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Evaluating the Effect of the Ketogenic Diet on the Reproductive and Metabolic Parameters in Iraqi Females with Polycystic Ovary Syndrome

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Abstract

Polycystic ovarian syndrome is the prevailing endocrine condition among females in their reproductive age. Clinically, it is characterized by irregular or delayed ovulation, excessive androgen levels, and the appearance of polycystic in ovaries. It is linked to a greater incidence of metabolic syndrome. Although it is related to various hereditary and environmental factors, insulin resistance is an essential factor in its development. The objective of our conducted research was to observe the impacts of the ketogenic diet on the reproductive and metabolic indicators in females who have been diagnosed with polycystic ovary syndrome. Eighty females of reproductive age have participated in the current investigation. During three months of adhering to the ketogenic diet, high statistical reductions (P=<0.0001) were investigated in body mass index (-5.4 Kg/m^2), fasting blood sugar (-39.7 mg/dL), hemoglobin A1C (-1.03 %), insulin (-4.9 mIU/L), homeostatic model assessment for insulin resistance (-0.97), total testosterone (-0.29 ng/mL), luteinizing hormone (-6.9 mIU/ml), and LH/FSH ratio (-1.1). Conversely, highly statistical rises (P=<0.0001) were investigated in estradiol (29 pg/mL) and follicle-stimulating hormone (0.8 mIU/ml). The ketogenic diet and its advantageous impacts can serve as a supplementary treatment for polycystic ovarian syndrome.

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1. Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent medical condition that impacts females in years of reproduction and is marked by both reproductive and metabolic abnormalities [1]. The current clinically accepted criteria for diagnosing PCOS is 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 ovaries as determined by ultrasound examination [2]. A diverse range of factors can cause PCOS, but obesity and insulin resistance are considered significant factors in PCOS development [3]. There has been a reported correlation between the severity of obesity and insulin resistance and menstruation irregularity or infertility, which are essential clinical features of PCOS in women who are of reproductive age [4]. The traditional approach to treating PCOS has focused on addressing fertility issues and administering hormonal therapy. Furthermore, the main emphasis of research and clinical management has been on addressing the physical symptoms of PCOS through the use of medications, which has yielded diverse outcomes [5].

Lifestyle modification programs focusing on behavioral management and dietary changes have proven effective in reducing the risk of insulin resistance in metabolic syndromes. These programs also demonstrated preliminary efficacy in enhancing fertility rates in females who were diagnosed with PCOS [6]. Nevertheless, there are currently no specific dietary guidelines for women with PCOS. Uncontrolled experiments examining the effects of low-carbohydrate, hypocaloric, and ketogenic diets have shown that they can help obese women with PCOS lose weight [7]. A ketogenic diet (KD) is a dietary plan that is distinguished by a high content of fat, adequate protein intake, and just a tiny quantity of carbohydrates. KD is designed to replicate the metabolic state of fasting and stimulate the generation of ketone bodies [8]. KD has garnered widespread recognition as a practical dietary approach for treating intractable epilepsy. In recent years, KD has gained significant research interest due to emerging evidence of its potential therapeutic advantages for a multitude of diseases, ranging from obesity to malignancies [9]. Recent studies show that KD can improve insulin resistance through the progressive reduction in glycogen storage in the liver and muscles, resulting in a simultaneous decrease in blood sugar levels and a corresponding decrease in insulin concentration [10]. The rise in glucagon-induced lipolysis leads to elevated oxidation of fats originating from adipose tissue, which replaces glycogen depletion. As a result, ketone bodies, acetone, acetoacetate, and ß-hydroxybutyrate, are generated and function as metabolic fuel [11]. The study goal was to examine reproductive and metabolic parameters before and after three months of using KD for individuals who have been diagnosed with PCOS.

2.Materials and Methods

2.1. Study Participation

The current investigation comprised a cohort of 80 females who were diagnosed with PCOS. The age range of females who were diagnosed with PCOS is 18-35 years old. Our study was carried out in private clinics in Baghdad between January 2023 and August 2023. In our investigation, the females who were diagnosed with PCOS were determined using the revised Rotterdam criteria [12], which necessitate the presence of a minimum of two out of three signs: oligo-menorrhea or amenorrhea, clinical and biochemical excess of androgen levels, and the presence of multi-cysts on the ovary through ultrasonography. Our study was approved by the College of Science/Al-Nahrain University as a requirement for obtaining a doctoral degree in the philosophy of Chemistry Science. Additionally, the research ethics committee of the Iraqi Ministry of Health approved our research (2023114 on 14/1/2023). On the other hand, ethical consent was obtained from all subjects, and they were provided with comprehensive information about our study, including the purpose, procedures, benefits, and confidentiality of the research.

2.2. Exclusion Criteria

Individuals with cardiovascular diseases, hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumors, hypercholesterolemia, and hypertension, as well as those using medications such as metformin, dopamine, gonadorelin, and pills of contraceptives were not included in the current study.

2.3. Collection of Samples

Five milliliters of whole blood after overnight fasting for 8-12 hours were obtained from PCOS females during the first phase of the menstruation cycle, specifically days 2-4. All whole blood samples were taken in gel tubes and left to solidify for fifteen minutes. Three milliliters of blood serum were separated at room temperature after centrifugation at 1814 x g and analyzed immediately.

2.4. Assessment of Body Mass Index

Body mass index (BMI) can be established by splitting the weight of an individual (measured in kilograms, Kg) on the height squared (measured in meters, m^2) [13].

2.5. Analysis of Biochemical Parameters

The serum of total testosterone (TT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and insulin (INS) were determined using the ECLIA method (electrochemiluminescence-immunoassay) through the Roche Cobas e411 autoanalyzer system (Roche-Hitachi Diagnostics, Japan). Hemoglobin A1C (HbA1C) was determined using the FIA (Fluorescence Immunoassay) through I-CHROMA II (Boditech Med, South Korea). Serum Fasting blood sugar (FBS) was measured with the glucose MR kit supplied by Linear Company (Linear Chemicals S.L.U., Spain) with a semi-auto MINDRAY chemistry analyzer manufactured by (Shenzhen Mindray Bio-Medical Electronics Co.

LTD) in China. The HOMA-IR, which stands for homeostatic model assessment for insulin resistance, was computed by the subsequent formula: fasting blood glucose (mg/dL) multiplied by fasting blood insulin (mU/L)/405 [14].

2.6. Statistical Analysis

Our data were given in the form of the mean ± standard deviation. The probability of significant differences (P-value) was computed using a paired t-test at 0.05 degree of freedom via Prism computer program version 8.01 (GraphPad Prism software, San Diego, California, USA). If the P-value was under 0.05, a difference was viewed to be statistically significant.

3. Results and Discussion

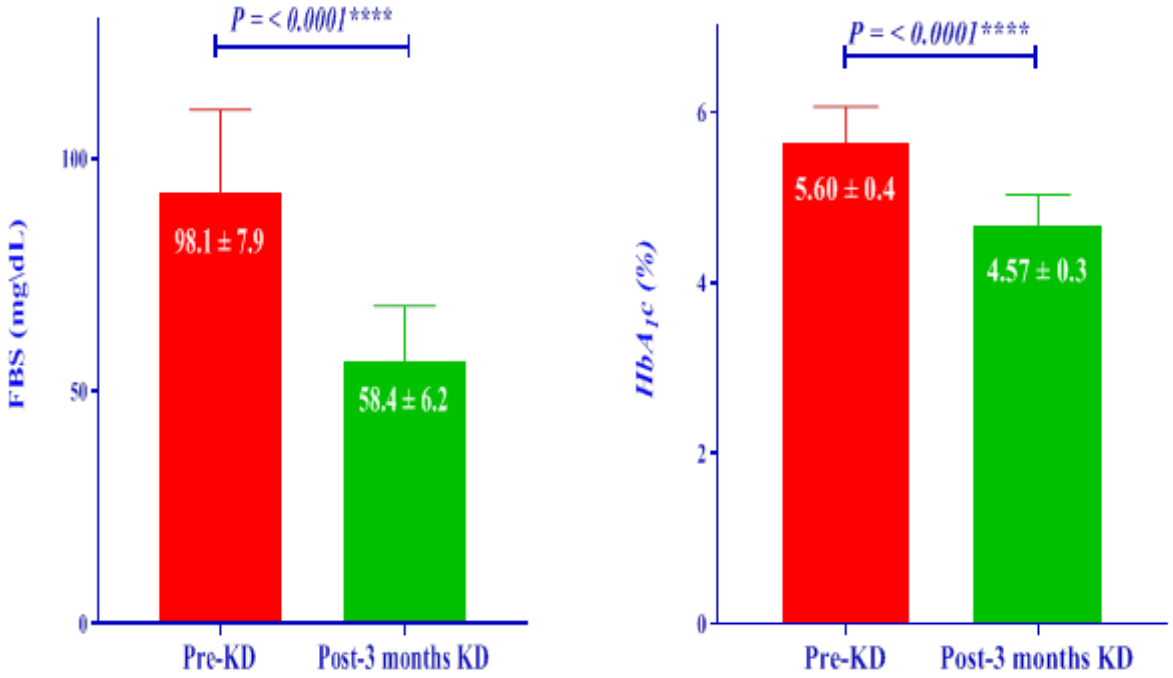
Table 1 presents the demographic, metabolic, and reproductive variables in the PCOS female studied group (before and after 3 months of KD). The findings revealed highly significant reductions (P-value=<0.0001) in BMI, FBS, HbA1c, INS, HOMA-IR, TT, LH, and LH/FSH ratio after 3 months of adhering to KD. On the other hand, highly significant rises (P-value=<0.0001) in E2 and FSH after 3 months of adhering to KD. Prior studies have found the importance of central obesity in developing metabolic syndromes. In women with PCOS, it has been found to have a prevalence of 43%. The presence of hyperinsulinemia and insulin resistance defines metabolic syndromes [15]. Hyperinsulinemia and insulin resistance are often observed in many young females with PCOS. These conditions are not reliant on weight but appear to be associated with overall body fat and fat distribution in the central region [16]. On the other hand, individuals with PCOS commonly have an abundance of androgens, which is frequently linked to metabolic abnormalities like central obesity, hyperinsulinemia, and insulin resistance [17]. Insulin resistance has been suggested as the primary underlying condition responsible for various hormonal and reproductive abnormalities seen in PCOS, including hyperandrogenism [18]. The most exciting findings in the present research were that three months of KD encourages a reduction in BMI, FBS, HbA1c, INS, HOMA-IR, TT, LH, and LH/FSH ratio in women with PCOS. Our study's findings are in agreement with those of the previous report [19], which demonstrated that three months of KD exhibit advantageous impacts on BMI, FBS, HbA1c, INS, HOMA-IR, TT, LH, and LH/FSH ratio in women diagnosed with PCOS. Instead, three months of KD encourages a rise in the level of E2 and FSH in women with PCOS. These findings are consistent with the findings of previous work [20], which investigated that three months of KD exhibit advantageous impacts on E2 and FSH levels in women diagnosed with PCOS. During the previous ten years, there has been growing interest in KD as a nutritional treatment due to its ability to ensure substantial weight loss and provide numerous benefits, particularly in cases of insulin resistance [21]. KD targets the resolution of insulin resistance and can undeniably ensure improvement from a metabolic and endocrinological standpoint, as these two aspects are highly interrelated [22].

Table 1. Statistical descriptive, metabolic, and reproductive parameters analysis before and after 3 months of adhering to KD.

Parameter	Pre-KD (Mean ± SD)	Post-3 Month KD (Mean ± SD)	P-value	Significant
BMI, Kg/m^2	34.9 ± 2.9	29.5 ± 2.3	< 0.0001	HS
FBS, mg/dL	98.1 ± 7.9	58.4 ± 6.2	< 0.0001	HS
HbA_1c, %	5.60 ± 0.4	4.57 ± 0.3	< 0.0001	HS
INS, mIU/L	15.8 ± 4.3	10.9 ± 5.2	< 0.0001	HS
HOMA_IR	2.68 ± 0.7	1.71 ± 0.6	< 0.0001	HS
TT, ng/mL	1.01 ± 0.2	0.72 ± 0.3	0.0031	S
E2, pg/mL	133 ± 40.2	162 ± 40.2	< 0.0001	HS
LH, mIU/ml	18.8 ± 6.5	11.9 ± 5.6	< 0.0001	HS
FSH, mIU/ml	7.4 ± 2.5	8.2 ± 2.3	0.021	S
LH/FSH ratio	2.6 ± 0.9	1.5 ± 0.9	0.001	S

BMI: Body Mass Index, E2: Estradiol, FBS: Fasting Blood Sugar, FSH: Follicle-Stimulating Hormone, HbA_1c: Hemoglobin A_1c, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HS: Highly Significant, INS: Insulin, KD: Ketogenic Diet, LH: luteinizing Hormone, S: Significant TT: Total Testosterone.

The excessive production of LH, along with a shift in the LH/FSH ratio in favor of LH and the concurrent decrease in FSH production due to the inhibitory effects of inhibin, underlies the failure of follicular maturation, anovulation, and the excessive stimulation of thecal cells by LH. Consequently, there is an excessive secretion of androgens and the formation of a self-sustaining negative cycle. Insulin and insulin-like growth factor (IGF), locally overproduced and further amplified by obesity, contribute to this cycle. They work together with LH to stimulate the synthesis of androgens, increasing their circulation [23]. Therefore, the KD intervention resulted in a reduction in the levels of glucose and insulin, as well as improved insulin sensitivity. This decreased androgen production and reduced estrogens from converting androgens into excess fatty tissue. Furthermore, the reduction in fat mass improved the LH/FSH ratio. Decreasing the surplus of LH results in a proportional rise of FSH, which in turn causes an improvement in the LH/FSH ratio [24]. Changes in body weight, level of testosterone, LH/FSH ratio, and insulin enhance the body's ability to reestablish endocrine system functions. Dietary intervention and lifestyle management have a positive impact on treating PCOS individuals and obesity.



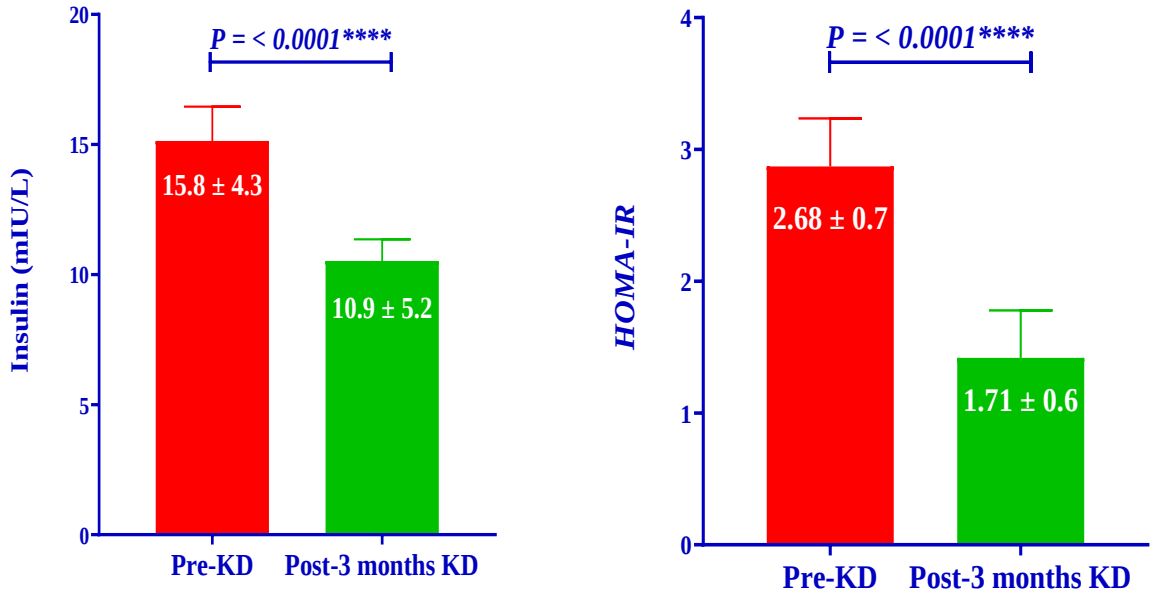


Figure 1. Show mean ± SD for FBS, HbA1c, insulin, and HOMA-IR before and after 3 months of adhering to KD.

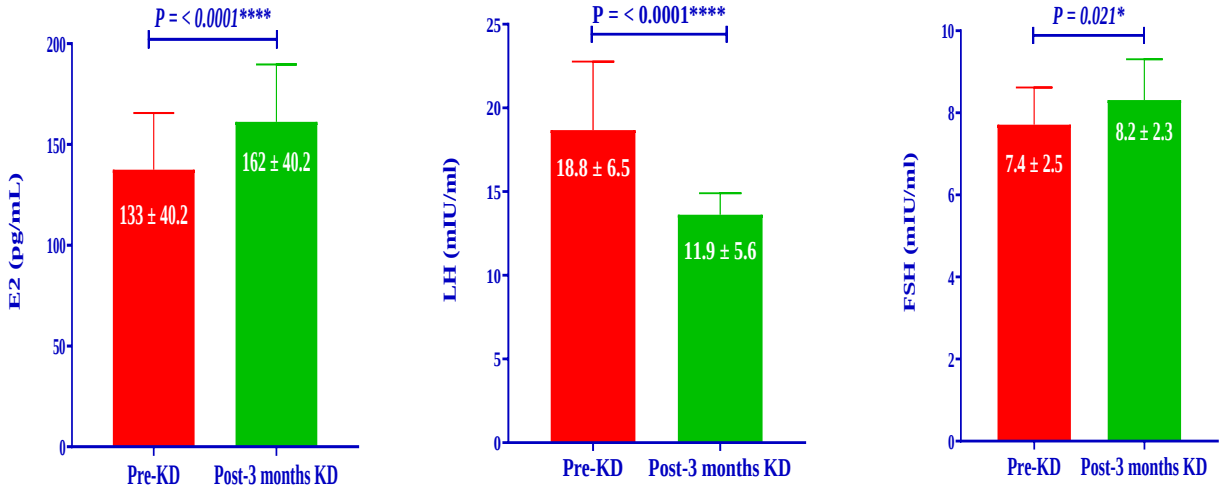


Figure 2. Show mean ± SD for E2, LH, and FSH before and after 3 months of adhering to KD.

4. Conclusions

The findings obtained from our research speculated that the ketogenic diet could be regarded as a beneficial non-pharmacological intervention for the regulation of metabolic and reproductive variables in women diagnosed with polycystic ovarian syndrome.

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Conflicts of Interest

Non-conflicts of interest.

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