British Journal of Medicine & Medical Research
20(3): 1-10, 2017; Article no.BJMMR.31503
ISSN: 2231-0614, NLM ID: 101570965

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Some Altered Trace Elements in Patients with Polycystic Ovary Syndrome

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/BJMMR/2017/31503
Editor(s):
(1) Yinhua Yu, Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University,Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, China.
Reviewers:
(1) Nirvana Samy, National Research Centre, Cairo, Egypt.
(2) Anna Benrick, University of Gothenburg, Sweden.
(3) Liudmila Ivanova, Kuban State Medical University, Russia.
Complete Peer review History: http://www.sciencedomain.org/review-history/18146

Original Research Article

Received 9th January 2017
Accepted 24th February 2017
Published 10th March 2017

ABSTRACT

Background: Insulin resistance is common in patients with polycystic ovary syndrome (PCOS). Trace elements and its correlation with insulin resistance are well documented.
Aim of Study: The current study aimed to determine possible correlations between insulin resistance and some trace elements (molybdenum, manganese, selenium and chromium) in patients with PCOS.
Study Design: Case-control study.
The study was performed in the infertility clinic at Babylon hospital for children and maternity. The duration of this study was from October 2014 to December 2015.
Methodology: The study involved sixty women (thirty women had PCOS and thirty women were controls).
Aspectrophotometrically procedure was used to analyze trace elements (molybdenum, manganese, selenium and chromium) in the serum. In addition the blood glucose and serum insulin during fasting were measured and insulin resistance (IR) was determined using the homeostasis model assessment (HOMA).
Results: Body mass index (BMI) in patients with PCOS was increased compared to controls. HOMA and fasting serum insulin were significantly higher in women with PCOS in comparison with controls. There was no difference in blood glucose in women with polycystic ovary in comparison with controls.

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The cohort was divided into insulin sensitive (NIR) and insulin resistant (IR) patients with PCOS. Women with PCOS-IR had significantly lower serum chromium, selenium and molybdenum and higher serum manganese than women with PCOS-NIR (p-value <0.05).
Conclusion: There was a correlation between the levels of serum chromium, selenium, molybdenum and manganese and IR in patients with PCOS.

Keywords: Trace elements; PCOS; insulin resistance.

1. INTRODUCTION

Polycystic ovarian disorder is more widely recognized endocrine issue in women, influencing 6-18% of ladies of reproductive age [1].

PCOS is described by increased secretion of androgen from ovary and adrenal gland., hyperandrogenic metabolic disorder features, for example, hirsutism, alopecia and/or acne, [2,3].

Patients with PCOS have increased risk of developing insulin resistance, hyperinsulinemia and decreased glucose tolerance [4].

An increasing predominance of PCOS in patients with type two diabetes mellitus, in addition to confirmation of resistance to insulin and related Hyperinsulinemia [5,6,7,8].

Hyperinsulinemia and insulin resistance are more predominant in patients with PCOS than women without the condition irrespective of their obesity [9,10].

The insulin resistance and hyperandrogenemia might originate in the fetal life and may be detected in the adolescence [11,12].

The abnormality in the glucose metabolism in patients with PCO may also occur at a more youthful age and might exhibit a more fast change from impaired tolerance to glucose to type 2 diabetes mellitus [13].

The trace minerals had been identified for long period as having potential for enhancing metabolic diseases e.g prediabetes (metabolic disorder, obesity and insulin resistance) or diabetes mellitus. Distinguishing the targets of cells and sites of activity of trace minerals had reestablished interest for their therapeutic uses. The activation of signals of insulin receptor (chromium), antioxidant features (zinc, selenium), or phosphatases inhibition (vanadium) hence seemed important in insulin sensitivity and homeostasis of glucose [14].

The manganese was a component of dismutase enzyme which is an antioxidant that aids to fight the free radicals. It can neutralize superoxide ions which are highly reactive to hydrogen peroxide (H_2O_2), which is less reactive, and then this is immediately converted to H_2O by action of catalase and other different peroxidases into the matrix of mitochondria [15,16].

When the level of manganese is low, it may cause loss of fertility, mutations of bone in addition to convulsion. This supplement is present in entire grains, seeds and nuts [17].

Molybdneum is an essential basic element which is a part of a couple of compounds which includes xanthine, aldehyde and sulfate oxidase enzymes, which has a basic role involving the catabolic process of pyrimidines and sulfur. [18,19,20].

Enzymes that contain molybdenum can catalyze essential metabolic responses in the cycles of sulfur, nitrogen, and carbon. Molybdenum is joined into the proteins to form the molybdenum cofactor which is combined to sulfur atom of, molybdopterin. The enzymes that are containing Molybdenum-cofactor can catalyze the exchange of oxygen particle from or to a substance into a redox reaction containing two electrons [21,22].

2. MATERIALS AND METHODS

The current study was performed at the department of infertility between October 2014 and December 2015.

The study included sixty women. They are separated to two categories (patient group and control group).

Patient group comprised of thirty patients with age range from 16-43 years, PCOS was diagnosed according to the Rotterdam criteria.

The control group comprised of thirty women who are healthy (their age range between 17-30

years), with no biochemical or clinical components of hyperandrogenism, and their menstrual cycles were regular.

IR was found in 21 women with PCOS (group 1), whereas NIR was found in 9 patients with PCOS (group 2).

IR was diagnosed in women with HOMA-IR more than 2.5.

2.1 Inclusion Criteria

PCOS was diagnosed based on the 2003 Rotterdam consensus workshop that includes at least 2 out of following 3 criteria should be existed:

1. Oligoovulation -or failure of ovulation.
2. Biochemical and /or clinical features of increased androgen
3. Polycystic ovaries on ultrasound (>12 follicles which are 2-9 mm or ovarian volume >10 ml).

2.2 Exclusion Criteria [23,24]

A: Causes of hyperandrogenism apart from PCOS

1. Cushing' syndrome.
2. Congenital adrenal hyperplasia.
3. Virilizing ovarian/ adrenal tumours.

B: Factors that will affect serum trace elements determination:

Multivitamin supplementation for last 2 months.

C: Factors that will effect hormonal determination

1. Hormonal drugs in past 6 weeks.
2. Thyroid disorders.
3. Pregnancy and lactation.
4. Renal disorders.
5. Diabetes mellitus.
6. Oral contraceptive pills.

2.3 Body Mass Index BMI

BMI is determined from division of weight (measured in kilogram) on height (m^2) [25]

Normal BMI 18.5-24.9.
Overweight BMI 25-29.9.
Obesity BMI ≥30

The collection of blood samples was done following fasting overnight between 2^{nd}_3^{rd} day of spontaneous menstrual cycles or steroid challenged periods.

The serum concentrations of molybdenum, manganese, selenium, chromium, FSH, LH, TSH prolactin, testosterone, fasting insulin and fasting blood glucose are measured.

The transvaginal ultrasound examination is performed on the same day to all women involved in the study.

Criteria for determination of insulin resistance

Insulin resistance was diagnosed when HOMA ≥ 2.5.

Insulin resistance is determined from using equation below:

HOMA-IR=fasting insulin (μu/ml) x fasting glucose (mmol/l)/22.5 [26].

Measurement of molybdenum, manganese, selenium and chromium.

The collection of blood samples was performed between 2^{nd}_3^{rd} day of menstrual period.

The isolation of serum through centrifugation with duration of five minutes for 5000rpm and kept at - 20 degree centigrade till analysis was performed.

Blood levels of molybdenum, manganese selenium and chromium are determined by nuclear absorption spectrophotometer with sensitivity of less than 0.001.

Serum FSH, LH, TSH, prolactin, testosterone and fasting insulin were measured through Enzyme Linked Fluorescent Assay (ELFA) utilizing Tosoh device.

The measurement of Fasting blood glucose was performed spectrophotometrically utilizing glucose oxidase strategy gave by Biolabo, France.

2.4 Statistical Analysis

Analysis of data is done through utilizing SPSS form 18 programming. The information was communicated as mean ±SD.

t-test was used to analyze the data. The correlation among the variables was assessed by calculation of Pearson's correlation coefficients.

P-value less than 0.05 considered as significant statistically.

3. RESULTS

Table 1 revealed patients with polycystic ovary had higher BMI than healthy control which is statistically significant (p-value <0.05).

Table 1. Demographic criteria, hormonal and biochemical criteria of women with polycystic ovary and control groups

Criteria	Control (n=30) mean±SD	PCOS (n=30) mean±SD	P-value
Age (years)	22.7±3.2	25.2±7.3	> 0.05
BMI	25.3±4.6	29.3±5.8	< 0.05
LH	4.4±1.1	6.5±4.3	>0.05
FSH	5.9±0.9	6.3±2	>0.05
TSH	2.4±0.7	2.3±0.9	>0.05
Prolactin	9.6±2.3	17.4±9.4	<0.05
Testosterone	8.5±1.5	30.2±25.9	<0.05
FBS (mmol/L)	5.5±0.6	5.5±0.6	>0.05
F.Insulin (miu/ml)	8 ±5.2	16.5±11	<0.05
HOMA	1.9±1.2	4±2.8	<0.05

The body mass index of women with insulin resistance was significantly higher than patients with normal insulin resistance.

Table 1 shows the hormonal levels of PCOS and control groups. Patients with polycystic ovary had higher values of serum prolactin and testosterone in comparison with control. This difference is statistically significant.

The level of testosterone is higher in patients with PCOS-IR in comparison with patients who had normal insulin resistance (p-value <0.05).

Table 1 there was significant variation in fasting blood insulin and HOMA in patients with polycystic contrasted to controls. There is no significant variation in fasting blood sugar in patients with polycystic contrasted with controls.

Patients with PCOS-IR had significantly higher fasting insulin and HOMA values than patients with PCOS-NIR.

Table 3 shows that patients with polycystic ovary had significantly lower serum chromium (mean = 0.3±0.1) compared to the control group (mean =0.7±0.2).

Table 2. Demographic criteria, hormonal and biochemical criteria of women with polycystic ovary with insulin resistance and women with normal insulin resistance

Criteria	PCOS-IR (n=21"a") mean±SD	PCOS-NIR (n=9"a") mean±SD	p-value
Age (years)	25.7±8.4	24.0±3.8	>0.05
BMI	30.9±5.4	25.5±5.2	<0.05
LH	6.5±4.8	6.4±3.1	>0.05
FSH	6.0±1.6	6.9±2.8	>0.05
TSH	2.2±0.9	6.9±2.8	>0.05
Prolactin	16.4±8.7	19.7±11.2	>0.05
Testosterone	37.1±27.4	14.2±11.8	<0.05
FBS (mmol/L)	5.5±0.5	5.3±0.8	>0.05
F.Insulin (miu/ml)	20.9±10.4	6.3±1.8	<0.05
HOMA	5.2±2.7	1.5±0.4	<0.05

Table 3. Trace minerals of women with PCOS and control groups

Trace element (ug/dl)	Control (n=30 "a") Mean±SD	PCOS (n=30 "a") Mean±SD	p-value
Chromium	0.7±0.2	0.31±0.1	<0.05
Selenium	4.8±1.1	2.9±0.9	<0.05
Manganese	2.2±1.2	7.3±1.7	<0.05
Molybdenum	11.3±2.3	2.5±1.3	<0.05

Serum selenium is lower in patients with polycystic (mean= 2.9±0.9) than healthy control. The difference was highly significant.

Women with PCOS had significantly higher serum manganese (mean=7.3±1.7) than healthy women (mean= 2.2±1.2). The difference was highly significant.

Table 4. Trace minerals for women with insulin resistance and normal insulin resistance

Trace mineral Element (ug/dl)	PCOS-IR (n=21 "a") Mean±SD	PCOS-NIR (n=9 "a") Mean±SD	P-value
Chromium	0.3±0.1	0.3±0.9	>0.05
Selenium	3.1±0.9	2.6±0.7	>0.05
Manganese	7.3±1.8	7.2±1.6	>0.05
Molybdenum	2.5±1.2	2.4±1.7	>0.05

Serum molybdenum is lower in polycystic patients (mean= 2.5±1.3) than healthy group which is highly significant.

Table 4 above shows that there was no significant difference in serum chromium, selenium, manganese and *molybdenum between women with PCOS-IR and PCOS-NIR.*

3.1 Correlations

The correlation was for PCOS patients (30 women) Table 5.

4. DISCUSSION

Over production of responsive oxygen species (ROS) is a typical component in women with polycystic ovary [27,28].

Copper, zinc and manganese are fundamental micronutrients which joined into numerous proteins and metalloenzymes and they are dependable in cell metabolic system and oxidative stress pathways which may contribute to oxidative stress [29].

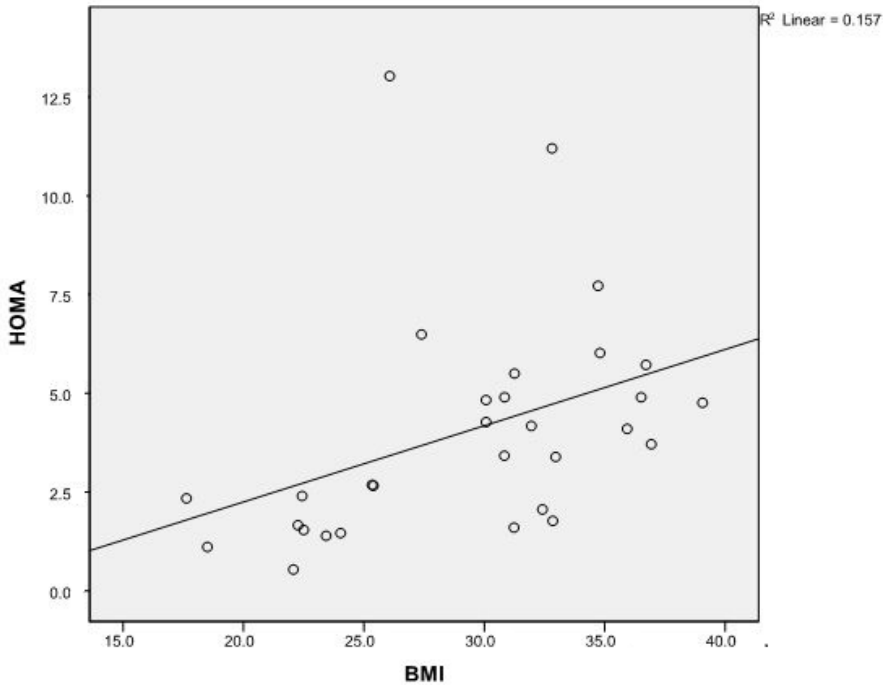
Numerous studies had revealed the role of increment of oxidative stress which could result from excessive production of reactive oxygen species in pathogenesis of polycystic ovary [30,31].

In the current study there is statistically no significant difference in blood glucose between patients with PCOS compared to the control.

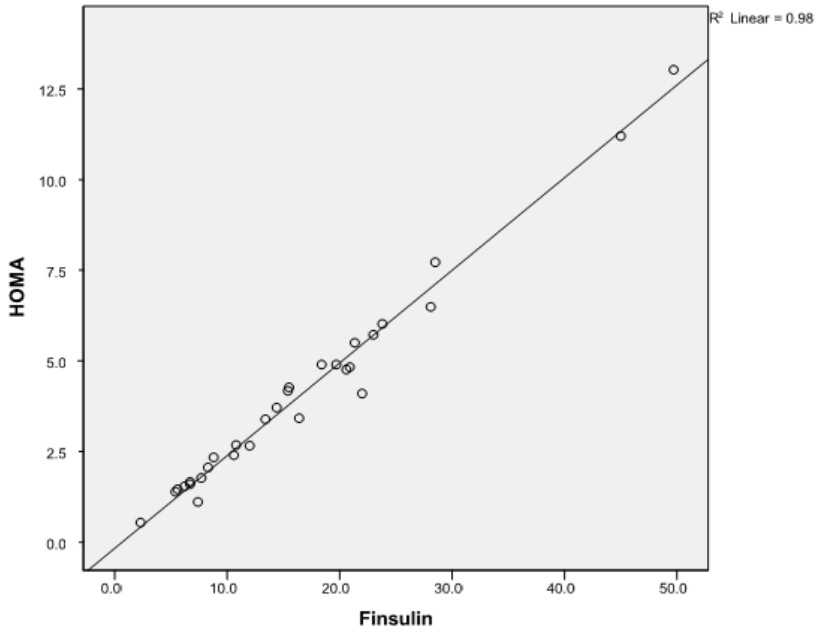
This result is in concurrence with Vinodhini et al. who demonstrated no significant variation in the value of fasting blood glucose in patients with PCOS and the controls [23]. While, a study conducted by Azevedo MF et al. found that the values of fasting blood glucose were higher in women with polycystic ovary which are significant statistically [32].

Table 5. Correlation of HOMA and BMI with trace elements in patients with PCOS

		Selenium	Manganese	Molybdneum	Chromium	HOMA	BMI
HOMA	Pearson Correlation	-.001-	.358	.001	.098	1	.396*
	Sig. (2-tailed)	.996	.052	.997	.605		.030
	N	30	30	30	30	30	30
	Odds ratio	0.999	1.430466	1.001001	2.664456		1.485869
BMI	Pearson Correlation	.063	.008	.347	-.059-	.396	1
	Sig. (2-tailed)	.740	.966	.061	.758	.030	
	N	30	30	30	30	30	30
	Odds ratio	1.01005	1.002002	1.081123	0.999	1.212883	



Graph 1. Showed correlation of HOMA with BMI



Graph 2. Correlation of HOMA with fasting insulin

In the current study, the HOMA and fasting insulin are higher in women with PCOS in comparison with the controls, the difference is significant statistically.

Current study, found there is a significantly higher levels of serum manganese in patients with polycystic ovaries in comparison with the control group. There is no significant variation in serum manganese in women with PCOS –IR and patients with PCOS-NIR.

This is as opposed to a study done at India in 2012 which found that serum manganese of PCOS patients was lower in comparison with control. In this study they clarified that because oxidative stress is increasing in women with PCOS, so that serum manganese value was diminished as a consequence of utilization in antioxidant defense system which includes MnSOD [33]

A few studies demonstrate that individuals with diabetes have decreased values of manganese in the blood.

A study revealed that individuals who have diabetes with higher blood values of manganese are protected more from low density cholesterol compared to patients with lower values of manganese [34,35].

In the current study serum chromium of PCOS women was lower in comparison with the control group, which is statistically significant.

Chromium was a trace element which improves the activity of insulin. Cell chromium enhances insulin signaling through increasing activity of insulin receptor kinase [36].

Supplementing women with chromium had been appeared in many studies to enhance the control of blood glucose in patients with type 2 diabetes mellitus [37,38,39,40,41,42,43].

Patients with PCOS were given 1,000mcg every day of chromium for two months could enhance the sensitivity of insulin by 30% and by 38% in obese patients with PCOS [44,45].

A study demonstrates that supplementing chromium picolinate at 200 mcg/day will not improve features of PCO [46].

Since mild derangement of control of blood sugar will increase the cardiovascular risk, so supplementation of chromium may lessen the rates of coronary heart disease [47].

In this study serum selenium of PCOS women is lower contrasted to the controls, which is statistically significant.

A study led at the AL-Kadhymia hospital included 25 women with PCO not treated by Clomiphene citrate and a second group involve 26 patients were treated by Clomiphene citrate. Selenium levels were lower in group who were not treated; this may be related to effect of oxidative stress [48].

A study performed by Melanie Ceko demonstrates that selenium is increased in healthy, large follicles of ovaries. Therefore assume basic part as antioxidant agent in the final phases of development of follicles [49].

Selenium will play a role as an antioxidant through selenoproteins that contains selenocysteins [50].

Diminished selenium values are found in diabetes associated with increased oxidative stress [51].

In the present study serum molybdenum of PCOS women is lower in contrast with the control, which is statistically significant.

Serum molybdenum is higher in patients with type II diabetes and is correlated with severity of diabetes [52].

A study in female rodent was given extra molybdenum with drinking water (5-100mg/l 0.0025 mg/kg with food) demonstrate that levels of 10 mg/l or higher will prolonge their estrus cycle [53].

In infertile men they found lower level of serum testosterone was associated with increased level of molybdenum [54].

Molybdenum influences the quality of oocyte perhaps through regulating the oxidative stress of ovaries through a dose-dependent way. It creates the impression that Molybdenum might enhance the function of ovaries at an appropriate concentration, which may be important in the treatment of infertility in female [55].

5. CONCLUSIONS AND RECOMMENDA-TIONS

Serum chromium, selenium, and molybdenum are lower in patients with PCOS than healthy control.

Serum manganese was higher in women with polycystic ovaries in comparison with control. There is no significant variation in trace elements between PCOS- IR and PCOS-NIR.

Further researches to assess effects of trace minerals will needed in order to prove hypothesis presented here.

CONSENT

Consent was obtained from the patients for both performing the study and publication of this paper.

ETHICAL APPROVAL

The necessary ethical approval was obtained from infertility department of Babylon Hospital.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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