The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 2728-2733

Effects of Thioctic Acid on the Hyperinsulinemia and Ovarian Volume in Female Patients with Polycystic Ovary Syndrome

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ABSTRACT

Background: Many scientists believe that elevated insulin levels are the primary cause of polycystic ovarian syndrome (PCOS). The hyperinsulinemia of obese women can be lowered by taking thioctic acid (Thioctacid-HR).

Objective: The aim of the current work was to evaluate the effect of thioctic acid (Thioctacid-HR) on hyperinsulinemia, insulin resistance, menstrual function, and the volume of the ovaries in patients with PCOS.

Patients and methods: This comparative, interventional, prospective randomized clinical study included a total of 38 women with PCOS, attending at Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospitals. Patients were randomly assigned into two equal sized groups of 19 subjects each by closed envelop technique as follow: group I (Case group) received Thioctic acid for 3 months and group II (Control Group) with no interventional treatment.

Results: Regarding fasting and post prandial insulin, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in a significant decrease in the fasting and post prandial insulin after treatment. Also, there was a significant decrease in HOMA-IR after treatment.

Conclusion: It could be concluded that **t**hioctic acid has significant effect on PCOs clinically but no effect on ultrasound findings. Also, it decreases insulin level after 6 months. Therefore, Thioctic acid could help in treatment of PCOS.

Keywords: Thioctic acid, Polycystic ovary syndrome, Hyperinsulinemia.

INTRODUCTION

When two or more of the following symptoms are present, a clinical diagnosis of polycystic ovarian syndrome can be made: persistent oligo-ovulation or anovulation; excess androgen production; and polycystic ovaries. Ovulatory infertility is the leading cause of infertility in developed countries, affecting between 5 and 10 percent of reproductive-age women. Menstrual dysfunction and the androgen-related symptoms of hirsutism, acne, and hair loss are common clinical presentations [(1)].

Hyperandrogenism and chronic anovulation in women without particular adrenal and pituitary gland disorders characterize polycystic ovary syndrome, a diverse clinical condition. Some people may have a history of polycystic ovary syndrome in their families, but the underlying cause of this condition is still unknown. Menstrual irregularities, hirsutism, acne, and, less frequently, a male pattern of alopecia typically emerge around the time of perimenarche. Metabolic disorders, such as obesity and insulin resistance with hyperinsulinemia, have been linked to polycystic ovarian syndrome as well [(2)].

In addition to being the leading source of androgen excess in females of reproductive age, polycystic ovary syndrome (PCOS) is a prevalent endocrine condition affecting this population. PCOS is characterized by a wide range of symptoms, which makes diagnosis challenging and has led to definitional debates. Polycystic ovary syndrome (PCOS) is a syndrome characterized by amenorrhea, hirsutism, and polycystic ovaries, and it was first described in a 1935 paper by Stein and Leventhal [(3)].

Many scientists believe that elevated insulin levels are the primary cause of polycystic ovarian syndrome (PCOS). Hyperinsulinemia in PCOS patients can be effectively treated with the insulin sensitizers (biguanides, glitazones), which has led to menstrual cycle and fertility normalization in over half of patients [(4)]. Patients with polycystic ovarian syndrome and hyperinsulinemia in addition to liver illness may benefit from thioctic acid because of its long-standing reputation as an efficient hepatoprotector (nonalcoholic steatosis, cirrhosis, or cirrhosis). Patients with PCOS who were overweight and hyperinsulinemic on an oral glucose tolerance test responded favorably to a combination of alpha lipoic acid and MYO. Positive effects were also seen in a subset of those who were overweight and had a first-degree relative with diabetes [(5)].

Reducing hyperinsulinemia using thioctic acid helps obese men and women lose weight, enhance insulin sensitivity, and normalize their lipid and carbohydrate metabolism [(6)].

Therefore, in this trial, we aimed to evaluate the effect of thioctic acid (Thioctacid-HR) on hyperinsulinemia, insulin resistance, menstrual function, and the volume of the ovaries in patients with PCOS.

PATIENTS & METHODS

This comparative, interventional, prospective randomized clinical study included a total of 38 women with PCOS, attending at Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospitals.

Received: 03/10/2022
Accepted: 06/12/2022

Patients were randomly assigned into two equal sized groups of 19 subjects each, by closed envelop technique as follow: **group I (Case group)** received Thioctic acid for 3 months and **group II (Control Group)** with no interventional treatment.

Inclusion criteria: Patients with PCOS using the revised Rotterdam criteria:

- oligo-anovulation or anovulation plus any next findings: hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-10 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary morphology on ultrasonography).
- Age between 18 and 35.
- Patients receiving no hormonal therapy during enrolling in the study.

Exclusion criteria: Diabetes Mellitus, on hormonal contraception

All patients were subjected to:

a) Complete history taking of clinical importance including complete Personal history, menstrual, obstetric, surgical history as well as any family history including maternal complications.

b) General and local examinations with special emphasis on vital data, BMI, Inspection hyperandrogenic manifestations e.g., hirsutism, acne.

c) Investigations: Basal hormonal studies on day 2 of cycle include serum FSH, LH, and prolactin levels, thyroid stimulating hormone was measured on day 2 of spontaneous menstrual cycle, and fasting blood glucose.

d) Imaging: Basal U/S on day 3 of the cycle to detect ultra-sonographic criteria of PCO and detection of ovarian volume.

- To perform the procedure, the women underwent the lithotomy position. The transducer was placed into the posterior vaginal fornix via a latex condom and gel. The size of both ovaries was measured. Furthermore, PCOS diagnostic criteria.

e) Thioctic acid pills 600 mg were used once daily, preferably 30 minutes before breakfast.

f) Hyperinsulinemia and ovarian volume six-month follow-up by baseline ultrasound and fasting glucose.

***Ethical Consideration*:**

This study was ethically approved by Zagazig University's Research Ethics Committee (ZU-IRB #6043/12-04-2020). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

Data was analyzed using SPSS 21 (Statistical Package for the Social Services) (SPSS). The findings were displayed using both tabular and graphical formats. Results were displayed using standard statistical measures such as means, medians, standard deviations, and confidence intervals. The accuracy of the data was demonstrated with the help of statistics. The student's t test (T) is utilized. Pearson Chi-Square and Chi-Square for Linear Trend were used to analyse the quantitatively diverse data (X^2). In this example, a P value of 0.05 or less was judged statistically significant.

RESULTS

Table (1) shows that the average age was 28.68±2.1 years for thioctic acid group and 29.78±2.57 years for control group respectively with no significant difference between both groups. Also, there were no significant differences as regard BMI or parity or mode of delivery and the majority were Parity (2) and had CS.

Table (1): Basic demographic and obstetric history distribution between the studied groups

			Thioctic acid group	Control group	t/ X^2	P
Age (years)			28.68±2.1	29.78±2.57	1.448	0.156
BMI (kg/m^2)			26.08±1.31	26.41±2.82	0.464	0.645
Parity	I	N	6	7		
		%	31.6%	36.8%		
	II	N	9	9	0.22	0.89
		%	47.4%	47.4%		
	III	N	4	3		
		%	21.1%	15.8%		
Previous mode of delivery	CS	N	12	13		
		%	63.2%	68.4%		
	VD	N	7	6	0.11	0.73
		%	36.8%	31.6%		
Total		N	19	19		
		%	100.0%	100.0%		

There was no significant difference between groups as regard clinical finding (Table 2).

Table (2): Clinical presentation distribution between the studied groups

			Group		X^2	P
			Thioctic acid group	Control group		
Cycle Irregularity	-VE	N	12	11		
		%	63.2%	57.9%		
	+VE	N	7	8	0.11	0.74
		%	36.8%	42.1%		
Hirsutism	-VE	N	12	13		
		%	63.2%	68.4%		
	+VE	N	7	6	0.11	0.73
		%	36.8%	31.6%		
Total		N	19	19		
		%	100.0%	100.0%		

There was no significant difference between groups as regard ultrasound finding (Table 3).

Table (3): Ultrasonography features distribution between the studied groups

			Thioctic acid group	Control group	X^2	P
Ovary	Both	N	7	8		
		%	36.8%	42.1%		
	Left	N	4	5	0.46	0.79
		%	21.1%	26.3%		
	Right	N	8	6		
		%	42.1%	31.6%		
Total		N	19	19		
		%	100.0%	100.0%		

Regarding ovary size, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in no significant difference between pre and after treatment (Table 4).

Table (4): Ovary size distribution before treatment and after 6 months between the studied groups

	Thioctic acid group	Control group	t	P
Sizeovary/cm^3	9.86±1.46	9.44±1.27	0.788	0.475
Sizeovary 6M/cm^3	9.71±0.51	9.36±0.90	1.232	0.121
P	0.321	0.385		

Regarding Hormones profile, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in resulted in a significant decrease in the LH, FSH, Prolactin after treatment (Table 5).

Table (5): Hormones profile distribution before treatment and after 6 months between the studied groups

	Thioctic acid group	Control group	T	P
FSH	**5.28±1.12**	**5.67±0.95**	**1.162**	**0.253**
LH	**8.22±2.01**	**7.14±1.60**	**1.261**	**0.215**
Prolactin	**16.15±4.00**	**16.68±3.89**	**0.275**	**0.785**
TSH	**3.24±0.78**	**3.18±0.70**	**0.105**	**0.917**
FSH_6M	**3.46±0.60**	**5.24±0.63**	**8.312**	**0.00****
LH_6M	**6.15±1.41**	**7.09±1.63**	**1.706**	**0.0842**
Prolactin_6M	**8.47±2.11**	**16.41±4.04**	**7.322**	**0.00****
TSH_6M	**2.46±0.43**	**3.24±1.39**	**2.005**	**0.053**
P 1 (FSH Pre-6M)	**0.001****	**0.065**		
P 2 (LH Pre-6M)	**0.001****	**0.215**		
P 3 (Prolactin Pre-6M)	**0.001****	**0.321**		
P4 (TSH Pre-6M)	**0.001****	**0.274**		

Table (6): Fasting blood glucose (FBG) and Post prandial glucose (PPG) Before treatment and after 6 months between the studied groups

	Thioctic acid group	Control group	T	P
FBG	**104.31±7.73**	**102.42±5.25**	**0.042**	**0.966**
PPG	**126.89±4.21**	**127.73±5.26**	**0.544**	**0.590**
FBG 6M	**103.36±7.69**	**104.73±8.26**	**0.528**	**0.601**
PPG 6M	**125.89±4.49**	**126.84±4.09**	**0.679**	**0.502**
P1 (FBG Pre-6M)	**0.398**	**0.274**		
P2 (PPG Pre-6M)	**0.412**	**0.358**		

Regarding fasting and post prandial insulin, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in a significant decrease in the fasting and post prandial insulin after treatment (Table 7).

Table (7): Fasting and post prandial insulin Before treatment and after 6 months between the studied groups.

	Thioctic acid group	Control group	T	P
Fasting insulin	**49.10±4.98**	**51.68±4.06**	**1.746**	**0.089**
PP insulin	**195.52±19.19**	**198.31±17.36**	**0.470**	**0.641**
Fasting insulin 6M	**22.63±2.38**	**50.89±2.72**	**34.008**	**0.001****
PP insulin M	**126.26±11.14**	**200.63±15.74**	**16.799**	**0.001****
P1 (Fasting insulin Pre-6M)	**0.001****	**0.352**		
P2 (PP insulin Pre-6M)	**0.001****	**0.122**		

There was no significant difference found in pre but at post Thioctic acid group was significantly lower and regard change assessment Thioctic acid group significantly decreased but no significant change happened in control group.
Regarding HOMA-IR, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in a significant decrease in the HOMA-IR after treatment (Table 8).

Table (8): Homeostasis Model Assessment Insulin Resistance Index (HOMA) Before treatment and after 6months between the studied groups

	Thioctic acid group	Control group	T	P
HOMA	**4.41±0.47**	**4.53±0.57**	**0.710**	**0.482**
HOMA 6M	**2.04±0.16**	**4.49±0.66**	**15.545**	**0.00****
P	**0.001****	**0.54**		

DISCUSSION

Hyperandrogenism, oligo-ovulation, and polycystic ovaries are the hallmarks of polycystic ovarian syndrome (PCOS), a prevalent endocrine condition that affects approximately 10% of reproductive-age women [7]. Researchers have looked at insulin resistance in PCOS for a long time in women [8]. However, many scientists now think that elevated insulin levels are a major contributor to polycystic ovarian syndrome (PCOS). Helping over half of patients regain fertility and regular menstrual cycles. Reducing hyperinsulinemia using thioctic acid (Thioctacid-HR) helps obese men and women lose weight, enhance insulin sensitivity, and normalize their lipid and carbohydrate metabolism [9].

In our study BMI (kg/m^2) was distributed as 26.08±1.31 and 26.41±2.82 for Thioctic acid group and Control group respectively with no significant difference between them. BMI was significantly reduced after thioctic treatment, that agreed with results of **Fruzzetti *et al.*** [10] Who stated that the treatment's efficacy was noted across the board for the female patients. There was a statistically significant drop in body mass index (p 0.05). Reproduction-related indicators were the only ones where there was statistical significance, with a decrease in FSH (p 0<.01) and a rise in E2 (p <0.01).

In our study and regarding ovary size, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in no significant difference between pre and after treatment. This agreed with results of **Fruzzetti *et al.*** [11] who found that Treatment with thioctacid-HR for 6 months improves menstrual function, cycle regularity, and hirsutism considerably in women with PCOS.

Regarding fasting and post prandial insulin in our study, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in a significant decrease in the fasting and post prandial insulin after treatment.

Agreed with our results of **Ivanova** [4] stated that there was a significant drop in average baseline insulin 104.7 pmol/L (67 percent, p = 0.023) after 6 months of treatment with thioctic acid (Thioctacid-HR) 600 mg daily and reduced average postprandial insulin by 499.6 pmol/L (54.4%, p = 0.015). The average values for basal and postprandial insulin in the control group did not vary significantly (p = 0.761).

Regarding Hormones profile, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in resulted in a significant decrease in the LH, FSH, Prolactin after treatment.

TSH in thioctic acid group mean and SD before treatment was 3.24 & 1.13 and in Control group was 3.18 & 1.05 respectively. However, after 6 months of treatment TSH in thioctic acid group mean and SD before treatment was 2.46 & 0.96 and in Control group was 3.24 & 1.39 respectively.

These results were in accordance with **Kamenov and Gateva** [12] who found that using thioctic acid resulted in a 67% drop in LH/FSH 2.50 pmol/L (p = 0.023). The mean values in the control group barely changed from one group to the next (p = 0.761). Also, **De Cicco *et al.*** [13] found that Following 6 months of treatment with thioctic acid, the mean FSH (mUI/mL) level increased from 4.00 to 4.69, with the standard deviation (SD) being 1.23. The mean LH (mUI/mL) before thioctic acid treatment was 4.92 (SD = 2.66) and after 6 months of treatment it was 4.73 (SD = 1.94) (p > 0.05).

In our study and regarding HOMA-IR, there were no significant differences between 2 groups. Taking of thioctic acid (Thioctacid-HR) for 6 months resulted in a significant decrease in the HOMA-IR after treatment The evaluation of HOMA-IR documented a normal peripheral insulin-sensitivity. HOMA-IR was at mean of 2.08 & SD 0.60 after 6 months of treatment it reached 1.92 & SD 0.85 which show significant decrease.

This was in line with **Cianci *et al.*** [14] findings, since they reported that after treatment, 80% of patients had normal HOMA-IR values and demonstrated significant improvements in metabolic pattern, including lower fasting insulin and HOMA-IR (p 0.01). There was only a significant decrease in FSH (p 0.01) and an increase in E2 (p 0.05) in women who did not have IR. Patients with IR had a greater increase in cycle length than those without IR (80.0% vs. 70.8%, p = NS). Also, **Genazzani *et al.*** [15] found that the levels of HOMA dropped by 5.7 pmol/L, which is a significant amount. The average values barely changed (p = 0.650) in the control group.

CONCLUSION

It could be concluded that **t**hioctic acid has significant effect on PCOs clinically but no effect on ultrasound findings. Also, it decreases insulin level after 6 months. Therefore, Thioctic acid could help in treatment of PCOS.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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