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Original Article

Resolvin D1 impacts on insulin resistance in women with polycystic ovary syndrome and healthy women

Nava Morshedzadeh [a], Ahmad Saedisomeolia [a, b, c], Mahmoud Djalali [a], Mohammad Reza Eshraghian [d], Sedigheh Hantoushzadeh [e], Maryam Mahmoudi [a, *]

[a] Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Pharmacy, School of Medicine, Western Sydney University, NSW, Australia
[c] School of Life and Environmental Sciences, Charles Perkins Centre, The University of Sydney, Sydney, Australia
[d] Department of Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[e] Maternal, Fetal and Neonatal Research Center, Vali-Asr Hospital, Imam Khomeini Hospital Complexes, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Aims: The aim of this study was to determine the association between the intake of omega-3 PUFAs and the serum level of resolvin D1 and insulin resistance in women with Polycystic Ovary Syndrome (PCOS) compared to healthy women.
Methods: A cross-sectional study was conducted in 2015–2016 in Tehran, Iran, among females referred to the infertility clinic at Valie-Asr Reproductive Health Research Centre. Thirty-one patients with PCOS (according to the criteria of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM)) and 29 healthy, normal cycling (NC) women of similar age, weight and height were enrolled. Anthropometric measurements, levels of resolvin D1, fasting insulin, glucose levels and insulin resistance index (HOMA) for each of the patients were determined.
Results: Intakes of macronutrients (protein, carbohydrates, and total fat) and omega-3 PUFAs were higher in the PCOS group compared to the control group; also, the PCOS group had significantly higher resolvin D1, fasting insulin, glucose levels and HOMA when compared with the control group. Moreover, resolvin D1 correlated negatively with HOMA and fasting insulin levels among both the PCOS and control women.
Conclusion: PCOS is associated with insulin resistance. We showed that omega-3 PUFAs can increase the synthesis of resolvin D1. Resolvin D1 is involved in insulin sensitivity by affecting insulin signaling and inflammatory pathways. Therefore, it can be a contributing factor in reducing insulin resistance in PCOS patients.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age with symptoms including an increase in androgens (clinical and biochemical), chronic anovulation, polycystic ovarian and oligomenorrhea or amenorrhea [1,2]. In addition to infertility, PCOS entails other risks, including increased insulin resistance, type 2 diabetes, dyslipidemia, hypertension, cardiovascular diseases and even mental complications such as depression and social stresses [3,4]. Recently, meta-analysis studies have indicated that women with PCOS have a 40-times higher risk of type 2 diabetes compared to healthy women [5]. Extensive studies indicated that insulin resistance plays a central role in the pathogenesis of PCOS in both obese and non-obese women with PCOS; however, obesity is a manifest feature of PCOS [2,6].

The etiology of insulin resistance is unclear; however, 50% of patients with PCOS have insulin receptor autophosphorylation, which suppresses the natural activity of tyrosine kinase [7]. Moreover, a decreased gene expression of GLUT4 can be involved in insulin resistance. Recently, studies have suggested that inhibition

* Corresponding author. Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.
E-mail address: m-mahmoudi@sina.tums.ac.ir (M. Mahmoudi).

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of insulin receptor substrate 1 (IRS-1) by induced serine phosphorylation of IRS-1 in muscle cells and decreased gene expression of GLUT4 can be involved in insulin resistance in these patients [8].

Chronic low-grade inflammation and oxidative stress play a critical role in the pathogenesis of insulin resistance in PCOS. Recent studies have suggested the role of adipose tissue and inflammation in insulin signaling pathways. This inflammation-induced IR (insulin resistance) originates from visceral abdominal fat by increasing the production of inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) [9,10]. Impairment of insulin signaling pathways was observed in the PCOS patients. Levels of proinflammatory markers such as C-reactive protein (CRP), as well as macrophage and monocyte counts, are higher in women with PCOS compared to healthy women [8,9].

Recent studies have attributed a new group of lipid mediators including E-series and D-series resolvins to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively. In D-series resolvins, DHA is transformed to active compounds of resolvins including RvD1, RvD2, RvD3 and RvD4 by 15-lipoxygenase enzyme [10].

Resolvin has an anti-inflammatory activity and immunomodulation actions. It blocks the production of inflammatory mediators, modulates leukocyte accumulation and polymorphonuclear neutrophil (PMN) infiltration into the inflammatory sites [10,11]. Increased intake of omega-3 PUFAs, such as EPA and DHA, causes an increased incorporation of these fatty acids in the membrane phospholipids of inflammatory cells [12]. It has also been shown that omega-3 PUFAs reduce the production of eicosanoids from arachidonic acid by decreasing cyclooxygenase and lipoxygenase enzyme activity. Therefore, EPA and DHA are the major substrates for RvD1 synthesis [10,13,14].

The aim of the present study is to determine the intake of omega-3 PUFAs and serum levels of resolvin D1, as well as their relationship to insulin resistance in PCOS patients compared to healthy controls.

2. Method and material

2.1. Subjects

This study was a case/control study. Thirty-one women with PCOS were recruited from the infertility clinic at Valie-Asr Reproductive Health Research Centre (Tehran Imam Khomeini Hospital). The diagnosis of PCOS was made according to ESHRE/ASRM criteria (the presence of at least two criteria of the disease: excess androgen activity, chronic anovulation, polycystic ovaries). Twenty-nine healthy female volunteers with regular menstrual cycles, of similar age, weight and height were enrolled as the control group.

The inclusion criteria for the study were: (i) a diagnosis of PCOS by the gynecologist; (ii) 18–38 years of age. All the women were Iranian, and had no history of glucose intolerance or intake of hormonal medications for the preceding six months. Exclusion criteria for all subjects were pregnancy, breastfeeding, smoking, current or previous (within the preceding six months) use of metformin or other hypoglycemic drugs, fat-reducing medications such as Orlistat, anti-inflammatory drugs (such as aspirin) and antioxidant supplements. None of the patients had any other disease such as cardiovascular disorders, hypothyroidism or systemic inflammation.

2.2. Clinical analysis

Personal information, records of diseases and drugs and supplements were recorded for all patients. Anthropometric measurements were taken for each patient including weight, height and waist circumference. Weight was measured using Seca scales to the nearest 0.1 kg (without shoes and with light clothing) and height (in a standing position) was measured to the nearest 1 cm without shoes. Waist circumference was measured to the nearest 0.5 cm (midway between the upper edge of the crest of the hip bone and the lower edge of the chest). Patients' usual dietary intake was evaluated by a 147-item self-reported food frequency questionnaire (FFQ) [15]. Frequency of consumption, or lack of consumption, of each food was recorded for every day, week, month, and year. The reported consumption amounts for each food were converted to grams per day before entering it into the software.

2.3. Biochemical analysis

Blood samples (10 ml) were taken in the laboratory after 10 12 h of fasting at around 7–8 am. Blood samples of 5 ml were collected in tubes containing 0.1% Ethylenediaminetetraacetic acid (EDTA) and these were centrifuged for 12 min to separate the plasma, and then stored at $-80\,^{\circ}$C. Fasting serum insulin was measured using ELISA kits (Diametra Company-Italy) at a sensitivity of 0.25 (μIU/ml). The plasma glucose was determined using the glucose oxidase method (Pars Test Kit, Iran). The Homeostasis Model Assessment (HOMA) score was used to estimate insulin resistance. The following formula was used:

$$\text{HOMA} = (\text{FPI}\ (\mu\text{U/ml}) \times \text{FPG(mg/dL)})\ /\qquad 405$$

2.4. The serum D1 resolution analysis

The serum resolving D1 level was measured using enzyme-linked immunoassay (EIA) kits (Cayman Chemicals-Ann Arbor, USA). Prior to the analysis of resolvin D1 levels, the plasma sample was purified via SPE Cartridges c18. This method was used for cleaning and concentration of samples prior to ELA essays for complicated chemical compositions.

2.5. Statistical analysis

All statistical analyses were performed using the SPSS (version 17, IBM CO). Nutritionist IV was employed in order to analyse daily dietary intakes. Means, standard deviations and medians were used to represent the data. The normality of data distribution was checked using the Kolmogorov-Smirnov test. We compared the means of the variables of the case group with the control group using an independent sample *t*-test and ANOVA in the adjusted models. Energy intake was adjusted by analysis of covariance (ANCOVA). The Pearson correlation test was used to determine the association between the variables and the resolvin D1 levels. Differences with P values of <0.05 were considered as significant.

3. Results

3.1. Findings associated with the anthropometric and hormonal properties of the PCOS patients and the healthy individuals

Among the 60 individuals enrolled in the study, 31 belonged to the case group (the group of patients meeting the inclusion criteria of the study) and 29 women belonged to the control group (the healthy group). With respect to age, BMI, and anthropometric measurements, there was no significant difference between the case ($n = 31$) and the control group ($n = 29$). Nevertheless, there was a significant difference in the average waist circumference between the two groups. In order to examine waist circumference as a confounding variable, statistical ANCOVA was used and the variable of waist circumference as a confounding variable between the two groups was not statistically effective (*P*-value = 0.4).

There were significant differences in the fasting plasma glucose and insulin levels between the women with PCOS and the control group. The average fasting blood glucose levels in the case group were higher than in the control group (*P*-value = 0.02). As expected, the fasting insulin levels in the case group were significantly higher than in the control group (*P*-value = 0.001); therefore, the insulin resistance index (HOMA) was significantly increased in the PCOS patients (*P*-value = 0.001). The anthropometric characteristics and hormonal profiles of the PCOS and control groups are shown in Table 1.

3.2. Daily energy, macronutrient and fatty acid intakes of the PCOS and control groups

Results of the evaluation of the daily dietary intake from the semi-quantitative food frequency questionnaire indicated that the mean intake of energy, protein and carbohydrates was higher in women with PCOS compared to the control group. Furthermore, the mean intake of total fat and omega-6 PUFAs was higher in the case group compared to the control group.

No significant difference was found in the intake of total fat and omega-6 PUFAs (Table 2). Unexpectedly, the average daily intake of omega-3 PUFAs was higher in the patients compared to the healthy group (*P*-value = 0.02).

3.3. The plasma level of resolvin D1

As shown in Tables 1–3, resolving D1 levels were higher in the PCOS group than in the control group, but there was no statistically significant difference. These observations related to a high consumption of omega-3 PUFAs in the patients (p-value = 0.19). According to the Pearson correlation test, there was a significant negative correlation between resolving D1 and the insulin resistance index (r = −0.654, p-value = 0.001). Moreover, in the PCOS group the correlation was more severe. There was a significant negative correlation between resolving D1 levels and fasting insulin levels.

4. Discussion

PCOS is the most common endocrine disorder among women and the leading cause of health problems, including mental disorders and metabolic complications [16]. The pathogenesis of PCOS is associated with insulin resistance and the elevation of insulin levels [17,18].

We determined the association between the daily intake of omega-3 PUFAs and resolvin D1 and found that resolvin D1 levels were associated with insulin resistance in patients with PCOS, as well as in healthy women. Previous studies have emphasized the role of hormonal profiles and metabolism on the pathogenesis of PCOS.

A study conducted by Macut D to determine oxidative stress and insulin resistance in non-obese women with PCOS indicated that insulin resistance in obese women is higher than in healthy women in the control group [19]. Stovall DW also evaluated the insulin resistance in obese and non-obese women with PCOS, and showed that diabetes mellitus, IGT (impaired glucose tolerance) and IR are far less common in lean women compared with obese women [20]. Results from both human and animal studies demonstrate that insulin resistance plays a critical role in the pathogenesis of PCOS.

Increased insulin resistance in women suffering from PCOS is primarily associated with an excess of central fat. One study showed that insulin resistance was higher in obese women rather than non-obese women (both those with PCOS and the control group); furthermore, insulin resistance had a strong correlation with women with abdominal obesity [9]. The studies suggested that women with PCOS have varying degrees of insulin resistance, and that overweight and obese women have greater insulin resistance. Yet, no studies have consistently confirmed that PCOS patients who are lean or of a normal weight have insulin resistance. Indeed, insulin resistance in cases of PCOS is more related to a disorder in insulin receptor signaling pathway, e.g. impairment in Ser/Thr phosphorylation, of insulin receptor substrate (IRS)-1 in insulin receptor signaling pathway [21]. In the present research, as expected, insulin resistance has been shown to be higher in the patients than in healthy women, which indicates impaired glucose tolerance in these patients.

In this study, we unexpectedly noted that an intake of omega-3 PUFAs (DHA) in women with PCOS was higher than in healthy women. Further, the intake of omega-6 PUFAs was higher in the patient group than in their healthy counterparts. However, results of other studies represent contradictory findings compared to our study.

According to the study by Alvarez-Blasco of women with PCOS and healthy women, it was found that obese women had more total fat regardless of whether they were a patient or not, and this fat intake was more likely to be associated with the intake of monounsaturated fatty acids. On the other hand, women with PCOS had a higher intake of omega-6 PUFAs and a lower intake of omega-3 PUFAs. This study concluded that dietary pattern and physical activity cannot be definite factors in the progression of PCOS in obese women [22]. In the present research, the intake of omega-3 PUFAs was higher than that of omega-6 PUFAs. Therefore, the results of the other research are consistent with those of the present study.

In the study on the effect of dietary patterns on endometriosis among women, a link was found between the daily intake of fat and fertility and endometriosis. However, an intake of trans fatty acids

Table 1
Anthropometric and metabolic characteristics of PCOS cases and controls.

Variable	Total (n = 60)	PCOS (n = 31)	Control (n = 29)	*P*-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (y)[a]	26.3 ± 3.9	25.9 ± 4.1	26.6 ± 3.9	0.4
Weight (kg)[a]	70.1 ± 12.1	70.6 ± 13.5	69.7 ± 10.9	0.7
Height (cm)[a]	161.5 ± 6.1	161.8 ± 6.4	161.1 ± 5.7	0.6
Waist (cm)[a]	89.8 ± 8.1	93 ± 8.1	86.4 ± 6.7	0.01
Fasting glucose (mg/dl)[a]	79.3 ± 4.4	81.0 ± 4.7	77.6 ± 3.4	0.02
Fasting insulin (μU/ml)[a]	10.5 ± 1.3	11.2 ± 1.1	9.7 ± 0.9	0.001
HOMA-IR[a]	2.1 ± 0.3	2.3 ± 0.3	1.8 ± 0.25	0.001
Resolvin D1 (pg/ml)	248.8 ± 175.7	277.4 ± 174.1	218.16 ± 175.3	0.19

[a] Independent-t tests performed ($P < 0.005$).

Table 2
Energy and macronutrient intakes of PCOS cases and controls.

Variable	Total (n = 60)	PCOS (n = 31)	Control (n = 29)	*P*-value	*P*-value[b]
	Mean ± SD	Mean ± SD	Mean ± SD		
Energy from food (kcal)[a]	2816.6 ± 444	3029.9 ± 431	2588.6 ± 378	0.001	–
Carbohydrates (g)[a]	454.2 ± 38.66	454.2 ± 62.78	380.6 ± 55.15	0.001	0.09
Protein (g)[a]	98.9 ± 16.1	103.4 ± 17.1	94.1 ± 13.5	0.024	0.04
Total fat (g)[a]	91.1 ± 17.2	96.9 ± 18.9	85 ± 12.8	0.07	0.1
Omega-3 PUFAs (g)[a]	1.3 ± 0.4	1.5 ± 0.4	1.2 ± 0.3	0.02	0.7
Omega-6 PUFAs (g)[a]	1.2 ± 0.34	1.1 ± 0.37	1.1 ± 0.33	0.06	0.5
DHA (mg)[a]	101.7 ± 30.5	110.2 ± 27.4	90.4 ± 33.3	0.015	0.6

[a] Independent-t tests performed (P < 0.005).
[b] *Energy* adjusted (based on covariance).

Table 3
Correlation between resolvin D1 and metabolic parameters.

Variable	Total (n = 60)		PCOS (n = 31)		Control (n = 29)	
	r	P	r	P	r	P
HOMA-IR[a]	−0.65	0.001	−0.87	0.001	−0.98	0.001
Fasting insulin (μU/ml)[a]	0.58	0.001	−0.79	0.001	−0.93	0.001
DHA (mg)[a]	0.71	0.001	0.82	0.001	0.85	0.01
Omega −3 PUFAs (g)[a]	0.81	0.001	0.85	0.001	0.75	0.001

[a] Pearson correlation tests performed (*P* < 0.005).

and palmitic acid increases the incidence of endometriosis, and omega-3 PUFAs containing 1% of the energy reduces the endometriosis and its complications such as infertility [23]. In the present research, despite the higher intake of omega-6 PUFAs by PCOS patients, the average intake of omega-3 PUFAs has been shown to be higher in patients with PCOS compared to the control group. We assume that the disparity in the results of these studies may have been due to further nutrition knowledge and improved dietary behavior of patients with PCOS; therefore, common dietary patterns might have been changed due to self-diagnosis or treatment. A limitation of the current study was the use of only one method for evaluating the daily intake of nutrients; the assessment of dietary intake using other methods, such as 24-h dietary recall and food record, might present more consistent results.

The present study has demonstrated that the resolvin D1 plasma level was slightly higher in PCOS patients compared to healthy individuals; however, this difference was not significant. According to the endogenous synthesis of resolvin from omega-3 PUFAs, most studies have focused on the difference in omega-3 PUFAs in women with PCOS. The present research is the first to examine the resolvin D1 level in patients with PCOS and few studies have examined this relationship on human samples.

A high resolvin D1 level might be due to a higher consumption of omega-3 PUFAs by PCOS patients compared with the control group, as well as an increased synthesis of resolvin D1 by PCOS patients compared with the control group. When it comes to the relationship of omega-3 PUFAs and resolving, our results consistently confirm the results found by other studies. The study by Arita et al. on mice reported that the level of resolvin D1 (which was evaluated via chromotography) was higher in the mice fed with DHA than in the control group; indeed, a direct relationship was seen between omega-3 PUFAs and resolvin [24]. In another study by Mas on human samples, a direct correlation between serum levels of resolvin D1 and the daily intake of omega-3 PUFAs in subjects who take the supplements was reported [25].

Although the majority of related articles focus on the endogenous synthesis of resolvin D1 and the anti-inflammatory effects of resolvin, there are few studies that have assessed the correlation between resolvin and insulin resistance. One study has examined the protective effects of omega-3 PUFAs and resolvin D1 on ob/ob rats. The results showed that gene expression of inflammatory biomarkers was reduced in the "omega-3 PUFAs" group and also that insulin sensitivity had increased in this group. As a matter of fact, AMPK activity has a significant relationship with the increase of DHA in fat and muscle tissue in rats [26], which probably has a mediatory relationship between these variables.

Another mechanism whereby resolvin may influence insulin sensitivity is by increasing insulin-dependent phosphorylation of protein kinase B (PKB/Akt) in fat mass. One study on obese diabetic rats showed that resolvin D1 in the group intake of resolvin caused an improvement in glucose homeostasis and an increased activation of Akt. Thus, a negative correlation has been observed between resolvin and insulin resistance in the present research [10].

The findings in these two studies were similar to the present research suggesting the inverse correlation between resolvin and insulin resistance, except that, in the present research, we used human samples. One study has shown that lipid mediator production, including resolvin and protectin, was increased in rats with a higher intake of fats for 8 weeks. In this study, a negative relationship between lipid biomarkers and insulin resistance and stimulated phosphorylation of Akt was observed in muscle and liver tissues of PCOS patients [27]. Akt is an important mediator of glucose transport and glucose metabolism in skeletal muscle in vivo. Studies suggest that impaired phosphorylation of Akt at both Ser473 and Thr308 is associated with type 2 diabetes in PCOS [28].

Another mechanism relates to the relationship between the insulin receptor and the inflammatory process. In previous studies, Chemokine-like receptor 1 (CMKLR23) was introduced as the resolvin receptor and as a part of TNF-α receptor inhibiting leukocyte infiltration and proinflammatory gene expression. On the other hand, this receptor affects the process of insulin signaling. However, the relationship between resolvin and receptor requires further investigation [29–31]. The results obtained in this study suggest that a lipid mediator resolvin has a protective role in insulin resistance.

It can be concluded that a lipid mediator resolvin has a protective role in insulin resistance and type 2 diabetes, which are the major complications in PCOS. However, a significant negative correlation has been observed between resolvin and insulin resistance. Other factors also affect the severity of the mechanism of this relationship and this requires further research. Resolvin and other lipid mediators can be considered as new therapeutic approaches for diseases such as type 2 diabetes, cardiovascular disease and metabolic syndrome.

Conflicts of interest

All other authors have no conflict of interest.

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