Pharmacotherapy and Neoteric Dietary Approaches for Polycystic Ovary Syndrome: A Systematic Review

Polikistik Over Sendromu İçin Farmakoterapi ve Neoterik Diyet Yaklaşımları: Sistematik Bir Derlemesi

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Abstract
Polycystic ovary syndrome (PCOS) is an ovarian disorder secondary to the dysregulated hypothalamic-pituitary-adrenal axis leading to androgen excess. Numerous studies have documented that insulin resistance is the key pathophysiological element for the development of PCOS. Insulin acts synergistically with luteinizing hormone (LH) to increase androgen production in the theca of the follicles. PCOS is the most malignant endocrine disorder affecting females (7%; from adolescence to menopause). Clinical hallmarks in PCOS are dyslipidemia, impaired glucose tolerance, hyperandrogenism, microcysts in ovaries, menstrual irregularities, anovulation, and obesity. During clinical examination, a woman’s identity is markedly threatened due to hirsutism, acne, alopecia, obesity, irregular menses, and infertility symptoms. Diagnosis is based on European Society for Human Reproduction and Embryology/The American Society for Reproductive Medicine or Rotterdam consensus criteria. In this article, we present a precise and comprehensible glimpse of updated and efficient patient management via pharmacotherapy and diet therapy with the most practicable type of diets and their positive outcomes. Nutrients (inositol, isoflavonoids, omega-3) and their dose regimens are discussed. A calorie deficit of 500-1,000 kcal based on the patient profile has proven effective in re-vamping biochemical values and weight loss.

Keywords: PCOS; metformin; clomiphene; genistein; dyslipidemia; androgen

Anahtar kelimeler: PKOS; metformin; klomifen; genistein; dislipidemi; androgen

Özet
Polikistik over sendromu (PKOS), androjen fazlalığına yol açan hipotalamus-hipofiz-adrenal aksidaki bozulmaya se-konder bir over hastalıkıdır. Çok sayıda çalışma, insülin di-rencinin PKOS gelişiminde anahtar patofizyolojik unsur olduğunu ortaya koymıştır. İnsülin, folikülerlerin teka hücrelerinde androjen üretimini artırarak luteinize edici hormon (LH) ile sinerjik olarak hareket eder. PKOS, kadınların etkileyen (%7; ergenlikten endişelen de kızıl adetlen de kızıl) en kötü huylu endokrin bozukluktur. PKOS, yüksek androjen seviyeleri, düzeniz adetler, mikrokist oluşumu ve infertilite ile karakterize olan çocuk organ bozukluklarına neden olur. PKOS’un manifestasyonu polikistik overler (morfoloji), hiperandrogenemi ve hipperl inadvertently (metabolik bozukluklar) olarak belirlenir. PKOS’un klinik karakteristikleri dislipidemi, bozulmuş glukoz tolernansı, hiperandrojenizm, overde mikrokistler, adet dü-zensizlikleri, anovülasyon ve obezitedir. Klinik muayenede, kadınların özelliklerinin hirsutizm, akne, alopesia, obezite, dü-zensiz adet kanaması ve kısalık semptomları nedeniyle önemli ölçüde tehdit altında olduğu görülmektedir. Tani, Avrupa İnsan Üremini ve Embrilioloji Derneği (ESHRE)/Amerikan Üreme Tibbı Derneği (ASRM) veya Rotterdam konsensüsü kriterleri- ne dayanmaktadır. Bu yüzden, en uygulanabilir diyet türleri ve olumlu sonuçları ile diyet tedavisi ve farmakoterapi üzerinde genelde mesajımı ve etkili hata yönetimi dair kesin ve anlaşılmır bir başık sunmuştur. Besinler (inositol, izoflavonoid- ider, omega-3) ve bunların doz rejimleri tartışılmasıdır. Hasta profiline göre 500-1.000 kcal’lık bir kalori ağını, biyokim- yasal değerlere düzeltmesinde ve kilo kaybında etkili olduğu kanıtlanmıştır.

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Introduction
Polycystic ovary syndrome (PCOS) is the most malignant endocrine disorder affecting women (7%; from adolescence to menopause) (1). PCOS results in multi-organ derangements categorized by raised androgen levels, irregular menses, and infertility with microcysts formation. The manifestation of PCOS can be specified as polycystic ovaries (morphological), hyperlipidemia (metabolic derangements), and hyperandrogenemia (2). Clinical hallmarks in PCOS are dyslipidemia, impaired glucose tolerance, hyperandrogenism, microcysts in ovaries, menstrual irregularities, anovulation, and obesity. During clinical examination, a woman’s identity is markedly threatened due to hirsutism, acne, alopecia, obesity, irregular menses, and infertility symptoms (3). Diagnosis is based on the European Society for Human Reproduction and Embryology/The American Society for Reproductive Medicine (ESHRE/ASRM) or the 2003 Rotterdam consensus criteria. In this article, our objective is to present a precise and comprehensible glimpse of updated and efficient patient management via pharmacotherapy and diet therapy with the most feasible types of diets and their positive outcomes. Nutrients (inositol, isoflavonoids, omega-3) are discussed along with their dose regimen. A calorie deficit of 500-1,000 kcal based on the patient profile is effective in revamping biochemical values and weight loss (4).

Methodology
We conducted a joint literature search using PubMed, Elsevier, and Google Scholar for the period 2000 to 2020. Keywords used were PCOS, infertility, metformin, omega-3, nutraceuticals, insulin resistance, and diet therapy. Papers in the English language alone were considered. Initially, over 100 articles were reviewed, but only 23 research papers were shortlisted based on their acceptability and our set criteria. PRISMA flow chart diagram describes the selection of studies (Figure 1). A literature review aimed to highlight the importance of potential nutrients and types of diets with the most positive outcomes in the early management of PCOS. The ability of nutraceuticals was found to significantly ameliorate complications of PCOS and the prognosis of medical nutrition therapy.

Presentation
National Institute of Health (NIH), in 1990, proposed a list of internationally accepted diagnostic criteria. According to these criteria, both hyperandrogenemia and oligoanovulation, are mandatory to diagnose PCOS (5). However, NIH criteria were revisited by the ESHRE and ASRM in 2003. NIH 2012 and Androgen Excess Society 2006 guidelines are listed in Table 1. The revised criteria, internationally known as Rotterdam consensus criteria, are now widely used in the diagnosis and requires a minimum of two of the following three features to confirm PCOS: (i) Clinical or biochemical hyperandrogenism, (ii) anovulation/oligomenorrhea, and (iii) polycystic ovaries on ultrasound, with the exclusion of conditions having similar presentation (6). Polycystic and ovarian volume >10 mL in the absence of a dominant follicle or ovaries on ultrasound was defined as 12 or more follicles measuring 2-9 mm in at least one ovary. Nevertheless, as PCOS remains a diagnosis of exclusion, other endocrinopathies with similar presentation to PCOS should always be considered. PCOS is an ovarian disorder secondary to the dysregulated hypothalamic-pituitary-ovarianaxis leading to androgen excess (9). Numerous studies have also specified that insulin resistance is the key pathophysiological element for the development of PCOS. Insulin acts synergistically with luteinizing hormone (LH) to increase androgen release in the theca cells of the ovarian follicles (10). Raised levels of LH pulse frequency and an elevated ratio of LH to the follicle-stimulating hormone (FSH) in many women are reported. This abnormality of gonadotrophins is responsible for many of the ovarian features of PCOS, including increased androgen synthesis (11). Hyperandrogenism characteristically varies with race and ethnicity, but the most common manifestations include menstrual irregularities (predominantly oligomenorrhoea), hirsutism, central obesity, and even frontal alopecia (12-15). Furthermore, pregnant women with PCOS carry a greater risk of de-
veloping complications such as hypertensive disorders, gestational diabetes, premature delivery, and congenital abnormalities in their neonates (16). Due to underlying metabolic and hormonal disturbances associated with PCOS, women are more susceptible to cardiovascular diseases, particularly hypertension (HTN) (17,18). Wild et al. documented in a cohort study an increased prevalence of HTN in subjects with PCOS (19). Nevertheless, the association between hypertension and PCOS remains inconclusive as few studies have reported a counter link between systolic arterial pressure and insulin sensitivity in the subjects with PCOS (20).

**Treatment**

As the primary source of PCOS remains elusive, medication is usually directed at symptoms, such as menstrual irregularities, hirsutism, infertility, and psychological issues. The first step in management for PCOS is lifestyle modification, including diet and exercise, to reduce weight. Weight loss not only helps to decrease levels of androgen, LH, and insulin but also aids in regulating ovulation, thereby improving the chances of pregnancy (21). The treatment plan should be customized to individual patients. Bariatric surgery may be considered in obese patients and cases requiring lifestyle modifications.

**Induction of Ovulation in PCos**

PCOS is the principal cause of 70% of all anovulatory-related types of infertility (22). Hart et al. reported that infertility was ten times more common among women with PCOS in comparison to healthy controls.
For women without any plans for children, long term control can be achieved with oral contraceptive pills (OCPs). In individuals with reproductive desires, ovulation can be induced by several methods. Recently, clomiphene citrate (CC) has been universally acknowledged as the first-choice drug for inducing ovulation in PCOS individuals. After binding to estrogen receptors on the hypothalamus, the CC makes an antiestrogenic effect and stimulates a gonadotropin-releasing hormone pulse that induces gonadotropin secretion from the anterior pituitary gland. Although up to 15-40% of patients with PCOS show resistance to CC; anovulation persists despite treatment for three successive months, and such patients are considered to be “clomiphene-resistant” (24).

Interestingly, a recent study has documented an alternative therapy of gonadotrophins as standard second-line treatment (25). The study formulated a new CC treatment protocol, named “intermittent CC treatment (ICT) for non-responders to standard CC therapy (25). Under the protocol, the non-responders for five days were given 100 mg/day of CC for 1-3 months depending on follicular growth (size >10 mm), observed after completion of each phase of CC treatment. When the diameter of the follicle reached ≥18 mm, ovulation was induced by injecting 10,000 IU of human chorionic gonadotropin (hCG). Overall, ICT was effective in around 80% of the CC-resistant PCOS patients. However, gonadotrophins, letrozole, and laparoscopic ovarian diathermy therapies are also recommended in “clomiphene-resistant” subjects (24).

Role of Antiandrogens in the Treatment of Hirsutism

Hirsutism, a common manifestation in women with PCOS, is defined as an unnecessary growth of terminal hair at androgen-dependent areas in females analogous to male pattern. It can be managed in several ways, including by spironolactone, flutamide, finasteride, oral contraceptive pills, and laser beam. Souter et al. reported a diagnosis of PCOS on further evaluation in approximately 50% of women, who complained of unwanted excess facial hairs (26). Androgen excess is predominantly responsible for hirsutism, and thus, antiandrogens offer an excellent choice to counter hyperandrogenism effects. Competitive in-
hibitation of androgen-binding receptors or 5-alpha-reductase inhibitors decreases androgen production. Spironolactone is the most commonly used antiandrogen drug (standard dose, 25-100 mg/day), generally well-tolerated, and has shown more efficacy on hirsutism than by use of OCPs (27). Flutamide 250 mg/day and finasteride 5 mg/day are other antiandrogens but are inferior to spironolactone in terms of efficacy (28). Contraception is recommended when patients use antiandrogens for the treatment of PCOS as these drugs pose a risk to the developing male fetus (opposing genital formation). Hirsutic women usually show clinical improvement approximately six months after treatment with OCPs and also present an enhanced clinical effect when OCPs are combined with antiandrogens. Ezeh et al. found that combined treatment with OCP and spironolactone showed greater improvements than with either drug individually (29).

Role of Metformin in PCOS

To date, numerous studies have reported on the vital role of hyperinsulinemia in the development of metabolic abnormalities in PCOS, regardless of body weight index (30,31). Metformin, a biguanide, acts to improve insulin sensitivity and thus lowers free circulating insulin as well as androgens in the bloodstream, resulting in improvement of the clinical sequelae of PCOS (32). However, despite a well-established role in the management of PCOS, conflicting results regarding its efficacy are found in the literature.

Wahab et al. conducted a study (33) on 35 female patients with established PCOS, age 20-35 years. They were given metformin (850 mg twice a day). In order to improve compliance, at every follow-up visit, patients were educated properly regarding the use of metformin. A final assessment was completed two years later with repetition of the transvaginal scan and reevaluation of all laboratory values (random blood glucose, serum insulin, LH/FSH, testosterone, prolactin, etc.). Metformin therapy for two years has shown improvements in the laboratory values. Furthermore, metformin is an effective drug to improve menstrual irregularities, LH, FSH, and testosterone, as indicated in this study (33). Similarly, numerous studies have reported that insulin-sensitizing drugs and dietary/lifestyle modifications improve not only hyperandrogenism but also menstrual irregularities, rate of ovulation, fertility, hirsutism, and weight in patients suffering from PCOS (34-36); these findings are confirmed in the current study. However, two recently published meta-analyses and systematic reviews (in which metformin efficacy was evaluated in improving reproductive outcomes for women with PCOS) concluded no significant evidence of improved rates of live births and clinical pregnancy with metformin alone or in combination with clomiphene (37,38).

In summary, metformin is an appropriate choice and plays a positive role in improving menstrual irregularities and weight reduction in females with PCOS, but current findings do not suggest its use as a first-line drug for ovulation induction. For medical practitioners, we outlined a schematic representation of an efficient clinical approach for PCOS patients in Figure 2. This provides quick insight into the management of PCOS assessment and treatment protocols.

Role of Diet Therapy in PCOS

Though PCOS is associated with overweight, central obesity with insulin resistance is markedly prevalent. In this article, we focused on how macronutrients and micronutrients strongly influence PCOS management. We also highlight the relationship of the type of diet with PCOS and the importance of calorie deficit for the treatment of PCOS. Besides nutritional management and pharmacotherapy, genetics, lifestyle, and ethnicity have a strong influence on the outcomes. Increased insulin resistance causes the overproduction of androgens in response to LH in ovaries. Previous studies confirm the significant role of short term calorie deficit therapy in correcting LH levels and menstrual irregularities. Levels of leptin (energy expenditure hormone) and ghrelin (ligand-increase appetite) levels get deranged in PCOS and can be corrected via calorie deficit therapy (39). Nutritional assessment and biochemical lab findings, along with physical assessment conducted by registered dietitian/nutritionist (RDN), calculates patient BMI and BMR according to
Harris-Benedict Equation. Based on the patient profile, the Dietitian (RDN) recommends a daily calorie deficit of 500-1,000 kcal.

Inositol present in whole grains, seeds, and fruits has two isomers D-chiro-inositol and Myo-inositol. Myo-inositol, a nutrient, belongs to the vitamin B complex. Studies have indicated the beneficial role of Myo-inositol in correcting hormonal profile, oxidative stress, and metabolic factors among PCOS patients. The dose of 4 g/d Myo-inositol along with 400 mcg/d folic acid has shown proven effects in diminishing serum androgen levels and improving glucose tolerance (40). Administration of 2-3 g/d myo-inositol plus 200 mcg/d folic acid has a beneficial role in the amelioration of plasma LH (41). D-chiro-inositol improves glucose levels and enhances uptake via post-receptor mediation of inositol phosphoglycans (IPGs), a mediator of insulin signaling pathways (42). Administration of 600-1,200 mg/dL D-chiro-inositol (DCI) for a period of 6 to 12 weeks in PCOS patients has shown positive outcomes with improving insulin resistance, serum androgen levels (43). Isoflavonoids (genistein and daidzein) found in soybean, chickpeas have promising effects on LDL-c levels. Administration of 18 mg genistein (twice a day) for three months significantly lowers LDL-c profile. Isoflavonoids also have

Diary guidelines for PCOS: 30-60 min moderate to intense exercise. Maintain a calorie deficit of 500 to 1,000 kcal based on patient profile. Achieve a 0.5 kg minimum weight loss per week.

Introduce fish (two servings) per week. Add LGI foods to the patient’s diet and remove HGI foods from the meal. Maintain blood sugar level with or without pharmacotherapy.

Figure 2. Schematic representation of an efficient and multipronged clinical approach for PCOS patients.

GI: Glycemic index; LGI: Low glycemic index; HGI: High glycemic index; FA: Fatty acid; FSH: Follicle stimulating hormone; IR: Insulin resistance; LH: Leutinizing hormone; BD: (bis in die in Latin) twice daily.
a positive impact on reproductive hormones (44). Mohammadi et al. conducted an 8-week study on 61 subjects of PCOS (overweight/obese) and administered omega-3 mcg/d in one group and compared placebo therapy in another group (45). A significant increase was reported in HDL. TC and LDL-c levels decreased, and insulin, glucose, and HOMA returned to optimum levels. Type of diets with the most feasible and positive outcomes are summarized in Table 2. However, the type of diet to be prescribed is based on individual nutritional assessments and biochemical lab reports. We strongly recommend calorie deficit therapy (500-1,000 kcal) for PCOS patients with monitoring at regular intervals. Calories from carbohydrates should range from 40-45%, the protein starts with 15% and may increase as per patient profile. Fats should not exceed 30% of total calories. Moderate to an intense exercise of 30 min or more is effective. Exercises such as brisk walk, swimming, arm exercise while seated in a chair for 10 min have been shown to improve glycemic control.

**Conclusion**

There is an urgent need to conduct extensive research at a genomic and molecular level to understand the pathophysiology of PCOS and the development of metabolic and cardiovascular outcomes in women suffering from the disorder. PCOS is a complex disorder, and the pharmacological approach is limited to the presentation and concern of the patient since the etiology of the disorder remains poorly understood. Nutraceuticals have offered new opportunities for PCOS management and show promising results.
(such as omega-3, myo-inositol, folic acid, vitamin-D, and calorie deficit diet therapy); all reduce weight and improve deranged reproductive hormones, insulin resistance, and lipid profile.

To sum up, this paper will be immensely useful for professionals and researchers and would offer a guidepost for future larger, multicentric, studies for the prevention and treatment of PCOS.

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**Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

**Authorship Contributions**


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