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Assessing the efficacy of spironolactone on adult acne in subjects with polycystic ovary syndrome

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Abstract---Aim: The present prospective clinical study was conducted to assess the long-term spironolactone therapy and its effect with and without dietary-induced weight-loss, on insulin levels, lipid profile, and clinical features in females with PCOS (polycystic ovary syndrome). Methods: The present study included 22 females 12 normal weight and 10 obese within the age of 17-32 years having symptoms of PCOS including hyperandrogenism with clinical or biochemical evidence with amenorrhea and/or oligomenorrhea. These subjects were assessed before spironolactone therapy and after 100mg/day spironolactone orally for 12 months. Lifestyle modification was advised for obese females. Before starting and following antiandrogen therapy, metabolic, endocrine, and clinical parameters were assessed. Results: Spironolactone orally resulted in a significant reduction of triglycerides in overweight females and an increase in HDL (high-density lipoproteins) in subjects who were lean and have normal weight. After 12 months of oral spironolactone therapy, the area under the curve of insulin, insulin resistance with hemostasis model, and levels of insulin during OGTT at 60 minutes were significantly reduced in obese females. In females with PCOS following

therapy, no negative change in insulin sensitivity and secretion and weight loss was seen after pharmacologic treatment. Conclusion: The present study concludes that spironolactone therapy is effective on androgenic clinical aspects in subjects with PCOS. It was also seen that long-term spironolactone therapy has no negative impact on glucose metabolism and lipid profile. These beneficial effects on lipid metabolism and glucose metabolism were seen with weight loss in PCOS subjects who were overweight.

Keywords---Adult acne, Efficacy, polycystic ovary syndrome, spironolactone, overweight females.

Introduction

Polycystic ovary syndrome (PCOS) is seen in nearly 7% of the females in the reproductive age group with associated hyperinsulinism and insulin resistance seen in most of these females. Obesity-associated with insulin resistance which is seen in nearly half of the females with PCOS increases the risk of insulin resistance in these females leading to diabetes mellitus. Insulin has various effects on the female ovary in various ways which may finally lead to increased androgens and disturbed ovulation in many females with PCOS.[1]Alternatively, insulin resistance may be caused by androgens via changes in the fiber structure of the muscles. Hyperinsulinemia and an increase in androgens can lead to PCOS of varying degrees in females. Various therapeutic efforts have been made on agents that could modify or treat the clinical manifestations associated with these conditions.[2]

Previous literature data has established that when lipid profiles of subjects with PCOS are assessed, the results have shown that a decrease in high-density lipoproteins is seen along with an increase in triglycerides, very low-density lipoproteins, low-density lipoproteins, and total cholesterol levels. These abnormal values in lipid profile variables can lead to concerning atherogenic consequences.[3] High-density lipoproteins and low-density lipoproteins are reliable biomarkers to predict the occurrence of coronary cardiac diseases in the affected subjects as well established by the previous literature data.[4] In females with PCOS, overweight is associated with menstrual disorders as clearly linked in previous literature data. Also, weight loss can cure infertility and menstrual disorders associated with excess weight in females. In addition, lifestyle modification including physical activity and food restrictions is the first method and approach in obese females having PCOS.[5] The present prospective clinical study was conducted to assess the long-term spironolactone therapy with an oral dose of 100mg/day and its effect with and without dietary-induced weight-loss, on insulin levels, lipid profile, and clinical features in females with PCOS (polycystic ovary syndrome) in normal-weight and obese females. Also, all the overweight females were suggested to take a low-calorie diet along with pharmacologic therapy.

Materials and Methods

The present prospective clinical study was conducted to assess the long-term spironolactone therapy and its effect with and without dietary-induced weight-loss, on insulin levels, lipid profile, and clinical features in females with PCOS (polycystic ovary syndrome). The study was conducted after obtaining clearance from the concerned Ethical committee. The study population was comprised of the females visiting the Outpatient department of Obstetrics and gynecology of the Institute.

The present study included 22 females 12 normal weight and 10 obese within the age of 17-32 years having symptoms of PCOS including hyperandrogenism with clinical or biochemical evidence with amenorrhea and/or oligomenorrhea. The subjects were referred for alopecia, acne, and/or hirsutism. All the included females had the non-systemic disease and did not take any medication that can affect the hormonal levels. PCOS was diagnosed based on endocrinological abnormalities including increased and Androstenedione, DHEA-S, and testosterone levels in the early follicular phase, chronic anovulation including amenorrhea and/or oligomenorrhea, hypergonadism signs including hirsutism, seborrhea, alopecia, and/or acne, and FG (modified Ferriman-Gallwey scores) of more than 8. Prolactin and thyroid functions were normal in all the subjects. Informed consent was taken from all the subjects before final inclusion after explaining the detailed study design.

The parameters recorded at baseline in all the study subjects were OGTT, blood pressure, BMI, acne (Luck's score), alopecia (Ludwig's score), FG scores. Endocrine factors include Luteinizing hormone (LH), FSH (Follicle-stimulating hormone), prolactin, Androstenedione, DHEA-S, and testosterone, and metabolic parameters including triglycerides, total cholesterol, and high-density lipoproteins. All the blood parameters were assessed after collecting 10 hours fasting blood sample intravenously. After completion of 12 months of taking oral spironolactone 100mg/day with food restrictions and lifestyle modification in obese females with PCOS, the parameters reassessed were $HOMA_{IR}$, $AUX_{insulin,}$ OGTT, HDL, triglycerides, total cholesterol, FG scores, BP, BMI< and menstrual history. The immunometric assay was used to measure plasma insulin and immunoradiometric assay for measuring androgens. The collected data were subjected to the statistical evaluation using SPSS software version 21 (Chicago, IL, USA) and one-way ANOVA and t-test for results formulation. The data were expressed in percentage and number, and mean and standard deviation. The level of significance was kept at $p<0.05$.

Results

The present prospective clinical study was conducted to assess the long-term spironolactone therapy and its effect with and without dietary-induced weight-loss, on insulin levels, lipid profile, and clinical features in females with PCOS (polycystic ovary syndrome). The present study included 22 females 12 normal weight and 10 obese within the age of 17-32 years having symptoms of PCOS including hyperandrogenism with clinical or biochemical evidence with amenorrhea and/or oligomenorrhea. The subjects were referred for alopecia,

acne, and/or hirsutism. In 5 females even after therapy, diet restriction, and lifestyle modification, the weight did not change these females constituted Group I and Group II constituted females whose weight reduced significantly after 1 year of spironolactone therapy. The study results have shown that at baseline acne was seen in 3 females having normal weight and 2 overweight females, alopecia was seen in 6 females including 2 normal weight and 4 overweight females which decreased in 2 females post spironolactone therapy. The menstrual cycle was irregular in all the study subjects at baseline with oligomenorrhea in 19 females and amenorrhea in 3 females. Following treatment, the menstrual cycle improved in 4 overweight females and 1 from group I and 3 from group II. Polymenorrhea was seen inn3 females postoperatively who were overweight.

On assessing the baseline and post-treatment clinical and metabolic parameters in normal weight and overweight females of the study subjects, it was seen that nearly all parameters were statistically comparable in all the subjects except a few (Table 1). The mean age in normal weight and overweight females was 23.6±4.7 years and 22.1±5.4 years respectively in the two groups. It was seen that OGTT (Oral Glucose Tolerance Test) in overweight females post spironolactone therapy reduced significantly from 67.1±13.7 to 51.6±24.5. Levels of high-density lipoproteins increased considerably in lean females from 1.13±0.5 to 1.49±0.3 following 13 months of spironolactone. This was a statistically significant increase. Levels of total triglycerides in obese females decreased from 1.56±0.3 to 1.22±0.8 which was statistically significant. Also, BMI improvement was seen in overweight females following pharmacologic therapy from 29.2±3.8 to 27.2±4.5. This difference was also statistically significant. Other parameters as $HOMA_{IR}$, AUCinsulin, fasting glucose, total cholesterol, blood pressure, and FG scores did not change significantly following spironolactone use for 1 year in either lean or overweight females (table 1).

The present study also assessed clinical and metabolic Baseline and post-treatment parameters in two groups of study females with PCOS (Table 2). The study results have shown that there were 4 females from the lean group and 5 females from the overweight group with a mean age of 19.6±4.8 and 23.8±5.5 years respectively. The $AUC_{insulin}$ levels in overweight females showed a significant reduction from 6092±3789 to 4502±2118 with a non-significant reduction in normal weight females. $HOMA_{IR}$ levels also showed a significant reduction in overweight females from 3.4±0.2 to 1.8±0.6 with a non-significant increase in normal e=weight females. Fasting glucose levels showed a non-significant change in both lean and obese females following 12 months of spironolactone therapy. OGTT 60 mins showed a significant decrease following pharmacologic therapy in obese females from 62.8±14.2 to 41.1±24.5 mmol/l. Total triglycerides in lean females showed a significant reduction from 1.3±0.3 to 1.0±0.5 in lean females and a non-significant reduction in overweight females. Also, BMI showed a significant reduction in overweight females after spironolactone from 30.1±3.7 to 26.1±3.6. Non-significant changes in HDL, total cholesterol, and FG scores were seen following 12 months of spironolactone in both lean and overweight females (Table 2).

Discussion

The present prospective clinical study was conducted to assess the long-term spironolactone therapy and its effect with and without dietary-induced weight-loss, on insulin levels, lipid profile, and clinical features in females with PCOS (polycystic ovary syndrome). The present study included 22 females 12 normal weight and 10 obese within the age of 17-32 years having symptoms of PCOS including hyperandrogenism with clinical or biochemical evidence with amenorrhea and/or oligomenorrhea. The subjects were referred for alopecia, acne, and/or hirsutism. In 5 females even after therapy, diet restriction, and lifestyle modification, the weight did not change these females constituted Group I and Group II constituted females whose weight reduced significantly after 1 year of spironolactone therapy.

The study results have shown that at baseline acne was seen in 3 females having normal weight and 2 overweight females, alopecia was seen in 6 females including 2 normal weight and 4 overweight females which decreased in 2 females post spironolactone therapy. The menstrual cycle was irregular in all the study subjects at baseline with oligomenorrhea in 19 females and amenorrhea in 3 females. Following treatment, the menstrual cycle improved in 4 overweight females and 1 from group I and 3 from group II. Polymenorrhea was seen inn3 females postoperatively who were overweight. These results were consistent with the findings of Legro Rs et al[6] in 2001 and Vrbikova J et al[7] in 2005 where authors showed similar results to the present study.

Baseline and post-treatment clinical and metabolic parameters in normal weight and overweight females of the study subjects when assessed, it was seen that nearly all parameters were statistically comparable in all the subjects except a few. The mean age in normal weight and overweight females was 23.6±4.7 years and 22.1±5.4 years respectively in the two groups. It was seen that OGTT (Oral Glucose Tolerance Test) in overweight females post spironolactone therapy reduced significantly from 67.1±13.7 to 51.6±24.5. Levels of high-density lipoproteins increased considerably in lean females from 1.13±0.5 to 1.49±0.3 following 13 months of spironolactone. This was a statistically significant increase. Levels of total triglycerides in obese females decreased from 1.56±0.3 to 1.22±0.8 which was statistically significant. Also, BMI improvement was seen in overweight females following pharmacologic therapy from 29.2±3.8 to 27.2±4.5. This difference was also statistically significant. Other parameters as $HOMA_{IR}$, AUCinsulin, fasting glucose, total cholesterol, blood pressure, and FG scores did not change significantly following spironolactone use for 1 year in either lean or overweight females. These results were in agreement with the studies of Haas DA et al[8] in 2003 and Spritzer Tm et al[9] in 2000 where spironolactone showed efficacy in females with PCOS.

On evaluating the clinical and metabolic, baseline and post-treatment parameters in two groups of study females with PCOS. The study results have shown that there were 4 females from the lean group and 5 females from the overweight group with a mean age of 19.6±4.8 and 23.8±5.5 years respectively. The $AUC_{insulin}$ levels in overweight females showed a significant reduction from 6092±3789 to 4502±2118 with a non-significant reduction in normal weight females. $HOMA_{IR}$

levels also showed a significant reduction in overweight females from 3.4±0.2 to 1.8±0.6 with a non-significant increase in normal e=weight females. Fasting glucose levels showed a non-significant change in both lean and obese females following 12 months of spironolactone therapy. OGTT 60 mins showed a significant decrease following pharmacologic therapy in obese females from 62.8±14.2 to 41.1±24.5 mmol/l. Total triglycerides in lean females showed a significant reduction from 1.3±0.3 to 1.0±0.5 in lean females and a non-significant reduction in overweight females. Also, BMI showed a significant reduction in overweight females after spironolactone from 30.1±3.7 to 26.1±3.6. Non-significant changes in HDL, total cholesterol, and FG scores were seen following 12 months of spironolactone in both lean and overweight females. This was comparable to the findings of Ganie MA et al[10] in 2004 and Ganie MA et al[11] in 2013 where authors showed improved clinical and metabolic features in PCOS females following spironolactone use.

Conclusion

Within its limitations, the present study concludes that spironolactone is effective in treating hyperandrogenism in subjects with PCOS with no remarkable associated side-effects with the long-term use of spironolactone on glucose and lipid metabolism. Beneficial effects of spironolactone on lipid profile and insulin resistance are seen in subjects with PCOS who were exposed to a high risk of metabolic and cardiovascular disease. However, the present study had a few limitations including small sample size, cross-section nature, and geographical area biases. Hence, more longitudinal studies with larger sample size and longer monitoring period will help reach a definitive conclusion.

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Tables

Table 2
Clinical and metabolic Baseline and post-treatment parameters in two groups of study females with PCOS

Parameter	Normal weight females (BMI <25) (n=4)		Overweight females (BMI >25) (n=5)	
	Pre-op	Post-op	Pre-op	Post-op
Age (years)	19.6±4.8		23.8±5.5	
$AUC_{insulin}$	5882±1590	5006±2187	6092±3789	4502±2118*
$HOMA_{IR}$	4.3±1.3	4.4±1.6	3.4±0.2	1.8±0.6*
Fasting Glucose (mmol/l)	18.4±6.6	16.6±3.4	17.6±3.2	13.7±7.8
OGTT 60 min (mmol/l)	73.2±15.7	66.4±18.0	62.8±14.2	41.1±24.5*
OGTT 120 min (mmol/l)	40.6±13.5	44.8±21.4	31.8±23.5	15.55±6.6
HDL (mmol/l)	1.14±0.3	1.16±0.4	1.0±0.3	1.0±1.3
Total cholesterol (mmol/l)	4.54±0.3	4.70±0.6	4.47±0.2	4.87±0.2
Total triglycerides (mmol/l)	1.3±0.3	1.0±0.5*	1.4±0.3	1.0±0.4
BMI (kg/m^2)	28.4±4.9	28.8±5.6	30.1±3.7	26.1±3.6*
FG scores	10.4±2.9	5.4±2.9	9.5±3.5	4.8±3.0

Table 1
Baseline and post-treatment parameters in normal weight and overweight females with PCOS

Parameter	Normal weight females (BMI <25) (n=12)		Overweight females (BMI >25) (n=10)	
	Pre-op	Post-op	Pre-op	Post-op
Age (years)	23.6±4.7		22.1±5.4	
$AUC_{insulin}$	3862±1302	3633±1248	6004±2964	4712±2072
$HOMA_{IR}$	2.04±0.7	2.3±0.9	3.4±1.1	2.7±1.5
Fasting Glucose (mmol/l)	9.3±3.8	10.4±2.6	17.2±5.7	14.7±6.2
OGTT 60 min (mmol/l)	39.3±15.41	39.5±14.4	67.1±13.7	51.6±24.5*
OGTT 120 min (mmol/l)	40.5±32.3	31.4±14.23	38.4±20.6	27.6±20.3
HDL (mmol/l)	1.13±0.5	1.49±0.3*	1.18±0.1	1.17±0.13
Total cholesterol (mmol/l)	4.37±1.7	4.8±1.5	4.46±0.2	4.76±0.5
Total triglycerides (mmol/l)	0.88±0.4	0.95±0.5	1.56±0.3	1.22±0.8*
BMI (kg/m^2)	22.2±2.1	22.1±2.2	29.2±3.8	27.2±4.5*
Diastolic B.P (mmHg)	80.2±3.7	75.6±5.4	79.4±3.1	77.7±5.2
Systolic B.P (mmHg)	126.7±9.3	115.6±6.8	121.5±10.3	118.1±10.1
FG scores	12.4±2.7	6.6±3.67	10.3±2.9	5.4±2.8