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Effect of inositol and hypocaloric diet in PCOS

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Abstract

We conducted a longitudinal study to assess the effect of inositol and hypocaloric diet on body weight, free androgen index (FAI), and hormonal and metabolic parameters in obese women with polycystic ovary syndrome (PCOS). 36 participants were selected by convenience sampling and were advised to take 1200 mg of inositol oral administration daily and to follow a hypocaloric diet <1000 kcal/day for 8 weeks. The base line and 8 week post intervention the Body mass index, body weight, and hormonal and metabolic parameters were assessed and compared. The data were analysed using Epi info 7 software. The paired t test was used to compare the mean values. After eight weeks, participants experienced significant weight loss. There was also a trend towards a reduction in FAI. There was a significant increase in the sex-hormone-binding globulin and reductions in fasting blood glucose and waist-to-hip ratio. The inositol and hypocaloric diet has resulted in significantly greater weight reduction and was accompanied by more pronounced improvements in hyperandrogenaemia, body composition, and several metabolic parameters in obese women with PCOS as compared to the energy deficit approach.

Keywords: PCOS, Inositol, hypocaloric diet, BMI, Hyperandrogenaemia.

Introduction

Approximately 5–21% of women who are of reproductive age have PCOS, the most common endocrine disorder. [1,2] Depending on the definition used and the population being studied, these prevalence rates are reported to vary. [1,2] One of the main characteristics of PCOS is insulin resistance (IR), which leads to hyperandrogenism and other clinical symptoms like acne, hirsutism, and polycystic ovary morphology on ultrasound. [3] PCOS raises the risk of complications during pregnancy and is recognized as a major cause of anovulatory infertility. [3, 4] Women with PCOS are more likely to experience metabolic disorders such as type 2 diabetes mellitus (T2DM), metabolic syndrome, and cardiovascular disease, in addition to these unfavorable reproductive outcomes. In addition to the lower quality of life reported in this population, they are also more likely to have compromised psychological wellbeing, as demonstrated by a high prevalence of anxiety, depression, and body dissatisfaction [5,6,7].

It can be challenging for many PCOS-affected women to maintain a healthy body weight. In fact, studies have indicated that up to 75% of PCOS-affected women are overweight or obese [8–9], and that these women may gain more weight over time. Obesity and especially central type obesity seem to worsen reproductive disorders, hyperandrogenism, IR, cardiovascular risk factors, and psychological effects [9]. Weight loss, on the other hand, improves PCOS-related outcomes. As first-line therapy for PCOS, lifestyle changes (diet, exercise, and behavioral adjustments) and weight management are advised to improve hormonal imbalances and fertility. Prior to conception and the start of infertility treatments, lifestyle changes and weight loss are also advised,[3] and they may increase ovulation rates more than oral contraceptive treatment.[10] Additionally, new research indicates that PCOS patients' psychological outcomes improve after losing weight.[11]

While the effects of low-calorie diets (LCDs) remain understudied in this population, studies involving dietary energy restriction for weight loss in PCOS have primarily focused on moderate reductions in energy intake to induce a deficit of 500–1000 kcal/d with/without the use of anti-obesity/anti-diabetes medication.[12,13,14,15,16]They usually entail substituting some or all of a meal with artificial formulas (shakes, soups, bars, etc.), which are frequently nutrient-dense (i.e., contain enough vitamins and minerals to meet dietary requirements). Due to their sudden calorie restriction, LCDs are advised to be used for only brief periods of time (8–16 weeks) and under medical supervision. Nevertheless, they have the potential to produce rapid weight loss (20–30%) and even weight maintenance.[17]

Inositol is a member of the B complex vitamins, as are its metabolites, which are referred to as sugar alcohols. Moreover, there are nine stereoisomers of inositol, including the myo-, cis-, allo-, epi-, muco-, neo-, scyllo-, D-chiro, and L-chiro formats. As second messengers, lipid synthesis, signal transduction, oocyte maturation, oogenesis, cell morphogenesis, and cytoskeleton organization, inositol-derived metabolites play critical roles in insulin sensitivity.[18,19] Randomized controlled trials on women with PCOS who took inositol supplements report that the supplement improves nearly every pathologic condition associated with PCOS, including insulin levels, reduced testosterone, and recovery of reproductive abnormalities.[20]

Many studies are conducted separately in use of low caloric diet and Inositol in PCOS patients. But only

rarely the studies were conducted to find the effect of use of both inositol and low caloric diet in PCOS patients. In this context, this study is conducted to assess the efficacy of use of inositol and low calorie diet/hypocaloric diet in PCOS.

Objective

To compare the before and after effects of hypocaloric diet and inositol on body weight, hormonal and metabolic parameters in PCOS women.

Methodology

Methods: This longitudinal study among PCOS participants was carried out at medical college. The sample size was calculated using Epi info software with values(Mean 1+/-s.d 1 is 16+/-6.8 and mean 2+/-s.d2 is 22.8+/-7.7) as per Deshmukh et al., study.[22] The calculated sample size is 36 and participants were selected by convenience sampling. Inclusion criteria was women between the ages of 18 and 45 who wanted to lose weight and whose body mass index (BMI) fell between 30 and ≤45 kg/m2 . PCOS was diagnosed based on the Rotterdam criteria, which includes self-reported oligomenorrhea (cycle length > 35 days and nine or fewer periods per year) or amenorrhea (absence of menses for a period ≥ three months) and biochemical hyperandrogenism, as indicated by an FAI > 4). Participants had to have willingness to use an accurate non-hormonal form of birth control for the whole study period in order to be eligible for inclusion.

Women with hyperprolactinemia, Cushing's disease, androgen-secreting tumors as differential diagnoses, as well as non-classical 21-hydroxylase deficiency, were excluded from study. Menopause and perimenopause, pregnancy or intending to become pregnant, breastfeeding, weight loss greater than 5 kg in the previous 6 months, substance abuse, acute illness, diabetes diagnosis, history of gallstones or gout, poorly controlled thyroid disorder or celiac disease were additional exclusion criteria in place. Additionally excluded participants were participants who used any of the following substances during the previous three months- hormone-releasing implants and oral hormonal contraceptives; anti-androgens (spironolactone, flutamide, finasteride, etc.); metformin or other insulin-sensitizing agents; clomiphene citrate or estrogen modulators; gonadotropin-releasing hormone (GnRH) modulators (e.g., leuprolide); minoxidil; anti-obesity agents; or any other medication that may impact appetite (e.g., oral steroids).

The participants were advised to adhere to the hypocaloric diet schedule and also to intake 1200mg of D-Chiro inositol daily for 8 weeks.

During the first visit (Visit 1), participants underwent asocio-demographic , medical history and clinical examination, routine blood tests (such as a full blood count, liver function tests, urea and electrolyte tests, clotting screen), and anthropometric measurements to screen them against inclusion and exclusion criteria. For eight weeks, eligible participants were instructed to adhere strictly to the low-calorie diet. The participants underwent an assessment of their body composition as well as anthropometric measurements (weight, BMI, waist circumference, and hip circumference) during Visits 2 and 3, which were held between 4 and 8 weeks after Visit 1. In addition, blood samples were obtained for the following tests: total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), high-sensitivity C-reactive protein (hs-CRP), fasting glucose, fasting insulin, HOMA-IR, and total cholesterol. Blood pressure was also taken. Support and

information about using the food replacement sachets, taking prescribed fiber supplements, and drinking fluids were given to the participants. Following the eight weeks, participants received a stepped return that involved cutting back on meal replacement drinks until they consumed about 1600 kcal per day and increasing by 200 kcal every two weeks.

Measurements

Using a stadiometer and weighing scale, participants' height and weight were recorded while they were wearing loose clothing and no shoes. Weight (kg) divided by height (m2) is the formula used to calculate BMI. An automated device was used to measure the subjects' blood pressure; they had to sit quietly for at least five minutes and have their right arm supported at heart level. After taking three readings, separated by at least two minutes, the mean value of the readings was determined. A tape measure was used to measure the waist circumference. The iliac crest, or midway point between the top of the hips and the bottom of the ribs, is where the tape measure was placed around the waists of the participants.

Biochemical analysis

Venous blood samples were drawn while fasting following an overnight fast, two hours at baseline, and eight weeks. Chemiluminescent immunoassay was used to measure serum insulin. The homeostatic model assessment-insulin resistance (HOMA-IR = (fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L))/22.5) was used to calculate insulin resistance. Quantification was done on serum testosterone and sex hormone binding globulin. To calculate the FAI, multiply (total testosterone/SHBG) by 100. Significant hyperandrogenaemia was defined as an FAI of ≥4, and a follow-up FAI of <4 indicated PCOS biochemical remission. Elevated androgen levels can be identified with high accuracy using FAI and free testosterone. The interpretation of free testosterone levels is more challenging in women because a substantial portion of testosterone is bound to SHBG.

By accounting for it, the FAI makes up for this reliance on SHBG. Biochemical remission of PCOS is not well defined; however, FAI levels of 5 or greater are thought to be suggestive of PCOS.[21] The following parameters were also assessed: aspartate aminotransferase (AST), triglycerides, HDL-C, Alanine aminotransferase (ALT), and total cholesterol.

Statistical analysis

The continuous variables in the study were summarised as means ± SD, while the categorical data are presented as n (%). Mean changes from baseline to 8-week follow-up were analysed using a paired t-test. The Epi info version 7 software is used for analysis.

Results

36 participants with PCOS were recruited in our study. The mean age is 28.3+.-5.33 years.27.7% were educated up to high/high secondary school and 55.5% were educated up to undergraduate/postgraduate.(Table 1)

Table 1: Socio demographic data of study participants

Variables	N	%
Age mean+/-s.d	28.3+-5.33 years	
Education		
Upto primary	2	5.5
Upto middle	4	11.1
Upto high/high sec	10	27.7
Undergraduate/post graduate	20	55.5
Occupation		
Working	15	41.6
Not working	21	58.3
Residence		
Urban	12	33.3
Rural	24	66.6

Table 2 shows there is mean reduction in body weight, body weight, waist hip ratio, Total cholesterol and FBS after 8 weeks and the results were significant. There is no significant reduction in PPBS, HBA1C, Triglyceride, AST and ALT after 8 weeks post hypocaloric diet and inositol intake.

Table 2: Comparison of metabolic parameters before and after intervention

Variables	At baseline Mean+/-s.d	At 8 weeks after intervention Mean+/-s.d	P value
Weight in kg	9.7+/-3.2	6.22+/-2.26	0.0001
BMI (Kg/m^2)	38.99+/-2.28	33.25+/-1.98	0.0001
WHR	0.93+/-.26	0.81+/-0.1	0.01
Fasting blood glucose mg/dl	102.3+/-7.29	93.63+/-9.31	0.001
Post prandial blood glucose mg/dl	110.66+/-8.37	108.63+/-5.37	0.22
HBA1C (%)	4.8+/-1.6	4.7+/-1.8	0.802
Total cholesterol (mg/dl)	194.53+/-22.24	183.43+/-21.35	0.03
Triglyceride	23.55+/-3.25	22.54+/-3.33	0.179
ALT (Iu/l)	28.33+/-9.31	31.53+/-8.12	0.12
AST (Iu/l)	19.43+/-5.32	21.78+/-6.93	0.112
CRP (mg/l)	7.1(5.66)	6.23(5.3)	0.71

Table 3 shows FAI at baseline is 9.09+/-0.49 and at 8 weeks it is 6.35+/-0.46. The mean SHBG at baseline is 16.2+/-6.44 and at 8 weeks it is 22.9+/-7.12 nmol/l. The results were significant. There is no significant difference in Total testosterone, DHEAS, Androstendeione, LH and FSH between pre and post hypocaloric diet and inositol.

Table 3: Comparison of hormonal parameter before and after intervention

Variables	At baseline Mean+/-s.d	At 8 weeks after intervention Mean+/-s.d	P value
FAI	9.09(0.49)	6.35(0.468)	0.0001
Total testosterone (nmol/l)	1.51(0.73)	1.33(0.62)	0.263
DHEAS (nmol/l)	6.87(3.29)	7.79(3.25)	0.830
Androstenedione (nmol/l)	5.33(2.1)	4.68(1.56)	0.14
SHBG(nmol/l)	16.2(6.44)	22.9(7.12)	0.001
LH (Iu/L)	7.6(3.36)	8.48(4.8)	0.37
FSH(Iu/L)	7.1(1.89)	6.47(1.61)	0.057

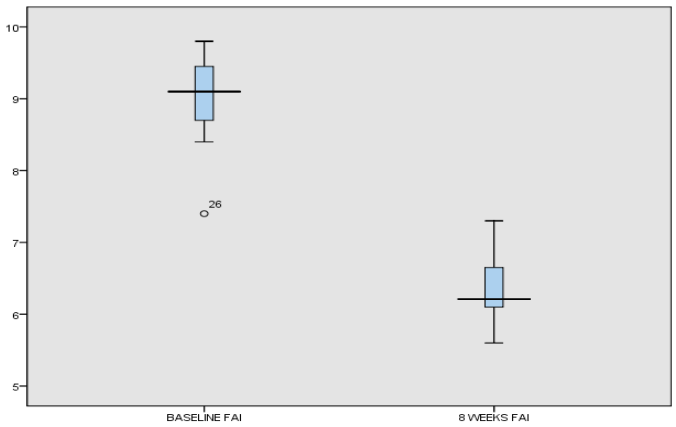

Figure 1: Comparison of FAI before and after intervention

Discussion

One common endocrine condition affecting women is PCOS. High levels of testosterone and aberrant insulin metabolism are its defining characteristics.[23,24] There is currently no proven cause of PCOS, and there is no efficient cure. The American Society for Reproductive Medicine (ASRM) 2018 Guidelines state that changing one's lifestyle, which includes controlling one's diet and exercising more, is the first line of treatment for

PCOS.[3] The term "LCD" describes a dietary pattern that lowers or limits the consumption of carbohydrates to less than 45% of the daily caloric intake in order to control symptoms or prevent disease.[25]

LCD and Inositol may successfully reduce insulin levels, improve insulin resistance and other endocrine deficiencies, and regulate body weight in overweight or obese individuals.[26,27] As of right now, the literature that has been published contains contradictory information about the impact of LCD and Inositol, which calls for more research and analysis on the effects of this dietary change on PCOS patients.[28]

Furthermore, stratified analyses showed that PCOS patients could significantly increase their levels of FSH and SHBG and decrease their testosterone levels with low-fat/low-CHO (less than 35% of fat and less than 45% CHO) and long-term (more than 4 weeks) LCD interventions. Therefore, LCD seems to be effective as an adjuvant treatment for PCOS-related manifestations, especially the low-fat/low-CHO LCD and the long-term LCD.The information currently available is consistent with the idea that LCD can effectively manage body weight in individuals who are overweight or obese, reduce insulin levels, and treat insulin resistance and other endocrine system deficiencies. A potential mechanism for these advantageous effects is a reduction in circulating insulin and glucose levels brought on by LCD.[28-30]

According to Zhang et al., meta-analysis, LCD can considerably lower BMI, serum TC and LDL-C levels, and BMI in PCOS patients. The results showed that LCD greatly reduces insulin resistance. In both obese and lean PCOS patients, a growing body of research indicates that insulin resistance and secondary hyperinsulinemia play a critical role in the development of hyperandrogenism, the maintenance of metabolic alterations, and an ovulation or irregular menstrual cycles. Furthermore, ovulation and follicular development can be hindered by hyperinsulinemia.[28]

In addition to inositol supplements, the control of inositol metabolism is also done by Low caloric diet which corrects the above dysfunctions. Inositol is a member of the vitamin B family and one of the nine stereoisomers of cyclohexanol. Two of the most prevalent cyclohexanol isomeres are D-chiro-inositol (DCI) and myoinositol (MI). Due to insulin dysfunction, PCOS patients have inhibited NAD/NADH-dependent isomerase activity, which converts the vast majority of intracellular pools of MI into DCI. Due primarily to the poor conversion of MI into DCI, the imbalance between MI and DCI is significant in IR. Consequently, dysregulation of inositol metabolism may result in hyperinsulinemia, decreased insulin sensitivity, inhibition of follicle maturation, and PCOS development.[31]

In a single-blind clinical trial by Mehrabani et al, a total of 60 obese and overweight PCOS women were enrolled to hypocaloric diet groups. The average testosterone level in the CHCD ranges from 1.31 ± 0.26 ng/ml to 1.15 ± 0.11 ng/ml ($p < 0.001$). The concentrations of luteinizing hormone (LH), follicle sensitizing hormone (FSH), and blood lipids remained unchanged, with the exception of low-density lipoprotein cholesterol (LDL-C), which decreased following a 12-week intervention. Insulin level, high-sensitivity C- reactive protein (hsCRP) concentration, and homeostatic model assessment for insulin resistance (HOMA) were all significantly reduced ($p < 0.001$) after low calorie diet. The results were similar to our study.[23]

Unfer et al., meta-analysis have shown that and rostenedione levels stayed unchanged, but there was a slight trend toward a reduction of testosterone concentration in Inositol intake group of PCOS oatient (SMD = -0.49, 95% CI: -1.072 to 0.092, P = 0.099). Inositol was given for at least 24 weeks showed a significant increase in serum SHBG throughout a subgroup's meta-analysis (SMD = 0.425 nmol/L, 95% CI: 0.050–0.801, P = 0.026).[20]

Therefore, based on the existing PCOS treatment strategies and the conclusions of the present analysis, we suggest that the most important therapy for PCOS patients is low caloric diet intervention and the medical treatment utilizing inositol to increase insulin sensitivity and to reduce hyper androgen state.

Conclusion

In summary, this study's findings regarding the impact of an inositol-rich diet and hypocaloric diet on PCOS patients imply that this strategy may be utilized to help this population lose weight temporarily. The study did discover, however, that this strategy produced more noticeable improvements in hyperandrogenism, body composition, and PCOS-related metabolic issues. Although these results are encouraging, they are based on a small, single-center study, and larger, multicenter RCTs are required to assess the general application of insulin intake and a hypocaloric diet in PCOS management.

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Abbreviations

PCOS: Polycystic ovarian syndrome

LCD-Low caloric diet

IR-Insulin resistance

HOMA IR-Homeostasis model assessment-estimated insulin resistance

LDL/HDL-Low/high density lipoprotein

FAI- Free androgen index

TG- Triglyceride

AST- Aspartate transmarine

ALT- Alanine transferase

BMI-Body mass index

References

1. D. Lizneva, L. Suturina, W. Walker, S. Brakta, L. Gavrilova-Jordan, and R. Azziz, ‘Criteria, prevalence, and phenotypes of polycystic ovary syndrome’, Fertil Steril, vol. 106, no. 1, 2016 p. 6–15, doi: 10.1016/j.fertnstert.2016.05.003.
2. W. M. Wolf, R. A. Wattick, O. N. Kinkade, and M. D. Olfert, ‘Geographical Prevalence of Polycystic Ovary Syndrome as Determined by Region and Race/Ethnicity’, Int J Environ Res Public Health, vol. 15, no. 11,2018, p. 2589 doi: 10.3390/ijerph15112589.
3. H.J. Teede, M.L. Misso, M.F. Costello, A. Dokras, J. Laven, L. Moran, T. Piltonen, R.J. Norman, ‘Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome’, Fertil Steril, vol. 110, no. 3, 2018 pp. 364–379 doi: 10.1016/j.fertnstert.2018.05.004.
4. A.H. Balen, L.C. Morley, M. Misso,S. Franks, R.S. Legro, C.N. Wijeyaratne, E. Stener-Victorin, B.C. Fauser,R.J. Norman, H .Teede, The management of anovulatory infertility in women with polycystic ovary syndrome: An analysis of the evidence to support the development of global WHO guidance. , Human reproduction update, vol. 22, no. 6, 2016, doi: 10.1093/humupd/dmw025.

5. X. Yin, Y. Ji, C. L. W. Chan, and C. H. Y. Chan, 'The mental health of women with polycystic ovary syndrome: a systematic review and meta-analysis', Arch Womens Ment Health, vol. 24, no. 1, 2021, pp. 11–27, doi: 10.1007/s00737-020-01043-x.
6. L. G. Cooney and A. Dokras, 'Depression and Anxiety in Polycystic Ovary Syndrome: Etiology and Treatment', Curr Psychiatry Rep, vol. 19, no. 11, 2017 p. 83, doi: 10.1007/s11920-017-0834-2.
7. 'Frontiers | The Effect of Free Androgen Index on the Quality of Life of Women With Polycystic Ovary Syndrome: A Cross-Sectional Study'. Accessed: Jan. 08, 2024. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fphys.2021.652559/full
8. 'Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group - PubMed'. Accessed: Jan. 08, 2024. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/22153789/
9. S. S. Lim, R. J. Norman, M. J. Davies, and L. J. Moran, 'The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis', Obes Rev, vol. 14, no. 2, 2013, pp. 95–109, doi: 10.1111/j.1467-789X.2012.01053.x.
10. G. Nf, c. Rh, f. W, g. Js, l. Rs, and c. E, 'American association of clinical endocrinologists, american college of endocrinology, and androgen excess and pcos society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome--part 1', Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, vol. 21, no. 11, 2015, doi: 10.4158/EP15748.DSC.
11. J.P. Domecq, G. Prutsky, R.J. Mullan, V. Sundaresh, A.T. Wang, P.J. Erwin, C. Welt, D. Ehrmann, V.M. Montori, M.H. Murad, 'Adverse effects of the common treatments for polycystic ovary syndrome: a systematic review and meta-analysis', J Clin Endocrinol Metab, vol. 98, no. 12, pp. 4646–4654, Dec. 2013, doi: 10.1210/jc.2013-2374.
12. D. Panidis, K. Tziomalos, E. Papadakis, P. Chatzis, E.A. Kandaraki, E.A.Tsourdi, I. Katsikis., 'The role of orlistat combined with lifestyle changes in the management of overweight and obese patients with polycystic ovary syndrome', Clin Endocrinol (Oxf), vol. 80, no. 3, pp. 432–438, Mar. 2014, doi: 10.1111/cen.12305.
13. R. Pasquali, A,. Gambineri, D. Biscotti, V. Vicennati, L. Gagliardi, D. Colitta, S. Fiorini, G.E. Cognigni,M. Filicori, M.Morselli-Labate., 'Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome', The Journal of clinical endocrinology and metabolism, vol. 85, no. 8, Aug. 2000, doi: 10.1210/jcem.85.8.6738.
14. E. Diamanti-Kandarakis, I. Katsikis, C. Piperi, K. Alexandraki, and D. Panidis, 'Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome', Clin Endocrinol (Oxf), vol. 66, no. 1,2007, pp. 103–109, doi: 10.1111/j.1365-2265.2006.02693.x.
15. K. I. Cheang, S. N. Sistrun, K. S. Morel, and J. E. Nestler, 'Effect on Insulin-Stimulated Release of D-Chiro-Inositol-Containing Inositolphosphoglycan

Mediator during Weight Loss in Obese Women with and without Polycystic Ovary Syndrome', Int J Endocrinol, vol. 2016, p. 7631804, doi: 10.1155/2016/7631804.

16. I. Kowalska, M. Kinalski, M. Straczkowski, S. Wolczyski, and I. Kinalska, 'Insulin, leptin, IGF-I and insulin-dependent protein concentrations after insulin-sensitizing therapy in obese women with polycystic ovary syndrome', Eur J Endocrinol, vol. 144, no. 5, 2001, pp. 509–515, doi: 10.1530/eje.0.1440509.
17. C. Rolland, K. L. Johnston, S. Lula, I. Macdonald, and J. Broom, 'Long-term weight loss maintenance and management following a VLCD: a 3-year outcome', Int J Clin Pract, vol. 68, no. 3, 2014, pp. 379–387, doi: 10.1111/ijcp.12300.
18. E.Diamanti-Kandarakis, I. Katsikis, C. Piperi, K. Alexandraki, D. Panidis. Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. Clin. Endocrinol. vol 66, 2007, p. 103–109.
19. K.I. Cheang, S.N Sistrun, K.S Morel, J.E Nestler, Effect on Insulin-Stimulated Release of D-Chiro-Inositol-Containing Inositolphosphoglycan Mediator during Weight Loss in Obese Women with and without Polycystic Ovary Syndrome. Int. J. Endocrinol. 2016,
20. I. Kowalska, M. Kinalski, M.Straczkowski, S. Wolczyski, S.Kinalska, Insulin, leptin, IGF-I and insulin-dependent protein concentrations after insulin-sensitizing therapy in obese women with polycystic ovary syndrome. Eur. J. Endocrinol. Vol.144, 2001, p. 509–515. [
21. C. Rolland, K.L. Johnston, S. Lula, I. Macdonald, J. Broom, . Long-term weight loss maintenance and management following a VLCD: A 3-year outcome. Int. J. Clin. Pract.vol. 68 2014, p. 379–387.
22. W.H. Daughaday, J. Larner, C. Hartnett . The synthesis of inositol in the immature rat and chick embryo. J Biol Chem. Vol 212, 1955, p.869–75.
23. E. Papaleo,V. Unfer, J.P Baillargeon, T.T. Chiu . Contribution of myo-inositol to reproduction. Eur J Obstet Gynecol Reprod Biol. Vol.147, 2009, p.120–3.
24. V. Unfer, G. Carlomagno, G. Dante, F. Facchinetti . Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. Gynecol Endocrinol.vol.28, 2012, p.509–15.
25. S. Hahn, W. Kuehnel, S. Tan, K. Kramer, M. Schmidt, S. Roesler, R. Kimmig, K. Mann, O.E. Janssen. Diagnostic value of calculated testosterone indices in the assessment of polycystic ovary syndrome. Clin. Chem. Lab. Med. Vol.45, 2007, p. 202–207.
26. H. Deshmukh, M. Papageorgiou, L.Wells, S.Akbar, T. Strudwick, K. Deshmukh, S.G Vitale, A. Rigby, R.V Vince, M Reid. The Effect of a Very-Low-Calorie Diet (VLCD) vs. a Moderate Energy Deficit Diet in Obese Women with Polycystic Ovary Syndrome (PCOS)—A Randomised Controlled Trial. Nutrients vol. 15, 2023
27. H.H Mehrabani, S. Salehpour, Z. Amiri, S.J. Farahani,B.J. Meyer, F. Tahbaz. Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. J Am Coll Nutr. Vol.31, no.2, 2012 , p.117-25.

28. C. C. Douglas, B. A. Gower, B. E. Darnell, F. Ovalle, R. A. Oster, and R. Azziz, "Role of diet in the treatment of polycystic ovary syndrome," Fertility and Sterility, vol. 85, no. 3, 2006, p. 679–688, 2006.
29. J. Wylie-Rosett, K. Aebersold, B. Conlon, C. R. Isasi, and N. W. Ostrovsky, "Health effects of low-carbohydrate diets: where should new research go?" Current Diabetes Reports, vol. 13, no. 2, 2013, p. 271–278.
30. R. B. Kostogrys, M. Franczyk-Żarów, E. Maślak, and K. Topolska, "Effect of low carbohydrate high protein (LCHP) diet on lipid metabolism, liver and kidney function in rats," Environmental Toxicology and Pharmacology, vol. 39, no. 2, 2015, p. 713–719,.
31. L. R. Saslow, S. Kim, J. J. Daubenmier et al., "A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes," PLoS One, vol. 9, no. 4, 2014. Article ID e91027
32. https://www.hindawi.com/journals/ije/2019/4386401
33. D. A. de Luis, O. Izaola, R. Aller, B. de la Fuente, R. Bachiller, and E. Romero, "Effects of a high-protein/low carbohydrate versus a standard hypocaloric diet on adipocytokine levels and insulin resistance in obese patients along 9 months," Journal of Diabetes and its Complications, vol. 29, no. 7, 2015, p. 950–954.
34. J. E. Chavarro, J. W. Rich-Edwards, B. A. Rosner, and W. C. Willett, "Diet and lifestyle in the prevention of ovulatory disorder infertility," Obstetrics & Gynecology, vol. 110, no. 5, 2007, p. 1050–1058.
35. A. S. Laganà, S. Garzon, J. Casarin, M. Franchi, and F. Ghezzi, "Inositol in polycystic ovary syndrome: restoring fertility through a pathophysiology-based approach," Trends in Endocrinology & Metabolism, vol. 29, no. 11,2018, pp. 768–780.