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Original Communication

Relationship of Body Mass Index and Dietary Inflammatory Index With Free Androgen Index and Insulin Resistance in Women With Polycystic Ovary Syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a leading endocrine disorder in reproductive-aged women. While dietary interventions are widely advocated, the distinct roles of adiposity and dietary inflammation in driving PCOS phenotypes remain unclear. Therefore, this study aimed to dissect the contributions of body mass index (BMI) and dietary inflammatory index (DII) to hyperandrogenism and insulin resistance (IR) in PCOS. **Methods**: This cross-sectional study included 115 women with PCOS who visited gynecology and infertility clinics affiliated with Tabriz University of Medical Sciences. Data from the DII were computed using a validated 168-item semi-quantitative food frequency questionnaire. The free androgen index (FAI) was calculated as follows: (total testosterone (nmol/L)/SHBG (nmol/L)) $\times$ 100. The relationships between the BMI and DII and FAI, the Homeostasis model assessment of insulin resistance (HOMA-IR), the Homeostasis model assessment of β-cell function (HOMA-β), the quantitative insulin sensitivity check index (QUICKI), sex hormone binding globulin (SHBG), testosterone, fasting insulin (FI), and fasting blood sugar (FBS) were assessed using descriptive and analytical statistics. The general linear model was applied to adjust for confounders. **Results**: The mean (standard deviation, SD) BMI and FAI among subjects were 26.27 (3.82) kg/m^2 and 1.5 $\pm$ 1.5%, respectively. The median DII (range: –3.66 (most anti-inflammatory) to 4.31 (most pro-inflammatory)) was 0.75. Significant direct relationships were observed between the BMI and FAI ($p < 0.001$), HOMA-IR ($p = 0.008$), QUICKI ($p = 0.002$), testosterone ($p < 0.001$), FI ($p = 0.017$), FBS ($p = 0.004$), and Ferriman Gallwey score ($p < 0.001$). No significant associations were found between DII and the aforementioned biomarkers ($p > 0.05$). A normal BMI was associated with a significantly lower hirsutism score ($\beta = –3.94$, $p = 0.003$), fasting blood sugar ($\beta = –10.02$, $p < 0.001$), fasting insulin ($\beta = –4.05$, $p = 0.042$), HOMA-β ($\beta = –1.20$, $p = 0.012$), QUICKI ($\beta = –0.19$, $p = 0.015$), testosterone ($\beta = –0.34$, $p < 0.001$), and free androgen index ($\beta = –0.96$, $p = 0.025$) compared to an obese BMI after adjusting for confounders. No significant associations were observed for DII categories (median split) across any biomarkers or hirsutism. **Conclusion**: Adiposity (measured by BMI)—not dietary inflammation—was independently associated with key PCOS manifestations, demonstrating significant positive relationships with hyperandrogenism markers (FAI, testosterone), insulin resistance (HOMA-IR), and clinical hirsutism. A normal BMI was correlated with clinically meaningful reductions in metabolic-androgen parameters compared to obesity. Thus, weight loss and a generally healthy diet may need to be combined to impact PCOS features significantly.

Keywords: polycystic ovary syndrome; insulin resistance; hormonal disorders; life style; body mass index; dietary inflammatory index

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder affecting 6–13% of women of reproductive age globally, making it the most prevalent hormonal imbalance in this population [1,2]. Recognized by the Rotterdam criteria, PCOS diagnosis is based on at least two of three features: oligo-anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound [3]. Beyond its reproductive manifestations, PCOS is increasingly characterized as a systemic metabolic disorder, with insulin resistance (IR), chronic low-grade inflammation, and visceral adiposity acting as interconnected drivers of its pathophysiology [4,5]. Emerging evidence underscores that women with PCOS face a fourfold increased risk of type 2 diabetes mellitus (T2DM), a 2.7-fold elevated cardiovascular disease (CVD) risk, and a higher prevalence of non-alcoholic fatty liver disease (NAFLD) compared to age-matched controls [6–10].

The hyperandrogenic milieu of PCOS arises from both ovarian theca cell hypersensitivity to luteinizing hormone (LH) and adrenal androgen excess, compounded by reduced sex hormone-binding globulin (SHBG) levels due to IR [11,12]. Free testosterone, quantified through the free androgen index (FAI), serves as a critical biomarker of hyper-

androgenism and correlates strongly with hirsutism, acne, and anovulation [13,14]. Concurrently, IR—present in 65–80% of women with PCOS regardless of body mass index (BMI)—exacerbates androgen synthesis via insulin-mediated stimulation of ovarian theca cells and inhibition of hepatic SHBG production [15–17]. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) are widely employed to assess these metabolic derangements [18–20].

Mounting evidence implicates chronic inflammation as a central component in PCOS pathophysiology. Women with PCOS exhibit elevated serum levels of pro-inflammatory cytokines (IL-6, TNF-α), acute-phase reactants (C-Reactive Protein (CRP), fibrinogen), and leukocyte adhesion molecules (ICAM-1, VCAM-1), even after adjusting for BMI [10,21–23]. This inflammatory cascade amplifies IR through TNF-α-mediated inhibition of insulin receptor substrate (IRS) phosphorylation and IL-6-induced suppression of adiponectin secretion [24]. Notably, adipose tissue dysfunction—particularly visceral adiposity—acts as both a source and amplifier of inflammation, with hypertrophic adipocytes releasing macrophage chemoattractants (e.g., MCP-1) that perpetuate a pro-inflammatory feedback loop [25].

Dietary modulation of inflammation has emerged as a promising therapeutic target in PCOS. The Dietary Inflammatory Index (DII), a validated tool assessing the inflammatory potential of diets, quantifies the cumulative effect of 45 food parameters on circulating IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP levels [26]. Pro-inflammatory diets (high DII scores), typically rich in refined carbohydrates, saturated fats, and processed meats, exacerbate oxidative stress and mitochondrial dysfunction in ovarian granulosa cells, potentially impairing folliculogenesis [27,28]. Conversely, anti-inflammatory dietary patterns—such as the Mediterranean diet abundant in omega-3 fatty acids, polyphenols, and fiber—demonstrate therapeutic efficacy in PCOS by improving HOMA-IR (mean reduction: 0.8 points), reducing free testosterone (15–20% decrease), and restoring menstrual cyclicity in 35–40% of cases [29,30].

While obesity amplifies PCOS severity through adipokine dysregulation (leptin resistance, reduced adiponectin) and androgen aromatization in adipose stroma [31], the independent contribution of dietary inflammation remains controversial. Recent Mendelian randomization studies suggest that genetic predisposition to IR accounts for 22–30% of the PCOS risk, highlighting the critical role of gene-diet interactions [32]. Nevertheless, current literature suffers from three key gaps: (1) limited data on DII's association with FAI and IR in PCOS-specific cohorts, (2) insufficient exploration of BMI-DII synergism in driving metabolic-hormonal dysregulation, and (3) reliance on cross-sectional designs unable to establish temporal causality.

This study addresses these gaps by investigating the dual impact of BMI and DII on FAI, IR, and associated metabolic parameters in a well-phenotyped PCOS women. Therefore, this study aimed to investigate the relationship of BMI and DII with FAI and IR in women with PCOS.

2. Materials and Methods

2.1 Study Design and Participants

This cross-sectional study enrolled 115 women aged 19–45 years diagnosed with PCOS according to the Rotterdam Criteria [33], recruited from the infertility and gynecology clinics of Al-Zahra and Taleghani Teaching Medical Centers of Tabriz between June 2019 and January 2022. Ethical approval was obtained from the (Ethics Approval and Consent to Participate: IR.TBZMED.REC.1398.458, adhering to the Declaration of Helsinki (2013 revision) [34]. Participants provided written informed consent after a detailed briefing on study objectives and procedures. Participants were required to meet the following inclusion criteria: (1) confirmation of PCOS diagnosis (Rotterdam Criteria) within the preceding year, (2) absence of pregnancy or lactation, (3) no history of endocrine disorders such as thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, or other endocrine disorders (verified by serum TSH, cortisol, and 17-hydroxyprogesterone levels), and (4) no history of insulin-sensitizing agents, hormonal contraceptives, or anti-androgen use within 90 days prior to enrollment. Exclusion criteria included: (1) diagnosis of type 1 or type 2 diabetes (HbA1c $\geq$6.5% or fasting glucose $\geq$126 mg/dL), (2) active inflammatory or autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease), and (3) recent participation in structured weight-loss programs or bariatric surgery within the past six months.

2.2 Demographic, Anthropometric and Clinical Assessments

A demographic and obstetric questionnaire was administered, consisting of items addressing age, educational attainment, occupation, duration of PCOS, previous treatments, the first day of the last menstrual cycle, menstrual cycle pattern, BMI, medications used by participants, etc. This questionnaire was developed based on study objectives and a review of scientific literature. It was then sent to 10 gynecology, obstetrics, and nutrition professors to assess content and face validity; revisions were incorporated based on feedback before implementation.

Anthropometric measurements were performed by trained clinicians using standardized protocols. Body weight was measured to the nearest 0.1 kg using a calibrated SECA digital scale (Hamburg, Germany), with participants wearing light clothing and no shoes. Height was assessed with a wall-mounted stadiometer (SECA; precision $\pm$ 1 mm), and BMI was calculated as weight (kg) divided by height squared (m^2).

Hirsutism was evaluated using the Ferriman-Gallwey scoring system, where two independent trained researchers, blinded to participant data, assessed hair growth across nine body regions. The scoring system evaluates hirsutism in nine areas: upper lip, chin, chest, upper back, waist, upper abdomen, lower abdomen, arms, and thighs. Each region is scored as follows: 0 = no hirsutism, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe hirsutism. Total scores range from 0 to 36. Inter-observer agreement was confirmed with a mean kappa value of 0.744 for the nine body areas [35].

Dietary intake was assessed using a validated and reliable semi-quantitative food frequency questionnaire (FFQ) capturing consumption over the past year. This FFQ includes 168 food items, with consumption frequency solicited in standard portion sizes (daily, weekly, monthly, or annually) by a trained investigator. Reported food quantities were converted to grams per day using the Iranian Household Measures Manual [36]. Nutrient intake was analyzed using Nutritionist IV software (N-Squared Computing, Oregon, USA) supplemented with the Iranian Food Composition Database. The DII was calculated according to Shivappa *et al.* (2014) [25], incorporating 44 food parameters with empirically derived inflammatory weights. Z-scores for each dietary component were computed relative to a global reference database and adjusted for total energy intake using the residual method to minimize confounding.

Fasting blood samples were collected between 8:00 and 10:00 AM during the early follicular phase (days 3–5 of the menstrual cycle) or following confirmation of amenorrhea (negative β-hCG pregnancy test). Serum was separated by centrifugation at 3000 rpm for 5 minutes at 4 °C and stored at –20 °C until analysis. Biochemical assays included:

- Total testosterone and sex hormone-binding globulin (SHBG): Quantified via electrochemiluminescence immunoassay (Siemens ADVIA Centaur XP; inter-assay CV <5%).
- Fasting insulin: Measured using a chemiluminescent microparticle immunoassay (DiaSorin LIAISON; CV <7%).
- Fasting blood glucose (FBG): Analyzed via the glucose oxidase method (Pars Azmoun Autoanalyzer; CV <3%).

Insulin resistance and sensitivity indices were derived as follows:

- Homeostasis Model Assessment for Insulin Resistance (HOMA-IR): (fasting insulin [µlU/mL] × fasting glucose [mg/dL])/405 [37].
- Quantitative Insulin Sensitivity Check Index (QUICKI): 1/(log(fasting insulin) + log(fasting glucose)) [38].
- Free Androgen Index (FAI): (Total testosterone [nmol/L]/SHBG [nmol/L]) × 100 [39].

2.3 Sample size

The sample size was determined a priori using G*Power software (Version 3.1.9.4, Düsseldorf, Germany) based on two primary outcomes: serum insulin and SHBG levels. For SHBG, we utilized the correlation coefficient (r = 0.293) between SHBG and total energy intake reported by Altieri *et al.* [40], with $\alpha = 0.05$ and power = 0.8, yielding a minimum sample size of 78. For insulin, the correlation coefficient (r = 0.235) between insulin and carbohydrate intake from the same study was used, with $\alpha = 0.05$ and power = 0.8, resulting in a required sample size of 115. To ensure robust statistical power for both parameters, the larger estimate (n = 115) was selected as the final sample size.

2.4 Quality Control

Laboratory tests were conducted using standardized kits approved by the reference laboratory, ensuring accuracy and reproducibility. All kits were manufactured under strict quality control protocols, and instruments such as ELISA readers were calibrated and validated by the reference laboratory. Intra- and inter-assay coefficients of variation (CV) were maintained below 5% for all biomarkers, including testosterone, SHBG, and insulin, confirming the reliability of the results.

2.5 Statistical Analysis

Normality of data distribution was assessed via the Kolmogorov-Smirnov test. Descriptive statistics included mean ± standard deviation (normally distributed variables), median (interquartile range) (non-normal variables), and frequency (%) (Categorical variables). Inferential analyses comprised Pearson's/Spearman's correlations, independent *t*-tests, Mann-Whitney U, Kruskal-Wallis, and one-way ANOVA. The general linear model (GLM) was applied to adjust for potential confounders (parity, family income, marital status, and education level) in associations of BMI and DII with metabolic-hormonal biomarkers. Analyses were performed in SPSS version 24 (IBM Corp, Armonk, NY, USA), with significance set at $p < 0.05$.

Inferential analyses included Pearson's/Spearman's correlations, independent *t*-tests, Mann-Whitney U, Kruskal-Wallis, and one-way ANOVA. The general linear model (GLM) adjusted for confounders (parity, income, marital status, education). Analyses used SPSS version 24 (IBM Corp.), significance at $p < 0.05$.

3. Results

The participant selection process is illustrated in Fig. 1. Among 115 women included in the final analysis, the mean (±standard deviation, SD) age and BMI were 29.28 ± 6.7 years and 26.27 ± 3.82 kg/m^2, respectively. Approximately two-thirds were married (69.5%), housewives (67.8%), and 55.6% held a university degree; 92.2% reported sufficient monthly income. No significant associations were observed between DII and age, marital

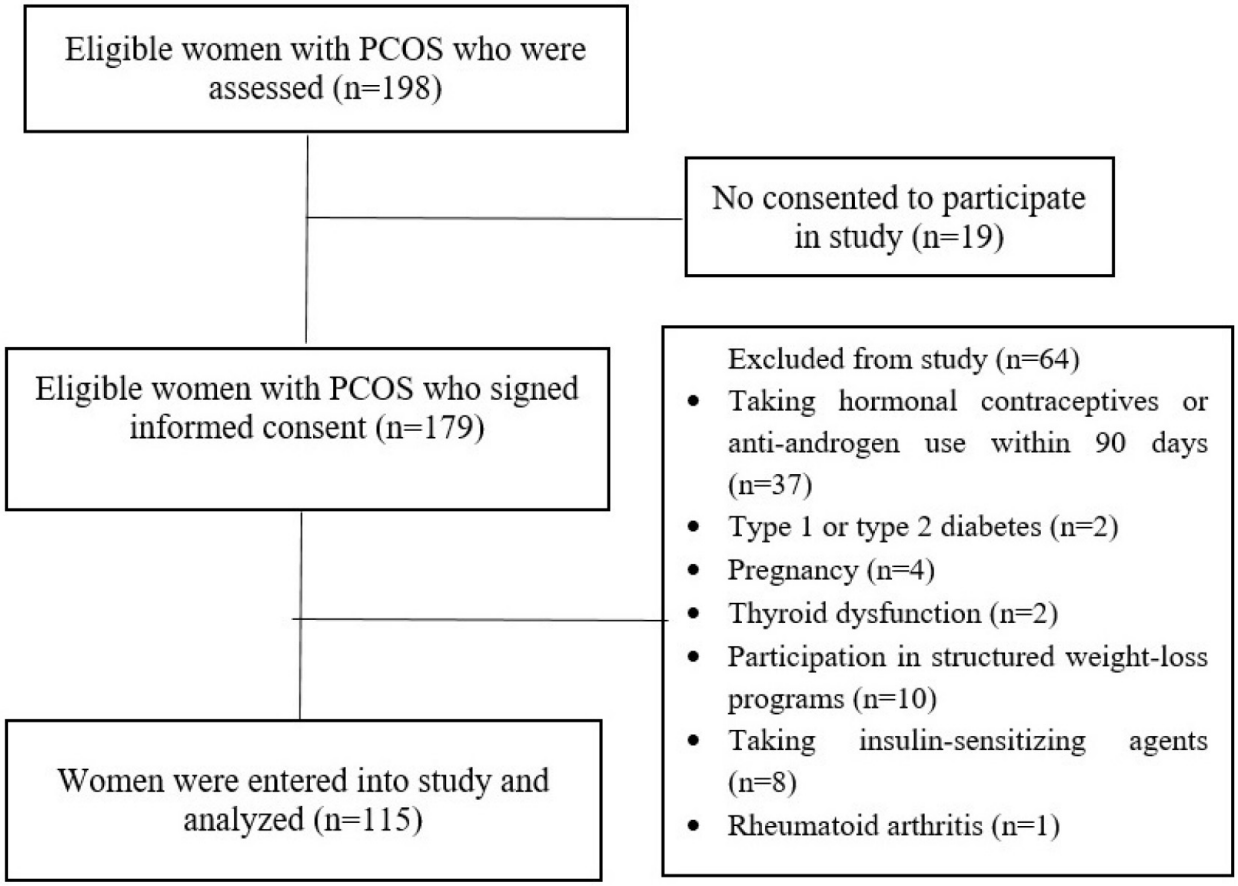

Fig. 1. Flow chart of selecting participants.

status, occupation, education, or BMI ($p > 0.05$). Most participants (74.8%) exhibited oligomenorrhea, 46.1% were nulligravid, 27.8% primiparous, and 83.5% reported no history of abortion. The mean duration of PCOS diagnosis was 3.45 ± 1.9 years.

DII showed no significant relationships with menstrual cycle pattern, pregnancy/abortion history, or PCOS duration ($p > 0.05$). However, mean DII differed significantly by parity ($p = 0.017$) (ANCOVA, adjusting for age as a confounder, indicated similar results; $p = 0.014$). DII values exceeded the median (0.75) in 53.9% ($n = 62$) of participants and were below the median in 46.1% (n =53). BMI distributions did not differ significantly across demographic or obstetric variables (Table 1).

DII ranged from –3.66 (most anti-inflammatory) to 4.31 (most pro-inflammatory), with 53.9% of participants scoring above the median (Table 2).

The mean fasting blood sugar (FBS), fasting insulin (FI), testosterone, Sex Hormone Binding Globulin (SHBG), Homeostasis Model Assessment of β-cell Function (HOMA-β), HOMA-IR, QUICKI, FAI, and Ferriman-Gallwey scores were 93.5 ± 9.3 mg/dL, 9.2 ± 6.7 µIU/mL, 0.6 ± 0.4 mg/dL, 65.4 ± 42.6 mg/dL, 2.2 ± 1.6, 106.3 ± 62, 1.4 ± 0.2, 1.5 ± 1.5%, and 12.9 ± 4.6, respectively (Table 3).

No significant correlations were found between DII and FAI (r = 0.089, $p = 0.346$), HOMA-β (r = 0.071, $p = 0.450$), HOMA-IR (r = 0.159, $p = 0.090$), QUICKI (r = 0.061, $p = 0.515$), Ferriman-Gallwey score (r = 0.053, $p = 0.778$), FBS (r = –0.080, $p = 0.395$), FI (r = 0.055, $p = 0.563$), testosterone (r = 0.108, $p = 0.249$), and SHBG (r = 0.049, $p = 0.603$) were not statistically significant. The results also revealed no significant differences between participants with DII values higher and lower than the median in the mean FAI ($p = 0.630$), HOMA-β ($p = 0.561$), HOMA-IR ($p = 0.329$), QUICKI ($p = 0.484$), FBS ($p = 0.463$), FI ($p = 0.504$), testosterone ($p = 0.214$), SHBG ($p = 0.829$), and Ferriman-Gallwey scores ($p = 0.869$) (Table 4).

BMI correlated positively and significantly with FAI ($r = 0.33$, $p < 0.001$), QUICKI ($r = 0.28$, $p = 0.002$), HOMA-IR ($r = 0.25$, $p = 0.008$), FI ($r = 0.22$, $p = 0.017$), FBS ($r = 0.004$, $p = 0.26$), testosterone ($r = 0.32$, $p < 0.001$), and Ferriman-Gallwey score ($r = 0.32$, $p < 0.001$). No associations were observed between BMI and HOMA-β ($p = 0.289$) or SHBG ($p = 0.154$) (Table 4).

General linear models revealed that normal BMI (vs. obesity) was associated with significantly lower hirsutism score ($\beta = –3.94$, $p = 0.003$), FBS ($\beta = –10.02$, $p < 0.001$), FI ($\beta = –4.05$, $p = 0.042$), HOMA-β ($\beta = –1.20$, $p = 0.012$), QUICKI ($\beta = –0.19$, $p = 0.015$), testosterone ($\beta = –0.34$,

Table 1. Associations between demographic/clinical characteristics and both Dietary Inflammatory Index (DII) and Body Mass Index (BMI) scores in women with polycystic ovary syndrome (PCOS) (n = 115).

Characteristic	Number (%) Mean ± SD	DII Mean ± SD	*p*-value	BMI Mean ± SD	*p*-value
Age (years)	29.28 ± 6.7	0.77 ± 1.8	0.718†	26.27 ± 3.82	0.406†
Marital status			0.858‡		0.069‡
Single	35 (30.4%)	0.81 ± 1.86		25.29 ± 3.4	
Married	80 (69.5%)	0.75 ± 1.79		26.7 ± 3.93	
Education			0.260§		0.183§
Less than diploma	12 (10%)	1.54 ± 1.98		26.38 ± 2.26	
Diploma	39 (33.9%)	0.78 ± 1.73		25.37 ± 3.94	
University	64 (55.6%)	0.62 ± 1.79		26.80 ± 3.91	
BMI (kg/m²)	26.3 ± 3.8	0.77 ± 1.8	0.206†	-	
Normal (18.5–24.9)	45 (39.1%)	0.89 ± 1.7			
Overweight (25–29.9)	54 (46.9%)	0.84 ± 1.8			
Obese (≥30)	16 (13.9%)	0.16 ± 2.06			
Occupation			0.845¥		0.360¥
Unemployed	2 (1.7%)	0.93 ± 0.52		26.35 ± 3.65	
Housewife	78 (67.8%)	0.70 ± 1.8		26.14 ± 3.44	
Work from home	29 (25.2%)	0.98 ± 1.9		28.12 ± 3.96	
Work outside home	5 (4.3%)	0.27 ± 1.4		26.60 ± 4.71	
Retired	1 (0.9%)	2.04 ± 0		20 ± 0	
Family income			0.152≠		0.054≠
Sufficient	106 (92.2%)	0.70 ± 1.8		26.47 ± 3.77	
Insufficient	9 (7.8%)	1.59 ± 1.71		23.92 ± 3.77	
Menstrual cycle			0.623¥		0.385§
Amenorrhea	13 (11.3%)	1.31 ± 2.06		26.48 ± 3.16	
Regular	14 (12.2%)	0.92 ± 2.02		25.67 ± 3.23	
Oligomenorrhea	86 (74.8%)	0.65 ± 1.70		26.42 ± 3.45	
Gravidity			0.583¥		0.419¥
0	53 (46.1%)	0.80 ± 1.84		26.21 ± 4.49	
1	26 (22.6%)	0.99 ± 1.84		25.91 ± 3.36	
2	24 (20.9%)	0.98 ± 1.90		27.29 ± 3.31	
≥3	12 (10.4%)	1.23 ± 7.00		25.22 ± 1.77	
Parity[£]			**0.017¥**		0.798¥
0	57 (49.6%)	0.77 ± 1.81		26.44 ± 4.46	
1	32 (27.8%)	1.12 ± 1.82		25.74 ± 3.2	
2	20 (17.4%)	–0.19 ± 1.46		26.72 ± 3.24	
3	6 (5.2%)	2.04 ± 1.42		26.07 ± 3.82	
DII < median	53 (46.1%)	-		26.38 ± 3.92	0.827‡
DII > median	62 (53.9%)	-		26.20 ± 3.76	

Abbreviations: DII, Dietary Inflammatory Index; BMI, Body Mass Index.

†Pearson correlation, ‡Independent *t*-test, §Kruskal-Wallis, ¥One-way ANOVA, ≠Mann-Whitney U test.

Bold: Statistically significant ($p < 0.05$).

[£] ANCOVA, adjusting for age as a confounder, showed similar results ($p = 0.014$).

$p < 0.001$), and FAI ($\beta = –0.96$, $p = 0.025$) after adjusting for confounders. No associations were observed for DII categories (median split) with any biomarkers or hirsutism (Table 5).

4. Discussion

This was a cross-sectional descriptive study that investigated the relationship between BMI and DII with FAI and IR (HOMA-IR, HOMA-β, and QUICKI) in women with PCOS. Findings underscore that BMI has an independent associations with hyperandrogenism and IR. Significant associations were observed between elevated BMI and in-

Table 2. Distribution of Dietary Inflammatory Index (DII) scores across percentiles in women with polycystic ovary syndrome (PCOS) (n = 115).

Percentile	DII value
Maximum	4.31
90th	3.13
75th	2.23
Median	0.75
25th	–0.69
10th	–1.61
Minimum	–3.66

Abbreviation: DII, Dietary Inflammatory Index.

creased FAI, testosterone levels, FI, and hirsutism severity. Women with PCOS and normal BMI exhibited significantly lower metabolic-hormonal biomarkers and hirsutism scores compared to obese individuals. Conversely, DII showed no independent associations with these outcomes, challenging the hypothesis that pro-inflammatory diets directly exacerbate PCOS phenotypes. These results align with and extend prior evidence while revealing novel complexities in PCOS pathophysiology.

4.1 Adiposity as a Central Driver of PCOS Pathogenesis

The robust correlation between BMI and hyperandrogenism mirrors findings from global cohorts. For instance, Cupisti *et al*. [41] demonstrated that obesity amplifies androgenicity through reduced SHBG and elevated free testosterone—a phenomenon attributed to adipose tissue-driven upregulation of 17β-hydroxysteroid dehydrogenase (17β-HSD), which enhances androstenedione to testosterone conversion [42]. This enzymatic activity, coupled with IR-mediated suppression of hepatic SHBG synthesis [43], creates a self-perpetuating cycle of hyperandrogenism in obese PCOS patients. Our results further corroborate Yasmin *et al*. [42], who identified BMI as a key determinant of FAI across both PCOS and non-PCOS populations. However, the absence of a BMI-total testosterone correlation in our cohort suggests that obesity may preferentially increase bioavailable androgens rather than total testosterone, possibly due to SHBG suppression [44–46]. Macrophages within obese adipose tissue release pro-inflammatory cytokines (TNF-α, IL-6), exacerbating IR by disrupting insulin signaling through IRS-1 serine phosphorylation [23,24]. The increased insulin levels also stimulate theca cell androgen production from increased CYP17A1 levels within the ovary [4]. Therefore, all these mechanisms contribute significantly to obesity as the predominant driver of hyperandrogenism and metabolic derangement in PCOS [47].

The link between BMI and IR (evidenced by HOMA-β and QUICKI associations) highlights adipose tissue as a nexus of metabolic dysfunction. Adipocyte hypertrophy in obesity triggers macrophage infiltration and pro-inflammatory cytokine release (e.g., TNF-α, IL-6), which impair insulin signaling via IRS-1 serine phosphorylation [24]. This inflammatory milieu not only exacerbates IR but also directly stimulates ovarian theca cell androgen production through insulin-mediated CYP17A1 activation [7]. These pathophysiological mechanisms may explain the concomitant associations between elevated BMI and both hyperandrogenism and β-cell hyperactivity (quantified by HOMA-β) observed in our study, a pattern corroborated by Cupisti *et al*. [48] in hyperandrogenic populations. While our findings demonstrate a significant association between elevated BMI and increased severity of hyperandrogenism (FAI) and IR in PCOS, it is critical to recognize the bidirectional nature of this relationship, wherein IR and hyperandrogenism may themselves exacerbate adiposity, thereby creating a cyclical interplay that amplifies metabolic and reproductive dysfunction in affected individuals.

4.2 The Paradox of Dietary Inflammation

PCOS is associated with chronic low-grade inflammation [49]. This inflammatory state involves immune cell dysfunction, cytokine imbalance, and autoantibody production, contributing to insulin resistance and hyperandrogenism [50]. Despite mechanistic plausibility, DII showed no association with IR or hyperandrogenism—a result contrasting with studies linking pro-inflammatory diets to metabolic syndrome [51–54]. Several factors may explain this discrepancy. First, chronic inflammation in PCOS is predominately driven by visceral adipose tissue as this accounts for ~30% of circulating IL-6 [55]. This adipose-derived inflammation may act as a confounding exposure, masking dietary influences. Second, the Iranian diet is rich in anti-inflammatory foods (e.g., legumes, vegetables, nuts, oils, and spices including saffron [56,57]), which may counteract the pro-inflammatory effects of high-DII diets. Third, the DII, based on 44 food parameters, may lack sensitivity to region-specific anti-inflammatory foods such as saffron and pistachios [58]. Additionally, the absence of direct inflammatory biomarkers (e.g., IL-6, CRP) limited our ability to assess dietary effects on phenotypes [59]. We believe that although pro-inflammatory diets may be implicated in PCOS development, their role in modulating established PCOS phenotypes is likely overshadowed by adiposity- driven inflammation.

Notably, two recent case-control studies [60,61] reported that high DII increases PCOS risk, but neither explored intermediary mechanisms such as IR or FAI. Another study found higher interleukin-6 levels in women with PCOS versus controls, despite comparable DII values [62]. Research in China linked pro-inflammatory diets to elevated PCOS risk, with DII positively correlated with inflammatory markers (platelet-

Table 3. Metabolic-hormonal-clinical profile of women with polycystic ovary syndrome (PCOS) related to glucose metabolism, androgen status, and clinical presentation.

Biomarker	Median	Interquartile range (IQR)	Mean ± SD
Fasting blood sugar (FBS)	93 mg/dL	10	93.5 ± 9.3 mg/dL
Fasting insulin (FI)	6.7 µIU/mL	6.5	9.2 ± 6.7 µIU/mL
Testosterone	0.6 ng/mL	0.6	0.6 ± 0.4 ng/mL
SHBG	54 nmol/L	51	65.4 ± 42.6 nmol/L
HOMA-β	1.6	1.6	2.2 ± 1.6
HOMA-IR	84.8	77.3	106.3 ± 62
QUICKI	1.3	0.4	1.4 ± 0.2
Free androgen index (FAI)	0.9%	1.3	1.5 ± 1.5%
Hirsutism score	11	6	12.9 ± 4.6

Abbreviations: FBS, Fasting Blood Sugar; FI, Fasting Insulin; SHBG, Sex Hormone-Binding Globulin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HOMA-β, Homeostasis Model Assessment of β-cell Function; QUICKI, Quantitative Insulin Sensitivity Check Index; FAI, Free Androgen Index; IQR, Interquartile Range (25th–75th percentile); SD, Standard Deviation.

Table 4. Associations of Body Mass Index (BMI) and Dietary Inflammatory Index (DII) with metabolic-hormonal biomarkers and hirsutism in women with polycystic ovary syndrome (PCOS) (N = 115).

Variable	Hirsutism score	FBS (mg/dL)	FI (µIU/mL)	HOMA -β	HOMA -IR	QUICKI	Testosterone (ng/mL)	SHBG (nmol/L)	FAI
BMI (Continuous)									
Correlation coefficient	0.322	0.267	0.223	0.247	0.100	0.280	0.327	–0.154	**0.330**
p-value†	**<0.001**	**0.004**	**0.017**	**0.008**	0.289	**0.002**	**<0.001**	0.100	**<0.001**
DII (Continuous)									
Correlation coefficient	0.053	–0.080	0.055	0.070	0.159	0.061	–0.108	0.049	–0.089
p-value‡	0.778	0.395†	0.563	0.450	0.090	0.515†	0.249	0.603	0.346
DII (Categorical)									
p-value¥	0.869	0.463≠	0.504	0.561	0.329	0.484≠	0.214	0.829	0.630¥

Abbreviations: BMI, Body Mass Index; DII, Dietary Inflammatory Index; FBS, Fasting Blood Sugar; FI, Fasting Insulin; SHBG, Sex Hormone-Binding Globulin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HOMA-β, Homeostasis Model Assessment of β-cell Function; QUICKI, Quantitative Insulin Sensitivity Check Index; FAI, Free Androgen Index.

†Pearson's correlation (continuous variables), ‡Spearman's correlation (non-parametric data), ≠Independent *t*-test (DII categorical: median split), ¥Mann-Whitney U test. Bold: Statistically significant ($p < 0.05$).

* We used General Linear Model to adjust the probable confounding role of parity for the relation of DII with Metabolic-Hormonal Biomarkers. However, no statistically significance results were observed.

to-lymphocyte and neutrophil-to-lymphocyte ratios) [54]. None of these studies investigated DII's relationship with IR or FAI in PCOS.

Our null findings suggest that while pro-inflammatory diets may contribute to PCOS development, their role in modulating established PCOS phenotypes is minimal relative to adiposity.

4.3 Clinical and Mechanistic Implications

The parity-DII association (higher DII in multiparous women) introduces a novel dimension to PCOS research. Notably, DII was higher in multiparous vs. nulliparous women independent of age. Postpartum metabolic shifts such as persistent IR, weight retention, and altered ghrelin signaling may predispose multiparous women to pro-inflammatory dietary patterns [63–66]. Additionally, cultural factors in Iran, where multiparity is often associated with sedentary lifestyles and calorie-dense traditional diets, could confound this relationship. Further research is needed to disentangle biological, behavioral, and sociocultural contributors.

4.4 Limitations and Future Directions

While this study benefits from rigorous exclusion criteria and standardized assays, its cross-sectional design precludes causal inferences. Temporal relationships between BMI and DII with outcomes cannot establish causal effects. Future research should prioritize longitudinal and interventional designs to clarify temporal relationships between diet, adiposity, and PCOS progression. Residual confounding by unmeasured variables (e.g., the amount of physical activity, stress, sleep quality, environmental toxins) may obscure diet-outcome relationships and insulin sensitivity. Given that sleep disturbances in women have demon-

Table 5. Adjusted associations of BMI and DII categories with metabolic-hormonal biomarkers and hirsutism in women with polycystic ovary syndrome (PCOS).

Different treatments		[€]Adjusted β 95% confidence interval	*p*-value		[£]Adjusted β 95% confidence interval	*p*-value
		Categorized BMI			Categorized DII	
Hirsutism Score	Normal to obese	–3.94 (–6.51 to –1.38)	**0.003**	DII < median to	–0.25 (–1.96 to 1.46)	0.775
	Overweight/obese	–1.55 (–4.05 to 0.94)	0.221	DII > median		
FBS (mg/dL)	Normal to obese	–10.02 (–15.14 to –4.91)	**<0.001**	DII < median to	–1.01 (–4.45 to 2.43)	0.562
	Overweight/obese	–8.63 (–13.61 to –3.64)	**<0.001**	DII > median		
FI (μIU/mL)	Normal to obese	–4.05 (–7.95 to –0.15)	**0.042**	DII < median to	–0.44 (–2.92 to 2.03)	0.723
	Overweight/obese	–1.91 (–5.71 to 1.89)	0.322	DII > median		
HOMA-β	Normal to obese	–1.20 (–2.13 to –0.27)	**0.012**	DII < median to	–0.17 (–0.77 to 0.43)	0.570
	Overweight/obese	–0.73 (–1.64 to 0.174)	0.112	DII > median		
HOMA-IR	Normal to obese	–10.94 (–47.8 to 25.92)	0.558	DII < median to	–11.65 (–34.16 to 10.86)	0.307
	Overweight/obese	0.04 (–35.88 to 35.95)	0.998	DII > median		
QUICKI	Normal to obese	–0.19 (–0.34 to –0.03)	**0.015**	DII < median to	–0.04 (–0.14 to 0.05)	0.360
	Overweight/obese	–0.09 (–0.24 to 0.05)	0.191	DII > median		
Testosterone (ng/mL)	Normal to obese	–0.34 (–0.54 to –0.14)	**<0.001**	DII < median to	0.04 (–0.09 to 0.18)	0.516
	Overweight/obese	–0.18 (–0.38 to 0.01)	0.066	DII > median		
SHBG (nmol/L)	Normal to obese	3.99 (–21.07 to 29.07)	0.753	DII < median to	4.0 (–11.92 to 19.92)	0.619
	Overweight/obese	–8.25 (–32.68 to 16.18)	0.505	DII > median		
FAI	Normal to obese	–0.96 (–1.80 to –1.21)	**0.025**	DII < median to	0.45 (–0.09 to 1.0)	0.105
	Overweight/obese	0.11 (–0.71 to 0.93)	0.789	DII > median		

Abbreviations: BMI, Body Mass Index; DII, Dietary Inflammatory Index; FBS, Fasting Blood Sugar; FI, Fasting Insulin; SHBG, Sex Hormone-Binding Globulin; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HOMA-β, Homeostasis Model Assessment of β-cell Function; QUICKI, Quantitative Insulin Sensitivity Check Index; FAI, Free Androgen Index.

BMI (kg/m^2) categorized as normal (18.5–24.9), overweight (25–29.9), and obese ($\geq$30) with obese considered reference. DII categorized as DII < median and DII > median, with DII > median as reference group.

[€] General Linear Model adjusted for family income, marital status, and education level.

[£] General Linear Model adjusted for parity and family income.

Bold *p*-values indicate the statistical significant (<0.05) levels.

strated associations with heightened inflammatory markers, IR, and psychosocial distress [67,68], coupled with evidence indicating physical activity's critical role in IR management among PCOS populations [69], we suggest that future research measure these variables in addition to DII. In addition, although BMI is a practical and clinically useful measure as an adiposity metric, visceral adiposity (via waist circumference or waist-to-hip ratio) is specifically linked to metabolic inflammation in PCOS. It might be helpful to report participant waist circumference or waist-to-hip ratio data alongside BMI in future studies.

Notably, the calculation of DII through food FFQs is susceptible to recall bias; concurrent validation using systemic inflammatory biomarkers (e.g., IL-6, TNF-α, and CRP profiles) is recommended to strengthen dietary inflammation assessments. Furthermore, the demographic homogeneity of the Iranian cohort (from a single region) may limit the generalizability of the findings to populations with divergent ethnic backgrounds, dietary norms, or obesogenic environments. Caution is therefore warranted when applying these results to Western or multiethnic groups characterized by varying eating practices. Exploring gene-diet interactions and adipose tissue-specific inflammatory pathways may elucidate novel therapeutic targets.

5. Conclusion

According to our findings, adiposity is the main factor influencing variation in hyperandrogenism and metabolic dysregulation in PCOS once the condition is established, with dietary inflammatory potential not demonstrating any independent correlation. Elevated BMI was consistently associated with worsened FAI, insulin resistance, and hirsutism, reinforcing weight management as a cornerstone of PCOS care. After adjusting for sociodemographic confounders, normal BMI correlated with clinically meaningful reductions in metabolic-androgen parameters compared to obesity. By demonstrating that weight status has a greater impact on PCOS metabolic-hormonal profiles than diet quality (in terms of inflammation), these findings suggest that weight loss combined with a generally healthy diet may be necessary to significantly affect PCOS features.

Abbreviations

PCOS, Poly cystic ovarian syndrome; LH, Luteinizing hormone; FSH, Follicle stimulating hormone; BMI, Body mass index; FAI, Free Androgen Index; FI, Fasting Insulin; DHEA, Dehydro Epi Androsteron Sulfate; SHBG, Sex Hormone Binding Globulin; DII, Dietary Inflamma-

tion Index; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HOMA-β, Homeostasis Model Assessment of β-cell Function; QUICKI, Quantitative Insulin Sensitivity Check Index; WHO, World Health Organization; CRP, C-Reactive Protein; FFQ, Food Frequency questionnaire; IR, Insulin resistance.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Author Contributions

NG and AFK were responsible for drafting the protocol, data collection, data analysis and interpretation and writing of the final manuscript. MS, KH, and MM were involved in drafting the protocol, data collection and editing the final version of the manuscript. All authors have contributed to the editorial changes made to the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics committee of Tabriz University of Medical Sciences with the code of IR. TBZMED. REC. 1398.458. All participants were ensured about the matter of confidentiality. Also, informed written consent was obtained from all participants and parent/legally authorized representatives of illiterate participants. All methods were performed in accordance with the Declaration of Helsinki. All of the methods were carried out in accordance with relevant guidelines and regulations.

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Conflict of Interest

The authors declare no conflict of interest.

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