

Review on

The Nutritional Managements to alleviate a Chronic Inflammatory condition- Polycystic Ovarian Syndrome

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Abstract-- PCOS or Polycystic Ovarian Syndrome is a common endocrinological condition seen in females which occur due to a variety of factors like stress and unhealthy diet. Various inflammatory responses and oxidative stress trigger the condition by altering metabolic programming and hormonal balance. The review describes a brief pathophysiology of PCOS and how different nutrients like vitamins, minerals, herbal medicine and complementary therapies like yoga, acupuncture will help in alleviating the adverse effects of the underlying condition. These therapies are natural and is recommended over medicines like Metformin as they promote hirsutism. The action of these therapies, entirely depends on the approach of patients, their genetics and the environment. The main aim is to depict the usefulness of therapies rather than taking dozens of medicines. Nearly 70% patients have successfully responded to supplementation of nutrients along with yoga and recommended them over medicine since their menstrual cycle regularized, LDL levels lowered and metabolism improved. Few supplements had no effect on hormone metabolism but they were excellent in controlling lipid profile. Nutritional supplements have shown the potential to alleviate oxidative stress thereby reducing inflammation and lowering insulin resistance. They normalized the levels of hormones, restored fertility and herbal medicine like cinnamon, mint have the same potential in managing PCOS.

Keywords-- PCOS, Nutrition, Mineral, Yoga.

I. INTRODUCTION

PCOS is a common endocrinopathy seen in reproductive age group females; those belonging to 15-25 years. The rate of occurrence is 12-18% as per studies. Anxiety, hyperandrogenism, binging on junk foods, lack of physical activities lead to PCOS. The problem in HPO axis triggers ovary to release excess androgen leading to male pattern hair growth [1]. The androgens convert to oestrogen by aromatization, thereby preventing LH surge and thus there is anovulation and amenorrhea.

USG findings reveal more than 10-12 follicles in either ovary and biochemical reports display altered FSH: LH ratio, increased free testosterone and decreased SHBG. The diagnosis is based on Rotterdam Criteria that tells that out of the three findings, if any two of them is seen in the patient, then she is said to be a case of PCOS. If the girl complains of secondary amenorrhea or no menstruation for 2-3 months or more, she has hirsutism; her hormonal levels are abnormal and her USG reports show many follicles or cysts in the ovaries then she is a PCOS patient. If the girl had complained about any two among the above said, then according to the Rotterdam criteria, she would be called as a patient PCOS [2]. The oestrogen levels are constantly raised, thus the hormonal levels and disturbed and the LH are also raised thus there is no typical LH surge that occurs normally in a female on the 14th day of her menstrual cycle. The absence of LH surge prevents ovulation and thus the Graafian follicle cannot rupture to release the ovum in the secondary oocyte stage. She does not menstruate due to no release of ovum. This continues for months and the follicles being unable to rupture eventually turns to cysts that is seen on ultrasound [3]. Effects of excess androgen causes hirsutism; excess facial, pubic growth of hairs and rarely it may cause male like deepening of voice and clitoromegaly. Testosterone, an androgen binds to Sex Hormone Binding Globulin (SHBG), a protein so that its half-life is stable and it releases when required. In this condition the testosterone is elevated and thus the SHBG cannot accommodate the humungous amount, thus SHBG levels are lowered that gets reflected on biochemical analysis [4]. Normally the FSH:LH ratio is 2:1 but in these patients the ratio gets altered to 1:2 or 1:3. Such patients develop abdominal fat and insulin resistance (IR) due to metabolic disorders. The cells cannot uptake insulin and there is hyperinsulinemia and hyperglycaemia. The prolonged effects of IR leads to type 2 Diabetes mellitus and obesity may lead to cardiovascular diseases, dyslipidaemia.

Obesity causes release of fatty acids and tumour necrosis factor alpha from adipose tissue to facilitate IR. High oestrogen levels may cause endometrial hyperplasia [5]. PCOS patients develop infertility and thus they cannot conceive. Oxidative stress leads to inflammatory conditions like PCOS and thus it must be controlled. IGFR1 signalling is reduced in them and there is elevated COX2 production that hinders oocyte maturation facilitating the infertility. Adiponectin levels are decreased and leptin increases in such patients leading to excess hunger. Hunger causes them to intake more food, leading to obesity [2]. The lipid profile is drastically degraded in such patients. They show elevated LDL level, high VLDL and TG level but HDL is lowered. The accumulation of fatty acid and cholesterol leads to this condition and paves the way for CVD, renal failure, etc [6].

PCOS can be treated by medicine like OCPs, metformin, danazol and others but they cause side effects like withdrawal bleeding, nausea, hirsutism, prevents pregnancy, etc. Nutritional therapy is a very big rescue to such adverse effects and have a potent role in treating PCOS [7]. Various vitamins, minerals, supplements, herbal medicine, yoga have played an immense role in the patients on whom studies were conducted. They normalized menstrual cycle, improved IR, hormone levels and lipid profile. They have a role in signalling thereby modulating the insulin and hormone metabolism [5]. Thus, the nutritional and complementary therapies can improve the lifestyle of PCOS females and replenish their fertility issues [7]. Stress, distorted body shape are important determinants of symptoms and the influence of psychological factors must be considered when treating the females [8]. An USA study in a population showed that the 8% black women and about 5% white women were affected with PCOS. The features of PCOS may differ from race to race due to certain factors like eating habits [9]. About 65-70% women have responded to nutritional therapy and yoga and have recommended them over medicines [2].

II. NUTRITIONAL THERAPY TO MANAGE PCOS

The roles of various nutritional supplements like vitamins, minerals, L-carnitine and others have been discussed along with the results observed on patients as per study conducted.

2.1 Role of Vitamins: -

The role of different vitamins on PCOS females are discussed below.

2.1.1 Vitamin D

Vitamin D helps in calcium metabolism. Its supplementation has led to improved insulin resistance and lowered LDL [10]. It indirectly influences carbohydrate metabolism by normalizing extracellular calcium and parathormone concentration [11]. It affects the expression metabolic genes that control inflammation by inhibiting pro-inflammatory cytokines which may contribute to the occurrence of IR [12]. Women with PCOS receiving 20,000 IU of cholecalciferol weekly benefited from improved carbohydrate metabolism and decrease in fasting glucose, triglycerides, and Estradiol were observed. Vitamin D stimulates the differentiation of granulosa cells and influences follicular maturation by targeting AMH, thereby restoring fertility [10].

2.1.2 Vitamin E

Tocopherol is a free radical scavenger, thus alleviates oxidative stress. It reduces LH, FSH and increases SHBG. It promotes thickening of endometrium and treats infertility [13]. According to a study, cosupplementation of 400 IU vitamin E with 1000 mg of ω -3 fatty acids for 12 weeks led to improvements in IR and androgen concentration. It is often supplemented with coenzyme Q10 [14].

2.1.3 Vitamin B9

Folic acid or vitamin B-9, is the synthetic form of folate derived from foods and supplements as it cannot be synthesized in the body. It acts as a coenzyme in several key reactions needed for nucleic acid synthesis and is essential for methylation of homocysteine to methionine [15]. Folic acid is proposed to have antioxidant, anticancer, and cardioprotective properties beneficial in PCOS women [2]. Moreover, supplementation with folate could normalize the typically elevated Hcy concentration observed in women with PCOS. CRP, MDA reduced on folate supplementation and its intake 5mg/day reduces insulin and LDL as per studies [16].

2.1.4 Inositol

Vitamin B8 has two stereoisomers, myoinositol and D-chiro inositol that play a major role in treating PCOS [17]. Current studies portrayed that myo-inositol is as effective as metformin in shaping the clinical and metabolic profile of PCOS females, but myoinositol showed no side effects like metformin [18]. Both MI and DI isomers are second messengers of insulin, stimulates glucose uptake and glycogen synthesis. 496 participants found that MI supplementation, alone or combined with DI, significantly reduced fasting insulin and increased SHBG was also observed [19].

2.2 *Role of minerals:*

The roles of various minerals are elucidated below.

2.2.1 *Selenium*

Selenium is an essential trace element and vital part of selenoproteins which assist in redox reactions and have important antioxidant and anti-inflammatory functions. Selenium is associated with a lower level of CRP [20]. Selenoproteins protect against oxidative stress caused by excessive concentrations of ROS and RNS. It is also involved in metabolic functions, and its plasma concentrations are thought to be decreased in women with PCOS, potentially leading to free radical accumulation and hyperandrogenism [21]. A study conducted in 2019 on PCOS identified 5 RCTs, where women with PCOS were supplemented with 200 µg Se daily for 8–12 weeks. Findings revealed reduced IR, inflammation, and oxidative stress, whereas results were inconsistent for BMI, weight, FBG, lipids, hormonal parameters, or other features of PCOS such as acne and hirsutism [22].

2.2.2 *Calcium*

Women with PCOS have abnormalities or reduction in calcium concentrations [23]. Calcium and vitamin D are often supplemented together as vitamin D improves calcium absorption, enabling it to carry out functions like the maintenance of bone, nerve transmission, and endocrine secretions [24]. Combined magnesium, zinc, calcium, and vitamin D supplementation in a study showed significant reduction in hirsutism and total testosterone but no effect observed on SHBG level [2]. Improvement in lipid profiles, menstrual regularity, and follicular maturation, reduced serum insulin, IR, FBG has been reported too [1].

2.2.3 *Zinc*

Zinc, a micronutrient, plays a role in lipid metabolism, glucose metabolism and fertility. Low zinc intake is associated with hyperinsulinemia, increased inflammation, and worse lipid profile like high LDL [25]. It stimulates lipogenesis and glucose transport through GLUT4. Zinc deficiency plays a significant role in the pathogenesis of PCOS and is a prognostic marker of the same [26]. Studies showed that the average serum zinc levels of PCOS patients are significantly lower compared with healthy controls. A recent study found that 4–50 mg of Zn supplementation 1–2 times daily for 8–12-week improved IR and lipid profiles in women with PCOS, and reduced CRP, oxidative stress (MDA). Reductions in fT, FSH, and DHEA-Sulphate were also noted [27].

2.2.4 *Iron*

Iron is a trace element and is vital for human life for oxygen transport. It is an important cofactor of Haemoglobin. Serum ferritin concentrations are increased in some women with PCOS, especially in them who are insulin resistant [28]. This mild iron overload may be due to acquired or genetic iron-sparing mechanisms due to oligomenorrhea, or increased iron absorption from decreased hepcidin. Studies revealed insulin sensitivity and reduction in S. ferritin [29]. This suggests that body iron stores in PCOS are driven more by IR and hyperinsulinemia than by menstrual losses. However, studies examining the relations between iron metabolism and PCOS are ongoing [30].

2.2.5 *Chromium*

Chromium is a safe and highly tolerable trace element provided by dietary intake and dietary supplementation especially chromium picolinate. It is an essential element in glucose and insulin homeostasis. Studies have reported that 500–700 µg daily supplementation of Cr picolinate results in decreased blood glucose levels [31]. Some studies showed a positive impact of Cr supplementation on PCOS while other evidence revealed that Cr had unfavorable effects [32]. Meta-analysis revealed that Cr supplementation had no effect on FBS level but had a beneficial effect on fasting insulin. Random effect analysis revealed that supplementation had a beneficial effect on free testosterone but no effects on serum DHEA [3]. It also indicated that Cr supplementation could significantly reduce BMI. A meta-analysis by Onakpoya et al. including 11 RCTs showed that Cr could significantly reduce weight and body fat [5]. However, further research should be performed with higher doses, longer duration and with larger sample size to confirm the meaningful impact of Cr on insulin metabolism. It has been shown that PCOS is more common in subjects with insulin resistance, type 2 diabetes mellitus and metabolic syndrome. Cr supplementation has significantly decreased blood triglycerides and increased HDL [33].

2.3 *Role of Carnitine*

Carnitine is a quaternary ammonium compound synthesized from amino acids lysine and methionine [2]. It is involved in glucose and fatty acid metabolism. L-carnitine is responsible for β -oxidation of fatty acids. Women with PCOS are reported to have lower concentrations of L-carnitine, which has been associated with oocyte quality and accumulation of long chain fatty acids [6].

A daily dose of 3 g/Lcarnitine supplementation for 3 months improved insulin sensitivity, BMI, and reduced serum LDL in a study conducted on 80 women with PCOS [7].

2.4 Role of omega 3 fatty acids

It is an unsaturated fatty acid responsible for heart health. ω -3 fatty acids have anti-inflammatory, antioxidant, and antihypertensive properties and also regulate abnormal expression of some genes like decreased IGF1 signalling and increased COX2, worsening oocyte maturation. ω -3 fatty acids are found in fish oil supplements [34]. Granulosa cell cultures treated with 25–100 μ g of the ω -3 fatty acid EPA showed increased IGF-1 and lowered cyclooxygenase 2 (COX2) expression, both essential for follicle maturation and fertility [35].

III. HERBAL MEDICINE FOR MANAGING PCOS

Herbal medicine or supplements are naturally derived from plants and are often used for medicinal purpose. They have the ability to cure many diseases including PCOS that is discussed as follows. The main mechanisms of the effectiveness of medicinal plants in PCOS are not yet fully understood. Nevertheless, these mechanisms seem to improve the hormonal balance of LH, FSH, and testosterone, and enhance oxidative stress and metabolic disorders.

3.1 Curcumin:

Curcumin is a product derived from turmeric that reduces blood glucose level by inhibiting NF-kB pathway, attenuating TNF alpha and fatty acid levels. It activates PPAR γ and hepatic glycolysis [7]. 51 women reported improved IR on consuming 500 mg curcumin daily for 6 weeks and their fasting blood sugar levels decreased too. Curcumin had no effects on lipid metabolism as per studies [6].

3.2 Cinnamon:

Cinnamon or *Cinnamomum verum* and their bioactive agents extracted from it like eugenol, cinnamaldehyde can stimulate glycogen synthesis, glucose uptake by cells, and increase insulin sensitivity by activating insulin receptors by inhibition of dephosphorylation of the insulin receptors, altering the expression of PPAR- γ [36]. A study conveyed that cinnamon supplement decreased malondialdehyde level and elevated total serum antioxidant capacity thereby reducing oxidative stress [37]. Cinnamon supplementation along with celery decreases production of reactive oxygen species (ROS) from ovarian tissue, thus protecting against oxidative stress in PCOS [38].

Study conducted on 66 females showed improved IR, lowered LDL, regular menses on consuming cinnamon. Another study showed the same results along with lowered triglycerides and more HDL [2].

3.3 Pomegranate juice:

The fruit juice of *Punica granatum* or pomegranate is rich in flavonoids that improves gut microbiota and reduces oxidative stress; inflammation [39]. In a study, 86 women with PCOS consumed 300 mL of pomegranate juice for 8 weeks showed improved lipids, lowered blood pressure (BP), lowered IR, BMI, and testosterone [40].

3.4 Fenugreek:

Fenugreek and related compounds like linoleic acid decreased the level of LH by reducing leptin, nitric oxide, and gonadotropin [41]. A study conducted on 208 PCOS females for 12 weeks who were prescribed 1000mg fenugreek everyday showed improvements in levels of prolactin, FBS, testosterone, SHBG, LDL, and triglycerides and LH:FSH ratio; decreased number of cysts, hirsutism, and promoted regularity of menstruation; and reduced weight and circumference of hip: waist [42].

3.5 Black cumin:

Nigella sativa or cumin can reduce insulin, cholesterol, and triglyceride. A study on 10 females showed reduced cholesterol, TG, FBS, LH, LDL, FBS, insulin, and normalized the menstrual cycle. It regulated the menstrual cycles by decreasing the LH level in PCOS patients [43].

3.6 Spearmint, ginger, and citrus mixture:

They have anti-inflammatory and hypoglycaemic effects through active compounds that include camphene, flavonoids, and terpenoids [44]. Spearmint, ginger, and citrus mixture was consumed 100mg by 60 women with PCOS and infertility. This mixture with or without CC, improved serum antioxidant concentrations including catalase, glutathione peroxidase. Improvements were also observed regarding IR, FBG compared to CC alone. Mint has an antiandrogenic effect and restores follicular development [45].

3.7 Aloe vera, green tea:

Aloe vera, green tea (*Camellia sinensis*), chamomile (*Matricaria chamomilla*) and white mulberry (*Morus alba*) are medical herbs that regulate lipid and carbohydrate metabolism; thus, they can be used by all phenotypes of PCOS women. Green tea has endocrine properties and is extremely good in maintaining hormonal balance. It maintains LH, FSH levels in PCOS patients [46].

IV. COMPLEMENTARY THERAPIES FOR MANAGEMENT OF PCOS

Complementary therapies are those which are practiced along with intake medicine and proper diet to control PCOS. It is a natural booster for PCOS management and studies have shown various effects on patients.

4.1 Yoga:

Yoga, a mind-body therapy involves controlled breathing exercises and holding positions, often in a specific sequence and for a set amount of time. PCOS females were supervised for 12-weeks that included 90 one-hour sessions that included Suryanamaskar, asanas, pranayama breathing exercises, relaxation, and meditation in the yoga group [47]. Participants in the yoga group had lower LH, FI, IR, and AMH post-intervention. In an RCT with adult women with PCOS, the three-month intervention included a guided yoga class for one hour three days a week, with pranayama breathing exercises and meditation. Participants in the yoga group had lower fT, and lower DHEA [48]. Another systematic review identified 16 studies that suggested that yoga may have promising benefits for the management of stress, anxiety, fatigue, menstrual irregularity, concentrations of LH, FBG, lipids, testosterone, and IR [49]. In a more recent RCT, Mohseni et al enrolled 67 women with PCOS and reported that 90 min of daily yoga practice for 6-week reduced hirsutism and waist: hip circumference, but without improvements in BMI, BP, symptoms of acanthosis nigricans. The yoga study that investigated in adolescent girls with PCOS did find a decrease in LH and no change in FSH [50].

4.2 Aerobic Exercise:

In a three-month study, cycling for 30 min three days per week resulted in decreased fasting insulin levels with no significant changes in the sex hormones and SHBG [51]. Similar findings were reported following a 24-week structured program with the same cycling parameters, and the improved FI was not maintained in a 12-week program followed by 12-weeks of detraining. A six-month study that involved cycling for 45 min three days per week decreased FI and IR. A 16-week RCT with continuous aerobic training on a treadmill resulted in decreased total testosterone with no changes in SHBG, E2, LH, or FSH [52].

V. CONCLUSION

There are ample nutrient and related therapies that can manage PCOS. They are beneficial in ameliorating the adverse health outcomes associated with PCOS.

The exercise interventions studied to date do not appear to consistently alter LH or FSH. The effects observed on different patients vary greatly due to their lifestyle, genetics and the way they follow up. Vitamin supplementation could be inserted into the therapeutic options of PCOS women regardless of BMI because of its cost effectiveness. The review describes the roles of these therapies on certain patients according to the studies conducted. More studies are going on to correlate the exact mechanisms behind the role of vitamins, herbs, yoga on PCOS patients. Studies has to be conducted on large scale of patients to come to a clear conclusion.

VI. LIST OF ABBREVIATIONS

PCOS- Polycystic Ovary Syndrome

IR- Insulin Resistance

LH- Luteinizing Hormone

FSH- Follicle Stimulating Hormone

SHBG- Sex Hormone Binding Globulin

RCT- Randomized Control Trial

E2- Estradiol

FBS/FBG- Fasting Blood Sugar/ Glucose

TSH- Thyroid Stimulating Hormone

fT – Free Testosterone

DHEA- Dehydroepiandrosterone

COX2- Cyclooxygenase 2

IGFR1- Insulin Growth Factor Receptor 1

AMH- Anti Mullerian Hormone

REFERENCES

- [1] Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocr Rev* 2016;37(5):467–520.
- [2] Simon Alesi, Carolyn Ee, Lisa J Moran, Vibhuti Rao, and Aya Mousa. Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome; *Nutr* 2022; 13:1243–1266.
- [3] Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies. *Hum Reprod* 2016;31(11):2619–31.
- [4] Jeanes YM, Reeves S, Gibson EL, Piggott C, May VA, Hart KH. Binge eating behaviours and food cravings in women with polycystic ovary syndrome. *Appetite* 2017; 109:24–32.

- [5] Szczuko, M.; Zapalowska-Chwyć, M.; Maciejewska, D.; Drozd, A.; Starczewski, A.; Stachowska, E. Significant Improvement Selected Mediators of Inflammation in Phenotypes of Women with PCOS after Reduction and Low GI Diet. *Mediat. Inflamm.* 2017, 2017, 5489523.
- [6] Barber, T.M.; Kyrou, I.; Randeva, H.S.; Weickert, M.O. Mechanisms of Insulin Resistance at the Crossroad of Obesity with Associated Metabolic Abnormalities and Cognitive Dysfunction. *Int. J. Mol. Sci.* 2021, 22, 546.
- [7] Kempegowda, P.; Melson, E.; Manolopoulos, K.N.; Arlt, W.; O'Reilly, M.W. Implicating Androgen Excess in Propagating Metabolic Disease in Polycystic Ovary Syndrome. *Adv. Endocrinol. Metab.* 2020, 11.
- [8] Eshre TR, Asrm-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1): 19–25
- [9] Ozcan Dag Z, Alpua M, Isik Y, Buturak SV, Tulmac OB, Turkel Y. The evaluation of temperament and quality of life in patients with polycystic ovary syndrome. *Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology.* 2017;33(3):250–3.
- [10] Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod.* 2016;31(12): 2841–55.
- [11] Celik O, Acbay O. Effects of metformin plus rosuvastatin on hyperandrogenism in polycystic ovary syndrome patients with hyperlipidemia and impaired glucose tolerance. *J Endocrinol Investig.* 2012;35(10):905–10.
- [12] Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007;370(9588):685–97.
- [13] Ong M, Peng J, Jin X, Qu X. Chinese herbal medicine for the optimal management of polycystic ovary syndrome. *Am J Chin Med.* 2017;45(03):405–22.
- [14] Mokaberinejad R, Zafarghandi N, Bioos S, Dabaghian FH, Naseri M, Kamalinejad M, et al. *Mentha longifolia* syrup in secondary amenorrhea: a double-blind, placebo-controlled, randomized trials. *Daru.* 2012;20(1):97.
- [15] Michael, P.J.; Stepani'c, V.; Nadja, T.; Panek, M.; Verbanac, D. Mild Plant and Dietary Immunomodulators. *Nijkamp Parnham's Princ. Immunopharmacol.* 2019, 561–587.
- [16] Ferro, D.; Baratta, F.; Pastori, D.; Cocomello, N.; Colantoni, A.; Angelico, F.; Del Ben, M. New Insights into the Pathogenesis of Non-Alcoholic Fatty Liver Disease: Gut-Derived Lipopolysaccharides and Oxidative Stress. *Nutrients* 2020, 12, 2762.
- [17] Giallauria, F.; Palomba, S.; Maresca, L.; Vuolo, L.; Tafuri, D.; Lombardi, G.; Colao, A.; Vigorito, C.; Francesco, O. Exercise training improves autonomic function and inflammatory pattern in women with polycystic ovary syndrome (PCOS). *Clin. Endocrinol.* 2008, 69, 792–798.
- [18] Buscemi S, Buscemi C, Corleo D, De Pergola G, Caldarella R, Meli F, et al. Obesity and circulating levels of vitamin d before and after weight loss induced by a very low-calorie ketogenic diet. *Nutrients.* 2021;13(6).
- [19] Kaminska K, Grzesiak M. The relationship between vitamin D3 and insulin in polycystic ovary syndrome - a critical review. *J Physiol Pharmacol.* 2021;72(1).
- [20] Barrea L, Verde L, Vetrani C, Savastano S, Colao A, Muscogiuri G. Chronotype: a tool to screen eating habits in polycystic ovary syndrome? *Nutrients.* 2022;14(5).
- [21] Muscogiuri G, El Ghoch M, Colao A, Hassapidou M, Yumuk V, Busetto L, et al. European guidelines for obesity management in adults with a very low-calorie ketogenic diet: a systematic review and meta-analysis. *Obes Facts.* 2021;14(2):222–45.
- [22] Barrea L, Verde L, Vetrani C, Marino F, Aprano S, Savastano S, et al. VLCKD: a real time safety study in obesity. *J Transl Med.* 2022;20(1):23.
- [23] Małgorzata Szczuko, Justyna Kikut, Urszula Szczuk, Iwona Szydlowska, Jolanta Nawrocka-Rutkowska, Maciej Zi'etek, Donatella Verbanac and Luciano Saso: Nutrition Strategy and Life Style in Polycystic Ovary Syndrome—Narrative Review. *Nutrients* 2021, 13, 2452.
- [24] Heimann, E.; Nyman, M.; Pålbrink, A.-K.; Lindkvist-Petersson, K.; Degerman, E. Branched Short-Chain Fatty Acids Modulate Glucose and Lipid Metabolism in Primary Adipocytes. *Adipocyte* 2016, 5, 359–368.
- [25] Matijašić, M.; Meštrović, T.; Perić, M.; Cipićić Paljetak, H.; Panek, M.; Vranešić Bender, D.; Ljubas Kelečić, D.; Krznarić, Ž.; Verbanac, D. Modulating Composition and Metabolic Activity of the Gut Microbiota in IBD Patients. *Int. J. Mol. Sci* 2016, 17, 578.
- [26] Kazemi, M.; Hadi, A.; Pierson, R.A.; Lujan, M.E.; Zello, G.A.; Chilibeck, P.D. Effects of Dietary Glycemic Index and Glycemic Load on Cardiometabolic and Reproductive Profiles in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv. Nutr.* 2021, 12, 161–178.
- [27] Martino, G.; Catalano, A.; Bellone, F.; Sardella, A.; Lasco, C.; Capri, T.; Langher, V.; Caputo, A.; Fabio, R.A.; Morabito, N. Vitamin D status is associated with anxiety levels in postmenopausal women evaluated for osteoporosis. *Mediterr. J. Clin. Psychol.* 2018, 6.
- [28] Azziz R, Marin C, Hoq L, Badamgarav E, Song P. 2005. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. *The Journal of Clinical Endocrinology and Metabolism* 90(8): 4650–4658.
- [29] Costello M, Shrestha B, Eden J, Johnson N, Moran LJ. 2007. Insulin-sensitising Drugs versus the Combined Oral Contraceptive Pill for Hirsutism, Acne and Risk of Diabetes, Cardiovascular Disease, and Endometrial Cancer in Polycystic Ovary Syndrome. *The Cochrane Library.*
- [30] Hussain, A., Polycystic Ovary Syndrome-diagnosis and treatment. 2015.
- [31] Onakpoya, I., P. Posadzki, and E. Ernst, Chromium supplementation in overweight and obesity: a systematic review and meta-analysis of randomized clinical trials. *Obesity Reviews*, 2013. 14(6): p. 496–507.
- [32] Ashoush, S., et al., Chromium picolinate reduces insulin resistance in polycystic ovary syndrome: Randomized controlled trial. *Journal of Obstetrics and Gynaecology Research*, 2015.
- [33] Jeejeebhoy, K.N., et al., Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. *The American Journal of Clinical Nutrition*, 1977. 30(4): p. 531–538.
- [34] Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J et al. 2004. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Annals of Internal Medicine* 140:778 – 785.

- [35] Pelusi B, Gambineri A, Pasquali R. 2004. Type 2 diabetes and the polycystic ovary syndrome. *Minerva Ginecologica* 56:41 – 51.
- [36] Hajimonfarednejad M, Nimrouzi M, Heydari M, Zarshenas MM, Raei MJ, Jahromi BN. Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: a randomized doubleblind placebo controlled clinical trial. *Phytother Res.* 2018;32(2): 276–83.
- [37] Grant P. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial. *Phytother Res: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives.* 2010;24(2):186–8.
- [38] Zhang J, Li T, Zhou L, Tang L, Xu L, Wu T, Lim DCE. 2010a. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. *The Cochrane Database Of Systematic Reviews* 9: CD007535.
- [39] Singh, S., Kooy, C., Der Kroy, F. (2013). Chemical characterisation of a herbal formulation for the treatment of polycystic ovary syndrome. Academic thesis (Bachelor of Medical Science Honours 1A), University of Western Sydney.
- [40] Moran LJ, Hutchison SK, Norman RJ, Teede HJ. 2011. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2: CD007506.
- [41] Kamel HH. 2013. Role of phytoestrogens in ovulation induction in women with polycystic ovarian syndrome. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 168(1): 60–63.
- [42] Arentz S, Smith CA, Abbott JA, et al. 2014b. A survey of the use of complementary medicine by a self-selected community group of Australian women with polycystic ovary syndrome. *BMC Complementary and Alternative Medicine* 14(1): 472.
- [43] Greenlee H, Atkinson C, Stanczyk FZ, Lampe JW. 2007. A pilot and feasibility study on the effects of naturopathic botanical and dietary interventions on sex steroid hormone metabolism in premenopausal women. *Cancer Epidemiology Biomarkers and Prevention* 16(8): 1601–1609.
- [44] Hickson SS, Miles KL, McDonnell BJ, Cockcroft JR, Wilkinson IB, McEnery CM. 2011. Use of the oral contraceptive pill is associated with increased large artery stiffness in young women: the ENIGMA study. *Journal of Hypertension* 29(6): 1155–1159.
- [45] March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ, Davies MJ. 2010. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Human Reproduction* 25(2): 544–551.
- [46] Bone K, Morgan M. 1996. *Clinical Applications of Ayurvedic and Chinese Herbs: Monographs for the Western Herbal Practitioner.* Phytotherapy Press: Queensland, Australia.
- [47] Thomson, R.L.; Buckley, J.D.; Noakes, M.; Clifton, P.M.; Norman, R.J.; Brinkworth, G.D. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 2008, 93, 3373–3380.
- [48] Grei Shele, Jessica Genkil and Diana Speelman: A Systematic Review of the Effects of Exercise on Hormones in Women with Polycystic Ovary Syndrome. *J. Funct. Morphol. Kinesiol.* 2020, 5, 35.
- [49] Nidhi, R.; Padmalatha, V.; Nagarathna, R.; Ram, A. Effect of a yoga program on glucose metabolism and blood lipid levels in adolescent girls with polycystic ovary syndrome. *Int. J. Gynaecol. Obstet.* 2012, 118, 37–41.
- [50] Welt, C.K.; Carmina, E. Clinical review: Lifecycle of polycystic ovary syndrome (PCOS): From in utero to menopause. *J. Clin. Endocrinol. Metab.* 2013, 98, 4629–4638.
- [51] Teede, H.J.; Deeks, A.A.; Moran, L.J. Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med.* 2010, 8, 41.
- [52] Farrell, K.; Antoni, M.H. Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: Biobehavioral mechanisms and interventions. *Fertil. Steril.* 2010, 94, 1565–1574.