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ORIGINAL ARTICLE

Isocaloric diet is as effective as the hypocaloric diet in ameliorating symptoms in PCOS patients

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Abstract

Background There is no randomized study comparing the isocaloric (ICHD) and hypocaloric diet (HCD) in PCOS subjects.
Objective To compare ICHD and HCD in weight-matched PCOS subjects.
Methods PCOS subjects were randomized to receive either a HCD or ICHD. Clinical, biochemical, hormonal and dietary assessments were performed at baseline, 3 months and at one year.
Results There were 168 PCOS subjects randomized to receive either ICHD ($n = 84$) or HCD ($n = 84$). We observed that while the hypocaloric diet was more effective in reducing weight, both the diets were effective in improving clinical symptoms. Around 50% patients showed improvement in clinical symptoms at 3 months and 30% were on diet alone therapy at one year in both the groups. The effect on hirsuitism was modest by both the diets at one year. The effectiveness of both the diets was similar with both the per protocol and the Intention to treat analysis; nevertheless, there was a greater loss to follow-up in patients on ICHD with high baseline caloric intakes.
Conclusion HCD and ICHD are equally effective in as many as 30% patients with mild symptoms over long term. Patients having higher caloric intakes at baseline should not be offered isocaloric diets.

Keywords Dietary pattern · Meal timing · Isocaloric diet · Hypocaloric diet · PCOS · Total caloric intake

Introduction

PCOS is a common disorder of the reproductive age group presenting with varying degrees of hirsuitism and oligoanovulation. Obesity can exacerbate the metabolic and reproductive abnormalities that are associated with the disorder. Weight loss in obese PCOS patients reduces circulating androgens and raises SHBG, enhances insulin sensitivity, and improves menstrual cyclicity and fertility rates [1–3].

There is no standardized prescribed diet for PCOS owing to the regional and cultural differences in the meal composition and diet preferences. The short-term beneficial effects of various diets including hypocaloric, isocaloric, low carbohydrate, and high protein diets have been studied [4–8]. However, there is paucity of randomized long-term studies comparing the different forms of diet.

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As compared to the Western cohort, we observed that Indian patients with PCOS were younger and had a lower BMI [9]. Indian diet differs from the West in having a greater proportion of carbohydrates and less proteins. In our previous study, we observed that our PCOS patients had comparable caloric and macronutrient distribution; however, they differed in food quality and meal timings in comparison to weight-matched controls [10]. It is not known if just a modification of relative macronutrient proportion is sufficient for these patients or a reduction of calories is also additionally needed. The present study aims to study the effect of a hypocaloric diet(HCD) compared to isocaloric healthy diet (ICHD) over a period of one year on different components of polycystic ovarian syndrome, i.e., obesity, menstrual cycles, hirsuitism, and biochemical parameters.

Materials and methods

Patients with PCOS diagnosed as per Rotterdam Criteria were included. Exclusion criteria were as follows [1]: endocrinological problems including hypothyroidism, androgen secreting tumors, Cushing's, prolactinoma, or CAH [2]; pregnant or lactating women [3]; those on oral

contraceptives or antiandrogens or insulin sensitizers within the past 6 months [4]; and use of antidepressants or lipid lowering medications. Blood pressure, height, weight, BMI, waist–hip ratio, hirsuitism score (by Ferriman Gallaway scoring), and acneform scoring as previously described [10, 11].

Blood was drawn at 0 h and 2 h after the oral administration of 75 gm glucose for both the subjects and controls. Glucose and lipid profiles were analyzed the same day and samples for insulin and other hormones (LH, FSH, testosterone, free testosterone, DHEAS, androstenedione and SHBG,TFT, Cortisol, ACTH, prolactin, and 17 OHP) were stored at – 20 °C and analyzed later.

Making a dietary record

PCOS subjects were trained by two dedicated dieticians to make a record of their eating patterns as previously described [10]. This included showing them models and pictures representing sample items viz chapattis, bowls, and glasses of different sizes commonly used in Indian households. The subjects were also asked to record the timings of the three major meals, tea, and mid meal snacks taken throughout the day. The mean of dietary recall over the past two days was noted. Dieticians spent additional 45 min to an hour on each patient enquiring about their dietary patterns, probing junk intake, physical activity, cross checking timings, and quantity of the meals taken. The total caloric intake along with differential carbohydrate, protein, fat, and fiber intake was calculated as per Indian standards established by NIN (National Institute of Nutrition) [12, 13]. Since NIN provides the nutritive data for raw foods, the relative proportion of various ingredients used in recipes for cooked foods was taken from recipe book published by the Institute of Home Economics [14]. The nutritional content of packaged foods was taken from the information provided overleaf.

Patients and controls were categorized as having late breakfast if they were taking breakfast after 10:00 AM, late lunch if they were having lunch after 3:00 PM, and late dinner if they were having dinner after 10:00 PM [15]. Physical activity in terms of number of days of regular physical exercise per week was categorized as previously described [16].

Dietary intervention

Subjects were randomized to receive either a hypocaloric diet (HCD) or an isocaloric healthy diet (ICHD) based on computer generated random number table. The ICHD diet

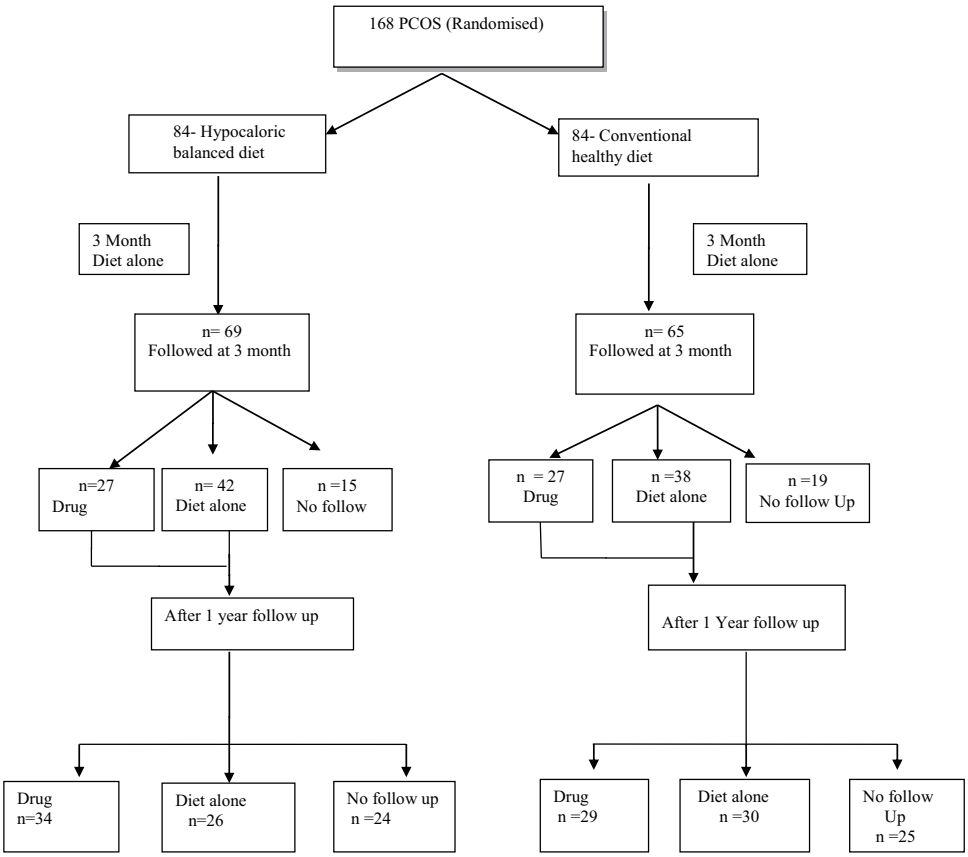

Fig. 1 Outline of PCOS patients

Table 1 Comparative clinical and biochemical parameters among PCOS patients assigned isocaloric diet versus hypocaloric diet

	Hypocaloric diet ($n = 84$)	Isocaloric diet ($n = 84$)	p-value
Age (years)	22.88 ± 5.23	24.74 ± 5.54	0.024*
BMI (kg/m^2)	26.38 ± 6.73	25.87 ± 6.14	0.64
Hirsuitism	56 (66.7%)	57 (67.9%)	0.50
Irreguiar periods	56 (66.7%)	54 (64.3%)	0.44
Acneform eruptions	52 (61.9%)	48 (57.1%)	0.31
Hirsuitism score	4.9 ± 3.19	7.6 ± 5.9	0.051
Menstrual cyclicity	63.58 ± 42.9 (45)	64.6 ± 45.27 (50)	0.76
WHR	0.86 ± 0.07	0.86 ± 0.08	0.86
RtOvvol (ml)	9.33 ± 3.83	10.36 ± 5.16	0.47
LOV	9.26 ± 4.62	9.29 ± 4.21	0.88
BP systolic (mm Hg)	117.58 ± 7.46	117.99 ± 7.95	0.79
BP diastolic (mm Hg)	72.13 ± 7.27	70.33 ± 6.33	0.06
GTT 0hour (mg/dl)	81.24 ± 11.02	78.33 ± 12.21	0.07
GTT 2hour (mg/dl)	103.00 ± 22.49	110.33 ± 29.48	0.08
Total cholesterol (mg/dl)	161.88 ± 35.05	158.56 ± 28.19	0.76
HDL cholesterol (mg/dl)	42.95 ± 9.13	45.96 ± 9.18	0.04*
LDL cholesterol (mg/dl)	96.80 ± 28.67	92.76 ± 23.22	0.32
VLDL cholesterol (mg/dl)	20.67 ± 8.23	19.76 ± 8.57	0.37
TRIGLYCERIDE (mg/dl)	103.87 ± 41.16	98.99± 42.64	0.36
TSH (UU/ml)	3.53 ± 6.51	2.93± 1.72	0.85
FSH (mIU/ml)	5.66 ± 1.91	5.48 ± 1.86	0.18
LH (mIU/ml)	10.88 ± 12.18	8.14 ± 12.44	0.01*
Prolactin (ng/ml)	16.56 ± 10.01	17.90 ± 12.58	0.97
Testosterone (nmol/l)	1.37 ±.72	1.32 ±.71	0.50
DHEAS (µg/ml)	2.29 ± 1.00	2.10 ± 1.19	0.06
Cortisol (nmol/l)	257.99±117.26	241.08 ± 99.09	0.59
Insulin 0H (µIU/ml)	14.33 ± 11.08	13.12 ± 8.88	0.59
Insulin 2H (µIU/ml)	54.81 ± 32.41	57.65 ± 41.00	0.85
17OHP (ng/ml)	2.69 ± 2.58	2.59 ± 2.28	0.32
Free testosterone (pg/ml)	3.17 ± 1.71	2.84 ± 1.70	0.13
SHBG (nmol/l)	83.58 ± 52.19	82.89 ± 54.82	0.92
Androstenedione (ng/ml)	3.60 ± 2.23	3.34 ± 2.28	0.16
Exercise >3 days/ week	22(26.9%)	15(17.8%)	0.30

*Denotes p value less than 0.05

was isocaloric to the calories being consumed by the subject prior to intervention. HCD diet was prescribed as either an energy reduction of 500 kcal/day or intake of 20 kcal /kg for overweight and obese PCOS subjects and 25 kcal/kg for normal weight individuals whichever was lower [7]. The macronutrient contents of both the diets were similar (60% carbohydrates, 15% proteins, and remaining by fat). A schedule of three main meals and at least 2 snacks was introduced for both the groups. They were advised to refrain from high glycemic foods and incorporate salads and fruits in their diet. A sample menu plan was provided for each patient, and the participants were encouraged to select foodstuffs suited to their preferences. Subjects were also encouraged to not miss their meals and take their major meals at appropriate timings (breakfast before 10:00 AM, lunch before 3:00 PM, and dinner before 9:00 PM). Participants in both the groups were encouraged to do regular physical activity of 20 min of walking for at least 3 days a week [16].

PCOS subjects were asked to make a hospital visit at 3 months, 6 months, and one year. During these visits, clinical symptoms, physical examination, and two-day dietary recall were performed. A verbal reinforcement for dietary compliance was done. Samples for biochemical and hormonal assessment were taken at three months and one year. Patients unsatisfied with the clinical response to diet therapy were put on medications (antiandrogens or insulin sensitizers or OCP).

Statistical analysis

Data was entered in excel sheet and analyzed in SPSS (Version 20 Chicago, IL, USA). The baseline mean values and delta changes in parameters from baseline in the two groups were compared with the independent sample Student's t test and the Mann–Whitney U test. Chi square test was used for non-parametric variables. Paired t test was used to compare the changes in mean values in parameters at three months. One-way repeated measure analysis of variance was used to compare the parameters at multiple timepoints. Multiple comparisons using Bonferroni corrections were performed to identify which pair showed significance. Further, the variables, failing normality assumption, were treated with Friedman's one-way repeated measures ANOVA. Both the groups were also compared by the intention to treat or per protocol analysis. p value less than 0.05 was considered as significant.

Assays

DHEAS, prolactin, and thyroid function tests were performed by chemiluminescence (Beckman CoulterDxI, 600). Insulin and testosterone were analysed by chemiluminescence (Vitros ECI, Johnson and Johnson). Plasma androstenedione, free testosterone, and SHBG were performed by ELISA (on Bio-Rad Evolis, Twin Plus)

Table 2 Mean changes in the clinical, biochemical, and hormonal parameters in PCOS subjects on isocaloric and hypocaloric diet at 0 and 3 months

PCOS patients on hypocaloric diet ($n = 69$)				PCOS patients on isocaloric diet ($n = 65$)		
Parameters	0 month	3 months	p value*	0 month	3 months	p value*
Weight (kg)	66.06 ± 18.09	64.71 ± 18.83	0.004*	62.39 ± 13.20	63.06 ± 13.57	.74
Cyclicity	67.47. ± 46.01(45)	53.76 ± .40.64(35)	0.00*	66.26 ± 47.38(47.5)	48.15 ± 27.53(35)	.00*
MODHIRSCO	5.33 ± 3.12	4.82 ± 3.07	0.002*	7.48 ± 6.04	7.43 ± 5.91	.28
Acne code	1.33 ± 0.47	0.61 ± 0.64	0.00*	1.21 ± 0.41	0.52 ± 0.50	.00*
GTT 0hour (mg/dl)	81.88 ± 10.95	81.55 ± 11.70	0.99	78.62 ± 12.27	79.17 ± 10.76	.78
GTT 2hour (mg/dl)	102.73 ± 22.52	108.00 ± 28.53	0.14	108.81 ± 30.49	108.28 ± 30.60	.88
Insulin 0H (μIU/ml)	13.67 ± 9.53	10.32 ± 5.25	0.01*	13.63 ± 9.41	10.37 ± 6.17	.01*
Insulin 2H (μIU/ml)	56.22 ± 31.58	55.60 ± 33.47	0.96	56.78+ 34.50	61.01 ± 46.63	.45
Total cholesterol (mg/dl)	162.33 ± 36.88	163.46 ± 34.83	0.61	155.88 ± 26.31	156.68 ± 29.04	.78
Triglyceride (mg/dl)	106.09 ± 41.66	107.96 ± 68.33	0.61	97.65 ± 41.61	96.97 ± 40.05	.90
TSH (UU/ml)	2.78 ± 1.64	2.89 ± 1.92	0.61	2.81 ± 171	3.45 ± 2.21	.004*
FSH (mIU/ml)	5.62 ± 1.61	5.61 ± 2.48	0.87	5.47 ± 1.85	5.49 ± 1.63	.08
LH (mIU/ml)	10.17 ± 10.46	9.12 ± 5.98	0.93	6.98 ± 5.07	7.71+6.01	.31
Prolactin (ng/ml)	17.18 ± 10.84	19.23 ± 13.50	0.51	17.29 ± 10.09	17.55 ± 9.33	.88
Testosterone (nmol/l)	1.35 ± .66	1.32 ± .43	0.98	1.29 ± .65	1.34 ± .74	.64
Free testosterone (pg/ml)	3.25 ± 1.78	3.19 ± 1.601	0.72	2.91 ± 1.83	2.56 ± 1.34	.23
SHBG (nmol/l)	86.98 ± 54.42	84.19 ± 50.88	0.73	92.09 ± 55.73	98.72 ± 63.77	.84
Androstenedione (ng/ml)	3.69 ± 2.36	3.68 ± 2.20	0.92	3.33 ± 2.29	3.29 ± 1.76	.72
AVR. energy (kcal)	1870.92 ± 453.77(1801.67)	1400.30 ± 310.89(1417.80)	0.00*	1510.85 ± 301.05(1563.36)	1650.39 ± 376.89(1618.98)	.00*
CHO(%energy	57.77 ± 5.00 (58.42%)	59.98 ± 15.86 (59.17%)	0.23	58.37 ± 7.7 (57.76%)	58.63 ± 5.87 (59.16%)	.80
AVR. protein (gm)	60.09 ± 19.43(54.50)	50.27 ± 13.45(47.83)	0.00*	48.57 ± 13.25(47.93)	55.26 ± 13.65(52.71)	.00*
PRO(%energy)	12.68 ± 2.18 (12.07%)	14.44 ± 2.72 (13.79%)	0.00*	12.91 ± 2.80 (12.28%)	13.39 ± 1.75(13.15%)	.13
FAT(%energy)	29.75 ± 5.51 (29.01%)	27.42 ± 4.50 (26.86%)	0.002*	29.92 ± 5.20 (30.18%)	28.27 ± 6.33 (26.79%)	.04*
Total fiber (gm)	32.77 ± 11.41(32.07)	34.35 ± 8.72(34.58)	0.19	29.23 ± 7.13(29.84)	38.63 ± 11.55(36.60)	.00*
Soluble fiber (gm)	6.29 ± 2.37(5.80)	7.15 ± 2.15(6.92)	0.00*	5.62 ± 1.52(5.88)	7.71 ± 2.76(7.34)	.00*
Pulse intake (gm)	126.74 ± 85.15(103.29)	143.26 ± 94.37(139.67)	0.22	112.90 ± 88.46(92.10)	168.72 ± 101.54(162.50)	.00*
Fruit intake (gm)	46.88 ± 62.52(17.90)	73.01 ± 56.33(67.20)	0.004*	25.89 ± 46.93(.00)	80.47 ± 86.20(51.55)	.00*
Dairy intake (gm)	188.14 ± 151.19(138.10)	162.01 ± 117.46 (145.37)	0.10	131.24 ± 140.22(108.75)	176.36 ± 135.82(138.1)	.02*
Junk intake (gm)	340.51 ± 201.89(305.28)	99.33 ± 105.11(67.46)	0.00*	273.89 ± 196.43(283.47)	156.46 ± 135.48(141.16)	.00*
Late/missed breakfast	24 (34.7%)	14 (20.2%)	0.026	33 (50.7%)	10 (15.3%)	.001*
Late/missed lunch	21 (30.4%)	10(14.4%)	0.011	20 (30.7%)	5 (7.69%)	.001*
Late/missed dinner	8 (11.5%)	3 (4.3%)	0.052	10 (15.3%)	4 (6.1%)	.042*

*Denotes p value less than 0.05

Results

Figure 1 gives the outline of PCOS patients randomized into two diet groups and their follow-up at 3 months and at one year. 168 patients were randomized to receive either HCD or ICHD ($n = 84$ in each group). Of 168 PCOS subjects, 134 followed at 3 months (69 in the HCD and 65 in the ICHD). 42(50%) patients in the HCD and 38(45%) in the ICHD continued with diet therapy at 3 months, while 27 patients in both the groups required drug therapy. 119 patients followed at one year, 60 in the HCD, and 59 in the ICHD diet subgroup. Of 49 subjects who did not follow at one year, 17 refused to come, 8 were transferred out of Delhi, 4 became pregnant, and 20 patients did not pick up telephone calls.

Table 3 Clinical, biochemical, and dietary profile of PCOS patients for PCOS subjects on hypocaloric diet only for one year

Parameters	0 month ($n = 26$)	3 months ($n = 26$)	1 year ($n = 26$)	p value*
Weight (kg)	64.31 ± 13.16	62.83 ± 14.37	63.52 ± 14.62	0.18
Cyclicity (months)	55.15 ± 32.87(50)	38.21 ± 10.68(35)	39.04 ± 14.19(35)	0.18[a,b]
MODHIRSCO	5.21 ± 2.74	4.47 ± 2.71	4.00 ± 1.987	0.004*[a]
Acne code	1.20 ± 0.41	0.57 ± 0.64	0.40 ± 0.63	0.00*[a,b]
GTT 0hour (mg/dl)	78.38 ± 9.54	80.79 ± 8.49	83.50 ± 13.31	0.025
GTT 2hour (mg/dl)	103.67 ± 21.00	100.54 ± 20.63	110.75 ± 23.80	0.64
Insulin 0H (μIU/ml)	12.15 ± 9.01	8.98 ± 4.38	8.25 ± 6.99	0.81
Insulin 2H (μIU/ml)	48.70 ± 28.75	53.48 ± 31.84	44.30 ± 35.05	0.44
Total cholesterol (mg/dl)	160.08 ± 40.63	160.08 ± 34.31	165.60 ± 45.74	0.44
Triglyceride (mg/dl)	95.54 ± 33.06	88.58 ± 52.73	111.80 ± 56.90	0.10
TSH (UU/ml)	2.88 ± 1.80	2.56 ± 1.21	2.54 ± 0.91	0.56
FSH (mIU/ml)	5.78 ± 2.17	6.36 ± 3.25	7.60 ± 3.25	0.02*[b]
LH (mIU/ml)	9.24 ± 9.36	9.21 ± 6.66	10.73 ± 12.06	0.94
Testosterone (nmol/l)	1.16 ± 0.51	1.25 ± 0.50	1.39 ± 0.79	0.37
DHEAS (μg/ml)	2.25 ± 0.95	2.83 ± 1.35	2.24 ± 0.84	0.18[c]
Free testosterone (pg/ml)	2.82 ± 1.19	3.39 ± 2.10	2.65 ± 1.56	0.44
AVR. energy (kcal)	1864.35 ± 526.25	1476.81 ± 358.73	1530.58 ± 384.51	0.00*[a,b]
CHO (%energy)	58.24 ± 5.24	57.99 ± 3.77	57.66 ± 6.02	0.88
PRO (%energy)	12.06 ± 1.25	14.01 ± 2.52	12.85 ± 1.59	0.004*[a]
FAT (%energy)	29.28 ± 5.20	27.48 ± 4.20	29.50 ± 6.08	0.42
Total fiber (gm)	34.11 ± 13.26	35.55 ± 9.47	31.13 ± 8.18	0.42
Soluble fiber (gm)	6.38 ± 2.57	7.18 ± 2.25	6.28 ± 2.17	0.44
Fruit intake (gm)	56.09 ± 68.09	86.65 ± 59.24	58.36 ± 94.06	0.06
Junk intake (gm)	307.02 ± 192.65	103.58 ± 116.50	208.57 ± 168.23	0.00*[a,b,c]
Late/missed breakfast	5 (19.2%)	4 (15.3%)	4 (15.3%)	0.747
Late/missed lunch	8 (30.27%)	5 (19.2%)	2 (7.69%)	0.111[b]
Late/missed dinner	3 (11.5%)	2 (7.69%)	1 (3.8%)	0.350

Parameters given as mean ± SD

*p value significant by repeated measures ANOVA or $a = 0$ m vs. 3 m; $b = 0$ m vs. 1 yr; $c = 3$ m vs. 1 y (post hoc analysis)

26 (31%) in the HCD and 30 (34%) in the ICHD group were satisfied with diet alone therapy at one year, while 34 patients in HCD group and 29 patients in the ICHD group required drug therapy at one year. While there was no difference in the effectiveness of the two diets either by the intention to treat or per protocol analysis at one year, around 30% patients in each group did not follow-up at one year.

Table 1 gives the comparative clinical and hormonal data of the HCD and ICHD subgroups at baseline. Patients in the ICHD group were slightly older; however, both the groups had comparable BMI and waist–hip ratios. The glucose, insulin, lipids, and physical activity were comparable in the two groups. Patients on ICHD had higher hirsutism score; however, menstrual cyclicity and androgen levels were comparable in the two groups. Patients on HCD had slightly higher total energy intake compared to the ICHD subgroup (mean 1750 kcal/day versus 1600 kcal/day, $p = 0.03$).

Table 2 gives the baseline and 3-month follow-up of PCOS patients on the HCD and ICHD groups. Only 50% patients (11/23) with caloric intakes (> 1800 kcal) followed in the ICHD group, whereas all 24 subjects in the HCD group with higher caloric intake followed at three months. There was a significant reduction in body weight in the HCD group while there was no change in weight in the ICHD group. Acne and menstrual cyclicity significantly improved in both the groups at 3 months (median 45 days vs. 35 days). While there was a mild reduction in hirsutism score with HCD, no change in hirsutism was observed with ICHD. There was no change in glucose or lipids or androgens; however, there was significant decrease in 0-h insulin levels with both HCD and ICHD. While the total energy reduced significantly with HCD, there was a slight increase in energy intake (100 kcal) with ICHD. This occurred as 24 out of 28 patients in ICHD group, who were missing any one major meal at baseline,

Table 4 Clinical, biochemical, and dietary profile of PCOS patients for PCOS subjects on isocaloric diet only for one year

Parameters	0 month ($n = 30$)	3 months ($n = 30$)	I year ($n = 30$)	p value*
Weight (kg)	58.15 ± 12.92	58.67 ± 13.38	58. 36 ± 12.35	0.25
Cyclicity (months)	50.90 ± 26.44(45)	41.63 ± 16.51(35)	38.37 ± 9.23(35)	0.27*[b]
MODHIRSCO	5.29 ± 4.81	5.13 ± 4.89	4.88 ± 4.54	0.04*
Acne code	1.22 ± 0.42	0.44 ± 0.51	0.11 ± 0.32	0.00*[a,b]
GTT 0hour (mg/dl)	79.33 ± 13.19	80.04 ± 11.30	89.55 ± 7.98	0.08*[c]
GTT 2hour (mg/dl)	110.74 ± 29.68	110.37 ± 27.90	114.50 ± 30.81	0.57
Insulin 0H (μIU/ml)	14.17 ± 7.44	10.35 ± 5.35	9.74 ± 4.09	0.51
Insulin 2H (μIU/ml)	60.94 ± 33.84	69.17 ± 47.14	56.19 ± 42.5	0.69
Total cholesterol (mg/dl) (TCH)	159.92 ± 30.11	157.92 ± 32.56	160.55 ± 28.2	086
Triglyceride (mg/dl)	97.88 ± 36.32	87.27 ± 30.93	90.68 ± 31.9	0.92
FSH (mIU/ml)	5.54 ± 1.62	5.48 ± 1.73	7.05 ± 2.55	0.008*[b,c]
LH (mIU/ml)	7.57 ± 5.41	10.11 ± 7.96	9.26 ± 7.94	0.58
Testosterone (nmol/l)(TESTO)	1.31 ± 0.65	1.42 ± 0.92	1.20 ± 0.51	0.48
DHEAS (μg/ml)	1.96 ± 0.92	2.04 ± 1.14	1.90 ± 0.87	0.20
Free testosterone (pg/ml)	2.71 ± 1.51	2.60 ± 1.51	3.05 ± 1.73	0.23
AVR. energy (kcal)	1554.26 ± 404.99	1704.46 ± 368.97	1539.25 ± 368.64	0.005*[a,c]
CHO (%energy)	59.03 ± 10.64	57.77 ± 6.34	57.86 ± 5.51	0.67
PRO (%energy)	13.40 ± 3.36	13.71 ± 1.80	13.31 ± 2.38	0.19[c]
FAT (%energy)	30.27 ± ± 6.52	28.60 ± 6.11	28.85 ± 5.25	0.48
Total fiber (gm)	30.09 ± 7.59	39.88 ± 12.43	33.20 ± 9.36	0.004*[a,c]
Soluble fiber (gm)	6.12 ± 2.05	7.88 ± 2.42	6.56 ± 1.71	0.00*[a,c]
Fruit intake (gm)	36.72 ± 57.19	86.13 ± 88.09	45.23 ± 52.19	0.006*[a]
Junk intake (gm)	311.95 ± 215.11	143.12 ± 123.42	148.84 ± 127.69	0.001*[a,b]
Late/missed breakfast	12 (40%)	4 (13.33%)	6 (20%)	0.031[a,b]
Late/missed lunch	7 (23.33%)	2 (6.66%)	6 (20%)	0.166[a]
Late/missed dinner	3 (10%)	2 (6.66%)	4 (13.33%)	0.391

Parameters given as mean ± SD

*p value significant by repeated measures ANOVA

a = 0 m vs. 3 m; b = 0 m vs. 1 yr; c = 3 m vs. 1 y (post hoc analysis)

now started taking all the three meals after dietary advice. There was a significant reduction in fat and junk intake whereas there was a significant increase in protein, fruits, and fiber in both the groups at three months. The meal timings significantly improved for breakfast, lunch, and dinner at three months for both the diet groups.

There was no change in the body weight, glucose, insulin, and androgens with both the diets at one year (Tables 3 and 4). There was a significant improvement in acne and menstrual cyclicity. There was a modest decrease in hirsutism score with HCD, while no change was observed with ICHD. There was a reduction in fat and junk intake and increase in fruit intake at one year compared to baseline; however, there was a deterioration compared to diet at three months in both the groups. There was an improvement in the meal timings compared to baseline diet (Fig. 2).

Table 5 compares the mean differences (delta change 0–3 months and 0-one year) in parameters between the two diets at three months and one year. Both the diets were similar in terms of changes in the clinical and biochemical parameters including menstrual cyclicity and hirsutism except weight which improved significantly with the HCD diet compared to the ICHD diet at three months.

Discussion

We studied the comparative effectiveness of hypocaloric versus isocaloric healthy diet (HCD vs. ICHD) in women with PCOS over a duration of one year. Isocaloric diet is a diet identical in total caloric intake but different in terms of macronutrient distribution. Previous studies have used different isocaloric diets (low-protein high-carbohydrate diet versus high-protein low-carbohydrate diet [17, 18] or low-carbohydrate high-fat diet versus high-carbohydrate low-fat diet) [19, 20]. Due to paucity of Indian studies on diet in PCOS patients, we have prescribed diet with macronutrient distribution as per diet for PCOS by Gower BA which is also are very close to the Indian recommendations [12,13,21]. On

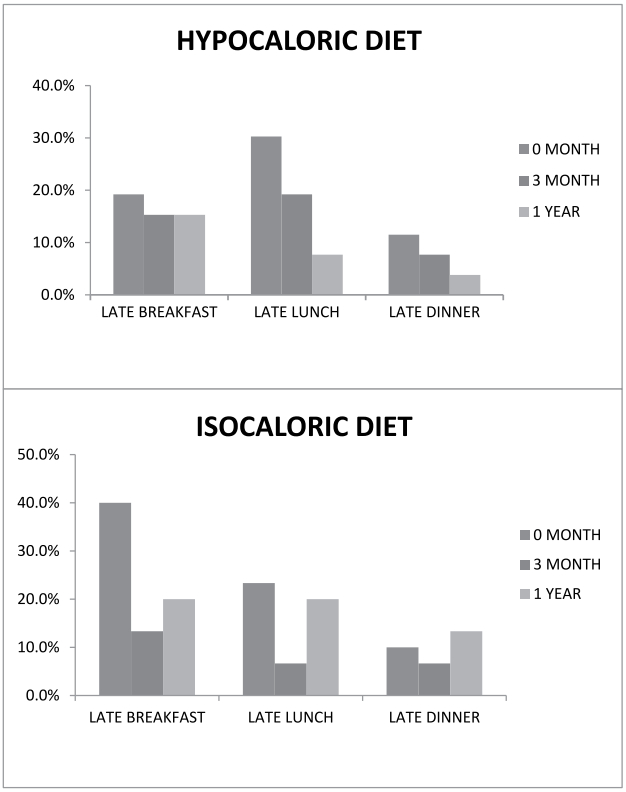

Fig. 2 Meal patterns of PCOS patients on two diets over a period of one year

the other hand, HCD is a diet low in calories aimed to sustain negative energy balance and, thereby, weight loss. The reduction in the calories consumed is variously described as absolute reduction from baseline (around 400–750 kcal/d) or a relative reduction from baseline (25%), or an intake below that required for weight maintenance [22, 23]. We have prescribed a hypocaloric diet with energy deficit of 500 kcal/day [22]. We added clause (20 kcal/kg for obese and 25 kcal/kg for lean whichever was lower) for patients who had baseline intake of more than 2500 kcal/day [7].

A systematic review by Moran et al. concluded that weight loss should be considered as the main approach to dealing with PCOS, regardless of dietary composition [24]. The short-term effectiveness of hypocaloric diets with varying macronutrient distribution has been shown earlier [7, 8, 22]. While there are more studies available on the hypocaloric diets, there is less data on isocaloric diets available in PCOS patients. Barr et al. for the first time demonstrated improvement in insulin sensitivity in 26 PCOS women on low glycemic index isocaloric diet in 2013 [25]. Subsequently, Goss et al., Gower et al., and Panico et al. also reported favorable metabolic effects and loss of fat mass with lower carbohydrate isocaloric diets [21, 26, 27]. However, to the best of our knowledge, we could not come across any randomized study comparing hypocaloric or isocaloric diets in PCOS subjects.

In the present study, both the HCD and ICHD groups were weight-matched and had comparable clinical and biochemical parameters except hirsutism at baseline. We observed that while the hypocaloric diet was more effective in reducing weight, both the diets were effective in improving menstrual cyclicity and acneform eruptions. While most of our patients had mild hirsutism (HS < 15), the effect on hirsutism was modest by both the diets at one year. The

Table 5 Mean difference in parameters between the isocaloric and hypocaloric diet at 0–3 months and 0–1 year

Mean difference in parameters from 0 to 3 months				Mean difference in parameters from 0 to one year		
Parameters	ICHD (66)	HCD (68)	*p* value	ICHD (30)	HCD (26)	*p* value*
Weight (kg)	− 0.66 ± 6.98	1.34 ± 4.60	0.011*	0.03 ± 3.09	− 2.02 ± 5.13	0.075
Cyclicity	18.10 ± 29.27	13.70 ± 31.46	0.31	12.53 ± 26.31	16.11 ± 28.90	0.43
MODHIRSCO	0.047 ± 1.12	0.51 ± 1.12	0.07	0.41 ± 0.87	1.21 ± 2.39	0.29
GTT 0hour (mg/dl)	− 0.54 ± 12.33	0.33 ± 12.79	0.80	− 12.90 ± 18.09	− 6.75 ± 13.92	0.33
GTT 2hour (mg/dl)	0.53 ± 28.50	− 5.27 ± 28.72	0.23	− 2.72 ± 24.32	− 8.93 ± 31.55	0.80
Insulin 0H (μIU/ml)	3.25 ± 11.01	3.35 ± 8.78	0.67	4.47 ± 8.51	1.49 ± 8.12	0.55
Insulin 2H (μIU/ml)	− 4.22 ± 55.08	0.62 ± 43.70	0.60	5.37 ± 51.26	1.82 ± 41.18	0.60
Total cholesterol (mg/dl)	− 0.80 ± 25.95	− 1.13 ± 19.01	0.90	− 1.29 ± 21.60	− 1.00 ± 20.68	1.00
Triglyceride (mg/dl)	0.67 ± 43.59	− 1.87 ± 49.89	0.61	9.23 ± 28.12	− 17.06 ± 50.79	0.14
FSH (mIU/ml)	− 0.31 ± 1.40	0.006 ± 2.51	0.24	− 1.54 ± 2.19	− 1.63 ± 2.83	0.90
LH (mIU/ml)	− 3.39 ± 11.97	1.05 ± 10.26	0.21	− 1.53 ± 10.23	− 2.15 ± 12.37	0.79
Testosterone (nmol/l)	− 0.05 ± 0.60	0.03 ± 0.58	0.59	0.11 ± 0.76	− 0.26 ± 0.93	0.16
Free testosterone (pg/ml)	0.34 ± 1.99	0.05 ± 2.16	0.44	− 0.54 ± 2.04	0.06 ± 1.75	0.17
SHBG (nmol/l)	− 6.63 ± 87.81	2.80 ± 67.59	0.70	40.62 ± 69.22	13.17 ± 54.50	0.26
Androstenedione (ng/ml)	0.03 ± 2.54	0.008 ± 2.38	0.79	− 0.90 ± 2.90	− 1.41 ± 1.44	0.42

p value* significant using Mann–Whitney *U* test

effectiveness of both the diets was similar (around 30% at one year) with both the per protocol and the intention to treat analysis. It is strange that in spite of no improvement in weight of the patients, the ICHD diet was as effective as the HCD diet in improving symptoms. The quality of food choices in those on ICHD improved with reduction in junk intake and increase of pulses, fruits, and fiber intake. The food choices given to our patients were closer to the DASH diet (rich in fruits, vegetables, fibers, legumes, low-fat dairy, and low in cholesterol, refined carbohydrates, and processed food), which has been shown to improve insulin sensitivity in PCOS subjects in a recent metanalysis [28]. Insulin reduced with ICHD at three months in our study. Apart from food choices, the meal timings also improved with significantly lesser number of patients taking late breakfast or late lunch at follow-up.

Late eating is associated with impaired glucose tolerance and carbohydrate oxidation, which may affect insulin action and thereby the PCOS phenotype [29, 30]. Jakubowicz et al. observed that increase in breakfast calories with reduction in caloric intake at dinner results in improved insulin sensitivity and decreased activity of cytochrome 17 hydroxylase, which improves hyperandrogenism and menstrual cycles in PCOS women [31]. We also observed for the first time that meal timings of PCOS patients were significantly different from weight-matched controls and that both the late breakfast and late lunch were significantly associated with hirsutism and irregular periods in subjects with PCOS [10]. We have randomized the same cohort published above into two groups on ICHD and HCD. It is possible that improved meal timings and improvement of food choices resulted in reduction of insulin levels with consequent improvement in clinical manifestations in our subjects on ICHD.

There were some limitations with the ICHD diet. Patients with baseline caloric intakes larger than 1800 kcal did not follow-up at three months thereby indicating ineffectiveness of ICHD with higher calorie intakes. Also, ICHD was ineffective in reducing weight over short term. While both the diets were equally effective, it should be noted that only 30% wanted to continue with diet alone at one year in both the groups. There was a deterioration of food habits at one year with subjects taking more fat and junk and lesser fruits, pulses, and fiber compared to diet at three months; nevertheless, food choices and meal timings were still better compared to their baseline diet. Such a non-compliance and lack of adherence to long-term diet therapy is well known [22–24]. A non-significant reduction in insulin levels with HCD over one year may be related to fewer numbers at follow-up, deterioration of food habits or other non-recorded stressful events in routine life.

We observed that HCD was effective in weight loss after 3 months; however, no significant change in weight was observed at one year. Long-term studies on low-calorie diets indicate that while the initial results may be impressive, around 75–80% of the people trying to reduce body weight fail in terms of long-term weight loss maintenance [23, 32]. The underlying mechanisms for weight regain or lack of effect over long-term hypocaloric diet are poorly understood. Adaptations in energy expenditure, increase in fractional energy absorption, and lack of compliance are mechanisms postulated in pathophysiology of less than expected weight loss with HCD [23]. Brain energy homeostasis is also suggested to play a role in failure of therapy over long term. Studies show that obese individuals display reduced levels of high energy phosphate and phosphocreatinine that predicts subsequent food consumption [32, 33]. NADH decrease induced by repetitive low caloric dieting could lead to boosted food craving and consumption to satisfy the cerebral energy needs [33]. This effect is known as weight cycling and describes repeated periods of initially successful weight loss followed by regain even beyond the initial body weight.

To the best of our knowledge, this is the third largest study with a long follow-up of one year [10]. Possibly, this is also the first comparative randomized assessment of hypocaloric and isocaloric diet in PCOS patients. Both the groups were weight-matched and had comparable waist–hip ratios, androgens, and glucose levels at baseline. Limitations include loss to follow-up, greater in the patients with high caloric intakes in the ICHD group. Nevertheless, we have tried to address this problem by the intention to treat analysis. Another limitation is a single blinded nature of the study, where dietician knew which study arm patients were allocated. While recall bias may be a limitation compared to weighted prospective methods, a recent review concluded that dietary recall is a convenient and valid method of dietary assessment that gives accurate dietary information when collected by a trained interviewer using standardized methods [34]. Previous studies have indicated that the recall bias can be reduced by multiple pass questioning by trained dieticians with special emphasis on forgotten foods and direct probing [35–37]. We believe that detailed interview by our experienced dieticians probing meal patterns and timings, direct probing of junk and snacks may have reduced the recall bias in the present study.

Conclusion

The present study demonstrated that isocaloric diets can be as effective in improving clinical symptoms as hypocaloric diets in about 30% of patients with mild symptoms over long term. However, hypocaloric diets cause a greater weight loss over short term. The improvement of clinical symptoms by eucaloric diets is related to the improvement of food choices and correction of meal timings. Isocaloric diets are not effective if patients have a high caloric intake at baseline.

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Author contribution BK conceptualized the study, was involved in all stages, and wrote the manuscript. SP, BP, and PS were involved in data collection, statistical analysis, and literature review including manuscript preparation. NS and LS were involved in data collection, laboratory data, and manuscript preparation. All the authors approved the final version of the manuscript.

Declarations

Ethics approval This study was approved by the Insti-tutional Ethics Committee (IRIS ID no. 2013-0976). Consenting subjects and controls underwent a detailed history and physical examination including anthropometry.

Conflict of interest The authors declare no competing interests.

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