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The Metabolic and Reproductive Effect of Exercise and Diet in Obese PCOS Women : Let the Evidence Guide Us

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ABSTRACT

One of the most strongly related reproductive diseases in obese women is a polycystic ovarian syndrome. PCOS also suffer other comorbidities, such as insulin resistance. This review focus on identifying the metabolic and reproductive effect of diet and exercise in obese PCOS women. We searched for articles published from January 2004 to February 2022 and used electronic databases. We used the purposive sampling method then these articles were selected by inclusion and exclusion criteria. Lifestyle modification programs with an emphasis dietary and exercise interventions have been successful in reducing the risk of comorbidities in the general population and improving reproductive and metabolic features in PCOS. Lifestyle modification should be incorporated in treating obese PCOS patients to reduce their long-term risks for diabetes, hypertension, dyslipidemia, and cardiovascular disease and to increase the probability of spontaneous pregnancy. However, the specific guideline for lifestyle modification emphazising in diet and exercise for PCOS patients requires the large size of clinical trial research to find the best type of interventions in lifestyle modifications with the same outcome parameters.

KEYWORDS

PCOS; diet; execises; obesity; metabolism

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Introduction

The number of people with obesity in the world has nearly tripled in the last four decades, this number is worst by pandemic conditions. The statistic data released by National Health and Nutrition Examination Survey (NHANES) in 2020 that prevalence for worldwide of adult in the age ≥ 20 years old with overweight and obesity are 73,6% and 41.9% (Stierman, 2021). The obesity rate for adult women is 29% and the obesity rate for adult men is 27% based on Health Survey for England in 2019. Indonesia Basic Health Research in 2018 reported that the prevalence of obesity and overweight in adult is 28,7% and 13,5%. Women with obesity was higher (44,4%) than among men with obesity (26,6%).

Until now, obesity is still a well-known risk factor for establishing metabolic and cardiovascular disease (Poirier et al., 2006). Moreover, obesity can also develop some specific problems, including fertility-related disease (Kulie, 2011). One of the most strongly related reproductive diseases in obese women at reproductive age is Polycystic Ovarian Syndrome (PCOS) which can lead to infertility (Sirmans et al, 2014).

The prevalence of PCOS in 2013 was 15-20% among the worldwide population. This is a burden because its responsibility for 90-95% of cases of anovulatory infertility. PCOS patients also suffer other comorbidities, such as insulin resistance. Insulin resistance appears in 50-70% of PCOS women (Sirmans et al., 2014). It increases the risk factors as well as the prevalence of metabolic syndrome, impaired glucose tolerance, and type 2 diabetes mellitus among PCOS women (Teede et al., 2010). Moreover, 84% of obese PCOS patient in Indonesia is also suffering from insulin resistance which contributes to early cardiovascular disease (Pangaribuan et al, 2012).

An important role in managing PCOS is played by lifestyle modifications including weight management with the help of diet and exercise. Some of the studies found that specific diet and exercise help the fertility status of PCOS patients. But somehow, it is still a debate matter what type of lifestyle intervention should obese PCOS patient does (Kim, 2022).

The purpose of this review is to identify some of the studies which show evidence of some specific diet and exercise as an incorporated treatment in managing PCOS and how they affect the disease metabolically and/or reproductively.

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Method

The independent variable that we used in this research is weight management and exercise while the dependent variable is the reproductive effect of obese women with PCOS. We searched for articles published from 1 January 2004 to 20 February 2022 and used these electronic databases: EBSCO, Proquest, Gale, Pubmed, Google Scholar, and Medline. We used the search terms including "obesity", "lifestyle modification", "PCOS", "exercise", "physical activity", "diet", "biomolecular effect of diet and exercise".

Initial screening of article titles and abstracts was done by the members of the review. Relevant articles were obtained in full text and read independently by the review team members to determine eligibility for inclusion. Articles eligible for inclusion were reported in English or Bahasa Indonesian since 2004 and were researched from any methods of studies. Studies had to report the obese patient with PCOS, or diet management in PCOS patients, or exercise management in PCOS patients, or infertility caused by PCOS in obese patients.

A wide range of studies was included in the literature: meta-analyses, single research reports including randomised controlled trails, small non-randomised studies, clinical guidelines, the consensus view, expert advice, case studies, demographic information, and physiological principles.

Results and Discussion

Diagnostic Criteria for PCOS

Polycystic Ovarian Syndrome has some diagnostic criteria that have been made by three groups: the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD), the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), and the Androgen Excess and PCOS Society (Xu et al., 2010)[1]. These criteria are summarized in Table 1.

Table 1. Macroscopic Observations of *Candida albicans* on SDA Medium

NIH/NICHD 1992	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders
Includes all of the following: 1. Clinical and/or biochemical hyperandrogenism 2. Menstrual dysfunction	Includes two of the following: 1. Clinical and/or biochemical hyperandrogenism 2. Oligo-ovulation or anovulation 3. Polycystic ovaries	Includes all of the following: 1. Clinical and/or biochemical hyperandrogenism 2. Ovarian dysfunction and/or polycystic ovaries

Based on Table 1, we can diagnose a patient as a PCOS patient if the patient has clinical and/or biochemical hyperandrogenism and ovary dysfunction and/or polycystic ovaries. The hyperandrogenism-clinical symptom as the first criterion clearly defined by the symptom like hirsutism, skin darkening, acne, and hair loss (Kim, 2022) while ovarian dysfunction can be defined by the symptom like oligo-anovulation (reduced ovulation), irregular menstrual cycles, and infertility. These two criteria is not caused by androgen excess or another disorder.

Epigenetics in PCOS

Research conducted in 2010 found that the pathogenesis of PCOS can be caused by exposure to excessive androgen during fetal growth, which affects modification of DNA methylation and gene expression predisposes to PCOS (Xu et al., 2010). PCOS has a significant genetic basis based on the evidence from family–based and association studies, although the genes predisposing to PCOS have yet to be clearly defined. Those genes thought to involve the regulation of ovarian steroidogenesis influence body mass index (BMI) and adiposity (Barber et al, 2006).

Role of Obesity in Pathomechanism of PCOS

Obesity, especially the central type, plays an important role in developing PCOS through hypertrophic adipocytes and macrophage accumulation in adipose tissue (Pujanek et al., 2013). There is a variety of proinflammatory and antiinflammatory factors, including the adipokines leptin, adiponectin, as well as cytokines and chemokines, such as TNF-a and IL-6 (Fantuzzi G, 2005) that are produced and released usually by adipose tissue in an obese patient (Ellulu, 2015). These conditions happen because adipose tissue contains various immune cells, either adaptive or innate. So that's why the adipose tissue is now considered as a *bonafide* immune organ, at the cross-road between metabolism and immunity (Makki K, 2013).

Tumor necrosing factor alpha (TNF) can bind competitively with peripheral insulin receptor subunit an alter the binding of insulin with its receptor. This condition with high level of Interleukin 6 (IL-6) will cause insulin resistance (IR) and develops systemic insulin resistance (Pujanek et al, 2013). Finally, the body will suffer a condition called hyperinsulinemia (Gonzalez et al, 2012). Hyperinsulinemia will stimulate increased luteinizing hormone (LH) secretion in ovarium and increased the conversion of estradiol and estrone to androgen (Pujanek et al, 2013) which

will end in hyperandrogenism, the main pathomechanism in PCOS. Adrenal androgen production can also be promoted by high level of cortisol due to the chronic inflammation induced by proinflammatory factors, which will give negative feedback for hypothalamus-pituitary-adrenal (HPA) axis which will increase secretion of adrenocorticotropic hormone stimulate adrenal androgen secretion (Farrel et al, 2010). TNF and IL-6 also stimulate the decreased sex hormone binding globulin (SHBG) secretion (Pujanek et al, 2013). The decrease in SHBG secretion causes increment of peripheral androgen bioavailability which will cause signs of virilization (Legro RS, 2012).

The over-expressed pro-inflammatory cytokines in obesity can also cause releasing Reactive Oxygen Species (ROS) and increasing oxidative stress. Oxidative stress can lead the damage of any organ, such as reproductive organ (Susantiningsih, 2015). This conditions with the abnormality of androgen signaling that happens inside the body will cause defect in ovary follicle. Primordial folicles will experience a development discontinuity. Then, the folicles will place themself in peripheral ovary zone, which will create a string of pearls appearance shown on ultrasound examination. Defect in androgen signaling will also cause defect on gonadotropin regulation and ovulation disruption that will promote subfertility condition inside the patient's body (Rosenfield et al, 2011).

Leptin, a hormone that is capable of effectively reducing food intake and body weight, in obese patient is incompetent to exert its anorexigenic effect. The lack of clinical utility of leptin in obesity is defined as leptin resistance (Izquierdo AG, 2019). Leptin also can specifically bind with obesity receptor (Ob-R) that significantly affect weight gaining which will make the condition worse (Pujanek et al, 2013).

Current Treatment Strategy for Obese Women with PCOS

Until now, the management of PCOS is only to treat the symptoms that appear with medication and lifestyle modification. Some of the symptoms of androgen disorders, menstrual disorders, and infertility (Sirmans et al, 2014). Androgen disorders usually appear as acne, hirsutism, and alopecia. Hormonal contraceptive pills (HCPs) or antiandrogens are commonly used to correct acne and hirsutism (Sirmans et al, 2014). Hyperinsulinemia that appear from another effect of androgen disorder can be treated by insulin sensitizer like metformin (Badawy et al, 2011). PCOS patients who have complaints menstrual disorders have a high risk of endometrial hyperplasia and carcinoma. To prevent proliferation of the endometrium and improve menstrual cycle HCPs containing progestin and estrogen at low doses can be prescribed (Sirmans et al, 2014).

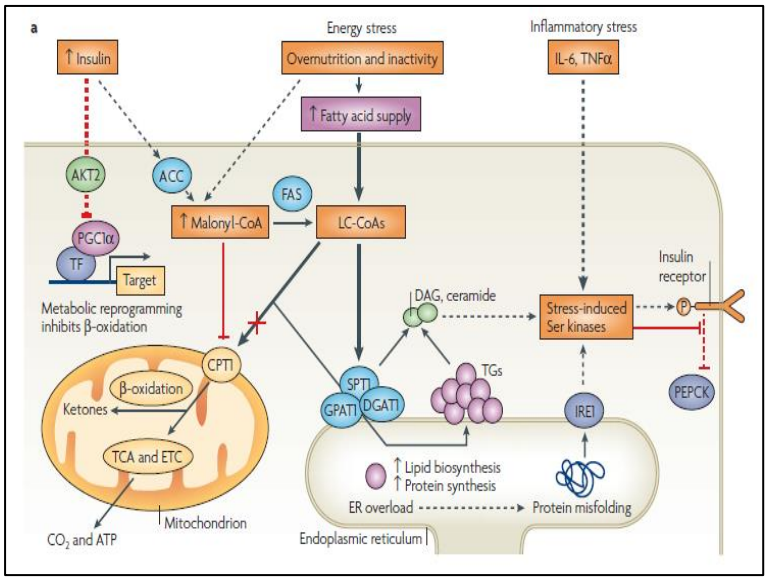
First-line treatment in patients with infertility is weight loss. Clomiphene citrate is the first choice of drugs used to induce ovulation (Badawy et al, 2011),. Although clomiphene is more effective, metformin can be used to increase in the rate of ovulation and pregnancy (Sirmans et al., 2014).

The possible second-line therapy infertil for PCOS patients are gonadotropin therapy and Laparoscopic Ovarian Drilling (LOD). Gonadotropin therapy is more preferred by women who do not want surgery. Meanwhile, LOD is preferred by women who are not able to follow a routine follow-up visit (Sirmans et al, 2014).

Third-line therapy recommended is In Vitro Fertilization (IVF). The pregnancy probability for infertile PCOS patients in this way is not much different from normal patients (Sirmans et al., 2014).

Biomolecular Effect of Diet and Exercise in Obese Women with PCOS

Liver is an essential metabolic organ that tightly controlled by insulin an other metabolic hormones. Glycolysis in the cytoplasm will metabolize glucose in to pyruvate and pyruvate is oxidized ATP in the mitochondria. Glycolytic products are used to synthesize fatty acids through lipogenesis in the fed state. the liver secretes glucose through breakdown of glycogenolysis and gluconeogenesis in the fasted state (Rui, 2014).

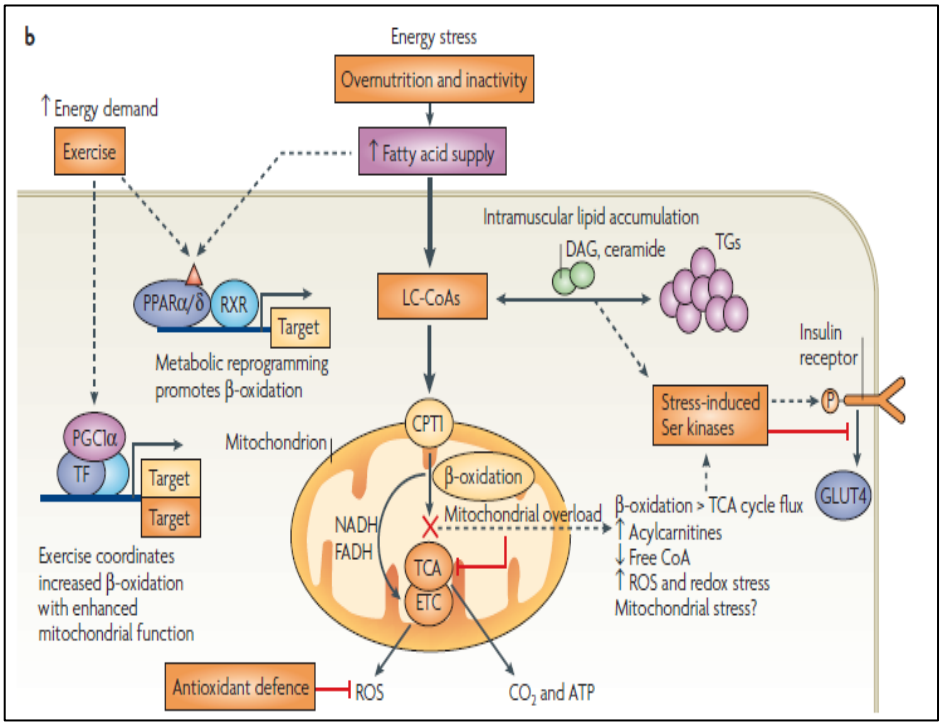


(Source: Muoio, 2008)

Figure 1. The metabolic overload caused by overnutrition and inactivity in liver

Overnutrition will increase the level of Coenzyme A (CoA) in every organ's cell. In the liver, elevated CoA level will stimulate new fatty acid synthesis and inhibit the activity of carnitine palmitoyltransferase-1. Biosynthetic enzymes will gain more long-chain acyl CoAs and produce more tiglycerids as well as signalling intermediates (for example, diacylglycerol and ceramide). Endoplasmic reticulum will have more heavy anabolic burden which contributes the occurence of protein misfolding and IRE1 activation. Together, these mechanisms will inhibit insulin-mediated suppression of gluconeogenesis through stress induced Ser kinases. In the contrary, they will stimulate more synthesis of lipid and inhibit β-oxidation (Muojo et al, 2008).

Meanwhile, in skeletal muscle, overnutrition will promote β-oxidation. It is stimulated by fatty acid influx and peroxisome proliferator-activated receptor (PPAR) α/δ-mediated activation of target genes. But, this promotion is not followed by an increase in tricarboxylic acid (TCA) cycle flux, so that the accumulation of acylcarnitines and reactive oxygen species exist in mitochondria. This accumulation is a result of metabolic by-products of incomplete fat oxidation. Ser kinases will be activated and it will hamper insulin signalling and glucose transporter-4 translocation (Muojo et al, 2008).



(Source: Muoio, 2008)

Figure 2. The metabolic overload caused by overnutrition and inactivity in skeletal muscle

ACC, acetyl CoA carboxylase; AKT2, Ser/Thr protein kinase; CPT1, carnitine palmitoyltransferase-1; DAG, diacylglycerol; DGAT1, diacylglycerol acyltransferase-1; ER, endoplasmic reticulum; ETC, electron transport chain; FAS, fatty acid synthase; GLUT4, glucose transporter-4; GPAT1, glycerol-3-phosphate acyltransferase-1; IL-6, interleukin-6; IRE1, inositol requiring kinase-1; LC-CoAs, long-chain acyl CoAs; PEPCK, phosphoenolpyruvate carboxykinase; PGC1α, PPARγ co-activator-1α; PPARγ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; RXR, retinoid X receptor; SPT1, serine palmitoyltransferase-1; TCA, tricarboxylic acid cycle; TF, transcription factor; TGs, triglycerides; TNFα, tumour necrosis factor-α.

Patients doing a calory restriction diet will decrease the CoA level so that the overnutrition-induced mechanism will be terminated. Meanwhile, patients doing exercise will have an increase in TCA cycle flux. It may compete lipid stress together with coupling ligand-induced PPARα/δ activity with PPARγ co-activator-1α-mediated remodeling of downstream metabolic pathways, which is also stimulated by exercise. These lifestyle modifications will finally result in improved mitochondrial performance, so that the sensitivity of insulin will be recovered (Muojo et al, 2008).

Beneficial chronic response effects of exercise can be reached after 8-12 weeks of regular physical activity. This chronic response can decrease oxidative stress as one of the PCOS pathomechanisms. The response can appear through several mechanism. The first is by improving proteasome activity and DNA-repairing enzyme activity. Proteasome will involve in oxidized protein proteolysis, so it will decrease the number of prooxidant. The involved DNA repairing enzymes are DNA glycosylase and uracil DNA glycosylase. There will be an increase in activity of both enzymes inside nucleus of myocyte and hepatocyte, followed by reduction of DNA mutation. Reduction of DNA mutation will make the cell more resistant to prooxidant attack. The next mechanism is by reducing DNA binding with sensitive transcription factors such as NF-κB, AP-1, MAPK, and CREB. This will result in inflammation reduction, which is related to prooxidant formation. The regular exercise is also able to increase enzymatic antioxidant activity

such as superoxide dismutase and glutathione peroxidase in hepatocytes. The mechanisms mentioned above will finally inhibit oxidative stress (Candrawati et al, 2012).

Weight Management for Obese Women with PCOS

Modest weight loss (5-10%) has been proved to help PCOS patient improved their metabolic and reproductive function. Weight management in PCOS patient not only assist importantly in weight loss along with symptoms appearance and fertility status but also long term health risk like CVD and type 2 diabetes (Marsh et al, 2005).

A study by Moran et al. in 2010 found that energy restriction followed by weight loss maintenance for 24 weeks reduces body fat up to 4 ± 2.2 kg, ($p < 0.05$). As we know hyperinsulinemia is one of major factor in developing PCOS, the subjects in this Moran's study have been shown lower insulin levels by 2.8 ± 1.1 mU/L, ($p < 0.05$). The subjects also shown reduction in total testosterone (0.3 ± 0.7 nmol/L, $p < 0.05$) and free androgen index (3.1 ± 4.6, $p < 0.05$) and improvement in menstrual cyclicity (57.1%). Low GI energy restriction also helps in improved menstrual cyclicity (Moran et al, 2010).

Oral anorexiant like sibutramine with and without diet therapy aid in 10% weight loss in the course of study and normalized OGTT in both groups ($p < 0.05$) also reduction free androgen index and testosterone in both groups but greater in sibutramine with diet therapy group ($p < 0.01$) (Florakis et al, 2007).

Another study in 2011 found the beneficial effect of walnut and almonds in metabolic and reproductive status of 31 obese women with PCOS. The decrease in apoprotein B is seen in both walnut ($p < 0.03$) and almond group ($p < 0.03$), also both group shown improvement in adiponectin. The studies also found that both groups shown improvement in their SHBG and free androgen index reduction (Kalgaonkar et al, 2010).

Some specific diet may have some effect in improving hormonal imbalances in PCOS like standard protein and high protein diet recommended by Danish Dietary Association. In this study both group appeared reduction in testosterone levels but greater in high protein diet (Sørensen et al, 2012). High protein diet also aid in lower fluctuation of blood glucose in PCOS obese patient (Douglas et al, 2006). Euvolemic and eucaloric meal in high protein increased cortisol and DHEA slower than simple glucose ($P < 0.01$) (Kasim-Karakas et al, 2007). Lowering carbohydrate also proved to be beneficial (Chavarro et al, 2007). A study with low carbohydrate diet with the macronutrient composition of 41% carbohydrate, 19% protein, 40% fat shows improvement in acute insulin level in obese PCOS patients ($p < 0.01$) and aid in faster weight loss ($p < 0.05$) (Kasim-Karakas et al, 2007).

Suplementation in vitamin D in obese women with PCOS helps improving the metabolic status such as blood pressure and total cholesterol ($p < 0.010$) (Pal et al, 2012). Suplementation with PUFA may also help PCOS patient. It is shown to have good metabolic and reproductive effect like increasing in plasma EPA ($p < 0.05$), reduction in bioavailable testosterone and androtenedione. In another study, PUFA also increases serum level of adiponectine, insuline, cholesterol, and trygliceride (Mohammadi et al, 2012).

Exercise Management in Obese Women with PCOS

The exercise that American College of Sports Medicine recommends is a minimum 150 minutes per week of moderate-intensity physical inactivity initially. This exercise is continued by a long-term weight loss 200-300 minutes per week are required or ≥2000 kilocalories (8400 kJ) with 500-1000 kilocalories energy intake reduction per day, concurrently with energy expenditure improvement (Stensel D, 2007). Another exercise that American College of Sports Medicine also recommends is low-moderate intensity (40-70% of maximum oxygen uptake) on minimum three non-consecutive days each week. The duration recommendation is 10-15 minutes initially then improved to 60 minutes per session over time (Stensel D, 2007).

The physical exercise program is the regular exercise that conducted in 16 wk, including brisk walking, cycling, or any other aerobic exercise at a self-selected pace described as "faster than normal walking at a pace that could be sustained for at least 30 min at least 3 days per week" found to be beneficial to decrease in estrone sulfate and 17β-diol-17 glucuronide ($p < 0.05$). There is also an improvement in menstrual frequency ($p < 0.05$)[46]. Especially with women with severe obesity, walking as exercise is considered less harmfull than high intensity aerobic training (Jedel et al, 2011).

Losing weight by exercise is more difficult in obese PCOS patients but regular exercise practiced at least 6 months improves weight loss. This has a beneficial because weight loss improves every parameter of PCOS (Khademi et al, 2010). Weight loss restores ovulation and pregnancy rates, diminishes acanthosis nigricans, improves psychological considerations, lowers testosterone levels while raising sex hormone binding globulin (SHBG) levels, and decreases insulin levels (Sirmans et al, 2014). Another study with 12 weeks of intensified aerobic exercise (3 h/wk) intervention showed that BMI was significantly reduced in PCOS ($P = 0.03$), total and abdominal fat mass were reduced after training ($P < 0.01$), visceral fat decreased in PCOS with exercise training ($P = 0.03$), insulin resistence (as measured by GIR) improved in PCOS after training by 16% ($P = 0.03$), and reduction in triglycerides (0.27 mmol/liter, $P = 0.02$) (Hutchison et al, 2011). Aerobic resistance exercise (three session of walking and two session of resistance training per week) when followed by 6000kj diet/day shows improvement in insulin sensitivity sensitivity ($p < 0.001$). We can also find an improvement level of testosterone, SHBG, FAI ($p < 0.001$) (Thomson et al, 2012).

In overweight and obese clomiphene citrate resistant PCOS patients, a 6-week intervention hypocaloric diet was effective in increasing the probability of ovulation under the treatment (Palomba et al, 2010). Moderate intensity exercise program in also gives beneficial metabolic effects such as an increase in peak VO_2 that indicates cardiorespiratory fitness, insulin sensitivity, and significant reduction in BMI (Sprung et al, 2012). An intervention of 12-week moderate intensity program in obese PCOS patients approximately 228 min/week at 40-60% peak VO_2 shows increase in peak VO_2 ($p = 0,033$), reduction of VLDL / chylomicrons concentration ($p = 0.007$), increase in large and

average HDL concentration (p = 0.002), and reduction of triglycerides and VLDL- triglycerides (p = 0.007) decrease in medium/small HDL (p = 0.031) (Brown et al, 2009).

Conclusion

The recommendation for weight management such as energy restriction followed by weight loss maintenance for 24 weeks, consumption of oral anorexiant like sibutramine, consumption of walnut and almonds, consumption of high protein and low carbohidrat, vitamin D and PUFA supplementation. This management can reduce the androgen level and improve the insulin level. Execise management that the previous research recommends is minimum 150 minutes per week of moderate intensity followed by a long-term weight loss 200-300 minutes per week. This lifestyle modification improves many aspects of PCOS although normal body mass index is not even reached. Even a few percent of weight reduction has clinical benefits. This clinical benefits happen because visceral fat is metabolically more active, and weight loss of a few percent is associated with significant loss of visceral fat.

Considering the reproductive and metabolism parameters measured in studies above, in treating obese PCOS patients, lifestyle modification should be incorporated to reduce their long-term risks for diabetes, dyslipidemia, hypertension, dyslipidemia, cardiovascular disease, and to increase the probability of spontaneous pregnancy. . However, the specific guideline for lifestyle modification emphazising in diet and exercise for PCOS patient needs futher research and investigation especially the large size of clinical trial research to find the best type of interventions in lifestyle modifications with the same outcome parameters.

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