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Research Article

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Evaluation of Cinnamon Supplementation on Insulin Resistance, BMI And Estradiol Levels in Women With Polycystic Ovary Syndrome: A Double-Blinded Randomized Controlled Clinical Trial

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Cinnamon reduces insulin resistance, BMI & estradiol in women with PCOS

Abstract

Background: Polycystic ovary syndrome (PCOS) is a serious multifactorial disorder. This study intended to assess the effect of cinnamon supplementation on estradiol level, and fasting- and two-hour (2 hpp) insulin and sugar levels in women with PCOS.

Material and Methods: This study was a double-blinded randomized clinical trial (RCT), conducted between January 2019 until December 2020, at Gynecology Clinic Sarem Women's Hospital in Tehran, Iran. Patients with PCOS, 130 subjects (65 person/ group) were diagnosed using Rotterdam diagnostic criteria. All participants received daily treatment consisting of 1500 mg metformin and 1000 mg cinnamon per day for 12 weeks. An evaluation of serum AMH level was conducted before and after the completion of therapy.

Results: Cinnamon supplementation significantly

reduced the estradiol, fasting glucose and 2hpp glucose, fasting insulin and 2 hpp insulin, BMI and weight levels after intervention. The highest reduction was observed in fasting glucose, 2 hpp insulin, and estradiol groups after intervention ($P<0.05$). There was a significant difference between the means of BMI ($P<0.01$), fasting sugar ($P<0.01$), and 2 hpp glucose ($P<0.01$) before and after intervention.

Conclusion: Cinnamon supplementation, as a safe herbal product, can be prescribed with metformin to improve the symptoms and complications of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a serious multifactorial disorder with heterogeneous and complex genetic causes that often leads to infertility in women. According to Rotterdam Diagnostic Criteria, PCOS has a prevalence of 15-20% in women in reproductive age. In PCOS, multiple immature follicles ("cysts") are formed within ovaries, which can thicken over time through fibrosis of the ovarian lining that prevents them from reaching and release. [1-3] Up to date, several classifications have been suggested for PCOS definition. According to the latest revise, the Rotterdam Revised Standard, the diagnosis of PCOS will be definitive when, 2 of the following three items to be observed in patients;

- Oligoovulation or anovulation
- Clinical or biochemical signs of excessive androgen level
- Observation of ovaries with poly cystic appearance (in one or both ovaries), the existence of more than 12 ovarian follicles with diameter of 2–9 mm and/or ovarian volume ≥10 cm^3.[4-8]

Despite extensive studies about the etiology of PCOS, the main reasons are still unknown. The outcomes of clinical and experimental studies have shown that PCOS is the result of various interactions between environmental factors and genetics.[9]

The role of environmental and genetics factors may involve the role of the anti-aging gene Sirtuin 1 that is now associated with PCOS. Sirtuin 1 is linked to insulin resistance and diabetes. Sirtuin 1 has effects on ovary aging and estrogen. Cinnamon and Metformin are activators of Sirtuin 1 and may be connected to the reduced estradiol, fasting glucose and 2hpp glucose, fasting insulin and 2 hpp insulin levels. [10-14] The measurements of Sirtuin 1 gene expression and plasma levels may assist with the improvement in the symptoms and complications of PCOS.

This syndrome is genetically characterized by dysfunction of the two axes of the brain; metabolic endocrine which is associated with hypothalamic-pituitary-adrenal axis. Over action of sympathetic nervous system leads to impairments in the regulatory pathways of steroid hormones, the regulatory pathway of gonadotropin action, the signaling pathway of insulin, and the regulatory pathways of glucose and fat metabolism. Therefore, it can be said that PCOS is a common endocrine and metabolic disorder with a possible genetic origin that is influenced by environmental factors including diet, lifestyle and social status.[15,16] On the other hand, considering the essential role of the liver in metabolic pathways, any dysfunction of the liver is classified as metabolic syndrome. Metabolic syndrome is generally characterized with symptoms such as enhancement of insulin resistance, elevated level of estrogen and inflammatory cytokines, as well as increased number and activity of fat cells, which are highly correlated with COS. [17]

Patients with PCOS may have normal levels of hormones, meaning that the cause of endocrine changes in these patients can be quite different. Currently, insulin resistance is the best well-known mechanistic reason for PCOS.[18] Insulin stimulates glucose homeostasis by increasing glucose uptake into muscle and adipose tissues. The effect of insulin is concentration dependent, so in patients with insulin resistance, the permeability of the cell membrane decreases toward insulin which leads to elevated insulin level.

Increased risk of developing diabetes type 2 is associated with insulin resistance. The prevalence of insulin resistance among women with PCOS is between 30 -35% and is greater in the obese than in lean population.

Often, women with PCOS and insulin resistance are young and have sufficient pancreatic B-cell reserve, thereby they are able to maintain normal glucose homeostasis. However, this state will turn to hyperinsulinemia. Comprehensive evidence-based data confirm that insulin resistance and hyperinsulinemia play an important role in the pathophysiology of PCOS.[19,20] According to the latest approvals of medical associations, control of insulin resistance, menstrual regulation, and modulation of androgen levels are the main recommendations for PCOS treatment. Up to date several medications have been developed to modulate PCOS symptoms such as menstrual and ovulatory dysfunctions, obesity, insulin resistance, lipid-metabolism dysfunction, androgen-related conditions, and estradiol levels. Yet, metformin is a lead compound for deterioration of insulin resistance, intra-ovarian androgens, and hyperinsulinemia in PCOS patients.[21,22] Literature reviews indicated that a wide spectrum of herbal products such as *Cinnamomum spp., Trigonella foenum-graecum, Cimicifuga racemosa, Tribulus terrestris, Glycyrrhiza spp., Paeonia lactiflora, and Vitex agnus-castus* are beneficial to improve different conditions of PCOS.[23,24]

One of the complementary therapies to correct metabolic disorders and to facilitate the entry of insulin into cells is the use of cinnamon compounds. *Cinnamomum zeylanicum* is one of the species of cinnamon which is obtained from the inner bark of a small evergreen tree belong the Lauraceae family.[25] The most important compounds in cinnamon are cinnamaldehyde, cinnamic acid, coumarin and eugenol and also, water-soluble polyphenols (e.g. catechin, procyanidin, cinnamtannin). It was shown that these compounds increase the activity triacylglycerol lipase that leads to fat hydrolysis of food, reduction of triglycerides, lowering the LDL cholesterol, increase in GLUT-4 receptor synthesis and its membrane translocation, inhibition of pancreatic and intestinal amylase and glucosidase, increase of hepatic glycogen production, and consequently elevation of glucose uptake and autophosphorylation of insulin receptors in fat cells and skeletal muscles.[26,27,28]

Taking to the account that hyperinsulinemia has been well recognized in women with PCOS, thus it is reasonable to assume that the use of insulin sensitizing compounds such as metformin and cinnamon can improve both the metabolic and reproductive functions. Cinnamon compounds are worth considering for investigations on insulin- and estradiol-related impairments in patients with PCOS. This clinical trial intended to assess the effect of cinnamon and metformin supplementation on estradiol level, as well as fasting and 2 hpp insulin and sugar levels in women diagnosed with PCOS.

Material and Methods

Study Design

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[29] This study was a double-blinded RCT, conducted in Gynecology Clinic Sarem Women's Hospital in Tehran, Iran, from January 2019 to December 2020. The patients were diagnosed by experienced Gynecologists. The sample size was estimated with 80% power and 95% confidence level to achieve the objectives of the study; 130 subjects (65 individuals per group). A questionnaire containing demographic and clinical information (e.g. height, weight, patient ultrasound information, taking medications, history of underlying diseases such as thyroid, hormonal disorders, and etc.) was completed for all participants in the study. A total of 130 women who passed the Rotterdam Criteria were selected and randomly divided into two groups; 1) the intervention group, and 2) the control group.

A number of patients in both groups, for various reasons, quit the study and ultimately, the intervention group contained 61 and the control group included 47 patients. The intervention group received cinnamon supplement capsules; CinnaBetic® (containing 500 mg cinnamon bark powder/2 times day) and the control subject received placebo capsules (2 g wheat flour). Both the placebo and cinnamon capsules were quite similar in shape and size.

Ethical Standards

This study was approved by Ethics Committee of

IRAN University of Medical Sciences (APPROVAL NUMBER/ID: IR.IUMS.REC.1397.1405). All experimental conditions were explained to participants and each one signed an informed consent from.

Inclusion Criteria

- Premenopausal women aging from 18 to 40 years
- All patients included in the study were diagnosed with PCOS according to the Rotterdam Criteria, who met two out of the following three features were met: clinical and/or biochemical hyper androgenism, polycystic ovaries, and/or oligo-/anovulation.
- All of patients included in the study were diagnosed with insulin resistance with abnormal estrogen level (higher or lower than normal)

Exclusion Criteria

- Patients who entered IVF cycle due to tubal, male, or unexplained infertility indications
- Loss to follow-up and poor continuity of treatment by the patient
- Hyper prolactinemia, hypertension, metabolic, liver, and cardiovascular diseases
- Taking beta-blockers and/or contraceptives pills within 3 months prior to study, due to interference with metformin mechanism

Outcome Measures

This is a RCT including PCOS women. We investigated the cinnamon 500 mg (2 times/day) and metformin 1500 mg supplementation effects on endocrine parameters including fasting and 2 hpp sugar, insulin and estradiol levels, and BMI.

Intervention Description

Following ultrasound and final diagnosis of PCOS, subjects entered into the treatment protocol and their height and weight were measured. Body mass index (BMI) calculated using (BMI= kg/m^2) formula. Subsequently diet and exercise were prescribed for all of them. Blood samples were collected and fasting and 2hpp blood sugar, as well as insulin and estradiol levels were recorded. Subjects were randomly allocated into two groups using block randomization method.

-Control group: received metformin + one capsule placebo (2 gr wheat flour), every 12 hours for 12 weeks.

-Intervention group: received metformin + one capsule cinnamon supplementation (500 mg cinnamon powder), every 12 hours for 12 weeks.

At the end of 12 weeks, fasting and 2 hpp sugar, insulin and estradiol levels, and BMI were rechecked again.

Statistical analyses

SPSS ver.22 statistical software was used to analyze the data obtained from both groups and was analyzed by t-tests and ANCOVA to identify two-group and comparison.

Results

As mentioned earlier, the median age of participants was 29.34, with an average height of 162 cm. In addition to PCOS, the most common underlying disease among participants was hypothyroidism, which was accounted for 56% of participants. 55% of participants were taking drugs. Table 1 represents the standard and non-standard regression coefficients for predictive variables. It was confirmed that the effect of intervention (cinnamon supplementation) on measured variables after elimination of the confounding effects including age, height, weight, underlying disease status, drug use, initial FBS and insulin levels, 2 hpp glucose and 2 hhp insulin, estradiol level, and BMI was significant.

According to the β value, it was elucidated that co-administration of cinnamon supplement and metformin had a significant impact on BMI, fasting and 2 hpp insulin levels, as well as sugar level, equaling to 3.18, 2.25, 1.82, 11.21 and 9.42 respectively. Thus, cinnamon supplementation was significantly effective on BMI, estradiol, FBS, insulin and 2 hpp insulin levels ($P<0.01$). Table 2 compares the effect of cinnamon supplementation on estradiol, fasting glucose and 2hpp glucose, fasting insulin and 2 hpp insulin, BMI and weight levels before and after intervention, as well as that of the control group. Data analysis exhibited that administration of cinnamon

Table 1. Standard and non-standard regression coefficients for predictive variables

Variables	Non-standard coefficients		Standard coefficients	t	Sig.
	B	Standard error	Beta		
Estradiol	0.12	3.24	-	0.04	0.971
	0.97	0.06	-18.13	16.21	0.001
BMI	0.36	0.38	-	0.95	0.344
	0.71	0.05	3.18	74.40	0.004
Fasting insulin	2.56	0.71	-	5.03	0.852
	3.91	0.004	2.25	20.18	0.004
2 hpp insulin	1.27	0.21	-	3.07	0.712
	2.74	0.03	1.82	9.27	0.003
FBS	0.31	4.11	-	0.07	0.847
	0.91	0.08	11.21	10.93	0.001
2 hpp	0.63	6.52	-	0.21	0.691
	1.14	0.13	9.42	8.37	0.008

*: Significant difference at P<0.01.

Table 2. Effect of cinnamon supplementation on estradiol, fasting glucose and 2hpp glucose, insulin and 2 hpp insulin, and BMI in comparison with the control group.

	Intervention group (n=60)			Control group (n=48)			
	Before	After	P- value interven-tion	Before	After	P-Value control group	P-value be-tween groups
BMI	28.01±5.6	27.60±5.53	< 0.01*	28.19±4.95	27.61±4.86	< 0.01*	0.748
Fasting glucose	94.62±9.66	96.03±10.55	< 0.05**	94.36±7.79	92.36±7.79	< 0.01*	0.068
2 hpp glucose	108.75±21.2	90.33±26.90	< 0.01*	102.74±19.86	83.17±20.79	< 0.01*	0.021
Fasting insulin	15.69±11.14	13.27±10.97	< 0.01*	14.41±6.71	12.03±6.5	< 0.01*	0.191
2 hpp insulin	71.61±59.63	60.41±57.70	< 0.05**	59.02±66.26	54.97±65.23	< 0.01*	0.457
Estradiol	48.46±32.18	40.33±22.65	< 0.05**	45.18±22.02	55.59±26.68	< 0.05**	0.005
Weight	74±15.99	72.94±15.89	< 0.01*	74.73±14.14	73.19±13.87	< 0.01*	0.0001

*: Significant difference at P<0.01.

**: Significant difference at P<0.05.

significantly reduced all the parameters that mentioned before and after the intervention. The highest reduction was observed in fasting glucose, 2 hpp insulin, and estradiol groups after intervention ($P<0.05$). There is a significant difference between the means of BMI ($P<0.01$), fasting sugar ($P<0.01$), and 2 hpp glucose ($P<0.01$) before and after intervention. It is noteworthy that the estradiol level increased in control group before and after the trial ($P<0.05$).

Discussion

This RCT study tended to investigate the effectiveness of cinnamon supplementation on glucose, insulin, estradiol and BMI levels in women with PCOs. Insulin resistance is one of the most important manifestations of PCO syndrome, which causes hormonal changes in the body. Obesity is one of the important morphological manifestations in PCO syndrome and studies also show that adipose tissue plays an important role in the development and persistence of PCO disorders.[30,31] Hyperandrogenism, is one of the another most important characteristics of PCOS which results in disturbance of ovarian function. Androgen enhances the production of ovarian steroids and high levels of androgen substrates and aromatase activity leading to higher estradiol concentration. Sufficient amount of estradiol not only reduces hypothalamic secretory activity but also decrease the sensitivity of the pituitary gland to GnRh. This effect depends on the amount of estradiol.[32] On the other hand, insulin receptors presented in the ovaries tissue in a complex with the FSH and IGF-1 hormones increase the estrogen production by granulosa cells. Therefore, increased insulin level due to insulin resistance synergistically lead to elevated estradiol production in PCOS.[21,33]

The efficacy and effects of different available treatments like metformin on various blood parameters like fasting and 2hpp glucose level was proved by multiple randomized clinical trials. By contrary, impacts of these medicines on the estradiol level neglected by most researchers. Therefore, it is crucial to provide and explore new alternative therapies to retard hyperandrogenism with minimal side effects. To the best of our knowledge our study is the first RCT which assess the efficacy of hyperandrogenism treatment combined with cinnamon therapy in Iranian women.

Up to date, numerous interventional studies have been performed on the effect of cinnamon supplementation on various aspects of PCOS. Borzoei et al. demonstrated that using three capsules/day, containing 500 mg of cinnamon for 8 weeks causing decrease in serum lipids and an increase in antioxidant activity in intervention group.[34] In another published RCT in 2017, Borzoei et al., evaluated the positive effect of cinnamon supplementation (3 capsules/day/8 weeks, containing 500 mg cinnamon) on glycemic indices, serum lipids and adiponectin in overweight women with PCOS.[35]

Previous studies have shown that decreasing estradiol level moderately, increases the insulin sensitivity and reduces the effects of insulin resistance.[36] Based on our results [Table 1], the effect of cinnamon consumption on lowering blood estradiol level in intervention group was statistically significant in comparison to control group. Decrease in estradiol level naturally increase insulin sensitivity in cells. However as depicted in Table 2, decrease in estradiol level per se could not statistically make a significant reduction in metabolism and BMI level of PCOS patients. It can be suggested that cinnamon supplementation has mostly played a regulatory role on estradiol level. In a similar study but on animal subjects (rats) in 2013, the effect of metformin and cinnamon supplementation was assessed on the 17β- estradiol, progesterone, testosterone, dihyrotestosterone, LH, FSH, insulin, insulin resistance, lipid profile (cholesterol, triglycerides, leptin), and total oxidant capacity (TOC). The authors reported that cinnamon supplementation significantly improved the disturbance of all parameters, particularly 17β- estradiol, which was elevated in rats with PCOS.[21]

Based on the data presented on Table 1, cinnamon supplementation has a positive effect on BMI of women who were participating in the intervention group. In accordance with our findings, Arentz et al., in 2017

conducted a study on overweight PCOS women and evaluated the combined effect of lifestyle and cinnamon supplementation on their weight. Their results exhibited that in combination group (Life style and cinnamon supplementation) significant improvements were observed in factors such as BMI, insulin level, blood pressure, depression, quality of life, and finally pregnancy rate.[36]

In several studies, stimulation of insulin secretion and hypoglycemia through modifying the insulin resistance introduced as the mechanism of action of cinnamon.[37,38] In the present study, we found that 1000 mg/day cinnamon supplementation over a period of 12 weeks significantly alleviated the fasting and 2 hpp glucose and insulin levels. Confirming our results, repeatedly it was reported that cinnamon can reduce the blood sugar and insulin level (fasting and 2 hpp).[39,40] Administration of cinnamon extraction mice fed a high-fat diet improved insulin resistance and decreased the blood lipid through modulation of transcription factors and changes in the expression of genes associated with enzymes such as ACLY and FAS and insulin resistance, glucose, and lipid metabolism.[41] In a pilot study by Wang et al., cinnamon extract significantly reduced the insulin resistance in the mice models.[42] Another study by Jain SG et al., showed that consumption of 6 capsules containing 3 g of cinnamon for 16-week period, reduced metabolic parameters such as glycemia measurement and adiposity including abdominal obesity, blood pressure and lipids of Asian Indians women with metabolic syndrome. [43] Although our study showed superiority of treatment regime contained cinnamon to other available options however some limitations should be noted. First, relatively small sample size and short follow-up time. Second we were unable to assess whether this type of treatment has any positive impact on fertility rate in future. Finally, we only evaluated the estradiol levels to reduce the medical cost of study.

Conclusion

Results of this study illustrate that cinnamon as a safe herbal supplement can be prescribed with metformin to improve the symptoms and complications of PCOS. However, the duration of the study should be considered in future studies with higher sample size and longer periods.

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Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the IRAN University of Medical Sciences (APPROVAL NUMBER/ID: IR.IUMS.REC.1397.1405).

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