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Assessment of the Efficacy of Adhering to the Ketogenic Diet on Adipokines (Betatrophin, Endotrophin, and Meteorin-Like Protein) in Obese Women with Polycystic Ovary Syndrome

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Abstract

Obesity increases the detrimental effects on both reproductive and metabolic indicators of polycystic ovarian syndrome (PCOS). The ketogenic diet affects the outcomes of reproductive and metabolic characteristics in PCOS women. Adipose tissue is recognized as a novel gland by releasing diverse peptides called adipokines, like betatrophin, endorphin, and Meteorin-like proteins. Although the ketogenic diet's impact on many adipokines in various diseases was examined, its effects on the adipokines level in PCOS have not yet been studied. Therefore, the current research attempts to investigate how the ketogenic diet affects the adipokines level in obese PCOS women. Because seventy obese women with PCOS did not follow our single-arm clinical trial design, they were excluded, and only 50 obese women with PCOS completed and concluded the study. Adipokines (betatrophin, endotrophin, and meteorin-like protein) level was measured for all obese PCOS before and after adhering to 3 and 6 months of the ketogenic diet. From the baseline (before adhering to the ketogenic diet), betatrophin was significantly reduced by 15% and 27% when obese PCOS women adhered to 3 and 6 months of the ketogenic diet, respectively. Furthermore, endotrophin was significantly reduced by 19% and 34% when obese PCOS women adhered to 3 and 6 months of the ketogenic diet, respectively. Conversely, meteorin-like protein significantly surged by 10% and 19% when obese PCOS women adhered to 3 and 6 months of the ketogenic diet, respectively. The findings suggested that the ketogenic diet and its advantageous impacts can serve as supplementary management to control PCOS complications.

Keywords: Adipokines, Betatrophin, Endotrophin, Ketogenic Diet, Meteorin-Like Protein, Polycystic Ovary Syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is a chronic endocrine condition among women throughout their reproductive age, with a prevalence ranging from 8% to 13% [(1)]. The recent clinically recognized criteria for PCOS diagnosis are based on the revised Rotterdam criteria, which call for the presence of at least two out of the following three characteristics after ruling out other possible causes: oligo-ovulation or anovulation, hyperandrogenism, and polycystic ovarian morphology as determined by ultrasound examination [(2)]. The precise identification of the etiology of PCOS remains unclear. Nevertheless, some prior research has indicated a potential association between PCOS and a multitude of factors, such as family history, an improper lifestyle, using personal care products containing endocrine-disrupting chemicals, and obesity [(3)]. About fifty percent of women diagnosed with PCOS have a body weight more than the healthy range, that goes considered overweight or obese [(4)]. Obesity increases the detrimental effects on both the reproductive and metabolic variables of PCOS due to an elevation of adaptive hyperinsulinemia (HI), which in turn causes insulin resistance (IR) [(5)]. Furthermore, obesity develops various complications related to PCOS, including glucose intolerance, dyslipidemia, and type 2 diabetes mellitus (T2DM) [(6)].

A ketogenic diet (KGD) is an eating regimen characterized by consuming a high amount of fat, an adequate amount of protein, and a very low amount of carbohydrates [(7)]. KGD is intended to replicate the metabolic state of fasting and

promote the generation of ketone bodies [8]. KGD has been widely recognized as a practical dietary approach for treating various conditions, including intractable epilepsy, malignancies, and obesity, as emphasized the use of KGD in the management of PCOS through its efficacy on the outcomes of weight, reproductive, and metabolic variables in women with this syndrome [10].

Adipose tissue (AT) is recognized as a novel gland because it releases a diverse range of signaling peptides that control many homeostatic processes, including nutrient intake, energy usage, and insulin secretion and functioning [11]. The main peptides released from AT are adipokines, including betatrophin (β-Trophin), endotrophin (E-Trophin), and meteorin-like protein (Metrnl). Recent evidence suggests that adipokine profiles change with the quantity and condition of AT due to obesity, which are important contributing factors in playing a pivotal function in metabolic syndromes [12]. Therefore, in obesity, changes in the secretion of adipokines can cause reproductive and metabolic disruptions, which may be a significant factor in the onset of IR and related disorders, particularly PCOS.

Betatrophin (β-Trophin), also called angiopoietin-like protein 8, is a novel adipokine that belongs to the angiopoietin-like protein family [13]. β-Trophin participates in many biological processes within the human body, particularly glucose tolerance during IR [14]. Moreover, previous studies have reported that β-Trophin regulates lipids metabolism [15]. Endotrophin (E-Trophin), or collagen type VI, is a soluble product from the breakdown of the alpha-3 chain of collagen type IV by proteolysis [16]. E-Trophin participates actively in diverse biological processes within the human body, like inflammation, angiogenesis, and fibrosis [17]. It has been identified that E-Trophin plays a pivotal role in responding to a metabolic problem [18]. Meteorin-like protein (Metrnl), also called Subfatin or Metrnl protein, is a novel adipokine mainly secreted by AT and during the exercise of skeletal muscles [19]. Metrnl participates in diverse biological processes within the human body, including anti-inflammatory and insulin-sensitizing activity [20]. Furthermore, increased Metrnl levels can stimulate energy usage and improve glucose tolerance [21].

Although the efficacy of KGD has been examined on many adipokine levels in various diseases, the effect of KGD on the level of adipokines in PCOS has not yet been studied. Therefore, this study aims to investigate the impact of KGD on β-Trophin, E-Trophin, and Metrnl levels, and their relationship with anthropometric, reproductive, and metabolic disruptions in obese PCOS women.

Materials and Methods

Study design and Participants

This single-arm clinical trial was conducted at private clinics in Baghdad City from June 2024 to February 2025. We enrolled one hundred twenty obese women with PCOS, ages 18 to 25, in this study. Seventy obese women with PCOS did not follow our study design because they did not meet the inclusion criteria, and only 50 obese women with PCOS completed and concluded the study as presented in "Figure 1". In our research, PCOS diagnosis was made based on the revised Rotterdam criteria [2], which calls for a minimum 2 of 3 of the following symptoms to be present: (1) oligo/or amenorrhea; (2) clinical/biochemical overproduction of androgens; (3) polycystic ovary morphology observed through ultrasonography (there are ≥12 follicles in each ovary with 2-9 mm in diameter, as well as a raised ovarian volume ≥10 mL). Women with other possible causes, rather than PCOS, such as tumors that secrete androgens, Cushing's syndrome, hypertension, diabetes mellitus, and congenital adrenal hyperplasia, were ruled out. The ethics committee of the College of Science/Mustansiriyah University approved our study (code: BCSMU/0524/0006C on 3/5/2024) under all Helsinki Declaration tenets. Additionally, all women gave their ethical consent and were provided comprehensive information about our study, including its purpose, procedures, benefits, and confidentiality.

The Protocol of adhering to the ketogenic diet

In our study, obese PCOS women have adhered to standard KGD. A certified nutritionist doctor determined the daily calories consumed by women with PCOS by measuring their body composition and basal metabolic rate, which gave an approximate range between 1400 and 1800 kilocalories per day (kcal/day). The total energy consumption per day included 6% carbohydrates (84-108 kcal) from vegetable sources (like cabbage, lettuce, onion, cucumber, tomato, garlic, and green pepper), 20% protein (280-360 kcal) from animal sources (like meat, eggs, chicken, fish, and shrimp), and 74% fats (1036-1332 kcal) like animal tallow, olive oil, coconut oil, and avocado fruit. The total calories required per day were taken from two meals. The adherence to KGD was evaluated by testing the ketone bodies in urine (≥ +15 mg/dL) through urine strips (CYBOW, Republic of Korea).

Collection of blood sampling

Five milliliters of venous blood were withdrawn from each participant during the early follicular phase (day 2, 3, or 4) of the menstrual cycle after overnight fasting for 10 hours at least by

using a 5 mL disposable syringe. 5 mL was drawn and transferred into tubes with gel and left to clot at room temperature (25 ℃) for 10 minutes. For at least 7 minutes, the tubes with gel were centrifuged to separate sera at 3000 rpm. The obtained sera by centrifugation were subdivided into two portions and stored until the hormonal, metabolic, and adipokine markers were measured.

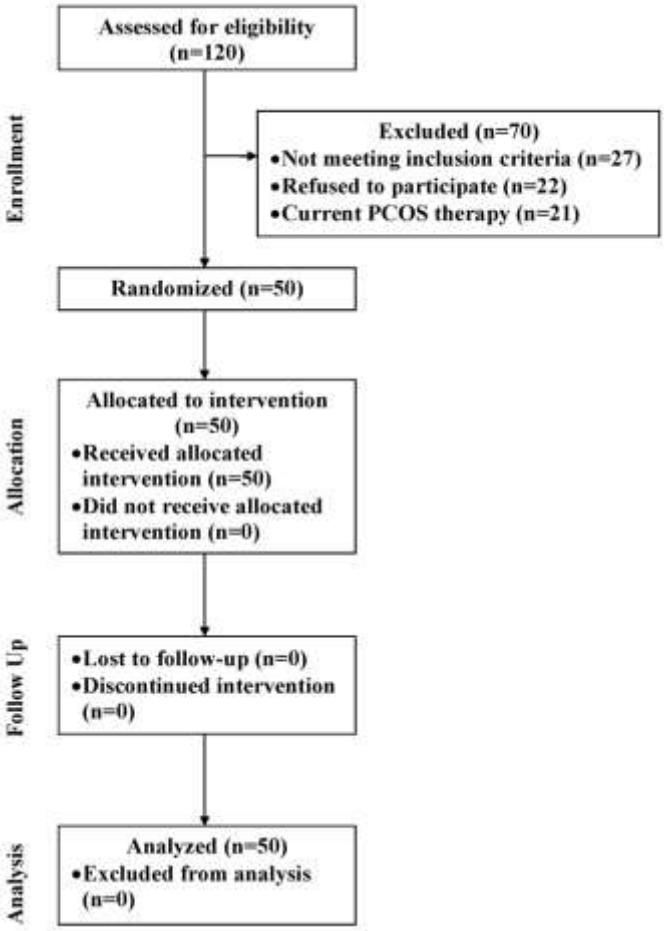

Figure 1. Flowchart of participant selection in the study.

Measurements of anthropometric and biochemical characteristics

An electronic scale, InBody-270S (InBody, UK), to the nearest 0.1kg was used to measure the body weight of each woman. A stadiometer, BSM-270B (InBody, UK), was used to measure each woman's height to the nearest 0.1cm. Body mass index (BMI) was determined by dividing a woman's weight (measured in kg) by her square height (measured in m^2). The ECLIA technique (Electro-Chemi-Luminescence-Immuno-Assay) by Roche Cobas e-411 autoanalyzer system (Roche-Hitachi Diagnostics, Japan) was employed to measure fasting sera of hormonal tests by commercial kits (Roche Diagnostics, Switzerland) [22], including luteinizing hormone (LH, mIU/mL), follicle-stimulating hormone (FSH, mIU/mL), total testosterone (TT, ng/mL), sex hormone-binding globulin (SHBG, nmol/L), insulin (µIU/mL), and metabolic tests, including blood glucose (FBG, mg/dL), total cholesterol (TC, mg/dL), triglyceride (TG, mg/dL), and high-density lipoprotein-cholesterol (HDL-C, mg/dL). The ratio of TT (ng/mL) * 2.5/SHBG (nmol/L), then multiplied by 100%, is used to calculate the free androgen index (FAI) percentage [23]. Moreover, to compute HOMA-IR (homeostatic model assessment-insulin resistance), the following standard formula was used: fasting glucose (mg/dL) * fasting insulin (µIU/L)/405 [24].

Measurements of adipokines characteristics

The ELISA (Enzyme-Linked-Immune-Sorbent-Assay) technique was employed to measure β-Trophin (0.5-100 ng/mL), E-Trophin (0.31-20 ng/mL), and Metrnl (31.2-2000 pg/mL) by commercial kits (MyBioSource, USA).

Statistical analysis

The computer program Prism, version 8.01 (GraphPad Software, Boston, New York, USA) was computed using a one-way ANOVA (analysis of variances) at 0.05 degree of freedom, then Tukey's test comes second to indicate the probability of differences (P-value) among before and post-3 and 6 months of KGD within PCOS women. The results are presented in terms of mean

± standard deviation (SD). To evaluate whether the studied parameters followed a Gaussian distribution (normal distribution), the Shapiro–Wilk normality test was utilized. The P-value at <0.05 has been considered statistically significant. The Pearson correlation coefficient was utilized to investigate the associations between adipokines with anthropometric, reproductive, and metabolic parameters among obese PCOS women at baseline (before adhering to KGD). The distinct letters (a, b, and c) found in the same row in the table predict that the three groups will differ significantly. Significant differences between the three groups within a single parameter are indicated when all distinct letters are found in the same row. In contrast, when the same distinct letter is found in the same row for two or three groups, it indicates no significant difference within a single parameter.

Results and Discussion

At baseline, although β-Trophin had a significant direct association with BMI (r=0.482, P=0.003), insulin (r=0.666, P=0.002), FBG (r=0.554, P=0.014), HOMA-IR (r=0.679, P=0.001), TC (r=0.564, P=0.004), and TG (r=0.597, P=0.016), β-Trophin had a significant inverse association with SHBG (r=-0.501, P=0.017). E-Trophin had a significant direct association with BMI (r=0.337, P=0.044), LH/FSH ratio (r=0.399, P=0.025), TT (r=0.321, P=0.035), insulin (r=0.573, P=0.021), FBG (r=0.351, P=0.018), and HOMA-IR (r=0.441, P=0.012). Metrnl has a significant inverse association with BMI (r=-0.481, P=0.015), insulin (r=-0.752, P=0.001), FBG (r=-0.807, P=0.001), HOMA-IR (r=-0.811, P=0.001), TC (r=-0.553, P=0.002), and TG (r=-0.271, P=0.011), as seen in "Table 1". On the other hand, the linear regression analysis in the present study did not indicate any significant correlation between β-Trophin and E-Trophin. Instead, Metrnl has a significant inverse association with β-Trophin (r=-0.399, P=0.021) and E-Trophin (r=-0.428, P=0.011).

Table 1. The correlations between the adipokines with anthropometric, reproductive, and metabolic parameters in obese PCOS women before adhering to KGD.

Parameters	β-Trophin		E-Trophin		Metrnl	
	***r*-value**	***P*-value**	***r*-value**	***P*-value**	***r*-value**	***P*-value**
Weight, kg	0.523	0.202	0.325	0.767	0.035	0.826
BMI, kg/m^2	0.482	0.003**	0.337	0.044*	-0.481	0.015*
LH, mIU/mL	0.279	0.089	0.158	0.152	0.053	0.911
FSH, mIU/mL	-0.112	0.654	0.386	0.067	0.121	0.630
LH/FSH ratio	0.081	0.852	0.399	0.025*	0.132	0.495
TT, ng/mL	0.273	0.109	0.321	0.035*	0.093	0.888
SHBG, nmol/L	-0.501	0.017*	–0.028	0.799	0.603	0.505
FAI, %	0.731	0.387	0.621	0.417	0.111	0.652
Insulin, µIU/mL	0.666	0.002**	0.573	0.021*	-0.752	0.001**
FBG, mg/dL	0.554	0.014*	0.351	0.018*	-0.807	0.001**
HOMA-IR	0.679	0.001**	0.441	0.012*	-0.811	0.001**
TC, mg/dL	0.564	0.004**	0.076	0.491	-0.553	0.002**
TG, mg/dL	0.597	0.016*	0.139	0.209	-0.271	0.011*
HDL-C, mg/dL	0.062	0.231	–0.107	0.331	0.070	0.696

β-Trophin: Betatrophin; **E-Trophin:** Endotrophin; **Metrnl:** Meteorin-like protein; **r:** linear Correlation Coefficient value. ***:** Significant association between the two variables (P<0.05); ****:** significant association between the two variables (P<0.005).

From the baseline, adhering to 3 and 6 months of KGD significantly reduced body weight (-13.4 kg *vs.* -29.4 kg; P<0.001), BMI (-4.1 kg/m^2 *vs.* -8.1 kg/m^2; P<0.001), LH (-3.5 mIU/mL *vs.* -6.1 mIU/mL; P<0.001), LH/FSH ratio (-1.5 vs. -2.1; P<0.005), TT (-0.58 ng/mL *vs.* -0.78 ng/mL; P<0.001), FAI (-6.2 % *vs.* -8.2 %; P<0.001), insulin (-2.3 µIU/mL *vs.* -7.8 µIU/mL; P<0.001), FBG (-9.8 mg/dL *vs.* -27.5 mg/dL; P<0.001), HOMA-IR (-1.1 *vs.* -2.8; P<0.001), TC (-21.1 mg/dL *vs.* -33.4 mg/dL; P<0.001), and TG (-14.6 mg/dL *vs.* -26.7 mg/dL; P<0.001) levels. In contrast, adhering to 3 and 6 months of KGD significantly improved FSH (2.3 mIU/mL *vs.* 4.4 mIU/mL; P<0.05), SHBG (10.6 nmol/L *vs.* 18.8 nmol/L; P<0.001), and HDL-C (14.1 mg/dL *vs.* 27.6 mg/dL; P<0.05) levels, as seen in "Table 2".

Table 2. The statistical changes in the anthropometric, reproductive, and metabolic parameters in obese PCOS women before and after 3 and 6 months of KGD.

Parameter	Pre-KGD (Baseline) *Mean ± SD*	Post-3 months of KGD *Mean ± SD*	Post-6 months of KGD *Mean ± SD*	*P*-value
Weight, kg	89.8 ± 10.7[a]	76.4 ± 16.3[b]	60.4 ± 14.9[c]	< 0.0001
BMI, kg/m^2	32.6 ± 3.9[a]	28.5 ± 2.3[b]	24.5 ± 2.1[c]	< 0.0001
LH, mIU/mL	18.8 ± 4.5[a]	15.3 ± 2.6[b]	12.7 ± 2.1[c]	< 0.0001
FSH, mIU/mL	5.5 ± 1.7[a]	7.8 ± 1.9[b]	9.9 ± 1.5[c]	0.0111
LH/FSH ratio	3.4 ± 1.7[a]	1.9 ± 0.4[b]	1.3 ± 0.6[c]	0.0011
TT, ng/mL	1.89 ± 0.41[a]	1.31 ± 0.11[b]	1.11 ± 0.14[c]	< 0.0001
SHBG, nmol/L	35.6 ± 12.6[a]	46.2 ± 19.5[b]	54.4 ± 21.2[c]	< 0.0001
FAI, %	13.3 ± 4.6[a]	7.1 ± 1.4[b]	5.1 ± 2.3[c]	< 0.0001
Insulin, µIU/mL	16.9 ± 7.2[a]	14.6 ± 4.6[b]	9.1 ± 6.6[c]	< 0.0001
FBG, mg/dL	109.6 ± 7.9[a]	99.8 ± 6.5[b]	82.1 ± 10.9[c]	< 0.0001
HOMA-IR	4.6 ± 1.9[a]	3.5 ± 1.4[b]	1.8 ± 0.7[c]	< 0.0001
TC, mg/dL	192.2 ± 42.9[a]	171.1 ± 28.4[b]	158.8 ± 33.5[c]	< 0.0001
TG, mg/dL	154.5 ± 72.7[a]	139.9 ± 40.2[b]	127.8 ± 38.1[c]	< 0.0001
HDL-C, mg/dL	39.2 ± 12.8[a]	53.3 ± 11.2[b]	66.8 ± 10.8[c]	0.0389

KGD: Ketogenic Diet; **SD:** Standard Deviation; **BMI:** Body Mass Index; **LH:** Luteinizing Hormone; **FSH:** Follicle-Stimulating Hormone; **TT:** Total Testosterone; **SHBG:** Sex Hormone-Binding Globulin; **FAI:** Free Androgen Index; **FBG:** Fasting Blood Glucose; **HOMA-IR:** Homeostatic Model Assessment-Insulin Resistance; **TC:** Total Cholesterol; **TG:** Triglyceride; **HDL-C:** High-Density Lipoprotein-Cholesterol.

From the baseline, a one-way ANOVA revealed a significant reduction (P<0.005) in the β-Trophin level when obese PCOS women adhered to 3 and 6 months of KGD (75.1 ± 22.6 ng/mL *vs.* 63.6 ± 25.8 ng/mL *vs.* 54.7 ± 30.3 ng/mL) as seen in "Figure 2". Moreover, a significant reduction (P<0.005) in the E-Trophin level when obese PCOS women adhered to 3 and 6 months of KGD (17.1 ± 3.4 ng/mL *vs.* 13.8 ± 4.1 ng/mL *vs.* 11.2 ± 5.6 ng/mL), as seen in "Figure 3". On the contrary, a significant surge (P<0.005) in the Metrnl level was observed when obese PCOS women adhered to 3 and 6 months of KGD (1485.5 ± 288.3 pg/mL *vs.* 1641.1 ± 197.9 pg/mL *vs.* 1749.8 ± 156.4 pg/mL) as seen in "Figure 4".

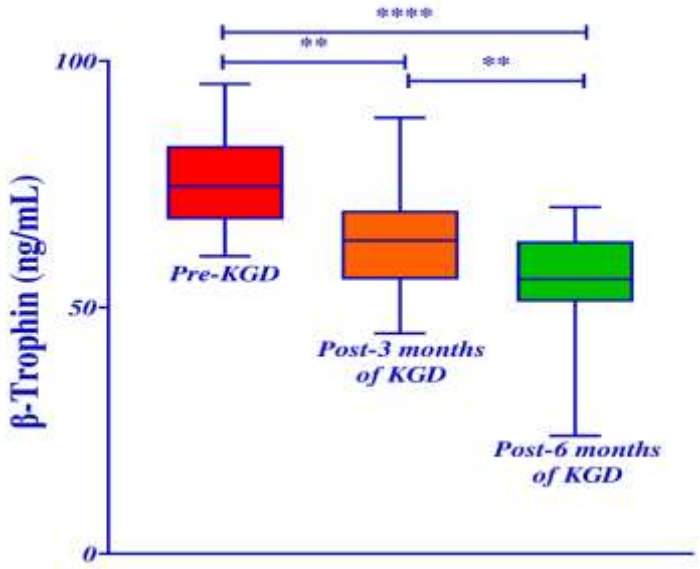

Figure 2. Changes in the betatrophin level before and after adhering to 3 and 6 months of KGD. **: indicates change among means is statistically significant (P<0.01); **: indicates change among means is highly statistically significant (P<0.0001).**

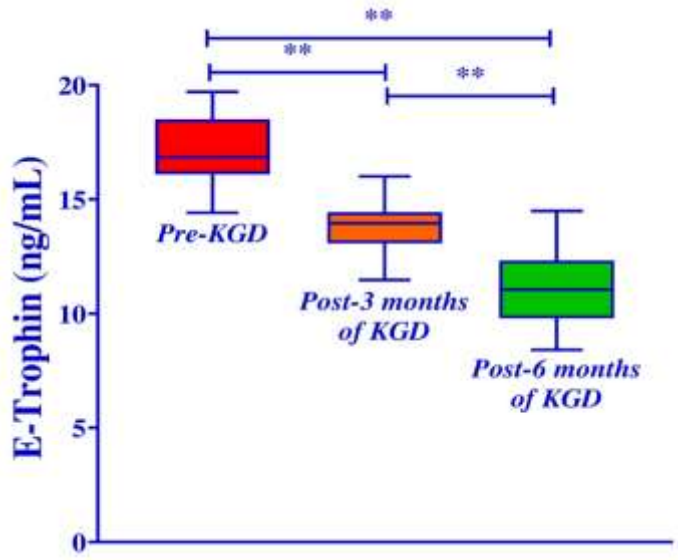

Figure 3. Changes in the endotrophin level before and after adhering to 3 and 6 months of KGD. **: indicates change among means is statistically significant (P<0.01).

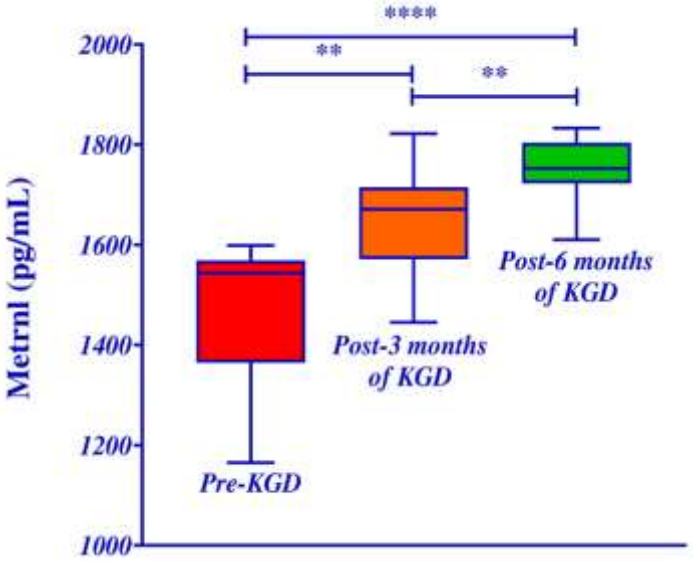

Figure 4. Changes in the meteorin-like protein level before and after adhering to 3 and 6 months of KGD. **: indicates change among means is statistically significant (P<0.01); **: indicates change among means is highly statistically significant (P<0.0001).**

One interesting finding in the current investigation is statistical changes (P<0.001) in the anthropometric, reproductive, and metabolic parameters when obese PCOS women have adhered to 3 and 6 months of KGD, as seen in "Table 2". Although the findings align with those observed by Paoli et al. [25], who noted that significant changes were seen in the anthropometric, reproductive, and metabolic parameters when 14 overweight women with PCOS adhered to 12 weeks of KGD, the present study provides more substantial evidence due to a longer follow-up period and larger sample size. KGD is viewed as an effective weight loss regimen due to ketone bodies' appetite-suppressing properties by decreasing ghrelin (hunger hormone) and increasing satiety peptides, which significantly reduce calorie intake [26,27]. In the same way, several reports have supported the positive advantages of nutritional ketosis by KGD in preventing metabolic syndromes in many obesity-related diseases [28]. Gluconeogenesis and ketogenesis pathways are stimulated in the liver when carbohydrates are restricted to ≤ 50g daily. The ketogenesis pathway occurs when endogenous glucose production is exhausted and insulin levels in the bloodstream decrease, thereby decreasing body glucose and fat storage. On the other hand, HI has significant effects on the production of androgens from the ovaries through decreasing SHBG in obese conditions [29]. Although PCOS, as shown in the study, is mainly characterized by

hyperandrogenism and IR, many researchers have suggested that the circulation of SHBG is influenced by certain common genetic variations in the SHBG alleles, which could contribute to PCOS phenotype development [30,31]. However, several studies have been conducted in this field, and no one has been able to establish a specific association, and the findings of these investigations are likewise unclear. Altogether, our investigation speculated that KGD would decrease HI, reducing the stimulation of the synthesis of ovarian androgens, and this synergistically restricts the levels of free androgens in the circulation. Moreover, a reduction in the LH/FSH ratio, as elevated LH relative to FSH is commonly linked to disrupted ovulation, is considered favorable in PCOS to normalize the hormonal balance, potentially improve ovulation and chances of conceiving, and regulate the menstrual cycle [32]. Therefore, KGD intervention helps lower the LH/FSH ratio that could restore the endocrine's normal function and is generally considered beneficial for PCOS women.

What is surprising in in such investigation is that there were statistical reductions in the β-Trophin and E-Trophin levels when obese PCOS women adhered to 3 and 6 months of KGD, as seen in "Figures 2 and 3". At the same time, there was a statistical increase in the Metrnl level when obese PCOS women adhered to 3 and 6 months of KGD, as seen in "Figure 4". To the best of our knowledge, this is the first study to examine the relationship between KGD intervention and circulating β-Trophin, E-Trophin, and Metrnl in obese women with PCOS. Although the precise mechanism by which KGD regulates adipokine levels in PCOS remains unclear, four main possible explanations exist for these results. First, weight reduction is important in regulating metabolic adipokines in obesity conditions. Many authors have observed that a significant decrease in weight causes a notable mainstay regulation in the metabolic adipokines circulating in the bloodstream [33]. As shown in "Table 1", β-Trophin, E-Trophin, and Metrnl have significant associations with BMI. Therefore, these correlations in the current study confirm the association between weight reduction via KGD and substantial regulation of the adipokines circulating in the bloodstream in obese PCOS women. Second, the KGD causes a reduction in the visceral adipose tissues (VAT) and results in regulating blood biochemistry variables [34]. VAT can trigger reproductive and metabolic disorders by releasing various adipokines, which induce IR. Conversely, other adipokines are released by VAT and exhibit positive reproductive and metabolic effects through a rise in insulin sensitivity and reducing glucose intolerance [35]. A significant reduction in the VAT by KGD was reported to reduce abdominal obesity and improve its complications [36]. Therefore, the decrease in VAT via KGD is essential and could reflect the high level of VAT, which leads to constant reproductive and metabolic disorders, including PCOS, due to irregularities in the secretion of adipokines from AT. Third, it has been known that obesity and metabolic syndromes are related, and the main factor for this relationship is obesity's ability to result in IR [37]. Most adipokines are affected by IR in metabolic syndromes, especially in PCOS [38]. Our study demonstrated significant associations between β-Trophin, E-Trophin, and Metrnl with insulin, FBG, and HOMA-IR "Table 1". When obese PCOS women adhered to KGD, the HOMA-IR with compensatory insulin levels significantly decreased, which in turn caused a notable decrease in the β-Trophin and E-Trophin levels and a notable surge in the Metrnl level. On the other hand, obesity is correlated with the incidence of dyslipidemia. Dyslipidemia, which is characterized by excessive TC and TG, as well as reduced HDL-C levels, is generally acknowledged to be a risk for cardiovascular diseases (CVD), particularly in PCOS [37]. Studies indicated that IR could be the fundamental mechanism that connects obesity and dyslipidemia [39]. Also, numerous adipokines secreted from AT are dysregulated due to excess adiposity and adipocyte malfunction, which causes changes in the lipid balance [40]. The current study demonstrated significant associations between β-Trophin and Metrnl with TC, TG, and HDL-C. In PCOS, KGD has a significant role in controlling lipid levels [41]. In recent years, there has been a rising body of evidence demonstrating that treatment with KGD results in a significant drop in body weight and a marked reduction in liver fat. Reducing hepatic lipids improves hepatic IR by lowering compensatory insulin and excessive hepatic glucose production. Also, lower glucose and insulin levels in KGD limit cholesterol biosynthesis by mediating β-Hydroxy β-methyl glutaryl-CoA reductase, which insulin activates [42]. Therefore, our findings regarding the effects of KGD on the β-Trophin, E-Trophin, and Metrnl levels further support the fact that there is a strong pathophysiological correlation between adipokines with IR and dyslipidemia in metabolic syndromes, particularly PCOS. Fourth, several studies demonstrated that systemic inflammation is increased in PCOS women due to obesity and IR [43]. Producing and inhibiting inflammatory cytokines controlling systemic inflammation, resulting in the overexpression of related adipokines from AT [44]. Although prior studies have shown that diet can influence systemic inflammation, there has recently been growing evidence that KGD is an anti-inflammatory via its effects on reducing inflammatory adipokines [45]. On the other hand, a recent study has shown that the level of carbon reactive protein (CRP), a

systemic inflammatory marker, is significantly increased and statistically directly correlated with E-Trophin in PCOS women and confirms that adipokines are associated with systemic inflammation in PCOS [46]. Therefore, the decrease in systemic inflammation by KGD is essential and could reflect a substantial reduction in the adipokines circulating in the bloodstream in obese PCOS women from AT.

Many essential limitations need to be considered. For instance, the number of participants was relatively small, the follow-up duration was short, relying on the urine strips to evaluate the ketone bodies during the KGD period, the absence of direct measurements to inflammatory markers, and the current research lacks a control group (non-KGD-PCOS women). Notwithstanding these limitations, further clinical trials and more intervention periods are needed to examine whether KGD has the same results more closely in large sample sizes in women diagnosed with PCOS or healthy women.

Conclusion

The present study can draw the following conclusion: KGD impacts on reproductive and metabolic characteristics by ketogenesis nutrition in preventing androgenic and metabolic disorders via weight loss. At the same time, KGD impacts the regulation of adipokines (β-Trophin, E-Trophin, and Metrnl), which are significantly correlated with reproductive and metabolic characteristics in women diagnosed with PCOS. Therefore, KGD could be considered a beneficial non-pharmacological intervention for PCOS management.

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Conflicts of Interest

There is no conflict of interest among the authors.

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Ethics Statements

The ethics committee of the College of Science/Mustansiriyah University approved our study (code: BCSMU/0524/0006C on 3/5/2024) under all Helsinki Declaration tenets. Additionally, all women gave their ethical consent and were provided comprehensive information about our study, including its purpose, procedures, benefits, and confidentiality.

Author Contribution

All authors wrote, read, and approved the final manuscript version and agree with all parts of the work in ensuring that any queries about the accuracy or integrity of any work component are appropriately investigated and handled.

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تقييم فعالية الالتزام بالنظام الغذائي الكيتوني على الاديبوكينات (بيتاتروفين، إندوتروفين والبروتين شبيه - المتيورين) لدى النساء البدينات المصابات بمتلازمة تكيس المبايض

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الخلاصة

تزيد السمنة من ألاثار السلبية على المتغيرات الانجابية والايضية في متلازمة تكيس المبايض. يؤثر النظام الغذائي الكيتوني إيجاباً على المتغيرات الانجابية والايضية لدى النساء المصابات بمتلازمة تكيس المبايض. تُعرف الانسجة الدهنية الان بأنها غدة جديدة من خلال تكوين وافراز مختلف البروتينات التي تعمل عمل هرمونات تسمى بالأديبوكينات، مثل البيتاتروفين، الإندوتروفين والبروتين شبيه – المتيورين. على الرغم من دراسة تأثير النظام الغذائي الكيتوني على عدد من الأديبوكينات في امراض مختلفة، إلا ان دراسة تأثيره على مستوى الأديبوكينات في متلازمة تكيس المبايض لم تُدرس بعد. لذلك، يَسعى بحثنا الى دراسة كيفية تأثير النظام الغذائي الكيتوني على مستوى الأديبوكينات لدى النساء البدينات المصابات بمتلازمة تكيس المبايض. تم أستبعاد ٧٠ امرأة بدينة مصابة بمتلازمة تكيس المبايض لأنهنَ لم يتبعنَ تصميم تجربتنا السريرية العشوائية، وقد أكملنَ ٥٠ امرأة بدينة مصابة بمتلازمة تكيس المبايض واختتمت دراستنا بهن. تم قياس مستوى الأديبوكينات (بيتاتروفين، إندوتروفين والبروتين شبيه – المتيورين) لجميع النساء المصابات بمتلازمة تكيس المبايض المشاركات في دراستنا قبل وبعد الإلتزام بالنظام الغذائي الكيتوني لمدة ٣ و٦ اشهر. من خط الاساس (قبل الإلتزام بالنظام الغذائي الكيتوني)، إنخفض مستوى البيتاتروفين احصائياً بمقدار ١٥٪ و ٢٧٪ عندما إلتزمت النساء البدينات المصابات بمتلازمة تكيس المبايض بالنظام الغذائي الكيتوني لمدة ٣ و٦ اشهر تواليا. إضافة الى ذلك، إنخفض مستوى إلاندوتروفين احصائياً بمقدار ١٩٪ و ٣٤٪ عندما إلتزمت النساء البدينات المصابات بمتلازمة تكيس المبايض بالنظام الغذائي الكيتوني لمدة ٣ و٦ اشهر تواليا. في المقابل، إرتفع مستوى البروتين شبيه – المتيورين احصائياً بمقدار ١٠٪ و ١٩٪ عندما إلتزمت النساء البدينات المصابات بمتلازمة تكيس المبايض بالنظام الغذائي الكيتوني لمدة ٣ و٦ اشهر تواليا. تشير نتائج دراستنا الى النظام الغذائي الكيتوني وتأثيراته الايجابية على المتغيرات الانجابية، الايضية والاديبوكينات يمكن أن يكون تداخُلاً تكميلياً للسيطرة على متلازمة تكيس المبايض ومضاعفاتها.

الكلمات المفتاحية: الأديبوكينات، بيتاتروفين، إندوتروفين، النظام الغذائي الكيتوني، البروتين شبيه - المتيورين، متلازمة تكيس المبايض.