A pilot study of The Efficacy of Using Chromium Salts in Reducing Hirsutism Scoring & BMI in Polycystic Ovary Syndrome Patients: Double Blinded Randomized Controlled Trial

Running title:

Chromium Salts in Reducing Hirsutism scoring

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Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most frequent endocrinopathies in women in reproductive age. the clinical image of the disease is heterogeneous. Hirsutism is one of the gynecological symptoms of PCOS with prevalence ranging from 70-80% in affected cases.

Objective: To assess the effect of chromium salts in addition to metformin on hirsutism scoring and Body Mass Index in polycystic ovary syndrome patients.

Methods: This double blinded randomized controlled trial at Ain Shams University Maternity Hospital included sixty cases of PCOS complaining of hirsutism, age between 18 and 40 years were included, while Patients known to be diabetic, hypertensive, receiving corticosteroids, psychotropic drugs, diuretics, Ovulation induction drugs, known hypersensitivity or contraindications to the used medications or those who used permanent methods of hair removal were excluded. . The patients were randomly divided into two equal groups. Group S were thirty cases who received metformin and chromium picolinate and Group C were thirty cases receiving metformin and placebo in the form of vitamin C retard.

Results: There was a highly statistically significant difference between two groups as regard weight loss, BMI, hirsutism score and menstrual regularity in favor to intervention group after 4 months follow up as p- value was <0.001. There was No significant difference between two groups as regard side effects reported about the drugs as p-value was >0.05.

Conclusion: Adding chromium picolinate to metformin in PCOS patients caused further improvement of Hirsutism score and regularity of menses, and further decrease in BMI.

Trial registration number:

PACTR202209735208004,retrospectively registered.

Keywords: Polcystic ovaries; hirsutism; chromium.

Background

Polycystic ovary syndrome (PCOS) is defined by having at least two of the following criteria: irregular or absent ovulation, elevated levels of androgenic hormones and enlarged ovaries containing at least 12 follicles each[1].

Hyperandrogenism manifests by androgenic alopecia, hirsutism, acne lesions, increased hair loss, oily skin, seborrheic lesions. Hirsutism is one of the most frequent symptoms, assessed according to the Ferriman– Gallwey score, is the presence of gruff, thick and pigment-saturated hair in women in places typical for men, e.g. upper lip, chin, chest, nape of the neck, lumbar region, abdomen, thighs and feet[2]. The increased insulin levels found in patients with PCOS appear to directly enhance LH stimulated androgen secretion from the ovary[3]. Androgens are the key factors in the growth and development of sexual hair. Androgens act on sex-specific areas of the body, converting small, straight, fair vellus hairs to larger, curlier, and darker terminal hairs[4]. Hirsutism is very common, very distressing to patients and often improves with medical management. Prompt medical attention is important because delaying treatment makes the treatment more difficult and may have long-term health consequences[4].

Metformin is one of the insulin-sensitizing medications, which reverses the majority of metabolic abnormalities of PCOS[5] by increasing its sensitivity, increasing estrogen secretion and decreasing androgen production, thus, decreasing hirsutism[6].

Another agent is chromium (III) the synthetic salt form of Cr chloride the naturally occurring trivalent variety of chromium, which is a microelement that facilitates the maintenance of normal blood glucose level by activating insulin signal transduction and sensitivity[7], thus minimizing insulin resistance, which can play a significant role in controlling PCOS[8]. Picolinic acid may serve to improve chromium absorption9 Adequate intake (AI) was set based on estimated mean intakes and amounts of 25μg/day for young women. It is indicated as a microelement facilitating in maintaining normal glycaemia[7].

The aim of the current pilot study was to assess the effects of chromium compared to placebo in addition to metformin in women with polycystic ovary syndrome patients for improving hirsutism scoring & Body Mass Index.

Materials and Methods

This is a pilot double blinded Randomized Controlled parallel arm trial has a1:1 allocation for each arm (metformin / chromium in the active arm and the placepo/metformin in the control arm) .It was conducted in Ain Shams University Maternity Hospital from November 2020 to May 2021 study included 60 patients complaining of hirsutism attending outpatient Gynaecology clinic with polycystic ovary syndrome diagnosed according to Rotterdam criteria 1 which included the presence of at least two criteria from these three: oligo or anovulation, manifestations of hyperandrogenism and polycystic ovaries in ultrasound The study was conducted after approval of Research Ethical Committee, faculty of medicine of Ain shams University Number :(FMASUMS630/2020) .Written informed consent was obtained from each patient after full explanation of the procedure before enrolment

The study was registered in The Pan-African Clinical Trial Registry PACTR202209735208004. No important changes were done to methods after trial commencement.

Patients assessed for eligibility were 60 inclusion criteria included age between 18

and 40 years who agreed to participate in the study while Patients known to be diabetic, hypertensive, receiving corticosteroids, psychotropic drugs, diuretics, Ovulation induction drugs, known hypersensitivity or contraindications to the used medications in the study or those who used permanent methods of hair removal **were excluded**.

All patient participated in this study were undergone the following procedures: Full history, history of investigations and treatment. Menstrual history: criteria, average number of menstrual cycles per year, amount. infertility history Examination: Physical examination: measurement of BMI and BP measurement was done. General examination: For hirsutism Physical examination was begun with determination of the distribution and degree of hair growth using a scoring method Ferriman-Gallwey scale (according to this score. A score of 1 to 4 was given for nine areas of the body (upper lip, chin, back, chest, nape of the neck, lumbar region, abdomen, thighs and feet). A total score less than 8 was considered normal, a score of 8 to 15 indicated mild hirsutism, and a score greater than 15 indicated moderate or severe hirsutism. A score of 0 indicated absence of terminal hair. Skin examination: was done for acne or acanthosis nigricans.

All sixty women received metformin with dose of 500mg after main meal.

The first Group (chromium group): (n=30) received chromium (chromium picolinate, Mepaco) orally in a dose of 200microgram /day for 4 months' duration.

The second Group (placepo group) :(n=30) received placebo(same shape as chromium capsules).

Follow Up: The patients were followed up for taking the drug regularly by phone calls every two weeks. Follow up was for the frequency of hair removal every month for 4 months duration with usage of temporary method of hair removal and was stopped 2 weeks before Follow up. Body mass index (BMI) was also followed up monthly (Body weight was measured using analogue scales in light clothes; height was measured barefoot using a stadiometer) and calculated as follows: weight (kg)/height2 (m) Regularity of menses: The patient was asked about her menstrual history (time between cycles, frequency, duration), and any reported side effects of chromium salts or metformin: each month throughout the period of taking the drug.

The primary outcome was chromium effect in addition to metformin on hirsutism scoring, while **secondary outcomes were** its effect on BMI ,regulation of menses and side effects of chromium salts such as mood changes irritability headache, and side effects of metformin.

Sample size calculation:

At the beginning of the study there was no available information in literature assessing effect of chromium on hirsutism all studies were assessing its effect on insulin resistance so it was considered pilot study included 60 patient (30 in each group).

And were randomly assigned using computer –generated random sequence in a ratio of 1:1 Allocation for each arm of the study .each patient was assigned a, sealed ,opaque envelope with her number (Sequentially numbered) containing either chromium tablets or placepo .doctors and patients were blinded to which group the candidate was assigned to ,only the nurse in the clinic who chose each envelop for each patient was not blinded.

Statistical analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, unpaired student t-test was used to compare between two groups in quantitative data, paired Student T-test was used to compare between related samples and chi square test was used to compare between

groups in qualitative data by (IBM SPSS

Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). p value of< 0.05 was considered significant.

Results

Between November 2020 to May 2021, a total of 60 women(n=30 per group) were recruited for the study.. They were followed for 4 months duration ,Figure 1 (consort flow diagram)shows the allocation and follow-up of patients. Group 1 is the patients received chromium (chromium picolinate, Mepaco) orally in a dose of 200microgram /day .And group 2 received placebo(same shape as chromium capsules).

There were no statistically significant differences between both groups regarding age, Body Mass Index (BMI), period of infertility ,number of cycles per year (p value >0.05) as shown in table 1.

There were highly statistically significant difference between both groups as regard hirsutism scoring, weight loss and consequently BMI in favour of the intervention group after 4 months follow up (pvalue-<0.001) –as shown in table 2.

There was highly statistically significant difference between 2 groups as regards regularity of menses (pvalue <0.001) as shown in table 3

There was no statistically significant difference between two groups regard drugs reported side effects (pvalue <0.05) as shown in table 3.

Discussion

Up to 70% of patients with PCOS demonstrate overt insulin resistance and hyperinsulinism. The administration of insulinsensitizing agents has been proposed for the treatment of hirsutism as these agents have various potential advantages over traditional therapies as they correct both the metabolic and the endocrine aberrations of the disorder; thus permitting the resumption of normal endogenous ovulatory function, with little or no risk of ovarian hyperstimulation and multiple gestation, in addition to, the possible decrease in the long-term risk of type 2 DM and CVD [10].

The current study found that there were significant difference between both groups as regard hirsutism, menstrual regularity, weight loss and consequently BMI in favor of the intervention group after 4 months follow up (p-<0.001) - although hirsutism decreased, weight loss increased and menstrual regularity increased in both groups probably due to the effect of metformin given.

Teede et al [11]., suggested the use of metformin, in addition to, lifestyle modifications could be considered in adolescent females complaining of symptoms of PCOS even before the diagnosis is made, as this was shown to reduce weight and improve hirsutism [12]. Both studies agree with the results of the current study as both groups showed weight loss and improvement of hirsutism although in different degrees, which suggests that chromium augments the effects exerted by metformin.

The results of the current study agree with the results of Jamilian et al 13who found a significant reduction in hirsutism on 30 patients taking chromium 200 μg compared to the same number taking placebo in his double blinded randomized controlled trial after a follow-up period of 8 weeks, and with Ashoush et al [14]. who found a significant reduction in BMI and more menstrual regularity in 100 cases of PCO who used chromium for 6months.

However; Amr and Abdel-Rahim15 , found no significant change in BMI, acne or hirsutism; while there was an insignificant reduction in the number of cases with oligo/ amenorrhea in cases receiving chromium picolinate for 6months.

The main side-effect reported in the current study was abdominal discomfort which is

a known side-effect of metformin use and occurred equally in both groups suggesting that adding chromium did not result in additional side-effects.

The advantages of the current study is that it is the first randomized controlled study addressing the hirsutism score as the primary outcome with a follow-up period of 4 months; however, the main limitation of this study is the relatively small number of cases recruited as it is a pilot study, and the lack of comparison between different doses of chromium to decide the most effective dose to be used.

Conclusion

Adding chromium picolinate to metformin in PCOS patients augmented the effect of metformin causing further improvement of Hirsutism score, regularity of menses, and further decrease in BMI.

Larger randomized controlled trials using different doses of chromium are needed to confirm or refute these findings.

Ethics approval and consent to participate

Study approved by Research Ethical Committee, faculty of medicine ,Ain shams University, Number :(FMASUMS630/2020)

Consent :consent was taken from each patient .

Availability and data material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors report there are no competing interests to declare

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Registration

The study was registered at Pan Affrican Clinical Trial Registry PACTR202209735208004.

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Authors' contributions

All authors jointly contributed to conception and design of the study.

Marwa Saber Snosi: Design of the study, helped in review of literature, revision of results and data analysis , writing the manuscript and submission to journal.

Dina yahia Aly Mansour: design of the study, revision of review of literature and revision of manuscript revision of results and data analysis.

Eid HS: registration of trial, obtaining ethical committee approval, reviewed the literature, shared in collection of Data, active participation in following up patients ensuring patients compliance by phone calls.

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Table (1): Comparison between two groups as regard descriptive data.

		Cases (N=30)	Control (N=30)	Tests	
				X^2/ t	P-value
Age (years)		27.80±5.67	27.93±5.23	0.095	0.925 NS
Marital status					
Single		30%))9	43.3%))13	1.148	0.284 NS
Married		70%))21	56.7%))17		
BMI (kg/m^2)		28.41 ± 2.19	28.72± 3.04	0.459	0.648 (NS)
Parity	0	6(28.6%)	952.9%))	2.77	0.44 NS
	1	9(42.9%)	529.4%))		
	2	5(23.8%)	17.6%))3		
	3	1(4.8%)	0.0%))0		
Parity	0	6(28.6%)	52.9%))9	2.34	0.13 NS
	>=1	15(71.4%)	47.1%))8		
Skin Examination					
Acne					
Present		30(100%))	30(100%)	0.000	1.000 NS
Acanthosis					
Present		19(63.3%)	19(63.3%)	0.000	1.000 NS
Absent		11(36.7%)	11(36.7%)		
Duration Of Infertility		1.95±1.18	1.91±0.96	0.107	0.915 NS
Average no of cycles per year		5.53±1.28	5.50±1.48	0.093	0.926

Table (2): Comparison between two groups as regard Weight loss , BMI and hirsutism scoring at different times (Baseline,1st month,2nd month, 3rd month and 4th month).

	Cases		Control		T-test	
	Mean±SD	% of change	Mean±SD	% of change	t	P-value
Weight						
Baseline	74.93 ± 10.83		76.40± 9.53		0.557	0.580 (NS)
At 1 mon.	68.43 ± 9.60	8.7%	75.67± 10.18	1.0%	2.831	0.006* (S)
At 2 mon.	66.60 ± 9.79	11.1%	73.93± 9.70	3.2%	2.915	0.005* (S)
At 3 mon.	63.63 ± 8.84	15.1%	72.10± 9.80	5.6%	3.514	<0.001* (HS)
At 4 mon.	60.90 ± 8.68	18.7%	70.37± 9.37	7.9%	4.060	<0.001* (HS)
BMI						
Baseline	28.41 ± 2.19		28.72± 3.04		0.459	0.648 (NS)
at 1 mon.	26.44 ± 1.97	6.9%	28.06± 3.61	2.3%	2.156	0.035* (S)
at 2 mon.	25.12 ± 1.54	11.6%	27.11± 3.46	5.6%	2.887	0.005* (S)
at 3 mon.	23.89 ± 1.38	15.9%	26.17± 3.36	8.9%	3.445	<0.001* (HS)
at 4 mon.	22.71 ± 1.23	20.1%	25.52± 3.43	11.1%	4.223	<0.001* (HS)
Hirsutism						
Baseline	15.23 ± 4.83		17.17±5.64		1.426	0.159 (NS)
at 1 mon.	13.97 ± 4.25	8.3%	16.60±5.57	3.3%	2.060	0.044*(S)
at 2 mon.	12.13 ± 3.40	20.4%	16.07±5.53	6.4%	3.317	0.002* (S)
at 3 mon.	11.00 ± 3.21	27.8%	15.43±5.73	10.1%	3.697	<0.001* (HS)
at 4 mon.	9.77 ± 3.35	35.9%	14.73±5.77	14.2%	4.077	<0.001* (HS)

Table (3): Comparison between two groups as regard Regularity of menses and side effects reported about the drugs and at different times (1st month,2nd month, 3rd month and 4th month).

Regularity of menses	Cases		Control		Total		Chi-square	
	N	%	N	%	N	%	X^2	P-value
Baseline								
present	1	3.3	1	3.3	2	3.3	0.00	1.00 (NS)
Not present	29	96.7	29	96.7	58	96.7		
At 1 mon.								
Present	10	33.3	2	6.7	12	20.0	6.667	0.010* (S)
Not Present	20	66.7	28	93.3	48	80.0		
At 2 mon.								
Present	22	73.3	16	53.3	38	63.3	2.584	0.108 (NS)
Not Present	8	26.7	14	46.7	22	36.7		
At 3 mon.								
Present	27	90.0	17	56.7	44	73.3	8.523	0.004* (S)
Not Present	3	10.0	13	43.3	16	26.7		
At 4 mon.								
Present	27	90.0	15	50.0	42	70.0	11.429	<0.001* (HS)
Not Present	3	10.0	15	50.0	18	30.0		
Side effects reported about the drugs								
at 1 mon.								
abdominal discomfort	3	10.0	3	10.0	6	10.0	0.000	1.000
No	27	90.0	27	90.0	54	90.0		
at 2 mon.								
No	30	100.0	30	100.0	60	100.0	0.000	1.000
at 3 mon.								
No	30	100.0	30	100.0	60	100.0	0.000	1.000
at 4 mon.								
No	30	100.0	30	100.0	60	100.0	0.000	1.000

Figure 1 recruitment and flow of patients