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Zinc status and polycystic ovarian syndrome: A systematic review and meta-analysis

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ABSTRACT

Several studies have investigated serum zinc levels in patients with polycystic ovarian syndrome (PCOS), but the results of these studies remain inconclusive. Therefore, to derive a more precise estimation, we conducted a meta-analysis to investigate serum zinc concentrations in women with PCOS in comparison with healthy subjects. Electronic search was performed in PubMed, Scopus, and Google scholar up to April; 4, 2018 without any restriction. Eligible studies that evaluated the levels of zinc status in subjects with PCOS were included. Weighted mean differences (WMDs) with corresponding 95% CIs in serum zinc levels were initially estimated using a random-effects model. Eight studies, measuring circulating zinc levels in 552 PCOS and 464 control subjects, were included. Pooled effect size suggested that serum zinc levels in women with PCOS were not statistically different than their controls (WMD = −4.43 mg/dL; 95% CI = [−10.30, 1.44]; P = 0.139). Exclusion of one study revealed that women with PCOS significantly have lower serum zinc levels compared to healthy controls (WMD: −6.60 mg/dL; 95% CI = [−12.43, −0.76], P = 0.027). Our study indicated that circulating zinc levels in women with PCOS were significantly lower than those in healthy controls when detailed analysis is conducted. Large scale studies are needed to elucidate clear relation between zinc status and etiology of PCOS.

1. Introduction

Polycystic ovarian syndrome (PCOS) is regarded as the most prevalent endocrine disorder among women with approximate prevalence rate of 6–10% in pre-menopausal women [1,2]. PCOS is specified with menstrual disorders, polycystic ovaries and excess androgen symptoms such as acne, alopecia and hirsutism [2]. It has been reported that the prevalence of insulin resistance (IR), type 2 diabetes (T2DM), dyslipidemia, cardiovascular disease (CVD) and obesity are higher in women with PCOS [3,4]. Previous reports indicated that 40–50% of women with PCOS are obese or overweight. IR has been reported to affect nearly 70% of patients with PCOS [5,6].

Zinc is an essential nutrient that reported to be fundamental in more than 300 enzymatic reactions as a component of hundreds of enzymes like superoxide dismutase and phophoslipase C [7]. Increased prevalence of hypertension, T2DM and CVD has been associated with low dietary zinc intakes and low circulating zinc [8]. Higher zinc intakes are associated with lower risk of T2DM in women [9]. Altered serum levels of trace elements like chromium, copper and zinc were reported to be associated with IR [10]. Zinc is involved in signaling pathways of insulin action, and also its synthesis and storage [11]. Zinc can combine with insulin hexamer and facilitates stability and the binding ability of insulin to receptors [12]. Zinc supplementation has been reported to improve IR in T2DM [13] and the homeostatic model assessment (HOMA)-IR in obese subjects [14,15].

Several studies have investigated serum zinc levels in patients with PCOS, but the results of these studies remain inconclusive. Some studies have reported that serum zinc levels are higher in women with PCOS compared with healthy women [16,17]. Other studies reported that circulating zinc levels are lower in women with PCOS [18,19]. While others found that there is no significant difference in the serum level of zinc between PCOS patients and matched controls [20,21]. Therefore,

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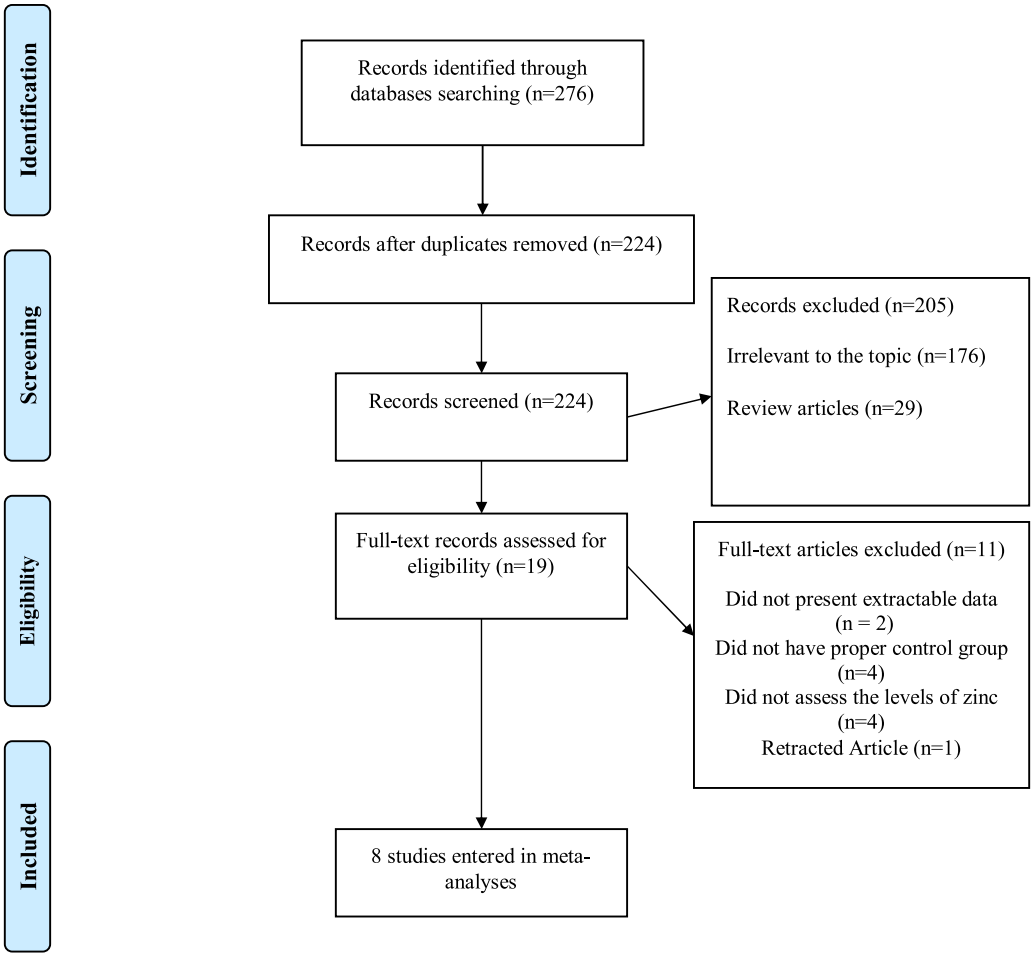

Fig. 1. PRISMA flow diagram of study selection process.

to clarify the above contradictory results we conducted a meta-analysis to investigate serum zinc concentrations in women with PCOS in comparison with healthy subjects.

2. Material and methods

2.1. Search strategy

We conducted a meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. The electronic search for the current systematic review and meta-analysis was performed up to April 4, 2018 in PubMed, Scopus and Google scholar. Above mentioned databases were searched utilizing Boolean operator tools, specifically using following terms: (PCOS OR Polycystic Ovarian Syndrome OR Polycystic Ovary Syndrome), in combination with (Zn OR Zinc supplementation OR Zinc therapy). No restrictions on language or publication date were imposed. An additional manual search was followed by reference lists of selected studies to detect other relevant trials.

2.2. Inclusion and exclusion criteria

Relevant articles were included if they: (1) examined the levels of zinc in PCOS subjects; and (2) provided sufficient information on serum/plasma zinc levels in both PCOS and control groups. Studies were excluded if they: (1) enrolled patients with a disease other than PCOS (2) without healthy control group, (3) reported duplicate data; and (4) were reviews, letters, editorial articles, or case reports.

2.3. Quality assessment

Two reviewers (M.A and H.M) assessed the quality of each selected study using the Newcastle-Ottawa scale [23]. This scale awards a maximum of 9 stars to each study: 4 stars belong to the selection (representativeness of the sample, sample size, non-respondents and ascertainment of the exposure), 2 stars belong to comparability (controls for the effect or factors), and 3 stars belong to the features of outcome (assessment of the outcome and statistical test).

2.4. Data extraction

M.A, H.M and A.H extracted the following data: first author's name, publication year, location of studies, methods of zinc measurement, the type of blood sample, body mass index and age of subjects in PCOS and control groups, sample size, matched variables between the case and control groups, criteria for diagnosis of PCOS and means and SDs for zinc levels.

2.5. Statistical analysis

Prior the calculation of effect size, the concentrations of zinc were converted to mg/dL. Weighted mean differences (WMDs) together with the corresponding 95% CIs in zinc levels were initially estimated using a random-effects model. Between-study heterogeneity was assessed using the I^2 statistic, which represents the percentage of the total variation across studies that is attributable to heterogeneity rather than to chance. I^2 was calculated using the formula: $I^2 = 100\% \times (Q–df)/Q$ (where Q is the chi squared statistic, and df is the degrees of freedom),

and an I^2 value of 75% or greater was deemed to indicate a high level of inconsistency. Significant heterogeneity was defined with a p-value of < 0.05. In order to explore reasons for heterogeneity, subgroup analysis was performed according to BMI. Sensitivity analysis was performed by omitting one study in each turn, to detect any significant changes in the results obtained. We used Begg's rank correlation test and Egger's regression asymmetry test to evaluate publication bias. Statistical analysis was performed using STATA 11 software (Stata Corp, College Station, Texas, USA).

3. Results

3.1. Literature search

We identified 276 publications from electronic search of the above mentioned databases. Of these, 224 citations were left after elimination of duplicates. In the title and abstract screening, 205 publications that were obviously irrelevant were excluded. Remaining studies (19 articles) were retrieved for full-text assessing. After reading the full texts, 11 articles were omitted for the following reasons: did not present extractable data (n = 2), did not have appropriate control group (n = 4), lack of measuring the plasma levels of zinc (n = 3) and retracted article (n = 1). To obtain non extractable data, we contacted the authors via email, but none of the authors replied. At the end, eight articles [16,17,19,24–28] enrolled in this meta-analysis. We did not find additional studies in the bibliographic search of articles and relevant reviews. The details of the systematic search and study selection process are depicted in Fig. 1.

3.2. General study characteristics

Included studies were published between 2012 and 2017 and reported data on 1016 subjects (552 PCOS patients and 464 controls). The mean age of participants ranged from 24 to 29 years. Four studies had been conducted in Turkey [16,19,25,27] and other studies had been conducted in Iran [26], China [28], India [17] and Iraq [24]. PCOS patients in all papers were diagnosed based on the Rotterdam criteria [29]. The method of measuring serum zinc levels in most studies was atomic absorption assay and only 1 studies [28] used inductively coupled plasma-mass method. The key characteristics of included publications are summarized in Table 1.

According to Newcastle-Ottawa scale, four studies [17,24,25,27] were regarded as moderate quality (4–6 stars), and the remaining studies [16,19,26,28] met the high quality criteria (7–8 stars). Last column of Table 1 provides results of quality assessment of the included studies.

3.3. Quantitative synthesis of data

Among eligible studies, one article [24] presented stratified statistics in terms of BMI values, therefore, present meta-analysis was performed on 9 datasets of the 8 selected studies. As indicated in Fig. 2, pooled effect size revealed that serum zinc levels in women with PCOS were not statistically different with those of healthy controls (WMD = −4.43 mg/dL; 95% CI = [−10.30, 1.44]; P = 0.139). However, significant heterogeneity was detected across the studies (I^2 = 90.4%, P < 0.001).

In order to explore reasons for heterogeneity, subgroup analysis was performed according to BMI (< 25, ≥25 and other). In two studies [19,25] mean of BMI was different for cases and controls and they put into the other BMI group. When the meta-analyses was sub-grouped by BMI, heterogeneity attenuated in other BMI group (I^2 = 0.0%, P = 0.534). Also, significant differences in pooled WMD of zinc levels were observed in studies in other BMI subgroup (WMD = −12.99 mg/dL; 95% CI = [−17.86, -8.12]; P < 0.001), there were non-significant differences in women with BMI lower than 25 (WMD = 3.14 mg/dL; 95% CI = [−6.03, 12.31]; P = 0.502) and higher than 25 (WMD = −11.72 mg/dL; 95% CI = [−34.47, 11.03]; P = 0.312). The results of subgroup analysis are shown in Fig. 3.

3.4. Sensitivity analysis

We performed a sensitivity analysis to ascertain whether our final results were affected by excluding one or more studies from the analysis. After exclusion of the study conducted by Kordouglu and colleagues [16] and reanalyzing the remaining articles, results revealed that serum zinc levels in women with PCOS were significantly lower than those of healthy controls (WMD: −6.60 mg/dL; 95% CI = [−12.43, −0.76], P = 0.027).

3.5. Publication bias

Although, we minimized publication bias by performing a comprehensive literature search, Begg's and Egger's tests were also applied to statistically assess publication bias. Finally, no evidence of publication bias was observed (Begg's test: P = 1.00, Egger test: P = 0.794).

4. Discussion

To the best of our knowledge, present study is the first systematic review and meta-analysis that evaluated the serum zinc status in patients with PCOS compared with healthy subjects. The results demonstrated that there are no significant differences in serum zinc levels between patients with PCOS and healthy subjects; however, there were considerable heterogeneity among included studies. In an attempt to find-out the source of heterogeneity we performed subgroup analysis, which showed that heterogeneity was attenuated in other BMI subgroup. In addition, sensitivity analysis indicated that after excluding one study [16] results changed. In fact, without that study pooled effect size showed that serum zinc levels in women with PCOS were significantly lower than healthy participants.

One of the possible mechanisms for linking zinc to PCOS could be through its effect on insulin signaling system. Studies have reported that insulin resistance in PCOS is due to post-receptor defect in insulin action [26]. Clinical and epidemiological studies have indicated that decreased zinc status is related to insulin resistance [30]. Improvement of insulin resistance after zinc supplementation has been reported in patients with PCOS [31].

PCOS has been described as a state of chronic inflammation mainly defined as an increased serum CRP compared to the weight matched controls [32]. Furthermore, PCOS patients are more likely to have increased visceral fat mass and higher waist to hip ratio [33]. Visceral fat may be a key factor describing components of metabolic syndrome and of low grade chronic inflammation through producing various cytokines and also adipokines [33,34]

In addition, recent studies highlighted the role of increased reactive oxygen species (ROS) and oxidative stress and also decreased antioxidant capacity in the pathogenesis of PCOS. Oxidative stress might have a role in the development of IR and hyperandrogenism in women with PCOS [35,36]. Zinc, as a remarkable antioxidant, protects the sulfhydryl groups of proteins against oxidation and its deficiency leads to increased oxidative damage in various organs [24,37]. Zinc reported as a key element involving in immune efficiency [38]. Multiple roles of zinc as a modulator of the inflammatory mechanisms have been investigated [39]. Zinc modulates the pro-inflammatory response by inhibiting nuclear factor kappa B (NF-κB), a transcription factor that is the master regulator of proinflammatory responses, which accordingly, results in decreased generation of inflammatory cytokines such as TNF-α and IL-1β [40,41]. On the other hand, zinc levels reported to be lower in obese subjects [42]. Chronic inflammation may reduce zinc absorption into the body in obese subjects [43]. In essence, lower zinc concentrations inside immune cells heightened inflammatory procedures and cytokine expression [43]. Therefore, zinc deficiency may act as an

Table 1
Characteristics of the included studies.

Author (Location; year)	Blood Sample	Method of Zinc assessment	Mean age (SD, years)	Mean BMI (SD, Kg/m^2)	Sample size		Zinc [mean (SD), μg/dl]	Matching	Definition of PCOS	Quality Score
					PCOS	Control				
Kurdoglu (Turkey; 2012)	Serum	Atomic absorption	PCOS 24.25 (4.68) Control 27.75 (5.45)	PCOS 21.72 (3.02) Control 22.63 (3.08)	35	30	PCOS 92 (20) Control 77 (19)	Age, BMI	Rotterdam	7
Chakraborty (India, 2013)	Serum	Atomic absorption	PCOS 28.93 (4.13) Control 28.33 (5.90)	PCOS 23.57 (5.62) Control 23.02 (1.15)	132	46	PCOS 60 (34.4) Control 56 (6.7)	Age, Weight	Rotterdam	6
Guler (Turkey, 2014)	Serum	Atomic absorption	PCOS 25.4 (6.7) Control 28 (5.9)	PCOS 27.4 (6.8) Control 23.5 (4.9)	53	33	PCOS 66.3 (13.2) Control 78.1 (14.7)	Age	Rotterdam	6
Zheng (China, 2015)	Serum	Inductively coupled plasma-mass	PCOS 27 (1.04) Control 29 (0.83)	PCOS 22.07 (0.88) Control 20.45 (0.58)	96	105	PCOS 84.36 (2.08) Control 89.15 (2.91)	Age, BMI,WHR	Rotterdam	7
Özer (Turkey, 2016)	Serum	Atomic absorption	PCOS 26.2(5.5) Control 29.4(8.8)	PCOS 26.9 (5.4) Control 23.8 (4.7)	71	53	PCOS 84.4 (25.5) Control 99.4 (19.9)	Age, BMI	Rotterdam	8
Kulhan (Turkey, 2017)	Serum	Atomic absorption	PCOS 24.06 (6.12) Control 25.34 (5.82)	PCOS 26.00 (4.52) Control 25.27 (2.68)	65	67	PCOS 95.45 (10.94) Control 89.22 (9.83)	NR	Rotterdam	6
Farhood (Iraq, 2017)	Serum	NR	PCOS 25.48 (3.56) Control 25.18 (3.1)	PCOS 28.34 (7.17) Control 28.28 (8.33)	40	40	PCOS 75.31 (33.91) Control 83.8 (10.11)	Weight	Rotterdam	5
Kanafchian (Iran, 2017)	Serum	Atomic absorption	PCOS 28.68 (5.08) Control 29.17 (5.03)	PCOS 29.14 (5.54) Control 27.92 (4.70)	60	90	PCOS 81.33 (24.28) Control 108.31 (63.29)	Age, weight, BMI	Rotterdam	8

NR: not reported.

initiator or promoter of the underlying mechanisms and metabolic features of PCOS [44], which could be different in obese subjects.

As mentioned, excluding the study of Kordouglu et al [16] changed overall results. Results without that study showed significantly lower serum zinc concentrations among women with PCOS compared with the healthy controls. After scrutinizing above-mentioned study, we found that this study was conducted on participants with an approximate BMI of 21 kg/m^2 that was lower than those of other articles. Worthy to note that the majority of people with PCOS are obese and overweight [45] and also some studies have shown a negative correlation between serum zinc levels and BMI in healthy subjects [46], as well as in PCOS patients [24]. Therefore, one of the possible reasons for higher levels of zinc in patients with PCOS in Kordouglu's study could be the lower BMI range in enrolled subjects compared to the

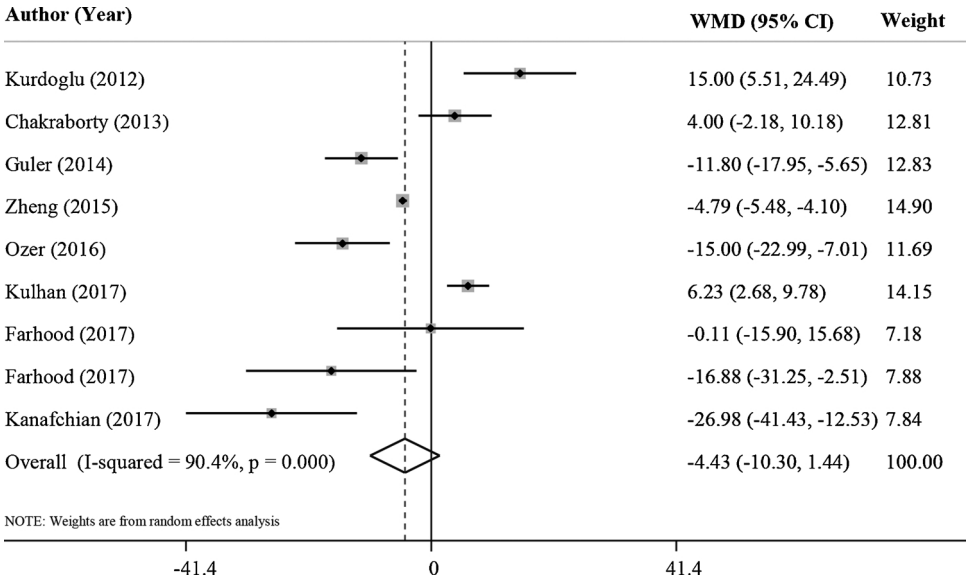

Fig. 2. Forest plot showing the differences of serum zinc levels in PCOS and control subjects.

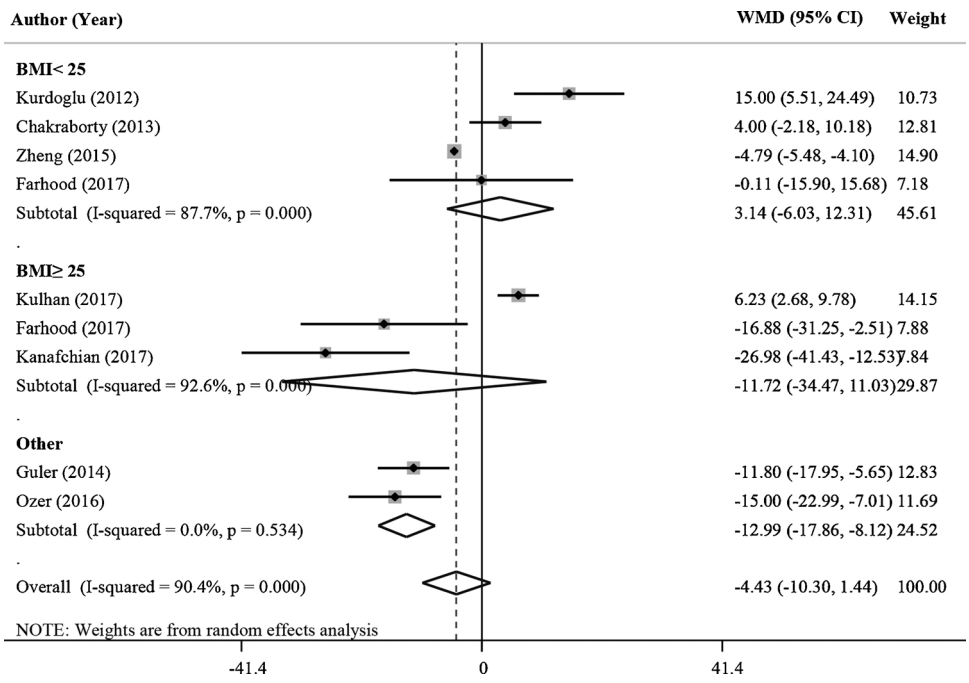

Fig. 3. Forest plot showing the differences of serum zinc levels in PCOS and control subjects stratified by BMI.

participants in other studies.

In subgroup analysis based on BMI, there were significant differences in serum zinc levels between PCOS and controls in studies in other BMI subgroup. Previous reports have shown that obesity is associated with low serum zinc levels [47,48]. Studies in other BMI subgroup recruited cases with higher BMI than controls (27 vs. 23), which maybe a possible reason for such significant association.

Limitations of this meta-analysis deserve to be acknowledged. First, the number of enrolled studies was small with small sample size. The largest study in our analysis was performed on about 200 subjects. Moreover, six included studies were BMI or weight matched, but in most records the mean BMI of the PCOS patients was higher than controls. This issue can lead to decreased serum zinc of PCOS subjects. Therefore, the results should be interpreted with caution. Included studies were heterogeneous regarding BMI, analytical method for measuring zinc serum levels, population, ethnic groups and quality score. Accordingly, further studies aiming to assess zinc serum levels as well as its dietary intake in patients with PCOS are warranted to explain the exact link between zinc status and PCOS.

5. Conclusions

We showed that when detailed analysis is conducted, there is a significant difference between women with PCOS and their healthy counterparts in terms of zinc status. Due to small number of subjects in previous works, large scale studies are needed before any solid conclusion could be drawn.

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References

[1] G. Bozdag, S. Mumusoglu, D. Zengin, E. Karabulut, B.O. Yildiz, The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis, Hum. Reprod. 31 (12) (2016) 2841–2855.

[2] R.S. Legro, S.A. Arslanian, D.A. Ehrmann, K.M. Hoeger, M.H. Murad, R. Pasquali, C.K. Welt, Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline, J. Clin. Endocrinol. Metab. 98 (12) (2013) 4565–4592.

[3] S. Iftikhar, M. Collazo-Clavell, V.L. Roger, J.S. Sauver, R. Brown Jr., S. Cha, D. Rhodes, Risk of cardiovascular events in patients with polycystic ovary syndrome, Neth. J. Med. 70 (2) (2012) 74.

[4] L.J. Moran, M.L. Misso, R.A. Wild, R.J. Norman, Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis, Hum. Reprod. Update 16 (4) (2010) 347–363.

[5] H. Chun-Sen, W. Chien-Hua, C. Wan-Chun, L. Ching-Tzu, C. Chun-Jen, H. Ming-I, Obesity and insulin resistance in women with polycystic ovary syndrome, Gynecol. Endocrinol. 27 (5) (2011) 300–306.

[6] K. Farrell, M.H. Antoni, Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: biobehavioral mechanisms and interventions, Fertil. Steril. 94 (5) (2010) 1565–1574.

[7] H. Tapiero, K.D. Tew, Trace elements in human physiology and pathology: zinc and metallothioneins, Biomed. Pharmacother. 57 (9) (2003) 399–411.

[8] M. Soinio, J. Marniemi, M. Laakso, K. Pyörälä, S. Lehto, T. Rönnemaa, Serum zinc level and coronary heart disease events in patients with type 2 diabetes, Diabetes Care 30 (3) (2007) 523–528.

[9] Q. Sun, R.M. van Dam, W.C. Willett, F.B. Hu, Prospective study of zinc intake and risk of type 2 diabetes in women, Diabetes Care 32 (4) (2009) 629–634.

[10] M. Basaki, M. Saeb, S. Nazifi, H. Shamsaei, Zinc, copper, iron, and chromium concentrations in young patients with type 2 diabetes mellitus, Biol. Trace Elem. Res. 148 (2) (2012) 161–164.

[11] F. Chimienti, Zinc, pancreatic islet cell function and diabetes: new insights into an old story, Nutr. Res. Rev. 26 (1) (2013) 1–11.

[12] D.N. Marreiro, B. Geloneze, M.A. Tambascia, A.C. Lerário, A. Halpern, S.M. Cozzolino, Participation of zinc in insulin resistance, Arq. Bras. Endocrinol. Metabol. 48 (2) (2004) 234–239.

[13] R. Kelishadi, M. Hashemipour, K. Adeli, N. Tavakoli, A. Movahedian-Attar, J. Shapouri, P. Poursafa, A. Rouzbahani, Effect of zinc supplementation on markers of insulin resistance, oxidative stress, and inflammation among prepubescent children with metabolic syndrome, Metab. Syndr. Relat. Disord. 8 (6) (2010) 505–510.

[14] K.J.C. Cruz, A.R.S. de Oliveira, J.B.S. Morais, J.S. Severo, P.M.V. Mendes, S.R. de Sousa Melo, G.S. de Sousa, D. do Nascimento Marreiro, Zinc and insulin resistance: biochemical and molecular aspects, Biol. Trace Elem. Res. (2018) 1–6.

[15] J. Kim, S. Lee, Effect of zinc supplementation on insulin resistance and metabolic risk factors in obese Korean women, Nutr. Res. Pract. 6 (3) (2012) 221–225.

[16] Z. Kurdoglu, M. Kurdoglu, H. Demir, H. Sahin, Serum trace elements and heavy metals in polycystic ovary syndrome, Hum. Exp. Toxicol. 31 (5) (2012) 452–456.

[17] P. Chakraborty, S. Ghosh, S. Goswami, S.N. Kabir, B. Chakravarty, K. Jana, Altered trace mineral milieu might play an aetiological role in the pathogenesis of polycystic ovary syndrome, Biol. Trace Elem. Res. 152 (1) (2013) 9–15.

[18] S. Mazloomi, N. Alizadeh, M. Aminzare, S. Niroomand, S.N. Mousavi, Serum zinc and adiponectin levels in patients with polycystic ovary syndrome, adjusted for anthropometric, biochemical, dietary intake, and physical activity measures, Biol. Trace Elem. Res. 10 (2017) doi.

[19] A. Özer, M. Bakacak, H. Kıran, Ö. Ercan, B. Köstü, M. Kanat-Pektaş, M. Kılınç, F. Aslan, Increased oxidative stress is associated with insulin resistance and infertility in polycystic ovary syndrome, Ginekol. Pol. 87 (11) (2016) 733–738.

[20] M.E. Sharif, I. Adam, M.A. Ahmed, D.A. Rayis, H.Z. Hamdan, Serum level of zinc

and copper in sudanese women with polycystic ovarian syndrome, Biol. Trace Elem. Res. 180 (1) (2017) 23–27.
[21] A. Milajerdi, S. Jazayeri, V. Bitarafan, N. Hashemzadeh, E. Shirzadi, Z. Derakhshan, M. Mahmoodi, A. Rayati, A. Djazayeri, S. Akhondzadeh, The effect of saffron (Crocus sativus L.) hydro-alcoholic extract on liver and renal functions in type 2 diabetic patients: a double-blinded randomized and placebo control trial, J. Nutr. Intermed. Metab. 9 (2017) 6–11.
[22] J. Picot, D. Hartwell, P. Harris, D. Mendes, A. Clegg, A. Takeda, The Preferred Reporting Items for Systematic Reviews and Meta-analyses Checklist, (2012).
[23] G. Wells, B. Shea, D. O'connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses, http www ohri ca/programs/clinical_epidemiology/oxford asp 2012Available from: URL (2011) http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[24] I.G. Farhood, Assessment of serum zinc level in patients with polycystic ovary syndrome, Iraqi J. Med. Sci. 15 (1) (2017).
[25] I. Guler, O. Himmetoglu, A. Turp, A. Erdem, M. Erdem, M.A. Onan, C. Taskiran, M.Y. Taslipinar, H. Guner, Zinc and homocysteine levels in polycystic ovarian syndrome patients with insulin resistance, Biol. Trace Elem. Res. 158 (3) (2014) 297–304.
[26] M. Kanafchian, S. Mahjoub, S. Esmaeilzadeh, M. Rahsepar, A. Mosapour, Status of serum selenium and zinc in patients with the polycystic ovary syndrome with and without insulin resistance, Middle East Fertil. Soc. J. (2017).
[27] M. Kulhan, N.G. Kulhan, U.A. Nayki, C. Nayki, N. Ata, P. Ulug, C. Mertoglu, Assessment of the relationship between serum vitamin (A, B 12, C, D, folate) and zinc levels and polycystic ovary syndrome, Archives of Medical Science-Civilization Diseases 2(1) 62-69.
[28] G. Zheng, L. Wang, Z. Guo, L. Sun, L. Wang, C. Wang, Z. Zuo, H. Qiu, Association of serum heavy metals and trace element concentrations with reproductive hormone levels and polycystic ovary syndrome in a Chinese population, Biol. Trace Elem. Res. 167 (1) (2015) 1–10.
[29] R. Azziz, Diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature, J. Clin. Endocrinol. Metab. 91 (3) (2006) 781–785.
[30] C.G. Taylor, Zinc, the pancreas, and diabetes: insights from rodent studies and future directions, Biometals 18 (4) (2005) 305–312.
[31] F. Foroozanfard, M. Jamilian, Z. Jafari, A. Khassaf, A. Hosseini, H. Khorammian, Z. Asemi, Effects of zinc supplementation on markers of insulin resistance and lipid profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial, Exp. Clin. Endocrinol. Diabetes 123 (04) (2015) 215–220.
[32] F.P.F. Tabrizi, B. Alipoor, A. Ostadrahimi, M.M. Sadagiani, Effect of zinc supplementation on inflammatory markers in women with polycystic ovary syndrome, Shiraz E Med. J. 12 (1) (2011) 30–38.
[33] C.C. Kelly, H. Lyall, J.R. Petrie, G.W. Gould, J.M. Connell, N. Sattar, Low grade chronic inflammation in women with polycystic ovarian syndrome, J. Clin. Endocrinol. Metab. 86 (6) (2001) 2453–2455.
[34] R. Pasquali, A. Gambineri, U. Pagotto, The impact of obesity on reproduction in women with polycystic ovary syndrome, Bjog Int. J. Obstet. Gynaecol. 113 (10) (2006) 1148–1159.
[35] M. Moti, L. Amini, S.S.M. Ardakani, S. Kamalzadeh, M. Masoomikarimi, Oxidative stress and anti-oxidant defense system in Iranian women with polycystic ovary syndrome, Iran. J. Reprod. Med. 13 (6) (2015) 373.
[36] F. González, N.S. Rote, J. Minium, J.P. Kirwan, Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome, J. Clin. Endocrinol. Metab. 91 (1) (2006) 336–340.
[37] N. Wiernsperger, J. Rapin, Trace elements in glucometabolic disorders: an update, Diabetol. Metab. Syndr. 2 (1) (2010) 70.
[38] A.S. Prasad, Zinc: mechanisms of host defense, J. Nutr. 137 (5) (2007) 1345–1349.
[39] A.S. Prasad, Clinical, immunological, anti-inflammatory and antioxidant roles of zinc, Exp. Gerontol. 43 (5) (2008) 370–377.
[40] N. Gammoh, L. Rink, Zinc in infection and inflammation, Nutrients 9 (6) (2017) 624.
[41] M. Jarosz, M. Olbert, G. Wyszogrodzka, K. Młyniec, T. Librowski, Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling, Inflammopharmacology 25 (1) (2017) 11–24.
[42] G. Di Martino, M.G. Matera, B. De Martino, C. Vacca, S. Di Martino, F. Rossi, Relationship between zinc and obesity, J. Med. 24 (2-3) (1993) 177–183.
[43] M.R. Nazem, M. Hedayati, M. Asadi, A. Emami, Jacobs J. Obes. (2016).
[44] F. Chimienti, M. Aouffen, A. Favier, M. Seve, Zinc homeostasis-regulating proteins: new drug targets for triggering cell fate, Curr. Drug Targets 4 (4) (2003) 323–338.
[45] C.R. McCartney, J.C. Marshall, Polycystic ovary syndrome, N. Engl. J. Med. 375 (1) (2016) 54–64.
[46] M. Ghayour-Mobarhan, A. Taylor, S. New, D. Lamb, G. Ferns, Determinants of serum copper, zinc and selenium in healthy subjects, Ann. Clin. Biochem. 42 (5) (2005) 364–375.
[47] G.M. Di, M. Matera, B.M. De, C. Vacca, S.M. Di, F. Rossi, Relationship between zinc and obesity, J. Med. 24 (2-3) (1993) 177–183.
[48] K. Torkanlou, B. Bibak, A. Abbaspour, H. Abdi, M. Saleh Moghaddam, M. Tayefi, E. Mohammadzadeh, H. Safarian Bana, M. Aghasizade, G.A. Ferns, A. Avan, M. Ghayour Mobarhan, Reduced serum levels of zinc and superoxide dismutase in obese individuals, Ann. Nutr. Metab. 69 (3-4) (2016) 232–236.