olivar L, Rojas M, Morillo J, Mejías J, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. International Journal of Reproductive Medicine. 2014;2014:1–17.

4. Mendonça HC, Montenegro Junior RM, Foss MC, Silva de Sá MF, Ferriani RA. Positive correlation of serum leptin with estradiol levels in patients with polycystic ovary syndrome. Brazilian Journal of Medical and Biological Research. 2004;37(5):729–36.

5. Yildizhan R, Ilhan GA, Yildizhan B, Kolusari A, Adali E, Bugdayci G. Serum retinol-binding protein 4, leptin, and plasma asymmetric dimethylarginine levels in obese and nonobese young women with polycystic ovary syndrome. Fertility and Sterility. 2011;96(1):246–50.

6. Rosenbaum M, Leibel RL. Role of leptin in energy homeostasis in humans. Journal of Endocrinology. 2014;223(1):1–23.

7. Morales AJ, Laughlin GA, Bützow T, Maheshwari H, Baumann G, Yen SS. Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. The Journal of Clinical Endocrinology & Metabolism. 1996;81(8):2854–64.

8. Koska J, Ozias MK, Deer J, Kurtz J, Salbe AD, Harman SM, et al. A human model of dietary saturated fatty acid induced insulin resistance. Metabolism: Clinical and Experimental. 2016;65(11):1621–8.

9. Guess N, Perreault L, Kerege A, Strauss A, Bergman BC. Dietary fatty acids differentially associate with fasting versus 2-hour glucose homeostasis: Implications for the management of subtypes of prediabetes. PLoS ONE. 2016;11(3):1–15.

10. Jakubowicz D, Froy O, Wainstein J, Boaz M. Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults. Steroids. 2012;77(4):323–31.

11. Jakubowicz D, Barnea M, Wainstein J, Froy O. Effects of caloric intake timing on insulin resistance and hyperandrogenism in lean women with polycystic ovary syndrome. Clinical Science. 2013;125(9):423–32.