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The Effectiveness of High Protein and Low Carbohydrate Diet on Reducing Pro-Inflamatory Activity in Rattus Norvegicus using PCOS Model

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ABSTRACT: Advanced Glycation End Products (AGEs) are highly reactive molecules formed through a non-enzymatic glycation process between reducing sugars and proteins, lipids, or nucleic acids. AGEs accumulate from exogenous sources, particularly foods cooked and processed at high temperatures, and contribute to reproductive and metabolic dysfunction associated with Polycystic Ovary Syndrome (PCOS) (2). Several studies have described the involvement of AGEs in elevated proinflammatory markers among women with PCOS, which exacerbates obesity and hyperinsulinemia (1). Management of women with PCOS includes calorie control and low-carbohydrate diets, both of which have been reported to improve the reproductive function of women with PCOS. This study aimed to combine a Low-Carbohydrate, High-Protein (LCHP) in an insulin-resistant PCOS (PCOS-IR) model to examine the proinflammatory contribution (AGEs and interleukin-6 [IL-6]) in PCOS-IR rats. To date, similar studies remain limited. The study used a post-test-only control design involving six rattus norvegicus aged 2–3 months, weighing 150–200 g. Animals were randomized into three groups (n = 6 each): K– (non-PCOS-IR, standard chow), K+ (PCOS-IR, standard chow), and P (PCOS-IR + LCHP). Serum samples were analysed for AGEs and IL-6 levels using ELISA. Data were analysed with ANOVA and post hoc tests to compare AGEs and IL-6 levels across groups. ANOVA revealed that IL-6 levels differed significantly ($p = 0.002$), indicating that the high-protein, low-carbohydrate diet reduced IL-6 levels in PCOS-IR rats. Significant differences were found between the K- and P groups ($p = 0.002$) and between the K+ and P groups ($p = 0.037$). However, IL-6 reduction between K- and K+ groups was insignificant ($p = 0.437$). Changes in AGEs levels among groups also differed significantly ($p = 0.015$). Post hoc analysis showed significant differences between the K- and P groups ($p = 0.023$) and between the K+ and P groups ($p = 0.047$). Nevertheless, the LCHP diet did not significantly reduce AGEs levels between K- and K+ groups ($p = 1.000$). At endpoint, between-group comparisons showed significant differences (one-way ANOVA), followed by Bonferroni pairwise tests. The high-protein, low-carbohydrate diet may be a potential dietary management modality for PCOS-IR.

KEYWORDS: AGEs, IL-6, LCHP diet, PCOS-IR

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders observed among women of reproductive age, typically between 4 and 20 years. The most frequent manifestations of PCOS include oligomenorrhea, hirsutism, insulin resistance (IR), obesity, and metabolic syndrome. According to the Rotterdam criteria for diagnosing PCOS, at least two of the following three features must be present: (a) oligomenorrhea or anovulation; (b) hyperandrogenism; and (c) polycystic ovaries, characterized on ultrasonography by ≥12 follicles measuring 2–9 mm in diameter and/or an ovarian volume >10 mL in at least one ovary (3). Previous studies have reported that women with PCOS experience inflammation that exacerbates insulin resistance. Dietary patterns, lifestyle, and environmental exposures adversely affect PCOS and directly influence both fertility and overall health (4).

The aetiology of Polycystic Ovary Syndrome (PCOS) remains unclear; however, it has been associated with several hypotheses, including environmental and genetic factors. Through a variety of metabolic pathways, including insulin resistance, dysregulation of adipose tissue, aberrant steroid hormone synthesis, and disturbance of the hypothalamic-pituitary-ovarian axis, these variables may result in systemic dysfunction (3). PCOS is often linked to an increased prevalence of comorbid conditions, particularly metabolic disorders such as obesity and insulin resistance. Furthermore, obesity usually makes PCOS more severe. There have been reports of increased circulating monocyte and lymphocyte counts, inflammatory infiltration within ovarian tissue, and greater levels of tumor necrosis factor (TNF) and C-reactive protein (CRP) in women with PCOS. Obesity and hyperinsulinemia exacerbate this chronic inflammatory condition. A reciprocal link between hyperinsulinemia, obesity, hyperandrogenism, and inflammatory state has been reported in earlier research (1). Adipocytes are among the cell types that produce cytokines, which are soluble chemicals involved in intercellular communication. Additionally, they are essential for biological mechanisms that encourage the recruitment of macrophages. Several researchers have found that women with PCOS have higher levels of macrophage inflammatory protein-

1α (MIP-1α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6) (5). According to other research, interleukin genes have a key role in mediating the inflammatory response and are implicated in apoptosis, differentiation, and cell proliferation (5).

The uncertainty regarding whether inflammation is caused by PCOS itself or by insulin resistance and obesity makes understanding the mechanisms underlying elevated inflammatory marker concentrations in women with PCOS particularly important. Several inflammatory markers, such as TNF, CRP, and various interleukins—including increased IL-6—may result from metabolic disturbances. IL-6 stimulates hepatic production of CRP under its influence, serving as one of the key inflammatory markers in women with PCOS. The primary role of aromatase is to maintain the balance of sex hormones during chronic inflammation. Decreased aromatase activity has been observed in women with PCOS, leading to elevated serum androgen levels (1). Proinflammatory cytokines stimulate aromatase activity, and inflammatory conditions convert androgens into estrogens. Additionally, testosterone inhibits aromatase activity. Various estrogen-mediated effects on inflammatory processes are linked to immune responses. Consequently, cytokines and other inflammatory factors can activate aromatase and alter the estrogen-to-androgen ratio. Interleukin-6 (IL-6) and TNF have been shown to activate aromatase in various cell types. These mechanisms are also involved in fertility and the implantation of fertilised oocytes in the uterus. Moreover, such alterations may result in dysfunction leading to miscarriage and infertility (6).

Advanced Glycation End Products (AGEs) are reactive molecules that have changed, according to earlier research. Reducing sugars react non-enzymatically with proteins, lipids, amino acids, or nucleic acids to generate AGEs. Higher levels of AGEs and higher expression of Advanced Glycation End Products receptors (RAGE) have been observed in women with PCOS (1). Through a positive feedback loop that increases RAGE receptor expression, the AGE–RAGE axis interaction triggers a number of intracellular inflammatory signaling pathways and oxidative stress signaling cascades, resulting in tissue damage. Immunohistochemical results in the ovaries of women with and without PCOS have revealed differences in the expression of proteins affected by AGE and RAGE. Granulosa cells in PCOS-afflicted women's ovaries express RAGE more strongly than theca interna cells do. These findings demonstrate that the multi-proinflammatory RAGE molecules and receptors are pathogenic and have a substantial role in reproductive disorders that result in ovarian dysfunction (2).

Women with Polycystic Ovary Syndrome (PCOS) who were given a high-AGEs diet for two months exhibited significantly higher serum levels of AGE, androstenedione, and free androgen compared with those who followed a low-AGE diet. The effect of AGE on granulosa cell function has been shown to induce granulosa cell proliferation in the ovaries; moreover, AGE decreases progesterone production by inhibiting the aromatase-mediated conversion of androgens into estrogens. This is associated with downregulation of luteinizing hormone (LH)/cyclic adenosine monophosphate (cAMP) receptor activity, leading to irregular menstrual cycles, increased follicle or cyst formation, thinning of the granulosa layer, and reduced serum progesterone levels (7). A low-carbohydrate diet comprises approximately 40% carbohydrates, 20% protein, and 40% fat. This dietary approach, developed in the early 2000s, emphasizes plant-based proteins, legumes, and phytosterols. Lipid profiles have shown improvements, including higher levels of high-density lipoprotein (HDL) cholesterol. Low-carb diets also improve body weight, serum insulin levels, fasting glucose, and waist circumference in women with PCOS, according to other research. 94 overweight and obese women with PCOS were given a low-carb diet consisting of 30% protein, 40% carbs, and 30% fat for 20 weeks. Thomson and colleagues found that this diet decreased lean mass and fat by about 2-3 kg. Furthermore, this diet has shown beneficial effects in several conditions, including type 2 diabetes mellitus, cancer, neurological disorders, obesity, and PCOS (8).

Research has validated the benefits of ketogenic and low-carb diets. Management of women with Polycystic Ovary Syndrome (PCOS) through carbohydrate restriction influences insulin secretion, thereby effectively reducing hyperandrogenism. However, these dietary interventions have not been based on therapeutic considerations related to differing etiologies. To our knowledge, no studies have specifically investigated inflammatory changes. Furthermore, whether such diets are more effective in treating PCOS remains uncertain. Therefore, the present study aimed to determine whether a high-protein, low-carbohydrate diet provides greater therapeutic benefits in improving PCOS by assessing serum levels of interleukin-6 (IL-6) and Advanced Glycation End Products (AGEs).

MATERIALS AND METHODS

2.1 Animals and experimental protocols

A three-month-old female white rattus norvegicus model PCOS-IR weighing between 100 and 200 grams served as the study's experimental unit. White mice were selected due to their simple handling, short estrogen cycle, shorter reproductive life, and stable genetics. The white rattus norvegicus was also employed as an insulin-resistant SOPK model in earlier studies in 2020. The trial started with a one-week adaption phase that included a usual vaginal swab result, predicted behavior, and a health condition. Anatomical abnormalities (e.g., ears damaged or not intact, short or stumpy tail, one or all four legs malformed, inability to stand, sores on body parts, and unclear eyes) and pregnancy during the adaption phase are factors for excluding white mice. These procedures have been approved by the Ethics Committee of the Faculty of Veterinary Medicine, Airlangga University, Indonesia.

This study used a post-test-only control group design and was carried out as a laboratory experiment. The PCOS model was used in the rattus norvegicus investigation. The rats were split into three main groups: the PCOS-IR rats model fed broiler standard chow (K+), the normal control group (K-), and the PCOS-IR rats model fed a low-carb, high-protein diet (LCHP) (P). This study was carried out in the laboratory of Airlangga University's Faculty of Veterinary Medicine in Indonesia. All of these procedures have been approved by the ethics committee of the Faculty of Veterinary Medicine, Airlangga University, Indonesia, No. 2. KE.062.04.2019 and the ethics committee of STIKES Husada Jombang, No. 002-KEPKSHJ on December 6, 2024.

Material protocols

Standard feed for rats consisted of commercial broiler feed containing 13% moisture, 21.5–23.8% protein, 5.0% fat, 5.0% fiber, 7.0% ash, 0.9% calcium (Ca), and 0.6% phosphorus (P), with a metabolizable energy of 3025–3125 kcal/g. In this study, the treatment groups received a pellet diet formulated with corn flour representing a low-glycemic index carbohydrate source (40%), egg white as a protein source (30%), and fish oil rich in omega-3 fatty acids (30% fat), following the formulation proposed by Itziar (2010) for a polycystic ovary syndrome with insulin resistance (PCOS-IR) diet (40% carbohydrate, 30% protein, and 30% fat). The low-carbohydrate high-protein diet and the standard broiler feed were administered for twenty days.

For 28 days, 0.1 mL of testosterone propionate was injected intramuscularly once daily to create the PCOS-IR model (9). Since another study in 2009 demonstrated that extended exposure to androgens, such as testosterone propionate, impacts the insulin resistance index and inflammation in the PCOS model rattus norvegicus serum, it was utilized to induce PCOS symptoms in this species. The Lemeshow (1997) formula was used to calculate the size of the rattus norvegicus sample in each group (9). The group that received testosterone propionate for 14, 21, and 28 days had a significantly greater insulin resistance score than the controls. A vaginal swab was taken both before and after therapy to observe any changes in the cycle brought on by the medication. On the 48th day, the rats were sacrificed by ether anesthesia and neck dislocation, and then the ovaries and blood samples were taken.

2.2. Biochemical assay for AGEs and IL-6 levels

The experimental animals fasted for 12 hours in order to collect blood before they were killed. An enzyme-linked immunosorbent assay (ELISA) was used to detect the amounts of AGEs and IL-6 in the blood drawn from the rats' blood vessels. As the gold standard of immunoassays, ELISA is a labeled immunoassay. Antibodies, antigens, and proteins are among the things that the very sensitive immunological test can identify and measure. At the conclusion of the investigation, blood samples were acquired for AGEs and IL-6; the units obtained are ng/mL. A ratio is the data scale. The German Bioassay Kit No. E0177Mo was used for the ELISA analysis that measured the levels of IL-6. An ELISA test was performed to determine the AGEs level using the Abbexa Cambridge UK Kit No. abx054078.

2.3. Statistical analysis

A data collecting form created specifically for this study to track AGEs and IL-6 levels in the PCOS-IR rattus norvegicus model will be used to capture the research data. The normalcy test, also known as the Kolmogorov-Smirnov test, is performed first. The analysis of variance, or ANOVA, test is applied when the distribution is normal. However, the Mann-Whitney or Kruskal-Wallis non-parametric tests will be used if the distribution is aberrant. When there is a significant difference in the variable across groups, the Bonferroni Post Hoc test will be used. SPSS version 22 software tools will be used for statistical computations.

RESULTS AND DISCUSSION

Measurement of IL-6 Levels

Table 1.1. Kolmogorov–Smirnov Test for IL-6 Levels

Kolmogorov-Smirnov	Asymp Sig	SD
.659	.778	.03221415

a. Test distribution is Normal.

b. Calculated from data.

The results of the One-Sample Kolmogorov–Smirnov test showed that the data were normally distributed. This conclusion was supported by an Asymptotic Significance (two-tailed) value greater than 0.05, indicating that the assumption of normality for the One-Way ANOVA test was satisfied.

Table 1.2. Test of Homogeneity of IL-6 Levels

Levene Statistic	df	Sig
.724	15	.501

According to the SPSS output for the *Test of Homogeneity of Variances*, the significance value (Sig) was 0.501. Since the significance value of 0.501 was greater than 0.05, it can be concluded that the variances of the compared serum IL-6 concentrations were equal (homogeneous). Therefore, the assumption of homogeneity required for the One-Way ANOVA test was satisfied.

Table 1.3. One-Way ANOVA Test for IL-6 Levels

ANOVA

Serum IL-6 Concentration

	Sum of Squares	df	Mean	F	Sig
Between Groups	.022	2	.011	9.526	.002
Within Groups	.017	15	.001		
Total	.038	17			

Based on the results of the One-Way ANOVA, the significance value (Sig) was 0.002, which was less than 0.05. Therefore, the mean serum IL-6 concentrations differed significantly among the three treatment groups.

Table 1.4. Post Hoc Test for IL-6 Levels

Groups	Group	Mean Difference	Std. error	Sig		
					Lower Bound	Upper Bound
K-	K+	-28.500	19.40695	.488	-80.7773	23.7773
	P	-83.333*		.002	-135.6106	-31.0561
K+	K-	28.500		.488	-23.7773	80.7773
	P	-54.8333*		.038	-107.1106	-2.5561
P	K-	83.333*		.002	31.0561	135.6106
	K+	54.8333*		.038	2.5561	107.1106

Based on the results of the post hoc analysis using the Bonferroni test, there were significant differences in serum IL-6 concentrations between the P group and the K- group (Sig. = 0.002 < 0.05), as well as between the P group and the K+ group (Sig. = 0.038 < 0.05). However, there was no significant difference in serum IL-6 concentrations between the K– and K+ groups (Sig. = 0.488 > 0.05).

Measurement of AGEs Levels

Table 1.5. Kolmogorov–Smirnov Test for AGEs Levels

Uji Kolmogorov-Smirnov	**Asymp Sig**	**SD**
.680	.745	.07936158

a. Test distribution is normal

b. Calculated from data

The results of the One-Sample Kolmogorov–Smirnov test indicated that the data were normally distributed. This was indicated by an Asymptotic Significance (two-tailed) value greater than 0.05, confirming that the assumption of normality required for the One-Way ANOVA test was satisfied.

Table 1.6. Test of Homogeneity of AGEs Levels

OD_{450} Values of AGEs

Levene Statistic	**df**	**Sig**
1.820	15	.196

According to the SPSS output for the *Test of Homogeneity of Variances*, the significance value (Sig) was 0.196. Since this value was greater than 0.05, it can be concluded that the variances of the compared OD_{450} values of AGEs were equal (homogeneous). Therefore, the assumption of homogeneity required for the One-Way ANOVA test was satisfied.

Table 1.7. One-Way ANOVA Test for AGEs Levels

ANOVA

	Sum of Squares	df	Mean	F	Sig
Between Groups	.072	2	.036	5.676	.015
Within Groups	.095	15	.006		
Total	.167	17			

Based on the results of the One-Way ANOVA, the significance value (Sig) was 0.015, which was less than 0.05. Therefore, it can be concluded that the mean OD_{450} values of AGEs differed significantly among the three treatment groups.

Table 1.8. Post Hoc Test for AGEs Levels

Groups	Group	Mean Difference	*P*	Sig	95% Interval	
					Lower Bound	Upper Bound
K-	K+	13.31	0.033	.595	110.88	227.97
	P	67.88		.014		
K+	K-	-13.31		.595	193.63	193.63
	P	54.57		.042		
P	K-	-67.88		.014	134.95	134.95
	K+	-54.57		.042		

The OD_{450} values of AGEs were significantly different between the P1 group and the K-group (Sig. = 0.023 < 0.05) and between the P1 group and the K+ group (Sig. = 0.047 < 0.05), according to the findings of the post hoc analysis using the Bonferroni test. The AGEs' OD_{450} values did not, however, differ significantly between the K– and K+ groups (Sig. = 1.000 > 0.05).

The results of the ANOVA test showed that serum AGEs levels decreased following the administration of a high-protein, low-carbohydrate diet in insulin-resistant PCOS model rats. P = 0.015, indicating a statistically significant difference from the dietary intervention. The reduction in AGEs levels after the high-protein, low-carbohydrate diet reflects one aspect of lifestyle modification—such as dietary adjustment and physical activity—recommended as the first-line therapy for women with PCOS. A hypocaloric diet has been reported to effectively regulate insulin secretion, endocrine balance, lipid levels, body weight reduction, and menstrual cycle improvement (11). Conversely, food processing involving high-temperature cooking, consumption of fast food, and high-calorie meals may increase AGEs secretion in the blood, contributing to ovulatory dysfunction. Disruption of the hypothalamic–pituitary–ovarian (HPO) axis plays a role in the etiology of PCOS related to elevated AGEs levels. Tissue damage results from the interaction of AGEs with their receptor (RAGE), which triggers a number of oxidative stress and inflammatory signaling pathways. The positive feedback loop that increases RAGE expression is even worse by such damage. Granulosa cells in PCOS-afflicted women express more RAGE than theca cells, a pathogenic change strongly linked to ovarian dysfunction and reproductive abnormalities (12). This study's observed decrease in AGEs levels is consistent with previous reports showing that low-AGEs foods can reduce circulating AGEs and improve metabolic, hormonal, and oxidative stress biomarkers in women with PCOS.

The post hoc test of AGEs levels in this study was conducted to compare the groups and identify which ones exhibited significant differences following the administration of a high-protein, low-carbohydrate diet. Significant differences were observed between the K– and P groups (p = 0.023) and between the K+ and P groups (p = 0.047), whereas no significant difference was found between the K– and K+ groups (p = 1.000, p > 0.05). Dietary intervention primarily benefits insulin sensitivity. Carbohydrate intake influences postprandial glucose levels, while a low-carbohydrate diet exerts anti-inflammatory effects relevant to endocrine and metabolic profiles. It is important to monitor dietary composition to ensure improvements in body weight, androgen levels, and fertility among women with PCOS. The quality and quantity of carbohydrate intake play a crucial role in dietary management for PCOS. The consumption of complex carbohydrates and unsaturated fats has been shown to reduce chronic inflammation, improve metabolism, insulin resistance, and hormonal imbalance in PCOS (13).

By raising insulin resistance, a high-protein diet may have an impact on PCOS management. Compared to healthy women, women with PCOS have less lean body mass. An essential endocrine organ, muscle can influence glucose and lipids and decrease the amount of insulin receptors. A diet rich in protein can improve insulin resistance, blood glucose and lipid control, and muscle mass (14). A week's worth of protein consumption can alter insulin sensitivity and cause a glucose imbalance. By inhibiting the inflammatory triggers TNF- α and IL-6, protein has anti-inflammatory benefits on overweight teenage girls (15).

In order to improve ovulation, control menstrual cycles, reduce hirsutism, improve insulin sensitivity, and lower androgen levels, women with PCOS should lose 5–10% of their body weight, according to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) guidelines (14).

As a result, it has been acknowledged that calorie-restricted eating habits are a significant dietary choice for PCOS individuals. Research examining how dietary changes, such as low-fat, low-carb, high-protein, and ketogenic diets, affect PCOS has shown promise in lowering central obesity and enhancing lipid metabolism and insulin levels (16).

Similarly, the ANOVA results for IL-6 levels in this study showed a significant difference, with p-value of 0.002 (< 0.05). The reduction in IL-6 levels reflected the influence of the lower AGEs concentrations observed in this study. The correlation of inflammatory markers such as IL-1, IL-6, and C-reactive protein (CRP) provides evidence that RAGE actively modulates inflammation, leading to impaired follicular growth and/or development in women with PCOS (19). Lower levels of chronic inflammation have been reported in overweight or obese patients with PCOS. According to the American Society for Reproductive Medicine (ASRM), first-line management for PCOS involves lifestyle modification, including dietary adjustment and physical exercise. Dietary interventions have been shown to alleviate clinical manifestations of PCOS, such as menstrual irregularities, hormonal imbalance, and anovulation. Regulation of macronutrient intake, particularly carbohydrate composition, is crucial; a diet containing approximately 10% carbohydrates can activate AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1), which exert beneficial effects on glucose homeostasis, inflammation, and reproductive function (11). A low-carbohydrate diet is similar to a high-protein diet model, as shown in previous studies where dietary interventions in PCOS resulted in differences in lipid levels (16). The post hoc analysis of IL-6 levels in this study also revealed significant intergroup differences ($p = 0.002$ and $p = 0.037$). However, K– vs K+ was not significant ($p = 0.437$). These findings suggest a high-protein, low-carbohydrate diet can improve metabolic and reproductive conditions through anti-inflammatory pathways. Experimental studies have shown that excessive fat intake reduces carbohydrate oxidation without significantly affecting fat oxidation. Conversely, excessive carbohydrate intake promotes fat accumulation through lipogenesis and lipid deposition in various tissues, resulting in cellular dysfunction, cell death, and the release of proinflammatory cytokines from adipose monocytes. Such mechanisms exacerbate the metabolic and reproductive disturbances associated with PCOS, underscoring the central role of glucose and saturated fat intake in its pathogenesis (13).

Dietary patterns play a significant role in regulating chronic inflammation. Diet-induced inflammation forms the basis of insulin resistance and hyperandrogenism, which are the key components of PCOS. Several dietary factors, such as glucose, have demonstrated this, which can induce chronic inflammation through oxidative stress. The Dietary Inflammatory Index (DII), developed by Shivappa *et al.*, is a quantitative tool designed to classify individuals according to the inflammatory potential of their diet. The DII evaluates the relationship between dietary components and inflammatory markers, including IL-1, IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). In contrast, a proinflammatory diet typically contains high amounts of saturated fats, refined cereals, fruit juices, red and processed meats, sugar-sweetened beverages, sugar, and honey. Recent studies have reported that higher DII scores are associated with an increased risk of PCOS. Lifestyle modification interventions—including weight reduction and regular physical activity—remain the primary approach in the management of women with PCOS. Dietary composition adjustments for treating and preventing PCOS have recently received growing attention. Therefore, identifying the most appropriate dietary pattern is crucial, particularly for women with PCOS (17).

CONCLUSION

The findings of this study are consistent with recent research demonstrating reductions in inflammatory markers such as IL-6 and AGEs in women with PCOS. It appears that dietary regulation—particularly of carbohydrate and glucose intake—can improve glucose secretion responses and modulate inflammatory pathways, thereby reducing the risk and severity of PCOS. Therefore, further investigation is warranted to establish personalized dietary approaches tailored to individual metabolic conditions, which should be considered in future studies.

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