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Research Article

Polycystic Ovary Syndrome: Effect of Inositols and Lipid Mediators. Pilot Study

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Abstract

Objective: to evaluate the effect of the combination of inositiol derivatives and lipid mediators on the metabolic and inflammatory profile of women with polycystic ovary syndrome.

Material and Methods: Experimental, prospective and longitudinal study carried out in patients diagnosed with polycystic ovary syndrome (Rotterdam criteria) without treatment or previous dietary intervention. The following nutritional preparations were administered orally daily:

- **Group A:** 300mg D-chiro-inositol, 1099mg myo- inositol + 30mg lipinova
- **Group B:** 4000 mg of myo -inositol + 30 mg of lipinova

The metabolic profile is compared before and after 4 weeks of treatment in each patient, determining the insulin levels and the HOMA index. The inflammatory profile was analyzed by determining the levels of IL-6 before and after treatment.

Results

- 41 patients with polycystic ovary syndrome subdivided into 20 from group A and 21 from group B were studied.
- Insulin levels before and after treatment were 17.9 +-9.3 SD and 10 +-4.09 SD, respectively, with statistically significant differences.
- The HOMA index pre-treatment was 4.1 +-2.1 SD and 2.1+- 1.1 SD post-treatment, with significant differences
- The level of IL-6 was pretreatment was 3.8 +- 1.5 Sd of 2.1 + -1.09 post treatment with significant differences

Conclusion: The results of the study show the positive effect of the combined administration of inositolic derivatives and pro-resolution lipid mediators on the metabolic, clinical and inflammatory profile of patients with polycystic ovary syndrome.

Keywords: Pro-Resolving Lipid Mediators; Inositol; Polycystic Ovary

Introduction

Polycystic ovary syndrome (PCOS) is highly prevalent and is the most common metabolic endocrine disorder in women of reproductive age. The first concrete medical report of PCOS in the contemporary medical literature was the highly influential report by Stein and Leventhal, [1]. who were the first to describe a series of patients, rather than isolated cases, with the triad of polycystic ovaries, hirsutism, and oligoamenorrhea, clinically linking what until then seemed unrelated features. However, despite significant progress in understanding the pathophysiology and diagnosis

of the disorder in the last 20 years, it is still underdiagnosed or misinterpreted by many clinicians [2]. Recently, interest has grown in the possibility of giving PCOS another name to better describe its endocrine-metabolic roots or to recognize the different phenotypes of the disorder. Furthermore, and regardless of what it should be called, it is clear that the medical community needs to be better prepared, informed and alert regarding this highly widespread disorder.

Definition

There are currently three diagnostic criteria in use for PCOS. Although there are minor differences in the diagnostic schemes for these criteria, they generally use the same features. Examination of the criteria indicates that two of them (ie, Rotterdam 2003 and Androgen Excess and PCOS Society 2006) represent extensions of the first (National Institutes of Health 1990) (Table 1). The 1990 National Institutes of Health criteria define two phenotypes: phenotype A (hyperandrogenism + oligoanovulation + polycystic ovarian morphology) and phenotype B (hyperandrogenism + oligoanovulation, but not polycystic ovarian morphology). Phenotype A is often referred to as the "full" PCOS phenotype; and both phenotypes A and B are often called "classic" PCOS. The Androgen Excess and PCOS Society 2006 and Rotterdam 2003 criteria include an additional phenotype, phenotype C (hyperandrogenism + polycystic ovarian morphology, but no oligoanovulation), the so-called "ovulatory" PCOS. Finally, the Rotterdam 2003 criteria introduced a fourth phenotype of PCOS, phenotype D (oligoanovulation + polycystic ovarian morphology, no hyperandrogenism), often referred to as 'non-hyperandrogenic' PCOS (Table 1). In 2012, a Congressional Consensus Panel of the National Institutes of Health recommended that the 2003 Rotterdam criteria be used, as long as the specific PCOS phenotypes identified are taken into account [3-5].

	NIH 1990	ESHRE/ASRM 2003 (Rotterdam)	Society AE-PCOS 2006	Consensus NIH 2012
Criteria	Are necessary two oftwo criteria: HE HAS OA	Are necessary two of 3 criteria: HE HAS OA PCOM*	Are necessary two of two criteria: HE HAS ovarian dysfunction (OA, pcom, either both*)	He recommended the use of 2003 Rotterdam Criteria,but with the specification of to identify the phenotypes specific included: phenotype A: HA+OA+PCOM* phenotype B: HA+OA phenotype C: HA+PCOM* phenotype D: OA+PCOM*
exclusions		Exclusion of disorders Similar or what it emulate		

Table 1

Epidemiology

The first study to establish the prevalence of PCOS in an unselected population was conducted in the southern United States and published in 1998 [6]. Since then, several studies have found a prevalence of PCOS affecting between 5 and 20% (1/20 to 1/5) of women of reproductive age, depending on the definition used [7]. In most of these studies, and despite variations in methodology, the prevalence of PCOS as defined by the 1990 National Institutes of Health has been relatively uniform, between 5% and 10%, while the prevalence of PCOS as defined by the Androgen Excess and PCOS Society of 2006 ranges between 10 and 15%; and according to Rotterdam 2003, it is between 5-20% [8]. In general, the prevalence of PCOS in a population is not related to the degree of obesity in that population, suggesting that it is not a consequence of the modern obesity epidemic [8].

Clinical presentation

Polycystic ovary syndrome is a clinical syndrome; that is, a collection of signs and symptoms, including clinical or biochemical hyperandrogenism, oligoanovulation, and polycystic ovarian morphology, which we define as follows.

Clinical hyperandrogenism

The most common clinical sign of hyperandrogenism is hirsutism or the presence of excess terminal hair in a male-like pattern. Terminal hair refers to hair that grows more than 5 mm in length (if not clipped), is modulated (with a central core of compact keratinocytes), and often has both shape and pigment. Body hair, on the other hand, is unmodulated, softer, generally less than 5mm long, may or may not be pigmented, and is uniform in shape. Male-type pattern refers to hair growth in areas where men typically develop terminal hair growth.

Clinically, the level of terminal hair growth in male-type areas is assessed using a visual scale, the modified Ferriman-Gallwey score [9]. This score is obtained by assigning a score of 0 (no visible terminal hair) to 4 (terminal hair growth consistent with that of a normal male individual) in nine areas of the body (upper lip, chin and neck, upper chest, lower back). upper abdomen, lower abdomen, or male pattern in shield, upper back, lower back, upper arms, and thighs) and then adding the values. Some considerations must be taken into account to assess the modified Ferriman-Gallwey score. It is worth mentioning that a color atlas has been published to help assess the modified Ferriman-Gallwey score reliably [9].

ovulatory dysfunction

Oligoovulation is usually detected by the length of the menstrual cycle (ie, the time between episodes of vaginal bleeding). Based on older epidemiological data, [10] oligoanovulation can be defined as menstrual cycles greater than 35 days in length, which in turn translates to 10 or fewer cycles per year. For greater rigor, some researchers prefer to use eight cycles or less per year as the definition of oligoanovulation, which is the equivalent of cycles longer than 45 days. However, not all oligoanovulation presents as clinically evident oligoamenorrhea [11]. In some women, ovulatory dysfunction will present as frequent menstrual bleeding (polymenorrhea), while other affected patients may have apparently "regular" monthly cycles (ie, eumenorrhea) [12]. In fact, up to 40% of hirsute women who claim to be eumenorrheic are oligoanovulatory [13,14].

Regarding hirsutism, the severity of menstrual dysfunction correlates directly with the degree of insulin resistance [15,16].

Polycystic ovary morphology

Although polycystic ovarian morphology can be detected histopathologically; clinically, most are detected by transvaginal ultrasonography. Polycystic ovarian morphology is defined as at least one ovary with an ovarian volume of more than 10 cm3 (or 10 mL) or a greater number of antral follicles (i.e., those that can be visualized as cysts in the ovarian cortex, measuring 2-9 mm in diameter). The exact number of antral follicles, that is, the antral follicle count, to establish the diagnosis of polycystic ovarian morphology using modern high-frequency transvaginal ultrasonography probes, is now at least 18 or more [17]. Although clinical symptoms are most pronounced in the reproductive years, the disorder causes symptomatology and morbidity throughout life [18]. Before menarche, affected girls may have exaggerated or premature adrenarche (excess production of adrenal androgens for age). On the other hand, in women, as they approach their later reproductive years and menopause, androgen biosynthesis progressively declines, and hirsutism and oligoanovulation may improve clinically.

Finally, we must recognize that the clinical phenotype of PCOS described by most researchers is based primarily on the evaluation of patients seen in the clinical setting. However, it is clear that there is significant referral bias for PCOS patients. Therefore, patients cared for in the clinical setting are often more severely hyperandrogenic and more obese than women with PCOS detected in epidemiological studies [9].

Pathophysiology

Although an in-depth analysis of this complex topic is beyond the limits of this study, there are a number of generalities about the pathophysiology of PCOS that can be addressed, focusing on the main defects observed and their interactions (Figure 1).

At the hypothalamic-pituitary level, PCOS patients show gonadotropin secretory abnormalities, including increased LH

pulse amplitude and frequency, and increased circulating LH levels, which is more evident in non-obese patients. In addition, the hypothalamic-pituitary axis appears to be somewhat resistant to the suppressive effects of progesterone on gonadotropin-releasing hormone pulse [19]. rate. daytime LH secretion, indicating that abnormalities in gonadotropin-releasing hormone release could be a primary defect in PCOS, at least in some patients. The increase in LH levels fulfills the role of stimulating the secretion of androgens by the ovarian theca cells.

At the ovarian level, the follicles show a relative resistance to follicle-stimulating hormone that, in part, may be intrinsic to the disorder. However, it may also be a consequence of the high levels of anti-Müllerian hormone secreted by a larger cohort of preantral follicles and the androgenic environment within the ovaries [20]. Other factors that may also contribute to abnormal follicular development in PCOS include elevated levels of circulating insulin and dysregulation of intraovarian factors that modulate follicular recruitment and growth; These include members of the transforming growth factor beta family (eg, anti-Müllerian hormone, inhibins, activins, bone morphogenetic proteins, and growth differentiation factors), other growth factors, and cytokines.

There is also evidence of adrenocortical steroidogenic dysfunction in PCOS [21] as approximately one-third of women with this disorder have an excess of dehydroepiandrosterone sulfate, an androgen metabolite or prohormone that is secreted almost exclusively by the adrenal cortex; however, the role of adrenal androgens in the development and maintenance of PCOS remains unclear.

Insulin resistance and compensatory hyperinsulinemia play a fundamental role in the pathophysiology of PCOS. Excess insulin, acting synergistically with LH, stimulates androgen production by ovarian theca cells [22] and, together with excess androgen, suppresses hepatic production of sex hormone-binding globulin [22]. Both factors favor the development of hyperandrogenism.

The etiology of decreased insulin sensitivity in PCOS remains unclear, although the various genetic and epigenetic dysfunctions all seem to lead to defects in the production and action of the major cellular glucose transporter, glucose transporter 4 (GLUT4)) and defects in insulin-mediated glucose disposal. Defects in insulin-mediated lipolysis are also evident in patients with PCOS. Furthermore, the degree of insulin resistance in PCOS worsens due to a state of chronic subacute inflammation, caused in part by the abnormal production and action of adipocytokines [12,16].

Finally, the contribution of obesity and fat distribution to the development of PCOS, regardless of its effect on insulin sensitivity, is unclear and probably modest at best, especially when studying patients identified in unbiased settings. medical. On the other hand, there is more evidence that the adipose tissue of women with PCOS has various defects that favor an inflammatory or insulin-resistant state; These include adipocytokine dysfunction, dysregulation of free fatty acid metabolism, and epigenetic alterations that affect GLUT4 function [6].

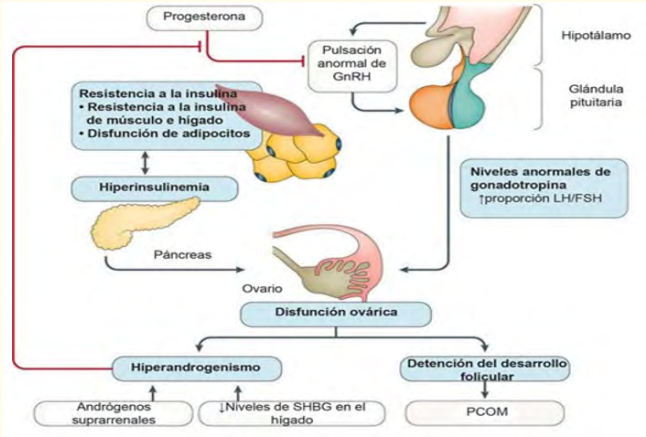

Figure 1: Pathophysiology diagram of polycystic ovary syndrome.

PCOS and insulin resistance

Patients with PCOS have chronic insulin resistance. Insulin resistance is defined as a decrease in the biological function of insulin with elevated plasma levels to maintain proper homeostasis. They are capable of producing insulin but to a lesser extent than expected, which suggests a dysfunction in the beta cells of the pancreas.

Insulin resistance and subsequent hyperinsulinemia are risk factors for developing type 2 diabetes and metabolic syndrome.

The prevalence of insulin resistance (IR) and compensatory hyperinsulinemia is increased in PCOS. Most studies show that at least 75% of women with the syndrome meet the diagnostic criteria for Rl.

Not all have metabolic syndrome (MS) according to the 2005 IDF diagnostic criteria [17]. In a recent study, 33% of non-diabetic women with PCOS develop MS before the age of 50, according to NHANES (MS between 30 and 40 years 30% of women with PCOS and MS have a first-degree family history of type 2 [12].

The determination of the degree of insulin resistance and the effect of the treatments on it will be determined by the levels of the HOMA resistance index and will be taken as normal values between 2.5-2.8 [20,21].

PCOS and inflammation

Analyzing the different pathophysiological alterations that cause polycystic ovary syndrome, we reach the conclusion that the inflammatory phenomenon is a key element in its development. This phenomenon has been directly related through the release of pro-inflammatory cytokines in the visceral tissue. Since PCOS is associated with obesity, we could think that only obese patients present this pro-inflammatory state; however, there are non-obese patients who also have a chronic inflammatory state associated with visceral adipose tissue.

PCOS patients have a pro-inflammatory genotype that leads to the production of pro-inflammatory cytokines such as TNF alpha and IL-6. The latter is a pro-inflammatory cytokine related to chronic inflammation such as insulin resistance. In patients with PCOS, it presents elevated serum levels of IL-6, not being intrinsic to this pathology, but it can acquire a crucial role in monitoring response to treatment [24,25].

Effect of inositols on PCOS

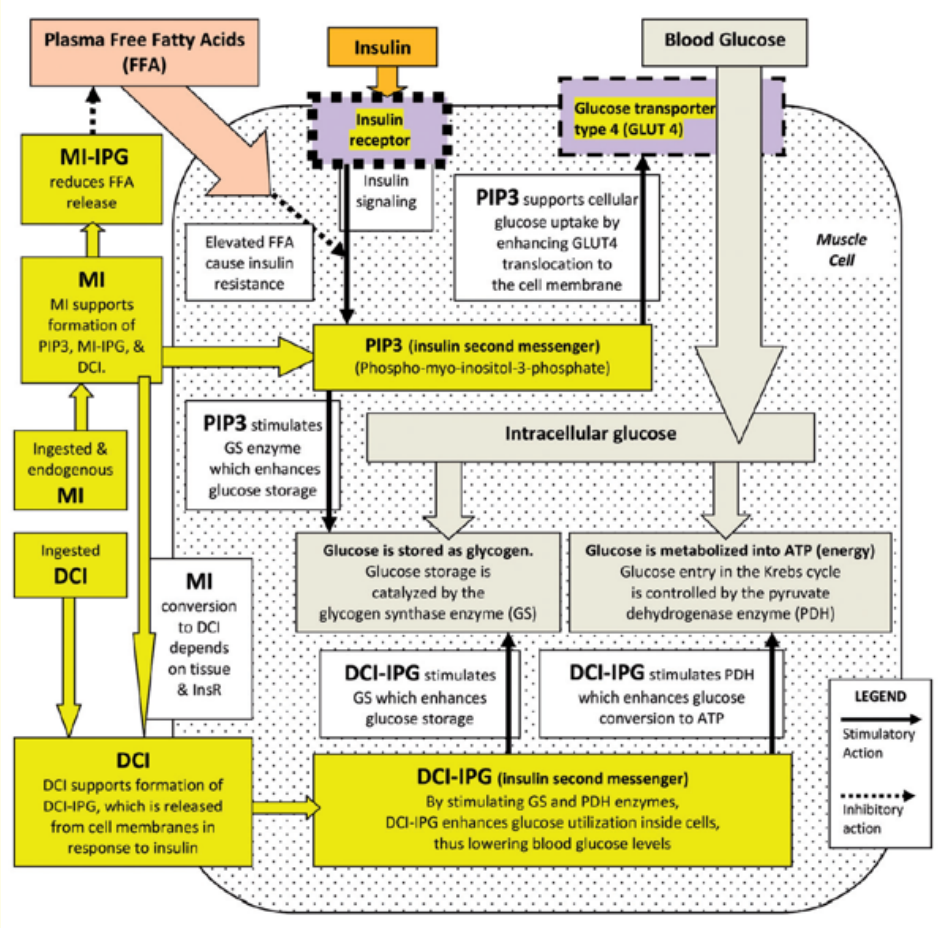

Figure 2: Effects of Inositols.

As we can see in the diagram above, both myo-inositol and d-chiro-inositol play a crucial role in glucose metabolism and insulin resistance. By existence, we understand insulin to be the deregulation of glucose and insulin metabolism, which leads to high blood levels of both. In this process, various cellular functions of organs such as the liver, muscle and adipose tissue are altered

- Alteration of cellular transport of glucose due to alteration of the GLUT4 enzyme
- Decreased pyruvate kinase activity not integrating glucose into the Krebs cycle.
- Alteration of glycogen synthase.
- Alteration of the adenylate cyclase that controls the mobilization of fatty acids, which causes their accumulation in the fatty tissue.

All these alterations improve with the use of insulin sensitizers such as insulin derivatives that are capable of reversing the cellular processes described [26-28].

Effect of lipid mediators in PCOS

We define inflammation as that response of the organism to different external or internal aggressions whose objective is to facilitate the repair and adaptation of the tissues to the new situation. A balance between inflammation and regulation is necessary for tissue survival. If the inflammatory component is excessive, it will cause the appearance of vascular, metabolic diseases.

The discovery of pro-resolution lipid mediators dates back more than a decade, but it is now that they have gained importance in many fields of medicine.

The origin of these pro-resolution mediators is the metabolization of omega-3 and omega-6 polyunsaturated fatty acids which, through interaction with different enzymes such as lipoxygenases, cyclooxygenases and cytochrome P450-dependent oxygenases, give rise to resolvins, protetin lipoxins and maresins [29]. figure 3.

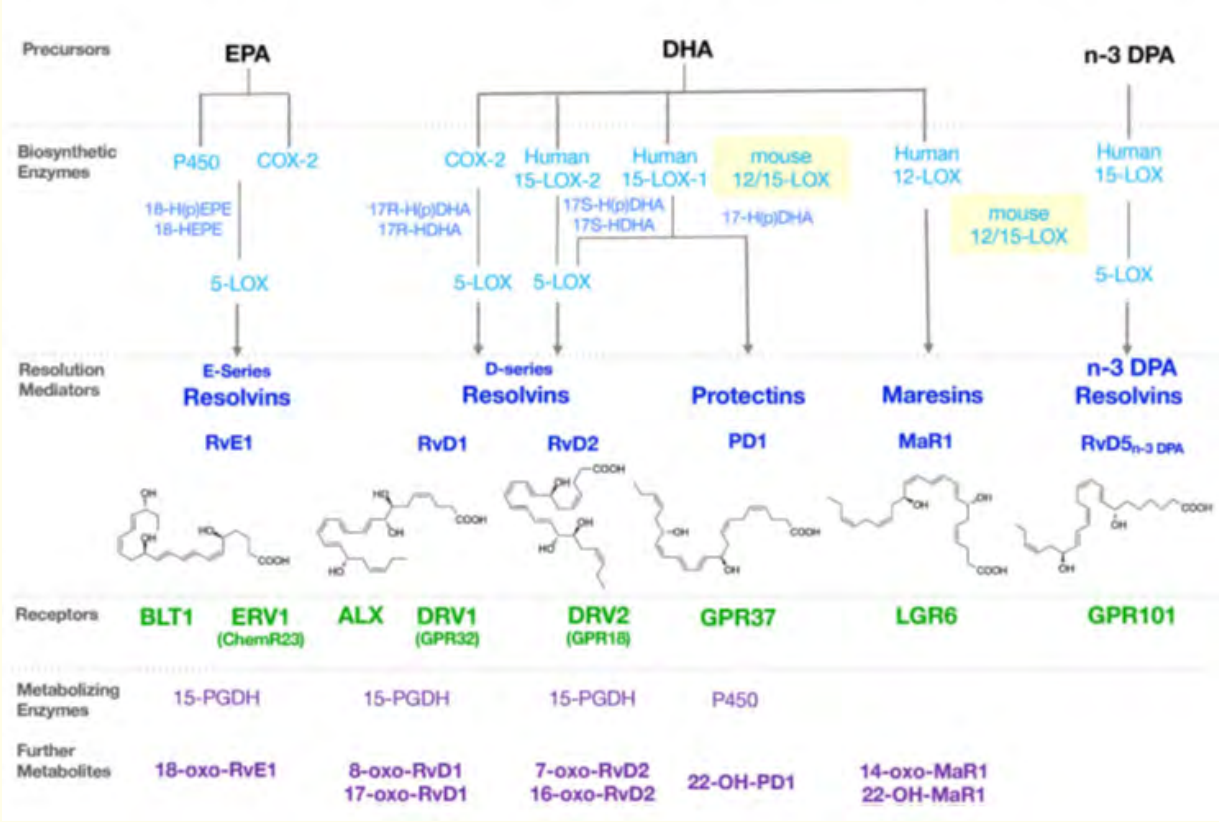

Figure 3: Types of pro-resolving lipid mediators.

The SPM will be aimed at the resolution of inflammation by cessation of the production of pro-inflammatory cytokines (TNF; ¡IL6IL8 I18" reduction of prostaglandin production. Figure 4.

Until recently, the phenomenon of resolution was believed to be a passive process. However, this resolving phenomenon is not consecutive to the inflammation, but it is at the beginning of the inflammation that its activity begins.

It is a highly active process, which involves the decrease in the proliferation and maturation of immune cells, the induction of apoptosis and active neutrophil spherocytosis by macrophages, the inhibition of the secretion of proinflammatory lipid mediators, as well as the secretion of essential lipid mediators for the resolution of inflammation derived from omega 3 fatty acids [30].

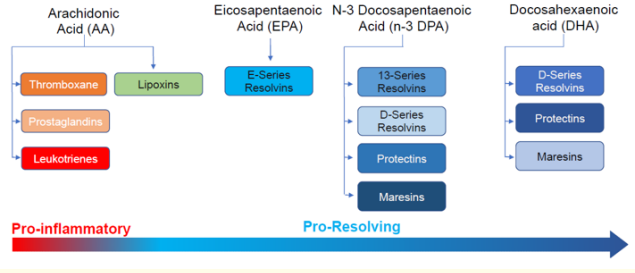

Figure 4: Essential lipid mediators for resolution.

After the description of the origin of the SPM, we expose their main functions:

- Limit the infiltration of polymorphonuclear cells.
- Reduce tissue damage by phagocytes
- Shorten the interval of resolution of the inflammatory response
- Increase phagocytosis and spherocytosis of macrophages
- Counteract pro-inflammatory agents
- Increase anti-inflammatory mediators IL-10.
- Improve tissue regeneration.

We have stated that the origin of these mediators are omega 3 and omega 6 acids. Therefore, an intervention from a nutritional perspective by increasing the intake of omega 3 would allow the balance of inflammation and resolution to reach equilibrium.

With regard to polycystic ovary syndrome, the therapeutic scheme has traditionally been based on addressing the existing symptoms, whether it is ovulatory dysfunction treated with anovulatory agents or with ovulation inducers, depending on the case, acne and hirsutism through the use of drugs that decrease testosterone or drugs that prevent the development of cardiovascular diseases [31].

PUFAs and their active forms have shown a beneficial effect in improving cardiovascular factors and an anti-inflammatory effect. There are numerous studies that analyze the effect of PUFAs in PCOS table 2 [31-34].

The SPM derived from PUFAs have a high anti-inflammatory power as demonstrated by *in vitro* and animal studies where a decrease in IL 6 levels is observed.

The HOMA index is a direct reflection of glucose metabolism, so together with IL6 it will be studied as a marker of response to treatment.

Object of Study	Design	Result
Influence of EPA on IGF-1 and Cox-3 expression in granulosa cells of PCOS women	In vitro cell culture of human granulosa cells from PCOS-affected women and healthy women. Exposition to EPA.	Significantly higher expression of IGF-1 m-RNA and lower expression of Cox-2 mRNA compared to non-treated control in both groups.
Effect of ω-3-PUFAs on metabolic and endocrine parameters	$N = 104$ women with PCOS. Effect of PUFA ω-3 supplementation on metabolic and endocrine parameters of a subgroup of $n = 22$ women;	Reduction of bioavailable plasma testosterone concentration. Modulation of lipid profile.
Effect of ω-3-PUFAs on obesity status and insulin resistance	$N = 61$ women with PCOS and BMI between 25 and 40 kg/m^2; double-blind randomized trial. Daily supplementation with 1200mg ω3-PUFA or placebo over 8 weeks	No significant effects on weight, BMI or waist circumference, but significant improvement in blood glucose level and insulin resistance
Effect of ω-3-PUFAs on PCOS	$N = 45$ non-obese PCOS women, daily supplementation with 1500mg ω-3-PUFA for 6 months	Decrease in BMI, insulin resistance, but not in blood glucose levels; Decrease in serum LH levels and testosterone levels; increase in SHBG levels

Table 2: Studies on the use of PUFAs in PCOS.

The objective of this study *to compare the effect of lipid mediators and inositol in patients with polycystic ovary and to determine if IL-6 and the HOMA index can be biomarkers of response to treatment.*

Material and Methods

Between April and August 2022, women who attended gynecology consultations and were diagnosed with sop were included in the study. The hospital ethics committee approved the study and informed consent was obtained.

The diagnosis of PCOS was confirmed using the Rotterdam criteria.

Hormonal tests and ultrasound were performed in the early follicular phase.

None of the patients were taking contraceptive drugs or insulin modulators. The ultrasound evaluation was performed with a GE brand ultrasound machine using a 5 MHz vaginal transducer.

Design

feasibility study (prospective cohort)

Procedures

Analytical determinations.

Patients who met the inclusion criteria underwent a blood test to determine baseline levels of interleukin 6 and the HOMA insulin resistance index.

Active intervention

DCI-inositol and Lipinova (Ovosicare, Ovusitol D Exelvit essential)were adminstrated for 4 weeks to all the patients who agreed to participate in the study. These preparations combined other vitamin components, sometimes duplicated, but without exceeding the limits of the European association of control nutrient intake.

The statistical analysis of the data will be carried out using the SPSS v. 25 (® IBM), and/or Wizard - Statistics and Analysis v.1.9 (© Evan Miller), and/or R software v. 4.0 (R Core theme, GNU).

Descriptive statistics will be used to summarize the epidemiological and clinical characteristics of the patients in the sample. In a first phase, the definition, control and validation of the variables included in the study will be carried out. Next, the descriptive and comparative analysis will be carried out. The quantitative variables will be analyzed using the measures of central tendency (mean, median) and dispersion (standard deviation, range) and the respective 95% confidence intervals. The qualitative variables will be described through proportions and the respective 95% confidence intervals.

Results

Demographic data is presented below

Descriptive statistics					
	N	**Minimum**	**Maximum**	**Half**	**Dev. Deviation**
Age	41	19.00	37.00	28,2000	7.48034

Table 3

None of the patients included was undergoing hormonal or insulin sensitizing treatment.

Regarding the BMI, the following results were observed

Statistics		
BMI		
N	Valid	41
	lost	0
Half		27,2000
Median		28,5000
Fashion		32.00
Dev. Deviation		4.73286

Table 4

In the group of patients studied, all presented menstrual disorders that improved after treatment.

The parameters studied before and after treatment are shown in the following tables

Pre-treatment markers

Post treatment result

Descriptive statistics					
	N	Minimum	Maximum	Half	Dev. Deviation
Insulin1	41	1.29	43.11	13,4927	9.90871
IL6pre	41	2.00	8.70	3.4883	1.40686
Homa1	41	,twenty-one	10.75	3.0796	2.52053

Table 5

Descriptive statistics					
	N	Minimum	Maximum	Half	Dev. Deviation
Insulin2	41	2.00	18.00	9,2321	4.09001
Il6pos	41	1.00	7.00	2.7393	1.33482
Homa2	41	,fifty	5:30	1.9607	1.14061

Table 6

Once the four weeks of treatment with DCI inositol and lipinova had elapsed, the levels of insulin resistance and inflammation parameters were compared with IL. 6- Both in the HOMA markers, IL-6 and in the levels of insulin, a significant decrease in them.

Paired Samples Statistics					
		Half	N	Dev. Deviation	Dev. average error
Pair 1	insulin1	16.7850	41	9.73152	1.83908
	insulin2	9,2321	41	4.09001	.77294
Pair 2	IL6pre	3.7786	41	1.54137	.29129
	IL6pos	2.7393	41	1.33482	.25226
Pair 3	homa1	3.8286	41	2.24959	.42513
	homa2	1.9607	41	1.14061	.21556

Table 7

Paired Sample Correlations				
		N	Correlation	Next.
Pair 1	insulin1 and insulin2	41	,837	,000
Pair 2	IL6pre and IL6pos	41	.643	,000
Pair 3	homa1 and homa2	41	,801	,000

Table 8

Study of the mean of the variables depending on the treatment used.

Group Statistics					
	TTO	N	Half	Dev. Deviation	Dev. average error
Insulin1	Inositol+LIPINOVA	Twenty-one	14,2905	9.42178	2.05600
	Caronositol+LIPINOVA	Twenty	15,1305	11.75106	2.69588
Insulin2	Inositol+LIPINOVA	Twenty-one	9,2000	4,47016	1.05363
	Caronositol+LIPINOVA	Twenty	9.2900	3.52624	1.11509

IL6pre	Inositol+LIPINOVA	Twenty-one	3.3333	1.36979	.29891
	Caronositol+LIPINOVA	Twenty	3.8632	1.58086	.36267
IL6pos	Inositol+LIPINOVA	Twenty-one	2.6611	1.45769	.34358
	Caronositol+LIPINOVA	Twenty	2.8800	1.13901	.36019
Homa1	Inositol+LIPINOVA	Twenty-one	3.2286	2.39669	.52300
	Caronositol+LIPINOVA	Twenty	3.3805	2.71688	.62329
Homa2	Inositol+LIPINOVA	Twenty-one	1.8222	1.23076	.29009
	Caronositol+LIPINOVA	Twenty	2.2100	.96661	.30567

Table 9

Levene's test for equality of variances		
	F	**Next.**
Insulin1	,550	.463
Insulin2	1,654	,210
IL6pre	.132	,719
IL6pos	.081	,778
Homa1	.010	,921
Homa2	1,080	,308

Table 10

There were no significant differences between the means of metabolic parameters depending on the type of treatment used.

Discussion

Polycystic ovary syndrome is a highly prevalent metabolic endocrine entity that affects around 5-20% of women of reproductive age and is not always correctly diagnosed. Its pathogenesis is not completely known and as a result of the existing metabolic alterations, comorbidities such as cardiovascular diseases, type 2 diabetes and metabolic syndrome may appear.

One of the basic pillars of the pathophysiology of PCOS is hyperinsulinemia as a result of existing insulin resistance. In addition, PCOS is considered a chronic inflammatory state evidenced by high levels of pro-inflammatory cytokinase such as IL-6. Some authors such as Ganadass [24] affirm that the inflammatory state in PCOS plays a crucial role and is commonly ignored.

Reviewing the literature, we reach the conclusion that, together with insulin resistance, the inflammatory state is the pillar on which the origin of PCOS rests. Currently, we have two analytical determinations that allow us to see and monitor the effect of drugs in the management of PCOS such as IL 6 levels and the HOMA resistance index.

The classic treatment of PCOS is limited to improving the existing symptoms based on the needs of the patient, but in view of the results of our work, in accordance with others in the literature that advocate synergies between inositols and different nutricellular components, it seems It is logical to recommend early treatment with nutritional complexes and lifestyle changes.

Health promotion interventions such as diet and exercise leading to weight loss improve metabolic parameters and fertility. The presence of acne hirsutism is treated with anti androgens and contraceptives. The desire for fertility involves the use of ovulation inducers and the improvement of the hyperinsulinemic state with the use of metformin.

However, the part of chronic inflammation and insulin resistance are not systematically treated. As stated by Regidor., *et al.* the use of pro-resolution mediators as an initial treatment for PCOS improves inflammation. There are different authors who have analyzed the effect of the association of inositols with other nutrients, observing a reduction in insulin parameters and IR HOMA in 8 weeks. Our research project has analyzed the effect of the union of inositolic derivatives and pro-solutive inflammatory mediators, observing a reduction of 20-70% in just 4 weeks, which makes us consider the synergistic effect of both

Critics of these studies by Unfer [36] state that these treatments only improve cardiovascular risks in patients with PCOS in the 40s and that due to their high cost and hypercaloric action they are not systematically indicated.

In this respect and based on our data with a population whose average age is 28 years, we must emphasize that many of the patients with PCOS will be diagnosed at an early age and that it is very likely that they will not have cardiovascular risk at that time and could develop it later. Our opinion, according to Regidor, is that the start of this therapy can and should be started immediately and that the possible OMEGA 3 side effects or the economic cost cannot be an obstacle that deprives patients of an opportunity for improvement. The results obtained allow us to consider the development of specific diets for PCOS, including foods that are a source of inositols and omega 3. The effect of the diet will affect three pillars of PCOS, obesity, inflammation and insulin resistance.

Note that PCOS patients are not always obese and that these patients do not usually benefit from specific diets, which means that PCOS alterations are not corrected through health promotion.

Altthough another reports are necessary to corroborate our data we believe, like other authors such as Paul [26], that open the door to carrying out combined treatments that cause synergy between both.- -The demonstration of the efficacy of SPM derived from omega 3 and the action of inositols can be the starting point for public health interventions through the consumption of foods that contain these components, designing diets for PCOS not only based on weight loss but also on the correction of insulin resistance and chronic inflammation.

Bibliography

1. Azziz R and Adashi EY. "Stein and Leventhal: 80 years on". *American Journal of Obstetrics and Gynecology* 214 (2016): 247.e1-247.e11.

2. Dokras A., *et al.* "Gaps in knowledge amongs regarding diagnostic criteria and management of polycystic ovary syndrome". *Fertility and Sterility* 107 (2017): 1380-1386.e1

3. Lizneva D., *et al.* "Criteria, prevalence and phenotypes of polycystic ovarian syndrome". *Fertility and Sterility* 106 (2016): 6-15.

4. National Institutes of Health. "Evidence-based methodology workshop on polycystic ovary syndrome. Executive summary". Final report (2012).

5. Lizneva D., *et al.* "Phenotypes and body mass in women with PCOS identified in clinical versus unselected populations: systematic review and meta-analysis". *Fertility and Sterility* 106 (2016): 1510-1220.

6. Azziz R., *et al.* "Screening for 21-hydroxylase deficient nonclassic adrenal hyperplasia among hyperandrogenic women: a prospective study". *Fertility and Sterility* 72 (1999): 915-925.

7. Knochenhauer ES., *et al.* "Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study". *The Journal of Clinical Endocrinology and Metabolism* 83 (1998): 3078-3082.

8. Bozdag G., *et al.* "The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis". *Human Reproduction* 31 (2016): 2841-2855.

9. Yildiz BO., *et al.* "Visually scoring hirsutism". *Human Play Update* 16 (2010): 51-64.

10. Treloar AE., *et al.* "Variation of the human menstrual cycle through reproductive life". *International Journal of Fertility* 12 (1967): 77-126.

11. Lizneva D., *et al.* "Androgen excess: investigations and management". *Best Practice and Research Clinical Obstetrics and Gynaecology* 37 (2016): 98-118.

12. Landay M., *et al.* "The degree of hyperinsulinemia, independent of androgen levels, is an important determinant of the severity of hirsutism in PCOS". *Fertility and Sterility* 92 (2009): 643-647.

13. Brower M., *et al.* "The severity of menstrual dysfunction as a predictor of insulin resistance in patients with polycystic ovary syndrome". *The Journal of Clinical Endocrinology and Metabolism* 98 (2013): E1967-1971.

14. Azziz R., *et al.* "Polycystic ovary syndrome". *Nature Reviews Disease Primers* 2 (2016): 16057.

15. Nestler JE., *et al.* "A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome". *The Journal of Clinical Endocrinology and Metabolism* 72 (1991): 83-89.

16. Nestler JE., *et al.* "Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using in ositolglycan mediators as the signal transduction system". *The Journal of Clinical Endocrinology and Metabolism* 83 (1998): 2001-2005.

17. The International Diabetes Federation: The IDF consensus worldwide definition of metabolic syndrome (2005).

18. Ehrmann DA., *et al.* "PCOS/Troglitazone Study Group. Prevalence and prediction of the metabolic syndrome in women with polycystic ovary syndrome". *The Journal of Clinical Endocrinology and Metabolism* 91 (2006): 48-53.

19. Lobo DR and Carina E. "The importance of diagnosing the polycystic ovary syndrome". *Annals of Internal Medicine* 132 (2000): 989-93.

20. Larsen R., *et al.* "Williams Textbook of Endocrinology by Elsevier Science (USA)" 627-636.

21. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. "Revised 2003 Consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome". *Fertility and Sterility* 81 (2004): 19-25.

22. Bonora E., *et al.* "Prevalence of insulin resistance in metabolic disorders". *The Brunik Study ll Diabetes* 47 (1998): 1643-1649.

23. Yeni-Konslrian H., *et al.* "Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers". *Diabetescare* 23 (2000): 171-175.

24. Abraham Gnanadass S., *et al.* "Association of metabolic and inflammatory markers with polycystic ovarian syndrome (PCOS): an update". *Archives of Gynecology and Obstetrics* 303.3 (2021): 631-643.

25. Peng Z., *et al.* "Interleukin-6 Levels in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis". *PLoS One* 11.2 (2016): e0148531.

26. Paul C., *et al.* "Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: state-of-the-art and future perspectives". *Gynecological Endocrinology* 32.6 (2016): 431-438.

27. Nordio M., *et al.* "Clinical Trial The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone". *European Review for Medical and Pharmacological Sciences* 16.5 (2012): 575-581.

28. Facchinetti F., *et al.* "Results from the International Consensus Conference on Myo-inositol and d-chiro-inositol in Obstetrics and Gynecology: the link between metabolic syndrome and PCOS". *European Journal of Obstetrics and Gynecology and Reproductive Biology* 195 (2015): 72-76.

29. Regidor PA., *et al.* "Chronic Inflammation in PCOS: The Potential Benefits of Specialized Pro-Resolving Lipid Mediators (SPMs) in the Improvement of the Resolutive Response". *International Journal of Molecular Sciences* 22.1 (2020): 384.

30. Alderman., *et al.* "PCOS: A Chronic Disease That Fails to Produce Adequately Specialized Pro-Resolving Lipid Mediators (SPMs)". *Biomedicines* 10.2 (2022): 456.

31. Serhan CN and Serhan CN. "Pro-resolving lipid mediators are leads for resolution physiology". *Nature* 510.7503 (2014): 92-101.

32. Calder PC. "Omega-3 polyunsaturated fatty acids and inflammatory processes: Nutrition or pharmacology?" *British Journal of Clinical Pharmacology* 75 (2013): 645-662.

33. Poudyal H., *et al.* "Omega-3 fatty acids and metabolic syndrome: Effects and emerging mechanisms of action". *Progress in Lipid Research* 50 (2011): 372-387.

34. Akinkuolie AO., *et al.* "Omega-3 polyunsaturated fatty acid and insulin sensitivity: A meta-analysis of randomized controlled trials". *Clinical Nutrition* 30 (2011): 702-707.

35. Phelan N., *et al.* "Hormonal and metabolic effects of polyunsaturated fatty acids in young women with polycystic ovary syndrome: Results from a cross-sectional analysis and a randomized, placebo-controlled, crossover trial". *The American Journal of Clinical Nutrition* 93 (2011): 652-662.

36. Rafraf M., *et al.* "Omega-3 fatty acids improve glucose metabolism without effects on obesity values and serum visfatin levels in women with polycystic ovary syndrome". *Journal of the American College of Nourishment* 31 (2012): 361-368.

37. Unfer VA. "Deeper Assessment of ω 3-Poly-Unsaturated Fatty Acids in Polycystic Ovary Syndrome Management. Comment on Regidor et al. Chronic Inflammation in PCOS: The Potential Benefits of Specialized Pro-Resolving Lipid Mediators (SPMs) in the Improvement of the Resolutive Response". *International Journal of Molecular Sciences* 22 (2021): 384.