© 2024 Journal of Pharmacy & Pharmacognosy Research, 12 (6), 1187-1195, 2024
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres24.2001_12.6.1187

Original Article

Clinical implications of dual therapy of acarbose plus myo-inositol on the thyroid profile in women with polycystic ovary syndrome

[Implicaciones clínicas de la terapia dual de acarbosa más mioinositol sobre el perfil tiroideo en mujeres con síndrome de ovario poliquístico]

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Abstract

Context: Polycystic ovary syndrome (PCOS) and thyroid are the most common endocrine disorders affecting women of childbearing age, causing anovulation and infertility. There is an increased prevalence of thyroid dysfunction reported among PCOS women.

Aims: To evaluate the benefits of acarbose plus myo-inositol therapy on the thyroid profile of PCOS.

Methods: An open-labelled, parallel randomised clinical trial on 80 PCOS women based on inclusion and exclusion criteria was performed at the Department of Gynaecology, SRM Medical College Hospital and Research Centre, Kattankulathur. Institutional ethics committee approval and prior informed consent were obtained. The trial was registered in CTRI (No: CTRI/2022/04/041877). Group A (n = 38) received metformin 500 mg TID, and group B (n = 39) received acarbose 50 mg TID along with myoinositol 1000 mg BID. Assessment of metabolic and hormonal profile was done at baseline and at the end of six months.

Results: Both groups showed significant reductions in luteinising hormone ($p < 0.0001$), total testosterone ($p<0.05$), thyroid stimulating hormone ($p<0.05$), fasting insulin ($p<0.05$), and homeostatic model assessment for insulin resistance ($p<0.0001$). The follicle-stimulating hormone was increased only in the metformin group. No significant changes in body mass index, free triiodothyronine, free tetraiodothyronine, and fasting glucose were observed in any group. Both therapies were safe, and no side effects or hypoglycaemia were recorded.

Conclusions: In consideration of the beneficial effects of the study, we conclude that the administration of acarbose plus myo-inositol exerts positive effects on the thyroid and other endocrinological profiles in PCOS women.

Keywords: acarbose plus myoinositol; excess androgen; insulin resistance; polycystic ovary syndrome; thyroid stimulating hormone.

Resumen

Contexto: El síndrome de ovario poliquístico (SOP) y la tiroides son los trastornos endocrinos más comunes que afectan a las mujeres en edad fértil, causando anovulación e infertilidad. Se ha informado una mayor prevalencia de disfunción tiroidea entre las mujeres con SOP.

Objetivos: Evaluar los beneficios del tratamiento con acarbosa más mio-inositol en el perfil tiroideo del SOP.

Métodos: En el Departamento de Ginecología del SRM Medical College Hospital and Research Centre, Kattankulathur, se llevó a cabo un ensayo clínico aleatorizado, paralelo y de etiqueta abierta en 80 mujeres con SOP basado en criterios de inclusión y exclusión. Se obtuvo la aprobación del comité ético institucional y el consentimiento informado previo. El ensayo se registró en el CTRI (nº: CTRI/2022/04/041877). El grupo A (n = 38) recibió metformina 500 mg TID, y el grupo B (n = 39) recibió acarbosa 50 mg TID junto con mioinositol 1000 mg BID. Se evaluó el perfil metabólico y hormonal al inicio y a los seis meses.

Resultados: Ambos grupos mostraron reducciones significativas de la hormona luteinizante, la testosterona total, la hormona estimulante del tiroides, la insulina en ayunas y la evaluación del modelo homeostático de resistencia a la insulina. La hormona foliculoestimulante se incrementó sólo en el grupo de metformina. No se observaron cambios significativos en el índice de masa corporal, la triyodotironina libre, la tetrayodotironina libre y la glucosa en ayunas en ningún grupo. Ambas terapias fueron seguras y no se registraron efectos secundarios ni hipoglucemias.

Conclusiones: Considerando los efectos beneficiosos del estudio, concluimos que la administración de acarbosa más mio-inositol ejerce efectos positivos sobre el tiroides y otros perfiles endocrinológicos en mujeres con SOP.

Palabras Clave: acarbosa más mioinositol; exceso de andrógenos; hormona estimulante del tiroides; resistencia a la insulina; síndrome de ovario poliquístico.

ARTICLE INFO
Received: February 28, 2024.
Accepted: June 3, 2024.
Available Online: June 30, 2024.

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Abbreviations: BID: two times a day; BMI: body mass index; CYPC17α: cytochrome P450C17alpha; FG: fasting glucose; FI: fasting insulin; FSH: follicle-stimulating hormone; HOMA-IR: homeostatic model assessment for insulin resistance; IGF1R: insulin-like growth factor-1 receptor; IR: insulin receptor; LH: luteinising hormone; OGTT: oral glucose tolerance test; PCOS: polycystic ovary syndrome; RCT: randomised controlled trials; SHBG: sex hormone binding globulin; fT3: free triiodothyronine; fT4: free tetraiodothyronine; TID: three times a day; TSH: thyroid stimulating hormone; TSHR: TSH receptor; TT: total testosterone.

INTRODUCTION

Polycystic ovary syndrome (PCOS) and thyroid dysfunction are the leading cause of anovulatory infertility among young women (Iqbal et al., 2021). In recent times, PCOS prevalence has hiked to 18% with Amsterdam criteria (Teede et al., 2010). PCOS is clinically manifested with anovulation, infertility, dermatological issues, and polycystic ovaries on the ultrasound (Dadachanji et al., 2018). It commences as a gynaecological and endocrinological problem and propagates into an intricate metabolic disorder in the long run (Louwers and Laven, 2020). Different types of thyroid dysfunction are reported in PCOS women, among which subclinical hypothyroidism is prominent, with a prevalence rate of 11 to 16.9% (Novais et al., 2015). Although the aetiology and pathogenesis of both disorders are different, both disorders share certain endocrinological and clinical features in common (Muderris et al., 2011). Therefore, it is important to rule out thyroid disorders before the diagnosis of PCOS (Williams et al., 2016). However, many PCOS patients who are co-morbid to thyroid illness have elevated TSH levels (Sinha et al., 2013). Therefore, it is of greater concern that PCOS be treated and that the altered thyroid levels be corrected simultaneously (Williams et al., 2016).

Most drugs used for treating PCOS are not FDA-approved or regulatory authority approved but are used in gynaecology clinics and are truly evidence-based (Vitek et al., 2015). Therefore, acarbose is a relatively three-decade-old safe drug for type 2 diabetes. It reduces the post-meal glucose and insulin levels (Joshi et al., 2015). It has recently been extended to show gynaecological and endocrinological effects on PCOS women (Tuğrul et al., 2008). Myo-inositol is a stable isomer of inositol, possesses insulin-sensitising effects, and has proven to decrease TSH and TT and, thereby, improve menstrual cyclicity (Jamilian et al., 2017; Raffone et al., 2010). Metformin, besides increasing insulin sensitivity, plays an important role in the reduction of FSH-mediated aromatase expression and also improves sex hormone binding globulin (SHBG), thereby indirectly decreases the circulation of excess androgen (Bertoldo et al., 2014). It has also been shown to ameliorate TSH levels in euthyroid glucose-intolerant patients (Karimifar et al., 2014). Therefore, the combination therapy of acarbose plus myo-inositol is anticipated to ameliorate and improve both disorders. The scope of the research is to determine the role of acarbose add-on therapy with myo-inositol against metformin alone on the metabolic, hormonal, and thyroid profile of PCOS.

MATERIAL AND METHODS

Study design and patient selection

A prospective, open-labelled, simple, randomised controlled trial was conducted on seventy-seven PCOS women who were enrolled between February 2023 and August 2023 at the Department of Obstetrics and Gynaecology of SRM Medical College Hospital and Research Centre, Kattankulathur. The study was approved by the institutional ethics committee (Ethics clearance no: 8230/IEC/2022), and prior informed consent was obtained from the patients. The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. The trial was registered in CTRI (No.: CTRI/2022/04/041877 https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2022/04/041877).

Inclusion and exclusion criteria

The inclusion criteria were established for patients aged 18 to 44 with Rotterdam criteria (Ajmal et al., 2019): chronic anovulation such as oligomenorrhea or amenorrhea; clinical or biochemical hyperandrogenism and/or PCO morphology on ultrasound. The study excluded those patients' who desired pregnancy and those with diseases and conditions that mimic PCOS, such as Cushing syndrome, congenital adrenal hyperplasia, idiopathic hirsutism, ovarian and adrenal secreting tumours, metabolic diseases other than thyroid disorders, and the use of hormonal therapy over the last three months.

Randomisation

After screening 138 patients, 80 were recruited and referred to gynaecology clinic based on inclusion and exclusion criteria. The principal investigator assigned the patients randomly into two groups using an open list of computer-generated random numbers, where 39 patients were allocated to group A and 41 to group B. One patient from group A and two patients from group B lost follow-up due to pregnancy and personal reasons, respectively. Group A (standard arm) received metformin 500 mg/TID, and group B (intervention arm) received acarbose 25 mg/TID with myo-inositol 1000 mg/BID for the initial four weeks, later the dose of acarbose was elevated to 50 mg/TID

along with myoinositol 1000 mg/BID until the end of study (see Fig. 1). The dose of acarbose was titrated slowly to avoid any gastrointestinal side effects.

Study procedure

The patients were subjected to physical examination. Thyroid, metabolic, and hormonal profiles were assessed at baseline and at the end of six months. The body mass index (BMI) was calculated by dividing weight in kg by height in m^2.

The blood samples were collected after an overnight fasting of 12 hours, the collected blood samples were centrifuged, and the sera were stored at -20°C. Serum concentrations of free triiodothyronine (fT3), free tetraiodothyronine (fT4), thyroid stimulating hormone (TSH), prolactin, luteinising hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), insulin were collected during the early follicular phase between day 2 and day 6 of a spontaneous or progestin induced bleeding and were determined by enhanced chemiluminescence assay performed at Neuberg diagnostics, Tambaram, Chennai. Fasting glucose (FG) was determined by hexokinase method. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as the product of fasting glucose in mg/dL and fasting insulin (FI) in µIU/mL by 405.

Statistical analysis

The sample size was estimated using the sample size formula for randomised controlled trials (RCT) where type one (α) and type two errors (β) were 0.05 (confidence interval at 95%) and 0.20 (power = 80%), respectively. The data was expressed by mean ± standard deviation and were analysed using the Statistical Program for Social Sciences (SPSS) version 18. The parameters were analysed using an independent t-test and Mann-Whitney u-test for parametric and non-parametric variables within and between groups. The level of significance was considered $p<0.05$.

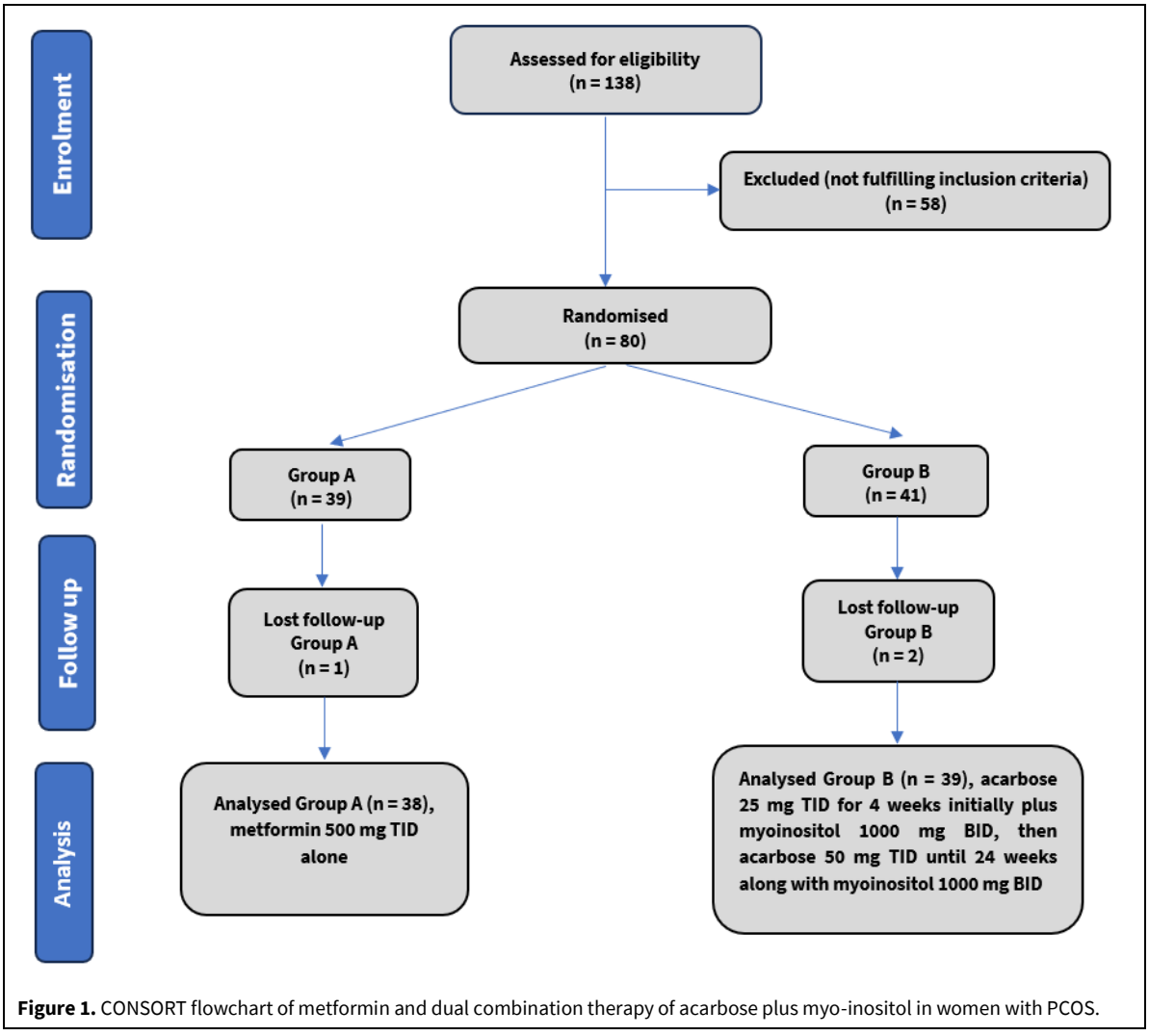

Figure 1. CONSORT flowchart of metformin and dual combination therapy of acarbose plus myo-inositol in women with PCOS.

Table 1. Determination of thyroid, metabolic, and hormonal parameters at baseline and after 6 months of treatment in group A (metformin) and group B (acarbose plus myo-inositol).

Parameter	Group A (n = 38)			Group B (n = 39)		
	Baseline	After 6 months	P-value	Baseline	After 6 months	P-value
Age	26.9 ± 7.1	-	-	27.3 ± 6.7	-	-
BMI (kg/m^2)	26.8 ± 5.5	26.45 ± 5.3	0.579	27.2 ± 5.7	26.7 ± 5.5	0.2365
LH (mIU/mL)	12.18 ± 1.35	8.24 ± 1.68	<0.0001**	13.42 ± 1.22	8.60 ± 1.65	<0.0001**
FSH (mIU/mL)	5.39 ± 2.02	6.48 ± 1.99	0.0063*	5.21 ± 1.60	5.52 ± 1.47	0.2101
FT3 (pg/mL)	3.69 ± 0.54	3.5 ± 0.54	0.1151	3.68 ± 0.57	3.52 ± 0.56	0.209
FT4 (ng/dL)	1.13 ± 0.16	1.113 ± 0.17	0.6389	1.13 ± 0.22	1.11 ± 0.23	0.618
TSH (uIU/mL)	2.77 ± 1.55	2.50 ± 1.43	0.0497*	2.74 ± 1.40	2.14 ± 1.09	0.0282*
Prolactin (ng/mL)	21.05 ± 4.36	19.35 ± 3.83	0.0758	20.56 ± 4.61	18.35 ± 4.21	0.0302*
TT (ng/mL)	0.633 ± 0.18	0.552 ± 0.16	0.0484*	0.639 ± 0.18	0.557 ± 0.15	0.0362*
FG (mg/dL)	95.92 ± 3.68	94.5 ± 3.66	0.0962	97.28 ± 5.93	94.89 ± 5.42	0.0678
FI (uIU/mL)	14.88 ± 5.14	13.61 ± 3.64	0.3778	15.22 ± 4.86	11.74 ± 2.03	0.0045*
HOMA-IR	3.52 ± 0.046	3.175 ± 0.032	<0.0001**	3.65 ± 0.07	2.75 ± 0.027	<0.0001**

Results are shown as mean ± SD; *p<0.05; **p<0.0001 with respect to baseline. BMI: body mass index; LH: luteinising hormone; FSH: follicle-stimulating hormone; FT3: free triiodothyronine; FT4: free tetraiodothyronine; TSH: thyroid stimulating hormone; TT: total testosterone; FG: fasting glucose; FI: fasting insulin; HOMA-IR: homeostatic model assessment for insulin resistance.

RESULTS

Pre-treatment values

The study recruited 80 PCOS women based on the inclusion and exclusion criteria. They were randomised into two groups: 39 patients in group A and 41 in group B. One patient from group A and two patients from group B lost follow-up due to pregnancy and personal reasons, respectively, and were excluded based on per-protocol analysis.

The pre-treatment serum concentration of all the parameters was in the normal range in both groups except LH and TT, which were slightly elevated in both groups; however, no significant difference between the groups was observed (see Table 1).

Baseline demographic analysis shows that the mean age was 26.9 ± 7.1 years in group A, 27.3 ± 6.7 years in group B, respectively, and the mean BMI was 26.8 ± 5.5 kg/m^2 in group A, 27.2 ± 5.7 kg/m^2 in group B, respectively. All other hormonal and metabolic parameters were determined at baseline and at the end of six months.

Post-treatment values

BMI reduction was reported more in the acarbose plus myoinositol group compared to the metformin group but was not significant.

LH (p<0.0001), TSH (p<0.05), TT (p<0.05), and HOMA-IR (p<0.0001) were significantly reduced in both groups (see Table 2). FSH (p=0.0063) was increased significantly only in the metformin group and not in the acarbose plus myo-inositol group. Significant improvement in prolactin (p=0.0302) and reduction in FI (p=0.0045) was found only in the acarbose plus myo-inositol group.

There was no change in fT3 and fT4 levels in both groups. A mild reduction of fasting glucose was observed in both groups but was not significant. The reduction was due to the effects of flattening of post-meal glucose and insulin-sensitising effects of the therapy. FG levels were reduced only in patients with high glycaemic levels and not in patients with normal plasma glucose. Both therapies were safe, and there were no side effects or hypoglycaemia recorded.

Comparison of post-treatment values between the standard and intervention arm

A significant difference in the reduction of TSH (p=0.0497), FI (p=0.0468), and HOMA-IR (p<0.0001) was observed in the acarbose plus myo-inositol group compared to the metformin group. Prompt recognition and treatment of the co-morbid conditions are essential to reduce the progression of the disorder into a complex syndrome. FSH (p=0.0171) reduction was significant only in the metformin alone group, thereby indirectly showing enhancement of follicular growth, restoration of ovulatory functions, regularisation of menses, and improvements in fertility.

Although LH (p<0.0001) was significantly reduced in both the groups, there was no difference between the groups stated. No changes in BMI, fT3, fT4, and fasting glucose levels were observed in both the groups.

Table 2. Comparison of post-treatment values of hormonal and metabolic parameters in group A (metformin) and group B (acarbose plus myo-inositol).

Parameter	Group A (n = 38)	Group B (n = 39)	P-value
BMI (kg/m^2)	26.45 ± 5.3	26.7 ± 5.5	0.4563
LH (mIU/mL)	8.24 ± 1.68	8.60 ± 1.65	0.3505
FSH (mIU/mL)	6.48 ± 1.99	5.52 ± 1.47	0.0171*
FT3 (pg/mL)	3.5 ± 0.54	3.52 ± 0.56	0.8499
FT4 (ng/dL)	1.113 ± 0.17	1.11 ± 0.23	0.9509
TSH (uIU/mL)	2.50 ± 1.43	2.14 ± 1.09	0.0497*
Prolactin (ng/mL)	19.35 ± 3.83	18.35 ± 4.21	0.28
TT (ng/mL)	0.552 ± 0.16	0.557 ± 0.15	0.8817
FG (mg/dL)	94.5 ± 3.66	94.89 ± 5.42	0.7082
FI (uIU/mL)	13.61 ± 3.64	11.74 ± 2.03	0.0468*
HOMA-IR	3.175 ± 0.032	2.75 ± 0.027	<0.0001**

Results are shown as mean ± SD; *p<0.05; **p<0.0001 with respect to baseline. BMI: body mass index; LH: luteinising hormone; FSH: follicle-stimulating hormone; FT3: free triiodothyronine; FT4: free tetraiodothyronine; TSH: thyroid stimulating hormone; TT: total testosterone; FG: fasting glucose; FI: fasting insulin; HOMA-IR: homeostatic model assessment for insulin resistance.

No serious adverse effects were reported in either group. One patient in the metformin group complained of abdominal discomfort in the first week of the study, but in the later weeks, the symptoms subsided, and the patient became tolerant to the drug. Meanwhile, no patients complained of any side effects in the acarbose plus myo-inositol group.

DISCUSSION

Our study showed a slight reduction in BMI in both the groups. The weight reduction might be due to an indirect rise in GLP-1 by delaying the post-meal absorption of glucose with acarbose (Penna et al., 2005). Parallelly, myoinositol is also hypothesised to reduce weight via lowering of leptin levels (Merviel et al., 2021).

Our study observed a significant reduction of LH levels in both groups. However, FSH was reduced only in the metformin-alone group. Several studies showed a marked decrease in LH with these agents (Özay et al., 2019; Tao et al., 2018; Tuğrul et al., 2008), but however, a study by Vandermolen et al. (2001) observed no change in these gonadotrophic hormones.

Acarbose does not directly impact LH release or hypothalamic response to GnRH activation. The drop in LH levels is made possible through a decrease in insulin levels (Ciotta et al., 2001; Tuğrul et al., 2008). A mild increase in serum progesterone levels was seen with the use of acarbose (Sönmez et al., 2005). Meanwhile, inadequate natural inositol in the ovary may cause impairment in insulin and FSH signal transmission. Therefore, external myoinositol administration would make the ovaries sensitive to these pituitary hormones, thereby boosting FSH release (Artini et al., 2013; Merviel et al., 2021). Another study states that the receptor-specific beta component of FSHR and LHR (g protein coupled receptors) interacts with insulin receptors (IR) and insulin-like growth factor-1 receptor (IGF1R) (i.e., tyrosine kinase receptors) with the use of metformin, thereby positively modifying the LH and FSH levels (Cannarella et al., 2021).

In our study, testosterone was reduced significantly in both groups, and a similar reduction was seen in a meta-analysis of acarbose by Zhang et al. (2014). However, in contrast, few studies did not mark any change in TT concentration (Baillargeon et al., 2010; Jamilian et al., 2017).

The enhanced insulin levels in PCOS are speculated to raise the androgen pool by either increasing the synthesis or decreasing the metabolism by acting at the pituitary, causing GnRH-stimulated LH release or inhibiting SHBG production at the hepatic level and/or by enabling the androgen production in the ovarian theca cells by increasing cytochrome P450C17alpha (CYPC17α) activity. Therefore, the mechanism of reduction of androgen levels with acarbose may be linked to a decrease in insulin re-

sponse to oral glucose tolerance test (OGTT) and probably related to a decreased ovarian CYPC17α activity (Ciotta et al., 2001). Although the exact mechanism is unknown, myoinositol decreases testosterone levels through improvements in FSH (Merviel et al., 2021; Özay et al., 2019). Metformin lowers total and free testosterone levels through the direct reduction of serum insulin levels and by subsequent lowering of CYPC17 action in the ovary (Soldat-Stanković et al., 2022). A study by Ohara et al. (2021) demonstrated that the reduction of androgen with metformin may be due to attenuation of androgen receptor (AR) expression and enhancement of HOMA10 expression in the ovary. A study by Hirsch et al. (2012) states that inhibition of androgen secretion with metformin is channelled independent of AMPK/MAPK/PKC signal routes but by fixing on hydroxy-delta-5-steroid dehydrogenase (HSD3B2) and CYP17-lyase via inhibition of mitochondrial complex I.

In our study, TSH levels were reduced significantly with both acarbose plus myo-inositol and metformin therapy but failed to mark any change in fT3 and fT4 levels. Acarbose is known to regulate thyroid activity at both peripheral and glandular levels, potentially regulating hypothyroidism. Thyroid hormones possess anti-peroxidative properties and, in addition, are recognised for being involved in the metabolism of glucose and and the alteration in these hormones may lead to increase in glycaemic levels. Therefore, the reduction of blood glucose levels and anti-oxidative abilities of acarbose may account for improvements in the thyroid profile (Rameshwar and Anand, 2006). Whereas, no change in prolactin levels was observed with acarbose (Ciotta et al., 2001).

TSH receptor (TSHR) is a G protein-coupled receptor constituting of α and β components; stimulation of receptor-specific beta component increases adenylate-cyclase action. TSHR has been shown to interact with tyrosine kinase receptors, such as IR and insulin-like growth-1 receptor (IGF1R). Metformin administration may make TSHR more sensitive to TSH through modification of insulin receptor substrate-1 (IRS-1), which is the main connection between thyroid and insulin signaling pathways (Cannarella et al., 2021). Another well-known mechanism demonstrates that basically, metformin activation of AMPK suppresses glucose synthesis in the liver, but in contrast, effects on CNS show that metformin inhibits hypothalamic AMPK, producing counter effects on fT3 levels (Karimifar et al., 2014). A meta-analysis states that TSH is decreased only in individuals with subclinical hypothyroidism and not in those who are euthyroid, and likewise, no changes in fT4 levels were observed (Rotondi et al., 2011). Metformin showed dose-driven action on prolactin and reduced only those that were elevated and not those at normal concentrations (Krysiak et al., 2016).

According to a study by Benvenga et al. (2021), individuals with hypothyroidism have a greater requirement for inositol, an element that mitigates thyroid failure by improving the accessibility of iodine. Myoinositol is an essential mediator for phospholipase C-dependent inositol phosphate Ca^{2+}/DAG cascade, required for the synthesis of H_2O_2, which is necessary for TH production and for organification of iodine. Depletion or any impairment in the available inositol or inositol-dependent TSH signalling may further aggravate hypothyroidism. Other mechanisms state that myoinositol uses IPG as secondary messengers for glucose, insulin, FSH, and TSH regulation (DiNicolantonio and H O'Keefe, 2022; Jamilian et al., 2017). Myoinositol reduces TSH with enhancement of thyroid profile in euthyroid individuals (Nordio and Basciani, 2017). Our research found that serum prolactin levels were reduced significantly with the dual therapy of acarbose, and myo-inositol effectively compared to the metformin alone group. Few studies showed a similar reduction of serum prolactin concentration with the use of myo-inositol (Genazzani et al., 2008; Pizzo et al., 2014).

Although there was a reduction in fasting glucose in the both groups in our study, none of them was significant. However, fasting insulin and HOMA-IR showed significant reductions in both groups, which was similar to studies reported with acarbose by Tuğrul et al. (2008), metformin by Tao et al. (2018), and myoinositol by Shokrpour et al. (2019). In contrast, few studies showed no positive changes with these medications (Geisthövel et al., 1996; Sathyapalan et al., 2008).

Acarbose minimises about 20% of post-meal glucose, thereby reducing the glucose spike and preventing its related toxicity and subsequent IR (Penna et al., 2005). In PCOS, impairment in the natural inositol levels in the ovary may predispose the afflicted women to insulin resistance; therefore, administration of myoinositol would act as a mediator in the inositol phospho-glycans (IPG) insulin signalling pathway and enhance glucose distribution to muscles, insulin sensitivity and would further restore central hormonal levels (Genazzani et al., 2008; Regidor and Schindler, 2016). On the other hand, metformin decreases plasma glucose by blocking its production in the liver and boosts insulin sensitivity by channelling its uptake into the tissues and also through lipid metabolism. These actions are AMPK dependent and are mediated by stimulation of AMPK and attenuation of cAMP, but however these effects rely on dose and the length of therapy (Regidor and Schindler, 2016).

Mild intestinal side effects emerging with metformin and acarbose are dose-driven and can be minimised by administering the medication along with the first bolus of food and by titrating the dose incrementally (Hanjalic-Beck et al., 2010; Sönmez et al., 2005). Myo-inositol is a highly safe and more suitable supplemental therapy for reproductive and endocrinological complications of PCOS (Merviel et al., 2021).

Most PCOS therapies are off-labelled and not approved by the FDA or national or international regulatory bodies. Acarbose, a three-decade-old safe medication for type 2 diabetes, reduces post-meal glucose and insulin levels and has recently extended to show reproductive and hormonal effects on women with PCOS (Joshi et al., 2015; Tuğrul et al., 2008; Vitek et al., 2015). Although the exact mechanism of the combination is not well known, acarbose is well tolerated in the Southeast Asian population and has proved to be effective along with myo-inositol in alleviating the thyroidal complications of PCOS.

The major disadvantage was the lack of use of novel biomarkers in the study. The research was basically done to find the effectiveness of combinational therapy of an alpha-glucosidase inhibitor (acarbose) with myo-inositol in the carbohydrate-consuming population. It was performed with the intention of delivering a cost-effective repurposed therapy for the complications of PCOS. Therefore, future research will be done on a larger population, and more specific markers will be used to confirm the effectiveness of dual therapy in PCOS in the long run.

CONCLUSION

Our findings show that the 24-week intervention of acarbose add-on with myo-inositol therapy decreased insulin resistance, TSH, LH, and TT levels. However, no significant reduction was observed in fT3, fT4, and fasting glucose levels. In general, combination therapy is anticipated to show better effectiveness by overcoming resistance and reversal effects of single therapy in the long run. Therefore, taking into account the relative safety and clinical effectiveness on insulin resistance and TSH, the combined therapy of acarbose plus myo-inositol would be suggestive for treating the metabolic, hormone, and thyroid complications associated with PCOS.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Contribution	Andavar M	Kamaraj R	Vijayakumar TM	Murugesan A
Concepts or ideas		x		
Design		x	x	x
Definition of intellectual content		x	x	x
Literature search	x	x		
Clinical trial	x			
Data acquisition	x			
Data analysis	x			
Statistical analysis	x			
Manuscript preparation	x	x		
Manuscript editing			x	x
Manuscript review	x	x	x	x

Citation Format: Andavar M, Kamaraj R, Vijayakumar TM, Murugesan A (2024) Clinical implications of dual therapy of acarbose plus myo-inositol on the thyroid profile in women with polycystic ovary syndrome. J Pharm Pharmacogn Res 12(6): 1187–1195. https://doi.org/10.56499/jppres24.2001_12.6.1187