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Eficacia terapéutica de la dieta cetogénica hipocalórica sobre la composición corporal y los parámetros bioquímicos en el síndrome del ovario poliquístico: un estudio de intervención

Therapeutic effectiveness of low-calorie ketogenic diet on body composition and biochemical parameters in polycystic ovary syndrome: an ıntervention study

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Data availability statement: The data presented in this study are available on request from the corresponding author due to privacy or ethical restrictions.

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Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Evaluation Board of Acıbadem Mehmet Ali Aydınlar University (Approvel no: 2019-14/17 and date of 12.09.2019). The written informed consent was obtained from all subjects involved in the study.

Registration in clinical trials: This research is registered with ClinicalTrials.gov under number NCT06469255.

Conflict of interest: The authors declare no conflict of interest.

Artificial intelligence: The authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

ABSTRACT

Introduction: the effectiveness of the ketogenic diet (KD) as a therapeutic approach for managing weight, hormonal, and metabolic aspects of polycystic ovary syndrome (PCOS) requires further clarification despite its growing popularity.

Objectives: this study evaluated the short-term effects of a 4-week low-calorie ketogenic diet (LCKD) on body composition, biochemical, and hormonal parameters in overweight or obese women with PCOS.
Methods: thirteen women with PCOS (mean age 29.77 ± 7.54 years, median BMI 27.2 kg/m²) participated in this clinical intervention study. Body composition (bio-electrical impedance), anthropometric measurements, and biochemical/hormonal parameters were assessed pre- and post-intervention.
Results: participants achieved a mean body weight loss of 6.90 % ± 2.04 %. Significant reductions were observed in body weight, BMI, fat percentage, fat mass, fat-free mass, waist, hip, and neck circumferences, and waist-to-hip/waist-to-height ratios ($p < 0.05$). LCKD also led to significant decreases in fasting glucose, insulin, HOMA-IR, HDL-cholesterol, prolactin, and IGF-1 levels ($p < 0.05$). Conversely, SHBG and TNF-α levels significantly increased ($p < 0.05$). Multiple regression analysis indicated that changes in waist (t = 4.196), hip (t = 3.983), and neck (t = -2.820) circumferences significantly impacted prolactin levels, while changes in fat percentage (t = -3.326, $p = 0.021$), fat mass (t = 3.501, $p = 0.017$), and hip circumference (t = 2.905, $p = 0.034$) influenced SHBG levels ($p < 0.05$).
Conclusions: short-term LCKD intervention shows potential as a therapeutic dietary strategy, yielding beneficial effects on both anthropometric and key biochemical parameters in overweight or obese women with PCOS.

Keywords: Ketogenic diet. Menstrual dysfunction. Polycystic ovary syndrome. Very low-calorie ketogenic diet. Medical nutrition therapy.

RESUMEN

Introducción: la dieta cetogénica (DC) ha ganado popularidad como tratamiento para el control del peso y los aspectos hormonales del

síndrome del ovario poliquístico (SOP), aunque su eficacia requiere más investigación.

Objetivos: este estudio tuvo como objetivo evaluar los efectos a corto plazo de una dieta cetogénica baja en calorías (DCE) de 4 semanas en mujeres con sobrepeso u obesidad y SOP.

Metodología: se incluyeron trece mujeres (edad media: 29,77 años, IMC: 27,2 kg/m²) en este estudio de intervención. Se midieron la composición corporal, las medidas antropométricas y los parámetros bioquímicos y hormonales antes y después de la intervención.

Resultados: Los resultados mostraron una pérdida media de peso del 6,90 %. Se observaron reducciones significativas en el peso corporal, IMC, porcentaje de grasa, masa grasa, circunferencias de cintura, cadera y cuello, así como en la relación cintura-cadera/cintura-estatura ($p < 0,05$). Además, se produjeron disminuciones significativas en los niveles de glucosa en ayunas, insulina, HOMA-IR, colesterol HDL, prolactina e IGF-1 ($p < 0,05$), mientras que los niveles de SHBG y TNF-α aumentaron ($p < 0,05$). El análisis de regresión múltiple mostró que la circunferencia de la cintura, la cadera y el cuello influyeron en los niveles de prolactina, mientras que los cambios en el porcentaje de grasa y la masa grasa impactaron en los niveles de SHBG.

Conclusiones: la intervención LCKD a corto plazo muestra potencial como estrategia dietética terapéutica, con efectos beneficiosos tanto en parámetros antropométricos como bioquímicos clave en mujeres con sobrepeso u obesidad y SOP.

Palabras clave: Dieta cetogénica. Disfunción menstrual. Síndrome del ovario poliquístico. Dieta cetogénica muy baja en calorías. Terapia nutricional médica.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (1). Affecting 8-13 % of women globally, PCOS extends beyond cosmetic concerns like hirsutism and acne, significantly elevating the risk for infertility, dyslipidemia, obesity, type 2 diabetes, cardiovascular disease (CVD), and certain cancers (1,2). While its etiology is complex, dysregulation of insulin action, particularly impacting the hypothalamic-pituitary-ovarian axis and adrenals, is considered a central mechanism rather than solely ovarian pathology (3).

Obesity is strongly linked to PCOS pathogenesis, exacerbating insulin resistance, which is present in 65 to 70 percent of cases, and androgen imbalances (3,4). Weight loss, even a modest reduction exceeding 5 %, is a cornerstone of PCOS management, demonstrably improving hyperandrogenemia, insulin sensitivity, lipid profiles, menstrual regularity, ovulation, fertility, and reducing long-term cardiometabolic risks (5,6). Lifestyle intervention focusing on weight loss is often more effective than medications targeting insulin sensitivity alone, especially in overweight women (7-10).

Ketogenic diets (KD), typically restricting carbohydrate intake to < 20-50 g/day, induce physiological ketosis and have gained attention for managing metabolic diseases like obesity and diabetes (11,12). Very low-calorie ketogenic diets (VLCKDs) are sometimes recommended for individuals with obesity and insulin resistance unresponsive to standard diets, aiming to improve metabolic and endocrine parameters (13,14). Preliminary evidence suggests low-carbohydrate diets might offer advantages over standard hypocaloric diets regarding fertility, endocrine profiles, weight loss, and satiety in women with PCOS (15,16). Studies have shown KDs can improve insulin sensitivity, reduce testosterone and insulin-like growth factor-1 (IGF-1), and potentially impact inflammatory markers like tumor necrosis factor-alpha (TNF-α) (17-19). For instance, a 12-week eucaloric KD improved metabolic markers and body composition (19),

while a 6-month low-carbohydrate KD pilot study showed reduced androgen secretion and increased sex hormone-binding globulin (SHBG) (20). However, it is believed that very low-carbohydrate diets may be superior to standard hypocaloric diets in ensuring fertility, endocrine and metabolic parameters, body weight loss, and increasing the feeling of satiety in women with PCOS; nonetheless, more controlled studies are needed to confirm these benefits (16). This study aimed to evaluate the short-term effects of a 4-week low-calorie ketogenic diet (LCKD) intervention on anthropometric measurements, body composition, and biochemical/hormonal parameters in overweight or obese women diagnosed with PCOS.

MATERIALS AND METHODS

Study design and participants

This single-arm intervention study was conducted between October 2019 and March 2020 on 13 volunteer women (mean age 29.77 ± 7.54 years; median BMI 27.2 kg/m²) diagnosed with PCOS according to the Rotterdam 2003 criteria by a gynecologist. Participants were recruited from a nutrition counseling center in İstanbul. The study was conducted according to the ethical rules in the Declaration of Helsinki, with ethical approval from the Acıbadem Mehmet Ali Aydınlar University Medical Evaluation Board (No: 2019-14/17, Date: 12.09.2019). It was registered at ClinicalTrials.gov (NCT06469255). All participants provided written informed consent. Exclusion criteria included other endocrine disorders, chronic liver/kidney disease, specific cardiovascular conditions, pregnancy/lactation, severe psychiatric disorders, oncological diseases, use of medications affecting biochemical parameters, and special dietary needs. In this study, Cohen's effect size ($r = 3.33$) was calculated based on the pre-test and post-test LH/FSH level values from the research conducted by Paoli et al. (19). The power analysis, performed using the G-Power 3.1 program, indicated that a minimum participation of 6 participants

would be sufficient to achieve a 95 % confidence interval, with 1-β set at 0.80 and α at 0.05.

Study protocol

The study intervention lasted for one inter-menstrual period (mean duration 30.92 ± 4.92 days). Participants attended four visits. At the first visit, the study was explained, and consent was obtained. The second visit (baseline, day 2-3 of menstruation) involved baseline blood collection for biochemical/hormonal analysis, anthropometric measurements, body composition analysis, and initiation of the LCKD plan. Urine ketone tests were performed at baseline (negative) and during follow-up visits (visits 3 and 4) to monitor ketosis and compliance. Diet compliance was also monitored via photo logs of meals shared with the researcher. The final visit (day 2-3 of the subsequent menstruation) included final blood collection, anthropometric/body composition measurements, and completion of the intervention. The study flow is depicted in the CONSORT diagram (Fig. 1).

LCKD planning

A personalized LCKD was designed for each participant. Total daily energy requirement was calculated using the Mifflin-St Jeor equation, adjusted for physical activity (factor 1.4) and thermal effect of food (10 %), then reduced by 500 kcal. Macronutrient distribution aimed for < 20 g/day carbohydrates and 0.8-1.2 g/kg/day protein, with the remaining energy from fat (> 30-40 g/day), following what Castellana et al. suggested (21). The average daily intake was 1582.53 ± 165.68 kcal, comprising 3.62 ± 0.77 % carbohydrates (13.55 ± 3.13 g/day), 21.46 ± 1.85 % protein (1.18 ± 0.14 g/kg/day), and 75.08 ± 1.85 % fat (133.42 ± 16.31 g/day). Energy and nutrient intake were analyzed using the Nutrition Information System (BeBiS) 8.2 (data provided as Supplementary Table I) (22). Participants were

allowed to eat unlimited green leafy vegetables, cruciferous vegetables, squash, and cucumbers during the intervention.

Anthropometric measurements

Body weight, height, and circumferences (waist, hip, neck) were measured following standard protocols (23). Body composition (fat percentage, fat, lean mass, total body water mass and phase angle (PhA)) was analyzed (TANİTA MC 780MA). Body mass index (BMI) (kg/m^2) was calculated using the following equation: body weight (kg) / height (m^2).

Biochemical measurements

Blood samples were collected before and after the intervention on days 2-3 of menstruation, after 8-12 hours of fasting. Analyses included fasting glucose, insulin, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, DHEA-SO4, androstenedione, LH, FSH, estradiol, SHBG, total testosterone, prolactin, IGF-1, and TNF-α. HOMA-IR was calculated using the formula: (fasting glucose (mg/dL) × fasting insulin (μU/mL)) / 405 (24).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences v.27 (IBM Inc., Chicago, IL, USA). Normality was assessed using the Shapiro-Wilk test. Descriptive statistics were presented, including the mean, standard deviation, median, minimum, maximum, and frequency distributions. Paired samples T-test or Wilcoxon's signed-rank test were used for pre-post comparisons based on data distribution. Pearson or Spearman correlation tests were used to examine relationships between variables. Multiple regression analysis tested the effect of anthropometric changes on biochemical parameters. Statistical significance was set at $p < 0.05$.

RESULTS

Anthropometric and body composition changes

After the 4-week LCKD intervention, participants achieved a significant mean weight loss of 6.90 % ± 2.04 % (p = 0.001). Significant reductions were observed in BMI, BMR, body fat percentage, fat mass, fat-free mass, muscle mass, and total body water ($p < 0.05$). Mean PhA increased from 5.75° ± 0.46° to 5.86° ± 0.51° (p = 0.289). Significant decreases were also noted in waist, hip, and neck circumferences, as well as waist-to-hip (WHR) and waist-to-height (WHeR) ratios (all $p < 0.05$) (Table I).

Biochemical and hormonal changes

Significant reductions were observed in fasting glucose, insulin, HOMA-IR, HDL-cholesterol, prolactin, and IGF-1 levels ($p < 0.05$). Notably, SHBG levels increased significantly (34.81 ± 15.42 to 60.58 ± 28.44 nmol/L, $p < 0.001$), and TNF-α levels also rose significantly (median 2.7 % to 2.9 %, p = 0.039). No significant changes were found in total cholesterol, LDL-cholesterol, triglycerides, FSH, LH, LH/FSH ratio, DHEA-SO4, total testosterone, androstenedione, or estradiol ($p > 0.05$). The average menstrual cycle duration decreased from 35.54 ± 13.28 days to 30.92 ± 4.92 days (p = 0.129) (Table I).

Correlations and regression analysis

Changes in body weight and BMI showed significant positive correlations with changes in insulin (r = 0.664, p = 0.013; r = 0.636, p = 0.020) and HOMA-IR levels (r = 0.703, p = 0.007; r = 0.686, p = 0.010). Change in fat percentage correlated positively with change in FSH levels (r = 0.601, p = 0.030). Change in hip circumference correlated positively with change in prolactin levels (r = 0.628, p = 0.022) (Table II).

Multiple regression analysis revealed that changes in waist (t = 4.196, p = 0.009), hip (t = 3.983, p = 0.010), and neck circumference (t = -

2.820, p = 0.037) significantly predicted changes in prolactin levels. Furthermore, changes in fat percentage (t = -3.326, p = 0.021), fat mass (t = 3.501, p = 0.017), and hip circumference (t = 2.905, p = 0.034) significantly influenced changes in SHBG levels (Table III). Changes in anthropometric parameters did not significantly predict changes in other hormonal parameters like FSH, LH, testosterone, or estradiol (data not shown).

DISCUSSION

This study demonstrates that a 4-week LCKD intervention in overweight women with PCOS leads to significant improvements in anthropometric parameters and favorable changes in several important biochemical and hormonal markers associated with the condition. While various dietary approaches are explored for PCOS management, the optimal strategy remains debated (15,19,25). KDs are theorized to benefit PCOS by improving hyperinsulinemia, a key driver of the syndrome (3,17).

Consistent with the established importance of weight loss in PCOS (5,6,26), our participants achieved a significant average weight reduction of nearly 7 %. This was accompanied by significant decreases in BMI, fat mass, and central adiposity markers (waist, hip circumference, WHR, WHeR). These findings align with previous studies showing beneficial effects of KD on body composition in PCOS (19,20). Reducing fat mass, particularly visceral adipose tissue which is often increased in PCOS (27,28), is crucial as it impacts androgen conversion and gonadotropin secretion (29).

Phase angle was negatively associated with inflammatory status and hyperandrogenemia, and PhA may be an indicator of PCOS severity (30). The non-significant increase in PhA, despite significant fat loss also accompanied by some lean mass reduction, is noteworthy. PhA is linked to cell integrity and muscle mass, and lower values are reported in PCOS (31,32). While the increase observed here might suggest a positive trend in cell health, the concomitant lean mass loss

likely tempered the significance. To our knowledge, this is the first study evaluating dietary intervention effects on PhA in PCOS, warranting further investigation.

Biochemically, the LCKD significantly reduced fasting glucose, insulin, and HOMA-IR, confirming improvements in insulin sensitivity. This effect is central to the theoretical benefit of KD in PCOS, as lower insulin levels can reduce IGF-1, which was also significantly decreased in our study, thereby suppressing ovarian and adrenal androgen production. (17). These findings are consistent with previous KD studies in PCOS (19,20). Furthermore, the strong correlation between changes in weight/BMI and changes in insulin/HOMA-IR highlights the connection between weight loss and enhanced insulin action.

We observed a significant increase in SHBG levels, which is crucial as low SHBG contributes to hyperandrogenism in PCOS by increasing free androgen levels (29,33). The increase in SHBG, influenced by reductions in fat percentage, fat mass, and hip circumference in our regression model, suggests a potential positive impact of short-term LCKD on the androgen profile, consistent with longer-term KD studies (20,3). However, we did not observe significant changes in total testosterone, DHEA-SO4, or androstenedione levels within the 4-week intervention period. This might be due to the short duration, as hormonal shifts, particularly in androgens like testosterone with longer half-lives or complex regulation (e.g., DHEA-S influenced by stress), may require more extended intervention (33,35). Similarly, gonadotropins (FSH, LH, LH/FSH ratio) and estradiol did not change significantly, although a correlation between fat reduction and FSH change was noted. Longer interventions have reported improvements in LH/FSH ratio and other hormones (19,36).

Interestingly, prolactin levels significantly decreased, correlating with reductions in hip circumference and influenced by changes in waist, hip, and neck circumferences. Elevated prolactin can occur in PCOS and may be linked to adiposity markers (37, 38). Our findings align

with Paoli et al. (19), suggesting LCKD might favorably modulate prolactin.

Lipid profiles showed mixed results. HDL-cholesterol significantly decreased, contrasting with some studies showing improved HDL with KD (19,35). Total cholesterol, LDL, and triglycerides did not change significantly. While participants increased unsaturated fat intake, overall fat and saturated fat intake also rose with the LCKD, potentially explaining the lack of improvement or even the decrease in HDL (39). The impact of long-term KD on CVD risk markers in PCOS needs further clarification.

Unexpectedly, the pro-inflammatory marker TNF-α significantly increased post-intervention despite improvements in other metabolic markers. While some animal studies suggest KDs reduce inflammation (40), human data, especially in PCOS, where baseline inflammation is often elevated (17), are unclear. This finding warrants further investigation into the specific effects of short-term LCKD on inflammatory pathways in PCOS.

Limitations

The current study has several limitations. First, the relatively small sample size limits the generalizability of our findings. While examining the therapeutic effects of a ketogenic diet combined with calorie restriction in overweight and obese women with PCOS, the findings are limited by the fact that the intervention lasted only 4 weeks, making the long-term efficacy and sustainability of the low-carbohydrate ketogenic diet uncertain. The scientific literature suggests that the majority of individuals with PCOS are overweight. However, given the heterogeneity of PCOS, future research is needed to investigate the metabolic effects of isocaloric ketogenic diet interventions, particularly in normal-weight PCOS patients. Addressing these limitations will be crucial for a more comprehensive evaluation of treatment effects in future studies.

CONCLUSIONS

This study demonstrates that a short-term (4-week) low-calorie ketogenic diet (LCKD) intervention effectively improves metabolic parameters and body composition, including insulin sensitivity (glucose, insulin, HOMA-IR), SHBG, IGF-1, and prolactin, in overweight or obese women with polycystic ovary syndrome (PCOS). In particular, multiple regression analysis revealed significant associations, with changes in waist, hip, and neck circumference predicting changes in prolactin levels, and changes in fat percentage, fat mass, and hip circumference influencing changes in SHBG levels. These findings suggest that LCKD holds promise as a therapeutic dietary approach for PCOS, particularly in reducing metabolic risks associated with excess body weight. Further research is needed to investigate its long-term efficacy and sustainability.

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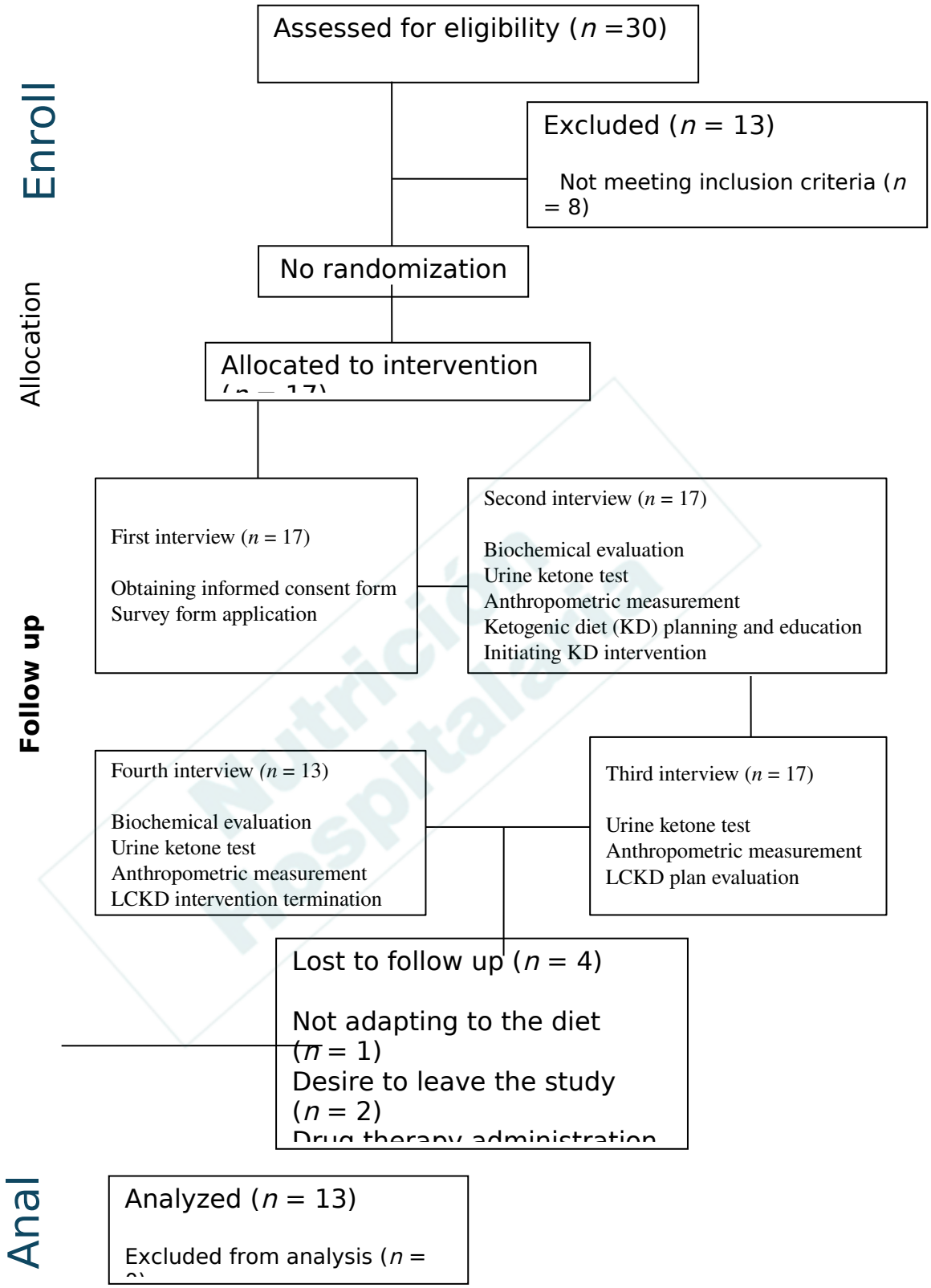

Figure 1. CONSORT flow diagram of the study.

Table I. Biochemical and anthropometric changes

	Pre-intervention	**Post-intervention**	***p***
Height, cm	162.08 ± 6.36	-	-
Body weight, kg	74.4 (58.8-112.7)	68.1 (55.2-106.2)	0.001†**
BMI, kg/m²	27.2 (25.1-42.9)	25.6 (22.8-40.5)	0.001†**
BMR, kcal/d	1472 (1197-1909)	1406 (1141-1826)	0.002†**
Fat, %	33.5 (30.8-46.9)	32.4 (29.2-45.8)	0.007†**
Fat mass, kg	24.4 (19.7-52.8)	22.0 (18.1-48.6)	0.001†**
Fat-free mass, kg	49.28 ± 5.57	46.98 ± 5.47	< 0.001‡***
Muscle mass, kg	46.78 ± 5.30	44.58 ± 5.19	< 0.001‡***
Total body water, kg	35.43 ± 4.02	33.78 ± 3.93	< 0.001‡***
PhA, °	5.75 ± 0.46	5.86 ± 0.51	0.289‡
Waist circumference, cm	96.0 (88.0-123.0)	89.0 (83.0-118.0)	0.001†**
Hip circumference, cm	111.0 (103.0-137.0)	105.0 (99.0-135.0)	0.001†**
WHR	0.9 (0.8-1.0)	0.8 (0.8-1.0)	0.011†**
WHeR	0.6 (0.6-0.8)	0.5 (0.5-0.7)	0.001†**
Neck circumference, cm	35.0 (31.0-40.0)	33.0 (30.0-40.0)	0.002†**
Glucose, mg/dL	88.00 ± 9.31	78.54 ± 12.39	< 0,001‡***
Insulin, mU/L	11.2 (4.9-27.7)	5.8 (2.4-19.4)	0.003†**
HOMA-IR, index	2.36 (0.99-6.36)	1.1 (0.4-4.3)	0.003†**
Total cholesterol, mg/dL	181.54 ± 46.00	178.38 ± 38.37	0.619‡
HDL-C, mg/dL	48.62 ± 13.46	40.92 ± 7.95	0.004‡**
LDL-C, mg/dL	128.85 ± 41.29	128.00 ± 37.64	0.901‡
Triglyceride, mg/dL	92 (48-195)	91 (61-184)	0.807†
FSH, U/L	5.42 ± 1.69	5.82 ± 2.13	0.391‡
LH, U/L	6.8 (4.3-16)	7.5 (3.8-13.6)	0.889†
LH/FSH	1.56 ± 0.60	1.39 ± 0.54	0.158‡
Prolactin, µg/L	17.9 (6.9-57.5)	13 (7.3-35.1)	0.025†*
DHEA-SO4, µg/dL	388.07 ± 125.66	419.63 ± 177.39	0.358‡
Total testosterone, µg/dL	0.49 ± 0.18	0.51 ± 0.22	0.559‡
IGF-1, µg/L	196.92 ± 63.71	156.04 ± 59.15	0.001‡
Androstenedione, µg/L	3.95 ± 1.55	3.19 ± 1.72	0.127‡

Estradiol (E2), ng/L	48.4 (31.2-153.4)	49.6 (39.7-121.8)	0.972[†]
TNF-α, %	2.69 (1.4-7.1)	2.9 (1.6-10.4)	0.039[†]
Menstrual cycle duration, days	36.54 ± 13.28	30.92 ± 4.92	0.129[‡]

[*]p <0.05, [**]p < 0.01, [***]p < 0.001; [†]Wilcoxon signed-rank test; [‡]Paired sample t-test, arithmetic mean ± standard deviation, median (minimum-maximum); BMI: body mass index; BMR: basal metabolic rate; DHEA-SO4: dehydroepiandrosterone sulfate; FSH: follicle stimulating hormone; HDL-C: high-density lipoprotein-vholesterol; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL-C: low-density lipoprotein-cholesterol; LH: luteinizing hormone; LH/FSH: luteinizing hormone/follicle stimulating hormone; PhA: phase angle; WHR: waist/hip ratio; WHeR: waist/height ratio; IGF-1: insulin-like growth factor 1; SHBG: sex hormone-binding globulin; TNF-α: tumor necrosis factor alpha.

Table II. Correlation between the intervention and the amount of change observed in anthropometric and biochemical parameters

		BW	**BMI**	**FP**	**FM**	**WC**	**HC**	**WHR**	**NC**
Glucose (mg/dL)	*r-s*	*r* = 0.189	*r* = 0.203	*r* = 0.273	*r* = 0.214	*r* = -0.088	*r* = 0.297	s = -0.341	*r* = -0.188
	p	0.536	0.506	0.367	0.484	0.776	0.324	0.254	0.539
Total cholesterol (mg/dL)	*r-s*	*r* = -0.094	*r* = -0.038	*r* = -0.040	*r* = 0.018	*r* = 0.116	*r* = -0.197	s = 0.045	*r* = 0.121
	p	0.761	0.901	0.897	0.953	0.706	0.519	0.884	0.693
HDL-C (mg/dL)	*r-s*	*r* = -0.104	*r* = -0.073	*r* = 0.357	*r* = 0.361	*r* = 0.298	*r* = -0.275	s = 0.308	*r* = -0.386
	p	0.736	0.813	0.231	0.225	0.322	0.363	0.305	0.193
LDL-C (mg/dL)	*r-s*	*r* = 0.036	*r* = 0.105	*r* = -0.243	*r* = -0.234	*r* = -0.087	*r* = 0.121	s = -0.076	*r* = 0.379
	p	0.906	0.732	0.423	0.442	0.778	0.695	0.806	0.202
Triglyceride (mg/dL)	*r-s*	*r* = -0.040	*r* = -0.015	*r* = -0.243	*r* = 0.004	*r* = 0.119	*r* = -0.425	s = 0.412	*r* = -0.231
	p	0.896	0.961	0.424	0.99	0.698	0.148	0.161	0.448
Insulin (mU/L)	*r-s*	*r = 0.664*	*r = 0.636*	*r* = -0.023	*r* = 0.438	*r* = -0.045	*r* = 0.099	s = -0.115	*r* = 0.261
	p	*0.013**	*0.020**	0.94	0.134	0.885	0.747	0.708	0.39
FSH (U/L)	*r-s*	*r* = -0.375	*r* = -0.317	*r = 0.601*	*r* = 0.259	*r* = -0.097	*r* = 0.241	s = -0.211	*r* = -0.009
	p	0.207	0.291	*0.030**	0.393	0.752	0.427	0.488	0.978
LH (U/L)	*s*	s = -0.118	s = -0.168	s = 0.415	s = 0.374	s = 0.061	s = 0.241	s = -0.111	s = 0.405
	p	0.7	0.584	0.158	0.208	0.842	0.428	0.718	0.169
LH/FSH	*r-s*	*r* = 0.183	*r* = 0.170	*r* = 0.307	*r* = 0.390	*r* = -0.097	*r* = 0.233	s = -0.118	*r* = 0.399
	p	0.55	0.578	0.308	0.188	0.751	0.444	0.701	0.177
Prolactin (µg/L)	*r-s*	*r* = 0.255	*r* = 0.157	*r* = -0.444	*r* = -0.350	*r* = 0.232	*r = 0.628*	s = 0.084	*r* = 0.167

	p	0.401	0.608	0.128	0.24	0.445	*0.022**	0.785	0.586
DHEA-SO4 (µg/dL)	*r-s*	*r = -0.383*	*r* = -0.213	*r* = 0.426	*r* = 0.184	*r* = -0.100	*r* = -0.393	s = -0.042	*r* = -0.085
	p	*0.196*	0.485	0.146	0.546	0.745	0.184	0.891	0.782
Total testosterone (µg/L)	*r-s*	*r = -0.194*	*r* = -0.014	*r* = 0.406	*r* = 0.205	*r* = -0.231	*r* = -0.281	s = -0.244	*r* = -0.223
	p	*0.524*	0.963	0.169	0.502	0.448	0.352	0.422	0.463
SHBG (nmol/L)	*r-s*	*r = -0.003*	*r* = -0.072	*r* = -0.003	*r* = 0.150	*r* = 0.049	*r* = 0.301	s = 0.143	*r* = 0.148
	p	*0.993*	0.814	0.993	0.624	0.874	0.318	0.641	0.629
IGF-1 (µg/L)	*r-s*	*r = -0.078*	*r* = -0.230	*r* = -0.315	*r* = -0.238	*r* = 0.503	*r* = -0.055	s = 0.504	*r* = 0.022
	p	*0.8*	0.449	0.294	0.433	0.08	0.858	0.079	0.944
Androstenedione (µg/L)	*r-s*	*r = 0.026*	*r* = 0.148	*r* = 0.389	*r* = 0.240	*r* = -0.454	*r* = 0.209	s = -0.527	*r* = 0.161
	p	*0.934*	0.63	0.189	0.429	0.119	0.493	0.064	0.6
Estradiol (ng/L)	*r-s*	*r = -0.336*	*r* = -0.347	*r* = 0.517	*r* = 0.235	*r* = -0.207	*r* = 0.121	s = -0.152	*r* = -0.004
	p	*0.262*	0.246	0.071	0.44	0.498	0.694	0.621	0.989
TNF-α (%)	*s*	*s = 0.184*	s = 0.061	s = -0.198	s = -0.132	s = 0.064	s = 0.448	s = -0.112	s = 0.489
	p	*0.547*	0.843	0.517	0.668	0.835	0.125	0.715	0.09
HOMA-IR (index)	*r-s*	*r = 0.703*	*r = 0.686*	*r* = -0.055	*r* = 0.407	*r* = -0.139	*r* = 0.180	s = -0.202	*r* = 0.222
	p	*0.007***	*0.010**	0.858	0.167	0.65	0.555	0.487	0.466

*$p < 0.05$, **$p < 0.01$; *r*: Pearson's product moment correlation coefficient; s: Spearman's rho correlation test; BMI: body mass index; BW: body weight; FFM: fat-free mass; FM: fat mass; FP: fat percentage; FSH: follicle-stimulating hormone; HC: hip circumference; HDL-C: high-density lipoprotein-cholesterol; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL-C: low-density lipoprotein-cholesterol; LH: luteinizing hormone; LH/FSH:

luteinizing hormone/follicle stimulating hormone; MM: muscle mass; NC: neck circumference; TBW: total body water; WC: waist circumference; WHR: waist/hip ratio. DHEA-SO4: dehydroepiandrosterone dulfate; IGF-1: insulin-like growth factor 1; SHBG: sex hormone binding globulin.

Table III. Effect of changes in anthropometric measurements after intervention on changes in biochemical parameters

						95 % C.I for β	
Variable		**β**	**S.E.**	**t**	***p*-value**	**Lower**	**Upper**
Prolactin	Body weight	3.131	6.396	0.490	0.645	-13.311	19.574
	BMI	-6.238	12.903	-0.483	0.649	-39.406	26.93
	Fat (%)	-1.203	4.267	-0.282	0.789	-12.173	9.767
	Fat mass	-2.773	5.546	-0.500	0.638	-17.03	11.485
	Waist circumference	2.583	0.615	*4.196*	*0.009***	1.000	4.165
	Hip circumference	4.968	1.247	*3.983*	*0.010**	1.762	8.175
	Neck circumference	-6.899	2.447	*-2.820*	*0.037**	-13.189	-0.609
SHBG	Body weight	-29.013	13.529	-2.145	0.085	-63.789	5.763
	BMI	25.512	27.29	0.935	0.393	-44.638	95.662
	Fat (%)	-30.022	9.025	*-3.326*	*0.021**	-53.223	-6.821
	Fat mass	41.065	Kas.73	*3.501*	*0.017**	10.911	71.218

	Waist circumference	0.125	1.302	0.096	0.927	-3.221	3.471
	Hip circumference	7.664	2.638	*2.905*	*0.034**	0.882	14.445
	Neck circumference	2.623	5.175	0.507	0.634	-10.68	15.926

**p*<0,05; ***p*<0,01; β: beta coefficient; C.I.: confidence interval; S.E.: standard error.

Supplementary Table I. Changes in energy and macronutrients after intervention

Parameters	**Pre-intervention**	**Post-intervention**	***p***
Energy (kkal)	1405.82 ± 294.21	1582.53 ± 165.68	*0.043*[†]
Carbohydrate (g)	129.21 ± 38.32	13.55 ± 3.13	*< 0.001*[†]
Carbohydrate (%)	37.31 ± 6.52	3.62 ± 0.77	*< 0.001*[†]
Fiber (g)	14.7 ± 4.65	11.3 ± 1.85	*0.055*[†]
Protein (g)	69.65 ± 18.03	82.93 ± 7.33	*0.019*[†]
Protein (g/kg)	0.92 ± 0.23	1.18 ± 0.14	*0.001*[†]
Protein (%)	20.64 ± 3.67	21.46 ± 1.85	*0.54c*[†]
Fat (g)	65.8 ± 15.88	133.42 ± 16.31	*< 0.001*[†]
Fat (%)	41.77 ± 6.13	75.08 ± 1.85	*< 0.001*[†]
Saturated fats (g)	23.34 ± 5.49	28.69 ± 6.72	*0.009*[†]
Saturated fats (%)	15 ± 2.27	16.25 ± 2.91	*0.146*[†]
Monounsaturated fatty acids (g)	27.53 ± 8.39	62.27 ± 8.02	*< 0.001*[†]
Monounsaturated fatty acids (%)	17.64 ± 3.5	35.41 ± 2.74	*< 0.001*[†]
Polyunsaturated fatty acids (g)	10.02 ± 2.74	33.6 ± 6.4	*< 0.001*[†]
Polyunsaturated fatty acids (%)	6.51 ± 1.5	19.01 ± 2.23	*< 0.001*[†]
Vitamin A (µg)	877.5	1301	*0.173*[‡]
Vitamin B1 (mg)	0.72 ± 0.2	0.78 ± 0.13	*0.457*[†]
Vitamin B2 (mg)	1.27 ± 0.48	1.51 ± 0.43	*0.152*[†]
Vitamin B3 (mg)	13.79 ± 6.29	16.87 ± 4.52	*0.106*[†]
Vitamin B6 (mg)	1.12 ± 0.4	1.25 ± 0.3	*0.295*[†]
Vitamin B12 (µg)	5.59	9.9	*0.087*[‡]
Vitamin C (mg)	92.89 ± 42.36	121.15 ± 48.97	*0.192*[†]
Vitamin D (µg)	2.37	3.1	*0.116*[‡]
Vitamin E (mg)	11.39	34.8	*0.001*[‡]
Folate (µg)	210.4	358.4	*0.005*[‡]
Sodium (mg)	3136.28 ± 631.6	3682.23 ± 768.04	*0.053*[†]
Potassium (mg)	2097.18 ± 627.71	2135.13 ± 215.61	*0.847*[†]
Calcium (mg)	660.27 ±	881.89 ± 229.95	*0.025*[†]

	163.3		
Magnesium (mg)	190.64	200.2	*0.507*‡
Phosphorus (mg)	1050.95 ± 249.24	1216.8 ± 167.17	*0.047*†
Iron (mg)	8.78 ± 2.07	12.08 ± 3.41	*0.012*†
Zinc (mg)	9.11	13.5	*0.055*‡

*$p < 0.05$; †Paired samples t-test; ‡Wilcoxon's sign test; arithmetic mean ± standard deviation, median.