

Adjuvant use of Angiotensin Receptor Blockers with Metformin in Patients with Polycystic Ovary Syndrome

¹Haider Fakhri Al-Tukmagi, ²Faris Anwar Rasheed and ³Saad Abdulrahman Hussain

¹Department of Clinical Pharmacy, College of Pharmacy,
University of Baghdad, Baghdad, Iraq

²Department of Gynecology and Obstetrics, Al-Kindi College of Medicine,
University of Baghdad, Baghdad, Iraq

³Department of Pharmacology and Toxicology, College of Pharmacy,
University of Baghdad, Baghdad, Iraq

Abstract: Background: PPAR γ agonists are used in type 2 diabetic patients to reduce insulin resistance. Recently, many AT1 receptor antagonists (ARBs) were reported to function as a partial agonist of PPAR γ based on *in vitro* experiments. The aim of the present study was to investigate the effects adjuvant use of ARBs (losartan, telmisartan or valsartan) with metformin on metabolic and hormonal status in women with polycystic ovary syndrome (PCOS). **Methods:** Using single-blinded clinical trial, we compared the effects of losartan, telmisartan or valsartan, when adjunctly used with metformin, on insulin sensitivity, body mass index, glycemic control the serum levels of various hormones (FSH, LH and testosterone). In total, 74 Iraqi females with PCOS were enrolled in the study and allocated into 4 treatment groups; metformin only (1000 mg day⁻¹) and metformin with losartan (25 mg), telmisartan (40 mg) or valsartan (40 mg) groups. **Results:** All ARBs significantly reduced BMI, FBG and C-peptide values compared to metformin only treated group; they also showed significantly greater effects in increasing plasma levels of FSH and decreasing both LH and testosterone levels compared to metformin only. The rank for the effects of the used ARBs in this respect was: telmisartan>losartan>valsartan after 4 months of treatment. **Conclusion:** Adjuvant use of ARBs with metformin improves its effect in treatment of women with PCOS, with most pronounced effect for telmisartan in this respect.

Key words: Metformin, losartan, telmisartan, valsartan, PCOS

INTRODUCTION

Poly cystic ovary syndrome is the most common disease among women during their childhood period (Glueck *et al.*, 2003), which is usually manifested by irregular or absence of ovulation, and/or increased serum level of androgenic hormones (Rotterdam ESHRE/ASRM, 2003) and increasing LH:FSH ratio which is usually 1:1, but may reach 2:1 or even 3:1 in some PCOS women (Hohmann *et al.*, 2005). About 50% of women having PCOS are obese and have the ability to have an android type of obesity (Franks, 1995) with hyperinsulinemia (Burghen *et al.*, 1980) and may develop, if not treated, cardiovascular diseases, hypertension (Orio *et al.*, 2006; Christian *et al.*, 2003), with increased Low Density Lipoproteins (LDL) and decreased High Density Lipoproteins (HDL) levels (Guizek, 2004). It was found that activation of PPARs, which play an important role in metabolism of cellular components like lipids,

carbohydrates and proteins (Berger and Moller, 2002), affect glucose and lipid metabolism (Little *et al.*, 2008; Samarasinghe *et al.*, 2009; Chatterjee, 2010) and so it can help in treatment of PCOS as it was found that 40% of female with loss-of-functions of PPAR- γ had PCOS (Semple *et al.*, 2006). The most commonly followed treatment of PCOS includes insulin sensitizing agents like metformin (Castello and Eden, 2003), PPARs activating agents (like thiazolidinediones) (Paradisi *et al.*, 2003) and the anti androgens (Legro *et al.*, 2007). The available PPARs activators may cause adverse effects or aggravate certain conditions that can limit the clinical utility and safety of these drugs. Recently, It was found that in addition to the classical action of ARBs as anti-hypertensives, they can decrease the risk of type 2 diabetes compared other types of anti-hypertensive drugs (Dahlof *et al.*, 2002). Additionally, they can improve insulin sensitivity in cases of insulin resistance and improvement of lipid metabolism in adipocytes and

adipose tissues (Henriksen *et al.*, 2001). Activation of PPAR- γ differs from one ARB to other according to their physicochemical properties, in which the high lipophylicity of telmisartan makes it more active than irbesartan and the lowest active losartan (Israili, 2000). The present study was designed to evaluate the difference in activity between losartan, telmisartan and valsartan, when used in lowest doses, as adjuvant with metformin during treatment of women with PCOS.

MATERIALS AND METHODS

This multicenter study was performed at Al-Elwiya Maternity Teaching Hospital and Al- Samarraee Maternity Teaching Hospital in Baghdad City from December 2009 till January 2011. Seventy four women with age range of 19-38 years, previously diagnosed as having polycystic ovary syndrome (PCOS) for at least 6 months before enrollment in the study and maintained on 1000 mg day⁻¹ metformin in two divided doses, they are classified according to the National Institute of Child Health and Human Development (NICHD) criteria (Zawadski and Dunaif, 1992). All patients fulfilled the ultrasonographic criteria of PCOS and had normal serum prolactin concentrations and thyroid function tests. Patients with hypertension, Cushing syndrome, early menopause, or congenital (non-classical) adrenal hyperplasia were excluded (Zawadski and Dunaif, 1992). Patients were not taking any drugs that interfere with those currently used throughout the study. All patients gave their written informed consent and the study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the College of Pharmacy, University of Baghdad and the Iraqi Ministry of Health. The patients were randomly assigned to 4 treatment groups: group 1, kept on their 1000 mg day⁻¹ metformin (Merck, France) (n = 20); group 2, metformin+25 mg day⁻¹ losartan (Ajanta, India) (n=19); group 3, metformin+ 40 mg day⁻¹ valsartan (Novartis, Switzerland) (n = 20) and group 4, metformin+40 mg day⁻¹ telmisartan (Boehringer Ingelheim, Germany) (n = 15).

These doses were employed because they are the lowest approved clinical use on the basis of Iraqi licensing. Patients were asked to adhere to their standard eating habits and physical activity throughout the study. Patients with impaired hepatic function (serum AST/ALT>40) or renal function (serum creatinine >1.5) were excluded from the study. Patients were assessed at baseline (first visit) and after 4 months' treatment including BMI measurements. Fasting (minimum 12 h) blood samples (10 ml) were obtained for laboratory evaluation of many biochemical parameters, including blood glucose (Barham and Trendoer, 1972), C-peptide (Lindstrom *et al.*, 1992) and serum levels of FSH, LH (Thomas and Segers, 1988) and testosterone (Ratcliffe *et al.*, 1982); the ratio of LH/FSH was also calculated as a parameter for evaluating progress in treatment. The data was analyzed using a computer program for windows XP, Microsoft Excel. All the results were expressed as Mean \pm Standard Deviation (SD). Paired Student t-test was used to pre- and post-treatment data months, while unpaired Student t-test was used to compare between the means of different groups. In all cases, a probability value of p<0.05 was considered statistically significant.

RESULTS

Table 1 showed that there is a highly significant decrease in BMI value compared to baseline after 4 months of treatment (p<0.01) in all groups; and the percent decrease is greatest due to the use of telmisartan with metformin compared to other groups. Meanwhile, fasting blood glucose level was also significantly decreased in all treatment groups compared to base line (p<0.05), with most pronounced percent decrease reported due to the adjuvant use of telmisartan with metformin compared to other types of treatment followed ; this effect was accompanied by significant decrease in C-peptide levels, which is also more pronounced in telmisartan group. In Table 2, all types of treatment followed significantly elevates serum levels of FSH; however,

Table 1: Effects of adjuvant use of either losartan, valsartan or telmisartan with metformin on BMI, FBG and C-peptide values after 4 months in Iraqi women with PCOS

Parameters	Patients groups							
	Met only (n)		Met+Losart (n)		Met+Valsart (n)		Met+Telmisart (n)	
	Baseline	4 Months	Baseline	4 Months	Baseline	4 Months	Baseline	4 Months
BMI (kg m ⁻²)	24 \pm 3.52	23.2 \pm 3.0 ^{a**}	24.5 \pm 3.3	22.8 \pm 2.6 ^{a**}	24.1 \pm 3.8	23.4 \pm 3.3 ^{a**}	24.5 \pm 2.8	22.3 \pm 2.1 ^{a**}
FBG (mg dL ⁻¹)	106.3 \pm 8.7	98.6 \pm 21.0 ^{a*}	100 \pm 7.5	90.7 \pm 6.5 ^{b***}	102.8 \pm 10.2	98.1 \pm 8.6 ^{a**}	100.1 \pm 8.0	87.1 \pm 4.9 ^{a**}
C-Peptide (ng mL ⁻¹)	4.2 \pm 1.1	3.9 \pm 0.9 ^{a*}	3.8 \pm 10.9	3.0 \pm 0.8 ^{b**}	3.8 \pm 1.1	3.7 \pm 1.0 ^{a*}	4.1 \pm 1.3	3.0 \pm 0.7 ^{a**}

Values were expressed as Mean \pm SD; n = No. of patients; significantly different compared to baseline value. * p<0.05, ** p<0.01; values with non-identical superscripts among different groups are considered significantly different (p<0.05)

Table 2: Effects of adjuvant use of losartan, valsartan or telmisartan with metformin on LH, FSH, Lh/FSH ratio and testosterone values after 4 months in Iraqi women with PCOS

Parameters	Patients groups							
	Met only (n)		Met+Losart (n)		Met+Valsart (n)		Met+Telmisart (n)	
	Baseline	4 Months	Baseline	4 Months	Baseline	4 Months	Baseline	4 Months
FSH (IU L ⁻¹)	4.0±0.4	4.6±0.4 ^{a**}	4.3±0.5	5.3±0.6 ^{b**}	4.6±0.8	4.9±0.8 ^{a**}	4.5±0.5	5.9±0.7 ^{c**}
LH (IU L ⁻¹)	9.3±1.4	8.7±1.1 ^{a**}	8.7±1.1	7.8±1.0 ^{b**}	9.1±0.9	8.4±0.9 ^{a**}	8.7±1.1	7.4±0.6 ^{b**}
LH/FSH ratio	2.3±0.5	1.9±0.3 ^{a*}	2.1±0.4	1.5±0.2 ^{b**}	2.0±0.3	1.7±0.2 ^{b*}	1.9±0.3	1.3±0.2 ^{c*}
Testosterone (ng mL ⁻¹)	1.0±0.2	0.9±0.2 ^{a*}	1.0±0.2	0.9±0.2 ^{a**}	1.1±0.2	0.9±0.3 ^{a*}	1.0±0.2	0.8±0.1 ^{b**}

Values were expressed as Mean±SD; n = No. of patients; significantly different compared to baseline value: *p<0.05, **p<0.01; values with non-identical superscripts among different groups are considered significantly different (p<0.05)

telmisartan and losartan found to augment the increase in FSH level already initiated due to the use of metformin alone, while such effect is not reported in case of using valsartan. Concerning serum LH, all types of treatment significantly decreased its level and telmisartan show the highest level compared to others (Table 2). The effects of all ARBs on both FSH and LH was reflected in significant decrease in LH/FSH ratio, with more pronounced effect reported for telmisartan followed by losartan and valsartan, respectively. Table 2 demonstrate the effects of adjuvant use of different types of ARBs on serum testosterone levels, where only telmisartan and losartan improve the effect of metformin in decreasing serum levels of testosterone significantly (p<0.05), while valsartan fails to produce such type of activity compared to others.

DISCUSSION

According to our knowledge, this is the first trial demonstrating that the angiotensin II receptor antagonists (losartan, valsartan and telmisartan), besides being an effective antihypertensive drug, may have beneficial effects in improving the effect of metformin in treatment of polycystic ovary syndrome patients; only one case study was reported about the use of telmisartan in hypertensive females with PCOS (Jensterle *et al.*, 2007). The present trial provides interesting new information about unexpected effect and possible new indication of the previously mentioned ARBs in patients with polycystic ovary syndrome. Since insulin resistance plays a major role in the pathogenesis of polycystic ovary syndrome, several trials have confirmed that insulin-sensitizing drugs, metformin (Harborne *et al.*, 2003; Castello and Eden, 2003) and thiazolidinediones (Rautio *et al.*, 2006; Dereli *et al.*, 2005) have favorable endocrine, reproductive and metabolic effects in polycystic ovary syndrome. Although there is no cure for PCOS, the aim of treatment is focusing on the underlying problems like insulin resistance, obesity and hyperandrogenism. Insulin resistance was found in most of the patients in followed in the present study. This

hyperinsulinemia in PCOS patients is independent but may be aggravated by obesity and reduced insulin sensitivity can be demonstrated in both lean and obese patients (Dunaif *et al.*, 1989). Hyperinsulinemia may be the cause of main features of PCOS and it may increase androgen production in PCOS by stimulating ovaries directly or indirectly through stimulation of LH secretion and inhibition of SHBG synthesis. Insulin may also stimulate adrenal androgen secretion (Nestler, 1997). Although ARBs are mainly approved for treatment of hypertension, some of them are considered as good lowering agent of the risk for type 2 Diabetes (Scheen, 2004) as the inhibition of RAS has been shown to increase insulin sensitivity and improve endothelial function (Henriksen *et al.*, 2001). Several studies have demonstrated that the PPARs can play an essential role in regulating lipid and carbohydrate metabolism and those ligands (especially for PPAR-γ) can improve insulin sensitivity (Berger and Moller, 2002). This direct activation of the ligand binding domain of PPARs by ARBs is independent of their angiotensin type 1 receptors blocking actions and it was found that this effect was strongest for telmisartan, followed by irbesartan and losartan but the effects of valsartan on PPAR-γ activation was minimal (Schiffrin *et al.*, 2003). In the present study, the reported effects for the utilized ARBs supported the previously mentioned idea about PPAR-γ activation, though they are adjunctly used with metformin. According to our results, it needs to be pointed out that the response to metformin and ARBs was observed in patients who were not considered severely insulin-resistant at baseline. Similarly, it has been reported previously that response to treatment with metformin (Kumari *et al.*, 2005) or rosiglitazone (Yilmaz *et al.*, 2005) was even shown in lean women with seemingly normal indices of insulin action and no clear predictors of a positive response to metformin or Thiazolidinediones (TZDs) have been identified. In the present study, we reported a highly significant change in both LH and FSH levels after 4 months treatment with metformin and its combination with one of the studied ARBs; however, the

effect reported for telmisartan and losartan is more pronounced. This finding is compatible with that reported in other studies, where the use of insulin sensitizers in PCOS patients decreases insulin levels with consequent improvements in LH and FSH levels (Balen and Rutherford, 2007; Lord *et al.*, 2003). Concerning the effects on testosterone level, we reported that only losartan and valsartan significantly lowered its levels after 4 months compared to metformin alone or its combination with valsartan; this finding was compatible with that reported by others which demonstrate a positive correlation between decreasing insulin sensitivity and androgen levels (Nagamani *et al.*, 1986). Moreover, Jayagopal *et al.* (2003) found that hyperinsulinemia is usually associated with a decrease in sex hormone binding globulin (SHBG) and increase androgen levels and treatment with insulin sensitizing agents greatly improve those hormonal abnormality (Jayagopal *et al.*, 2003). In addition, since the evaluated patients did not show remarkable impairment in BMI or insulin resistance, the reported reduction in testosterone and improvements in LH/FSH in our patients seemed to be independent of changes in BMI and fasting serum C-peptide levels, implying that the effects of ARBs reported in our study may involve mechanisms beyond the effect on insulin resistance. In fact, several lines of evidence support the notion that some PPAR- γ ligands, including TZDs, may have a direct effect on ovarian steroidogenesis apart from improved insulin sensitivity (Seto-Young *et al.*, 2005). Meanwhile, similar mechanisms may be involved for the ARBs-induced androgen suppression in our patients, but this should be proven with further research on the cellular and molecular level. Accordingly, our observation may provide a new basis for a potential new drug indication for certain ARBs in women with polycystic ovary syndrome. In conclusion, adjuvant use of certain ARBs with metformin in treatment of PCOS improves its metabolic and hormonal effects, with most predominant effect for telmisartan and losartan respectively.

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