VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2024, vol. 95, no. 2, 143–151

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.96864

How important are elements in polycystic ovary syndrome? Should they be supplemented? A systematic review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a multifactorial disorder with unknown etiology. The purpose of this systematic review is to analyze the available clinical trials on elemental supplementation in terms of improving biochemical parameters in women with PCOS. Electronic databases were searched from their inception until February 2023. Randomized controlled trials (RCTs) of PCOS during therapy with elemental supplementation alone or in combination with other elements were analyzed. Recommendations regarding supplementation with elements are not clear. There are many factors to consider, with the primary factor being the type of element and the possibility of supplementation and a balanced diet. Another aspect to consider is the presence of comorbidities, which may increase the demand for and absorption of elements. A final factor to be considered is the determination of the body's need for specific elements. Some elements may require supplementation (e.g., magnesium, selenium, iodine, calcium), while others (e.g., iron, copper, potassium, zinc, manganese, chromium) are in sufficient amounts in a proper diet, and some should be limited (e.g., sodium, phosphorus). It is necessary to determine the optimal dose of each element in order to improve the biochemical parameters of PCOS as much as possible, while at the same time avoiding the negative effects of excessive consumption.

Keywords: polycystic ovary syndrome; PCOS; element supplementation

Ginekologia Polska 2024; 95, 2: 143–151

INTRODUCTION

In recent years, extensive research has been conducted to better understand the physiological role of elements, including the consequences of deficiency or excess. Decreased levels of elements are found in various reproductive disorders, such as infertility, spontaneous abortion, pre-eclampsia, placental abruption, premature rupture of membranes, stillbirth and low birth weight [1]. However, there is a limited number of scientific publications in the literature on element levels among women with polycystic ovary syndrome.

More and more women with polycystic ovary syndrome (PCOS), guided by information on the advantages of taking various dietary supplements, also reach for element preparations [2]. Thus, it is important to expand research in order to understand how these supplements may affect the factors involved in PCOS, including metabolism, reproduction, and the psychological characteristics of the disease.

Despite emerging reports on the importance of elements, the optimal amounts of these components in the diet for women struggling with PCOS are not clearly delineated. However, it is known that lifestyle changes, including dietary

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Received: 7.08.2023 Accepted: 9.08.2023 Early publication date: 15.09.2023

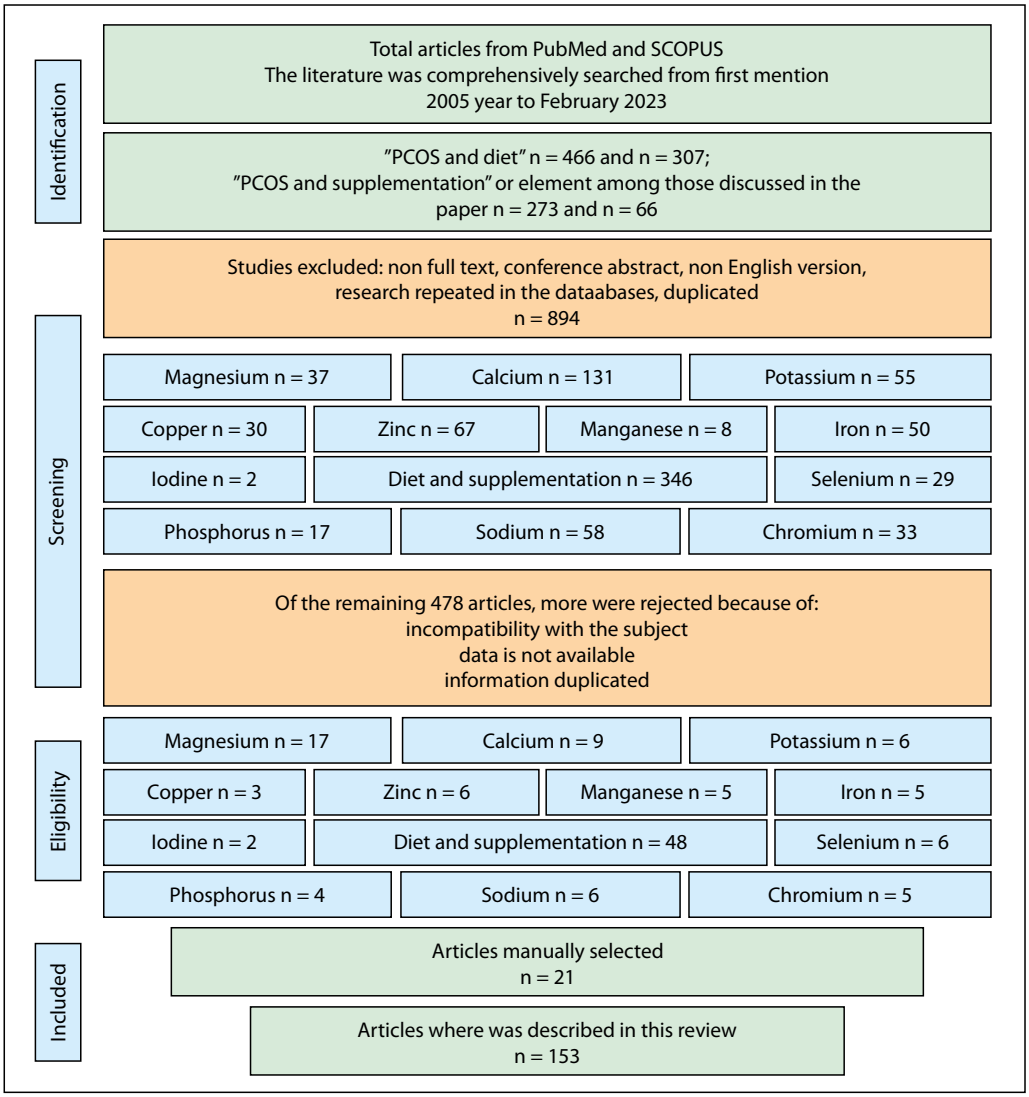

Figure 1. Flow chart of the review (created with BioRender.com https://app.biorender.com/, accessed on 12 March 2023); PCOS — polycystic ovary syndrome

modification, are considered one of the first-line therapies for metabolic syndrome in overweight and obese women with PCOS [1, 2]. Thus, a review of element supplementation in the course of PCOS seems a reasonable endeavor.

MATERIAL AND METHODS

This systematic review aims to discuss the effect of element supplementation on the biochemical parameters of PCOS patients. The literature was comprehensively searched from first mention (2005) to February 2023 in the PubMed and SCOPUS databases. The search scheme is shown in Figure 1. Two authors independently searched the literature, and after eliminating repetitive articles, assessed the eligibility of articles according to the above criteria.

The inclusion criteria: study sample was adult women diagnosed with PCOS; involved supplementation with one element or co-supplementation with other elements or vitamins; study design was randomized controlled trial (RCT).

The exclusion criteria: adolescent PCOS patients (age > > 18 years); the presence of comorbidities; no assessment of supplementation or no specification of the amount of dosage of supplements; lacking a control group; no access to the full text of the article.

RESULTS AND DISCUSSION

Element supplements are among the dietary supplements that are expected to provide improvement of the metabolic profile. The latest research on PCOS focuses on element supplementation to eliminate pathological situations in PCOS. Some elements (*e.g.*, magnesium, potassium, zinc) are often present in insufficient amounts, while some are in excess (*e.g.*, sodium and phosphorus) [1–2]. In this

work, an analysis of elements was made, from the most desirable elements, the supplementation of which seems necessary, to the least desirable, where care should be taken not to exceed the recommended amounts.

It has been shown that PCOS patients have lower serum **magnesium** (Mg) levels than healthy women [3]. Magnesium deficiency is associated with a wide range of complications in the female reproductive system [4–8]. Magnesium controls follicle stimulating hormone (FSH) binding to receptors in the ovary. Moreover, estrogen activity is magnesium dependent. Its deficiency increases the risk of infertility, miscarriage, premature birth and low birth weight [4]. Examples of magnesium supplementation are presented in Table 1 [9–34]. Recent research has suggested that magnesium may reduce the clinical symptoms of PCOS in two ways: by improving glucose homeostasis and androgen reduction as well as through its anti-inflammatory and antioxidant properties [5, 6]. As the cited studies have shown, magnesium in combination with vitamin E, zinc, or calcium significantly improves insulin resistance and inflammation [3, 7]. However, long-term studies are needed to confirm these associations and to demonstrate the benefits of using magnesium supplements in women with PCOS [8]. Considering the above and the fact that magnesium in the healthy population is often deficient, Mg supplementation in PCOS should be considered.

Women with PCOS often have **calcium** abnormalities; those who are obese are particularly at risk of deficiency of this element [14]. This may be due, in part, to the fact that the concentration of adiponectin is strongly related to the level of Ca and vitamin D [13]. It is suspected that abnormalities in calcium levels may be related to IR and contribute to the pathology of PCOS; however, the opinions of scientists are divided [13–18]. It is also suspected that there is a potential relationship between bone-derived markers and further disorders in women with PCOS [4, 5]. Due to its beneficial effect on ovarian follicles and the regulation of the menstrual cycle, calcium supplementation is recommended for women with PCOS. While these changes cannot be attributed to calcium alone, it is important to note that elements often work in complexes to regulate various metabolic processes and thus reduce the negative health effects associated with PCOS [14, 16–18]. Vitamin D increases calcium absorption. Latitude, season and climatic conditions are just some of the environmental factors that determine vitamin D production. Considering the above, it is recommended to supplement with vitamin D in regions with low insolation, along with calcium supplementation [13–15]. Calcium + vitamin D complex improves nerve transmission conduction, vasospasm, and dilatation as well as endocrine secretions. In addition, it has a positive effect on insulin secretion [18]. Studies also indicate that supplementation with Ca + vitamin D in women with PCOS improves lipid profile, increases QUICKI and decreases serum insulin concentrations, HOMA-IR,6 and testosterone (Tab. 1).

Adequate **potassium** intake can have a significant impact on glycemic control and diabetes risk reduction in women with PCOS, who are already at higher risk of developing additional comorbidities. It has been shown that the concentration of potassium in erythrocytes in women with PCOS is significantly higher than in healthy women [2] showed the existence of significant negative relationships between the amount of potassium in the erythrocytes of women with PCOS and saturated fatty acids in cell membranes. Saturated fatty acids cause a decrease in potassium influx into the cell by destabilizing the pH of the cytosol [35]. Although there is no information on potassium supplementation in women with PCOS, it seems reasonable to introduce this element to the diet, especially in cases where it is necessary to eliminate products with a high glycemic index (bananas, potatoes, sweet potatoes), which are the main source of potassium. Removing these products from the daily diet may increase the occurrence of deficiency of this element in PCOS patients. In addition, with a low consumption of vegetables, especially tomatoes, supplementation may be indicated.

Recently, attention has been paid to the importance of **zinc** in endocrine diseases such as PCOS [19]. Women following diets rich in fish and other seafood (*e.g.*, Mediterranean diet) usually have adequate levels of zinc, iodine, selenium and copper. For other diets, supplementation may be required. Zinc deficiency can lead to many disorders, including insulin resistance, diabetes, obesity, hyperglycemia and hypertriglyceridemia [19–21]. It can also cause oxidative damage in chronic diseases. Therefore, zinc may be a prognostic marker of PCOS [6, 20]. Table 1 shows the effect of zinc supplementation in women with PCOS. After zinc supplementation, an improvement in insulin resistance and lipid metabolism was found.

Thanks to its antioxidant and insulin-like properties, **selenium** has therapeutic potential for PCOS, especially since women with PCOS have a lower selenium content compared to healthy women [25]. Due to the generally insufficient intake of selenium, supplementation with this element is recommended [27]. Studies indicate a positive effect of selenium supplementation, as a result of which a reduction in IR, inflammation and oxidative stress was observed. However, not all parameters showed improvement (lipid and hormonal parameters or other features of PCOS such as acne and hirsutism) [25]. Clinical trial results are presented in Table 1. The results show a decrease in the level of HOMA-IR and HOMA-B and increase in QUICKI, as well as a lowering of the level of triglycerides (TG) and VLDL cholesterol [22–24, 26, 27]. There are also reports that

Table 1. Supplementation with selected elements in women with polycystic ovary syndrome (PCOS)

Element	Supplementation	Frequency/duration	Effect	Total number of patients	Author
Mg	Group 1: 500 mg glucophage, Group 2: 400 mg magnesium oxide, Group 3: 50 mg spironolactone	Twice a day/12 weeks	No effect was observed	Group 1 n = 14 Group 2 n = 10 Group 3 n = 12	[7]
Mg Zn Ca	100 mg Mg + 4 mg Zn + 400 mg Ca + 200 IU vit. D	Twice a day/12 weeks	Reductions in serum insulin levels, triglycerides, total cholesterol, HOMA-IR, serum triglycerides Increase in QUICKI	Group 1 n = 30 Group 2 placebo n = 30	[4]
Mg	125 mg/d Mg + 200 mg/d vit. E	Twice a day/12 weeks	Significant reduction in serum insulin levels Significant increase in QUICKI Significantly decreased serum triglycerides and VLDL--cholesterol concentrations	Group 1 n = 30 Group 2 placebo n = 30	[3]
Mg Ca	250 mg Mg + 47 mg Ca carbonate	Once a day/8 weeks	Significantly decreased BMI and serum testosterone An increase in the concentrations of serum DHEA and luteinizing hormone A significant increase in serum LH levels No effect: glycemic variables and lipid profile, FSH, SHGB {SHBG?}	Group 1 n = 30 Group 2 placebo n = 30	[5]
Mg	Group 1: 250 mg Mg oxide + 6 mg melatonin Group 2: 6 mg melatonin Group 3: 250 mg Mg oxide Group 4: Placebo	Once a day/8 weeks	A significant decrease in testosterone concentrations Mg + melatonin significantly reduced glucose homeostasis parameters (insulin and HOMA-IR), serum cholesterol, LDL-C	Group 1 n = 22 Group 2 n = 21 Group 3 n = 21 Group 4 placebo n = 20	[9]
Mg Zn	250 mg Mg oxide + 226 mg of Zn sulfate (containing 50 mg zinc)	Once a day/12 weeks	A significant decrease in hs-CRP A significant increase a plasma total TAC levels	Group 1 n = 30 Group 2 placebo n = 30	[6]
Mg	250 mg Mg oxide	Once a day/10 weeks	Significantly improved the components of quality of life (including physical functioning) No significant effect was observed on acne and alopecia	Group 1 n = 32 Group 2 placebo n = 32	[10]
Mg	250 mg/day Mg + 400 mg/day vit. E	Once a day/12 weeks	A significant reduction in hirsutism and serum hs-CRP A significant increase in plasma NO and TAC levels	Group 1 n = 30 Group 2 placebo n = 30	[8]
Mg	50-mg/day Mg + 6-mg/day melatonin	Once a day/8 weeks	No effect	Group 1 n = 22 Group 2 placebo n = 20	[11]
Mg	250 mg Mg oxide	Once a day/10 weeks	No significant effect on hyperandrogenism, hirsutism and sleep quality	Group 1 n = 32 Group 2 placebo n = 32	[12]
Ca	530 mg elementary Ca + vit. D 3533 IU	Once a day/8 weeks	Potential therapeutic benefits of vitamin D and Ca supplementation have been observed in alleviating the hormonal environment and PCOS-related sequelae in vitamin D deficient women	Group 1 n = 12 Group 2 placebo n =12	[13]
Ca	1000 mg Ca/ + Metformin1500 mg/ + vit. D 100000	Once a day/month	Significantly reduced BMI Menstrual cyclicity, follicular maturation, and pregnancy rates were affected positively, but the alterations were not statistically significant	Group 1 n = 25 Group 2 placebo n = 25	[14]

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Table 1. cont. Supplementation with selected elements in women with polycystic ovary syndrome (PCOS)

Element	Supplementation	Frequency/ duration	Effect	Total number of patients	Author
Ca	Group 1: 1500 mg/day metformin Group 2: 1500 mg/day metformin + 1000 mg Ca + + vit. D 3500 IU vit. D3 Group 3: Ca 1000 mg + vit. D 3500 IU vit. D3 Group 4: placebo group	Once a day	No effect	Group 1 n = 20 Group 2 n = 20 Group 3 n = 20 Group 4 placebo n = 20	[15]
Ca	Group 1: 1000 mg Ca + vit. D placebo, Group 2: 7000 IU vit. D + Ca placebo Group 3: 1000 mg Ca + 7000 IU vit. D Group 4: Ca placebo + vit. D placebo	Once a day/8 weeks	Calcium + vit. D supplements had greater decreases in HOMA-B; hs-CRP and MDA Significant increases in plasma TAC and GSH levels	Group 1 n = 26 Group 2 n = 26 Group 3 n = 26 Group 4 n = 26	[16]
Ca	Group 1. 200 IU vit. D, 90 µg vit. K + 500 mg Ca	Twice a day/8 weeks	A significant reduction in serum-free testosterone and DHEAS, TAC, luteinizing hormone and a significant difference in MDA concentrations No effect on prolactin, follicle-stimulating hormone, inflammatory markers, and glutathione levels	Group 1 n = 30 Group 2 placebo n = 30	[17]
Ca	Group 1: 1000 mg Ca + vit. D placebo Group 2: 7000 IU vit. D + Ca placebo Group 3: 1000 mg Ca + 7000 IU vit. D Group 4: Ca placebo + vit. D placebo	Once a day/8 weeks	Co-supplementation, led to decreased serum insulin levels, HOMA-IR,serum triglycerides and VLDL-cholesterol levels A significant rise in QUICKI No significant effects on FPG, total-, LDL-, HDL, and non-HDL--cholesterol levels	Group 1 n = 26 Group 2 n = 26 Group 3 n = 26 Group 4 n = 26	[18]
Zn	220 mg Zn sulfate (50 mg Zn)	Once a day/8 weeks	Significant decrease in serum insulin levels, HOMA-IR; HOMA -B; triglycerides, VLDL cholesterol Significant increase in QUICKI	Group 1 n = 26 Group 2 placebo n = 26	[19]
Zn	220 mg Zn sulfate (50 mg zinc)	Once a day/8 weeks	Decreased circulating MDA concentrations A significant on alopecia, hirsutism, and plasma MDA, No effect was observed on the hormonal profiles	Group 1 n = 24 Group 2 placebo n = 24	[20]
Zn	220 mg Zn sulfate (50 mg zinc)	Once a day/8 weeks	Decreasing serum hs-CRP and IL-6 levels Group 2 placebo n = 30	Group 1 n = 30	[21]
Se	200 µg Se	Once a day/12 weeks	Significantly increased insulin resistance and marginally significant increase in insulin levels	Group 1 n = 26 Group 2 placebo n = 27	[22]
Se	200 µg Se	Once a day/8 weeks	Significant decrease in triglycerides, VLDL-C, serum insulin levels, HOMA-IR; HOMA-B Significant increase in QUICKI	Group 1 n = 35 Group 2 placebo n = 35	[23]
Se	200 µg Se	Once a day/8 weeks	Significant decrease in DHEA levels, hs-CRP; MDA, acne, hirsutism	Group 1 n = 32 Group 2 placebo n = 32	[24]
Se	200 µg Se	Once a day/12 weeks	Significant decrease in testosterone No effect on serum lipids, SHBG	Group 1 n = 38 Group 2 placebo n = 38	[25]

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Table 1. cont. Supplementation with selected elements in women with polycystic ovary syndrome (PCOS)

Element	Supplementation	Frequency/ duration	Effect	Total number of patients	Author
Se	200 µg Se + 8×10^9 CFU probiotic	Once a day/12 weeks	A significant reduction in total testosterone, hs-CRP, MDA and improvements in hirsutism A significant increase in the TAC	Group 1 n = 30 Group 2 placebo n = 30	[26]
Se	200 µg Se	Once a day/8 weeks	Significantly decreased FPG, HOMA-IR, FSI and QUICKI Significantly reduced MDA levels	Group 1 n = 20 Group 2 placebo n = 20	[27]
Cr	200 µg Cr	Once a day/8 weeks	Significant increase in QUICKI significant reductions in FPG, insulin levels, HOMA-IR; serum triglycerides and total cholesterol concentrations	Group 1 n = 20 Group 2 placebo n = 20	[28]
Cr	200 µg Cr picolinate	Once a day/4 months	Improves glucose tolerance No effect was observed on the hormonal profiles	Group 1 n = 20 Group 2 placebo n = 20	[29]
Cr	200 µg Cr picolinate	Once a day/8 weeks	Significant decreases in serum insulin levels, HOMA-IR; HOMA-B, and a significant increase in QUICKI Decreasing serum triglycerides and cholesterol	Group 1 n = 32 Group 2 placebo n = 32	[30]
Cr	200 µg Cr picolinate	Once a day/8 weeks	Significant decreases in hs-CRP, MDA, in acne, hirsutism Significant increase in TAC	Group 1 n = 32 Group 2 placebo n = 32	[31]
Cr	200 µg Cr picolinate + 1000 mg carnitin	Once a day/12 weeks	Significant decreases in total testosterone; hs-CRP; MDA Significant increase in TAC levels Upregulated gene expression of IL-6 and TNF-α Significant decreases in BMI, glycemic control, lipid profiles except HDL cholesterol levels	Group 1 n = 27 Group 2 placebo n = 27	[32]
Cr	1000 µg Cr picolinate	Once a day/8 weeks	Significant reduction of BMI and FSI Significant rise in FGIR	Group 1 n = 50 Group 2 placebo n = 50	[33]
Cr	200 µg Cr picolinate	Once a day/8 weeks	Significant decrease in gene expression of IL-1 and serum hs-CRP levels Did not affect gene expression of IL-8, TNF-α, TGF-β, and VEGF	Group 1 n = 20 Group 2 placebo n = 20	[34]

BMI — body mass index; Ca — calcium; Cr — chromium; DHEA — dehydroepiandrosterone; FGIR — fasting glucose insulin ratio; FPG — fasting plasma glucose; FSH — follicle stimulating hormone; FSI — fasting serum insulin; GSH — glutathione; HOMA-B — homeostatic model assessment-beta-cell function; HOMA-IR — homeostasis model of assessment-insulin resistance; hs-CRP — high sensitivity C-reactive protein; TAC — total antioxidant capacity; IL-1 — interleukin-1; IL-8 — interleukin-8; MDA — malondialdehyde; Mg — magnesium; NO — nitric oxide; Se — selenium; SHBG — to sex hormone-binding globulin; TNFα — tumor necrosis factor α; TNF β — tumor necrosis factor β; QUICKI — quantitative insulin sensitivity check index; VDLD-C — very low-density lipoprotein cholesterol; VEGF — vascular endothelial growth factor; Zn — zinc

supplementation does not positively affect the improvement of parameters in PCOS [25]. Research results are conflicting; thus, supplementation should be considered with caution. However, it seems that in women who do not eat seafood and/or who have thyroid diseases, periodic supplementation may be indicated.

Chromium regulates the menstrual cycle, which contributes to increasing the chances of ovulation. Its deficiency contributes to the development of glucose intolerance, insulin resistance, hyperinsulinemia and a reduction in the number of insulin receptors [28]. Chromium is an important element in the treatment of PCOS, as it regulates hormonal profile disorders caused by this syndrome, improves body composition and reduces body mass index (BMI) [29–32]. Table 1 shows the results of chromium supplementation, especially in the form of chromium picolinate (CrP; chromium picolinate contains 12.4% elemental trivalent chromium) in PCOS patients. Chromium picolinate has been shown to improve IR, glycemic control and metabolic status, as well as lower body weight in women with PCOS [33, 34]. The results of clinical trials also indicate that chromium supplementation may reduce the HOMA-IR, HOMA-B index and increase the QUICKI index. Chromium, by enhancing the insulin signaling pathway, increasing activated protein kinase (AMPK) activity and increasing cellular glucose uptake, has a beneficial effect on improving diabetic parameters in PCOS patients [32]. Although there is evidence of a positive effect of chromium on biochemical parameters in PCOS, caution should be exercised when recommending supplementation with this element, as it is associated with increasing oxidative stress, DNA damage, genome instability and carcinogenicity [2, 27].

Polycystic ovary syndrome can cause dysregulation of systemic **copper** homeostasis. Many authors report higher levels of Cu in the blood serum of PCOS patients than in healthy women [2]. This can increase infertility rates by lowering progesterone levels, resulting in anovulation, implantation failure or luteal phase deficit. Moreover, a positive and statistically significant correlation was found between HOMA-IR and Cu [1]. In order to explain the relationship between high Cu levels in PCOS patients, studies should be extended to include reactive oxygen species. It is suspected that Cu supplementation may only be required in sporadic individual cases.

More than one-third of the world's people are at risk of **iodine** deficiency. An inadequate intake of iodine may lead to reproductive dysfunctions, congenital malformations or birth defects, and increased fetal and neonatal mortality. Deficiency of this element negatively affects folliculogenesis, contributing to the development of polycystic ovary syndrome [1, 2]. Recently, increased attention has been paid to the elimination of iodine deficiency, mainly due to the widespread introduction of iodized salt. However, the availability of this salt does not guarantee the optimal dose of iodine. In addition, in populations that do not require supplementation, it can cause harm to the body. Therefore, as in the case of selenium, supplementation may be indicated in people who do not consume fish and seafood or who consume them in insufficient amounts. Therefore, research on a larger scale is necessary to develop the best methods to eliminate the problem of iodine deficiency in the body.

Manganese may be involved in glucose metabolism disorders in women with PCOS; however, the research results are mixed. Many authors point to a lower level of manganese in women with PCOS than in healthy women. It is assumed that this is due to the consumption of this element in the antioxidant defense system, including manganese superoxide dismutase (MnSOD), in the event of increased oxidative stress [1]. Studies also indicate an increase in manganese deficiency in the case of insulin resistance. However, some researchers observed higher levels of this element in women with PCOS compared to the control group. Due to doubts regarding the impact of manganese on the body in women with PCOS, there are no studies on supplementation with this element.

Polycystic ovary syndrome is associated with excessive **iron** levels resulting from infrequent and scanty menstruation and reduced circulating hepcidin levels, which leads to increased iron absorption [2]. Many studies indicate significantly higher iron content in women with PCOS than in healthy women. Studies also show an association between elevated BMI (obese/overweight) with PCOS and higher serum ferritin, indicating the critical role of overweight/obesity. There are also reports of the lack of differences in the level of this element between women with PCOS and healthy women [1]. There are no studies on iron supplementation in women with PCOS, as this group usually does not require such intervention. Further research is suggested to focus on ways to lower iron levels in PCOS.

The last two elements: **sodium** and **phosphorus**, are among the elements found in excess in the diet. High sodium intake leads to increased production of glucocorticoids in adipose tissue and cortisol metabolites in urine. Sodium should be supplied systematically, in small amounts, because its excess is dangerous to health. The prevalence and excess of this ingredient in the diet makes supplementation harmful to health. Due to the excess in-take of sodium, especially in people who consume hidden sources of sodium (bread, rennet cheese), it would be advisable to limit sodium and eliminate the habit of adding salt.

Due to the widespread abundance of **phosphorus** in food, the element is found in excess in the diet. Elevated levels of phosphorus are especially dangerous in the case of calcium deficiency in the diet. The ratio of calcium to

phosphorus is then disturbed, which may lead to increased secretion of parathyroid hormone and increased calcium resorption from the bones. The correct proportions of these two elements can be maintained only by using a diet rich in milk and milk products. In women with a calcium deficit, especially in regions where dairy products are scarce (*e.g.*, Asia), other sources of calcium can be used, *e.g.*, sesame, hummus or vegetable milk. There are no previous publications on phosphorus supplementation in women with PCOS.

CONCLUSIONS

The small number of available publications on supplementation with certain nutrients suggests that additional high-quality research is necessary to determine the effectiveness of element supplementation. Clinical and review studies emphasize the positive effect of supplementation with selected elements on the improvement of reproductive, metabolic and hormonal disorders in PCOS. Supplementing the diet of women with PCOS with these elements had a positive effect on maintaining glucose and insulin homeostasis and improved the lipid profile. However, the available literature lacks a comprehensive approach to supplementation or co-supplementation with micronutrients, which makes it difficult to determine the extent to which these therapies could be effective in the treatment of PCOS symptoms. It should be remembered that there are many factors that can affect supplementation; there can be a positive but also a negative impact when the recommended amounts of a given element are exceeded. Thus, it is important to consider the type of diet used by PCOS patients as well as the comorbidities that may interfere with the processes of absorption and excretion of elements.

Article information and declarations

Author contributions

Conceptualization: KPN and MS; methodology: KPN and MS; validation: KPN, MZ, MSF and MS; formal analysis: KPN and MS; data curation: KPN and MS; writing — original draft preparation: KPN, MZ, and MS; writing — review and editing: KPN, MSF and MS; visualization: KPN and MS; supervision: KPN and MS; project administration: KPN and MS; funding acquisition: KPN, MZ, MSF and MS.

Funding

This research received no external funding.

Acknowledgments

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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