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RESEARCH ARTICLE

EFFECTS OF TELMISARTAN ON WEIGHT GAIN AND OBESITY IN PATIENTS WITH ESSENTIAL HYPERTENSION AND METABOLIC SYNDROME

D. Lalitha Devi, D. Arthi and K.S.N. Murthy

GSL Medical College, Rajahmundry

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ABSTRACT

Background: Abdominal obesity, which increases cardiometabolic risks is often associated with hypertension. Evaluation of antihypertensive drugs for their beneficial effects on weight gain may improve clinical management of obese patients with hypertension.

Objectives: To study the effects of Telmisartan treatment on weight gain and obesity in patients with essential hypertension and metabolic syndrome.

Methodology: Sixty patients who fulfilled the criteria for essential hypertension and metabolic syndrome, admitted to GSL General hospital Rajahmahendravaram constituted the study group. The study conducted with two angiotensin receptor blockers, Telmisartan and Losartan. These sixty patients are divided into two groups. First group received 40 mg Telmisartan per day and the second group received 50 mg of Losartan per day. The study period was 12 weeks from 1-3-2013 to 30-5-2013 in GSL General hospital, a tertiary care hospital in Rajahmahendravaram (A.P.). The following parameters are recorded in the proforma annexed. 1. Blood pressure 2. Random blood sugar 3. Body weight 4. Body mass index calclulated by using the formula BMI= Weight in kgs/ Height in square meters. Expressed as kgs per square meter 5. Waist circumference

Pre treatment and post treatment values of the above parameters are taken at the baseline and at the end of 3 months after giving the drug

Results : With Telmisartan all the post treatment values of blood pressure (both systolic and diastolic), body mass index, waist circumference and random blood sugar are highly significant (p value 0.000). With Losartan there is no statistical significance for body weight and BMI. Other values significant are SBP and DBP (p value 0.000), waist circumference (p value 0.045).

Interpretation and conclusions: The results showed that Telmisartan when compared to Losartan is effective in the management of hypertension as well as having additive benefits in reducing body weight, BMI and waist circumference. The drug is also beneficial in lowering blood glucose levels by increasing insulin sensitivity through its action on PPAR gamma receptors.

INTRODUCTION

Abdominal obesity, which increases cardiometabolic risks is often associated with hypertension[1]. Evaluation of antihypertensive drugs for their beneficial effects on weight gain may improve clinical management of obese patients with hypertension. Recently, clinical and experimental studies have shown that angiotensin receptor blockers have effect on weight gain and obesity, which indicate that these drugs could be beneficial for the management of obesity related hypertension.

Metabolic syndrome is a cluster of common cardiovascular risk factors, including hypertension, atherogenic dyslipidemia, insulin resistance and visceral fat obesity[2].

Metabolic syndrome is present in about 10-25% in industrialized countries.[3] The increasing availability of high calorie, low fiber foods and the adoption of sedentary life styles are leading to an increased prevalence of the metabolic syndrome in developing countries as well as in industrialized countries.[4] The presence of visceral fat plays an important role in the causation of metabolic syndrome.

The international diabetes federation consensus worldwide definition o f the metabolic syndrome (2006) is central obesity and any two of the following: Raised triglycerides >150 mg per dl or specified treatment of this lipid abnormality. Secondly, raised blood pressure systolic above 130 or diastolic above 85 or treatment for the previously diagnosed hypertension. Thirdly, raised fasting plasma glucose >130 mg or treatment for previously diagnosed type 2 diabetes mellitus.

The world health organization 1999 criteria require the presence of any one, diabetes mellitus, impaired fasting glucose, insulin resistance and any two of the following:

Blood pressure > 140/90 mm Hg
Dyslipidemia

Central obesity, Waist hip ratio > 0.85 male, >0.90 female, BMI > 30 kg/ square metre or micro albuminuria >20 microgms per minute

The present study is conducted with the following two drugs Telmisartan and Losartan belonging to the group of angiotensin receptor blockers which are used in the treatment of hypertension.

Telmisartan: It was believed that Telmisartan in addition to having antihypertensive effect has got some pleiotropic effects that interfere with metabolic pathways. Evidence suggests that it may partially activate PPAR gamma which may improve insulin sensitivity and dysregulation of adipokine secretion.[6] Activation of PPAR gamma by Telmisartan has got some additional benefits in patients with metabolic syndrome and essential hypertension.

Losartan: First drug in the group of angiotensin receptor blockers and is equally effective in controlling blood pressure as Telmisartan. But the additional benefits like PPAR gamma modulation seen with Telmisartan are not there.

The metabolic effect of Telmisartan and Losartan in hypertensive patients with metabolic syndrome was studied. According to a study conducted by ALESSANDRA *et al* (2005), Telmisartan, but not Losartan significantly reduced plasma glucose, blood pressure and body weight etc.[5]

In a study conducted by Takag H *et al* [7] Telmisartan has been proposed to be promising cardiometabolic sartan due to its unique PPAR gamma inducing property. In these randomized trials with Telmisartan versus control therapy, Telmisartan improved metabolic parameters in patients with metabolic syndrome.

Ozgur Bahdir *et al*[8] tested the clinical importance of Telmisartan in hypertensive patients with metabolic syndrome in comparison with Losartan. A total of 42 hypertensive patients were randomized either to Telmisartan 80mg/day or Losartan 50 mg / day. Biochemical assessments were made at baseline and at the end of 8 weeks. Insulin resistance was evaluated using HOMA –IR. Both the groups had similar reduction in systolic and diastolic blood pressure ($p<0.05$). But insulin resistance decreased in the Telmisartan group due to its molecular structure when compared to Losartan.

In an obesity research conducted by Tetsuya Kukuma *et al* [9] the results provide evidence that Telmisartan may improve glucose and lipid metabolism with the reduction of abdominal circumference and body weight in patients with type 2 diabetes and metabolic syndrome.

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity, and a healthy, reduced calorie diet according to FELDEISUN SE *et al* [10] .

MATERIAL AND METHODS

Aim and Objectives

Aim: To study the effects of Telmisartan on obesity and weight gain in patients with essential hypertension and metabolic syndrome.

Objectives

1. To study the beneficial effects of Telmisartan on body weight, body mass index and waist circumference in patients with essential hypertension and metabolic syndrome.
2. To study the other beneficial effect of maintaining good glycaemic control by improving insulin sensitivity in patients with metabolic syndrome
3. To compare the effects of Telmisartan with those of Losartan, another drug belonging to the same class of angiotensin receptor blockers

Study design: Prospective open label, randomized and controlled study

Study setting: GSL Medical College and General Hospital, a tertiary care hospital in Rajamahendravaram (A.P.)

Study period: A period of 3 months from 1-3-2013 to 30-52013

Study population: 60 patients who fulfill the criteria for essential hypertension and metabolic syndrome attending the medical out patient department of GSL General Hospital are taken as the study population. These patients are taking for the first time the two drugs Telmisartan and Losartan.

Thirty patients constitute group A and they receive 40 mg of Telmisartan per day by oral route.

The remaining 30 patients constitute group B and they receive 50 mg of Losartan per day by oral route.

Age group and sex: Patients of age group 45-75 belonging to both sexes were included in the study.

Selection criteria

Inclusion criteria

1. All the patients who fulfill the criteria for essential hypertension according to Joint national committee (JNC) eighth committee updated September 2011 are included in the study.
2. Patients with moderate hypertension are selected, the blood pressure ranging from systolic BP 140-160 mm of Hg and diastolic BP ranging from 90-100 mm of Hg.
3. Patients with metabolic syndrome fulfilling any 3 criteria like elevated blood pressure, elevated blood glucose, increased BMI or waist circumference or elevated triglycerides.

Exclusion criteria

1. Patients with severe hypertension who require more than two drugs as polypharmacy may obscure the results
2. Severe or uncontrolled diabetes.

The following parameters are recorded in the proforma annexed.

1. Blood pressure- Recorded with sphygmomanometer in millimeters of mercury
2. Random blood glucose- Recorded with a glucometer in millimeters per deciliter
3. Body weight – Measured with weighing machine in kilograms.
4. Waist circumference- Measured with measuring tape in centimeters

5. Body mass index (BMI)-Calculated using the formula

BMI= Body weight in kilograms/ Height in square meters

Expressed as kilograms / square meter

Pretreatment values of the above parameters are taken before giving the drug.

For group A, 40 mg of Telmisartan per day orally for three months given.

For group B, 50 mg of Losartan per day orally for three months given.

Post treatment values with both the drugs at the end of three months entered in the proforma annexed.

Ethical issues

Permission from the institutional ethics committee taken before starting the study

Informed consent taken from all the participants.

Statistical analysis

The following plan of statistical analysis was followed.

All statistical analysis was done by using SPSS software version 21 and in MS-EXCEL 2007.

Quantitative variables are presented and Mean ± standard deviation and qualitative variables were presented as percentages.

Student paired t test was used for comparison of pre and post treatment measurements.

For all statistical analysis, p-value less than 0.05 has been considered statistically significant.

OBSERVATION AND RESULTS

The following are the results of the experiment.

With Telmisartan, the drug which belongs to the group of angiotensin receptor blockers, the statistical values both systolic and diastolic blood pressure, random blood sugar, body weight, BMI and waist circumference are highly significant. With Losartan, another drug belonging to the same category of antihypertensives, the statistical values of systolic blood pressure, diastolic blood pressure and random blood sugar are highly significant. Waist circumference is also statistically significant. For body weight and body mass index there is no statistical significance. Finally, when both the drugs are compared, the post-treatment values of all the parameters are highly significant with Telmisartan, making it a choice of drug for the treatment of essential hypertension with metabolic syndrome by its specific action on PPAR-gamma receptors.

Table 1 showed age distribution, the mean age being 58.2 ± 12.2.

Table 1 Age Distribution of Cases (n = 60)

Age (years)	Number of cases	Percentage (%)
46 - 55	22	36.67
56 – 65	24	40
66 – 75	14	23.33

Mean Age (Years) = 58.2±12.2

Table 2 showed sex distribution, the male being 49 and11 females are in the study group.

Table 2 Sex Distribution of Cases (n = 60)

Sex	Number of cases	Percentage (%)
Male	49	82
Female	11	18

Table 3 showed the pre- treatment and post-treatment values in the telmisartan group. Mean + SD is shown for all the parameters. The p-values for all the parameters are highly significant.

Table 3 Telmisartan Treatment

Parameters		N	Mean	P value
SBP	Pre test	30	161±12.690	0.000*
	post test	30	141.83±13.031	
DBP	Pre test	30	103±7.94	0.000*
	post test	30	89.33±10.81	
BMI	Pre test	30	32.43±4.99	0.000*
	post test	30	30.84±4.83	
WC	Pre test	30	117.37±19.19	0.000*
	Post test	30	113.67±18.89	
BW	Pretest	30	75.17±5.46	0.000*
	Post test	30	73.20±5.14	
RBS	Pretest	30	216.33±42.21	0.000*
	Post test	30	181.73±38.47	

Table 4 showed the pre-treatment and post-treatment values in the losartan group. Mean + SD is shown for all the parameters. The p- values which are significant are given for both systolic and diastolic blood pressure, random blood sugar and waist circumference. The p- values for body weight and body mass index are not significant.

Table 4 Losartan Treatment

Parameters		N	Mean	P value
SBP	Pre test	30	161±10.94	0.000*
	post test	30	147.33±8.28	
DBP	Pre test	30	103.33±5.47	0.000*
	post test	30	92±6.64	
BMI	Pre test	30	27.05±2.81	0.085
	post test	30	26.95±2.85	
WC	Pre test	30	96.40±10.43	0.045**
	Post test	30	96.13±10.20	
BW	Pretest	30	67.70±9.88	0.493
	Post test	30	67.62±9.87	
RBS	Pretest	30	209.57±32.17	0.000*
	Post test	30	190.87±28.21	

Fig 5 is the box- plot showing pre and post treatment values with both telmisartan and losartan.

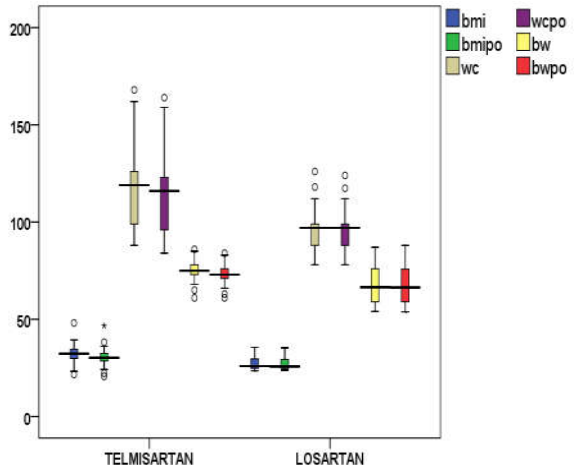

Fig 1 Box Plot

DISCUSSION

Sixty patients of essential hypertension with metabolic syndrome are selected for the study. Patients were divided into 30 patients each. One group received Telmisartan 40 mg per day and the other group received 50 mg of Losartan per day.

Metabolic and vascular abnormalities associated with metabolic syndrome are invetibly linked to the dysregulation of adipokines from accumulated visceral adipose tissues. Metabolic syndrome is present in about 10-25% of individuals in industrialized countries.

Telmisartan is an angiotensin 2 type 1 receptor blocker, originally developed for the treatment of essential hypertension. It was also reported to partially activate the peroxisonme proliferator receptor gamma (PPAR- gamma) which may improve insulin sensitivity and dysregulation of adipokine secretion. This activation of Telmisartan through PPAR-gamma activation has additional benefit in the treatment of essential hypertension with metabolic syndrome. Many animal studies have demonstrated the beneficial effects of Telmisartan on obesity, accumulation of visceral adipose tissues, insulin sensitivity and fatty liver.

Losartan is another angiotensin receptor blocker used for the treatment of essential hypertension. But with Losartan, antihypertensive effect was seen, but the other beneficial effects seen with Telmisartan were not observed like maintaining good glycaemic control and effect on body weight and visceral adipose tissue. However, in regard to the antihypertensive effect, both the drugs showed similar response.

The study hypothesis states that Telmisartan in addition to exerting good control on blood pressure, also having other beneficial effects on body weight, body mass index and waist circumference. Additionally, the drug is having long plasma half-life and strong binding affinity to angiotensin 2 type I receptors.

With Losartan good control of both systolic and diastolic blood pressure was achieved. But body mass index and body weight was not reduced. The waist circumference and random plasma glucose showed some statistical significance.

In the study conducted by KAKUTA *et al* [11] it was found that Telmisartan has the strongest binding affinity to angiotensin 2 type I receptor in comparison with other angiotensin receptor blockers. With other ARBs reduction in blood pressure is comparatively less and Telmisartan has got strongest binding affinity for the receptors. It has got long plasma half-life and can conveniently be given once in a day in a dose of 40-80 mg per day.

In another study conducted (HONGBO HE *et al*, 2010)[12], the hypothesis that Telmisartan prevents weight gain and obesity through activation of PPAR- gamma dependent pathways was tested.

In vivo, long term administration of Telmisartan significantly reduced visceral fat and prevented high fat diet- induced obesity in wild type mice and hypertensive rats but not in PPAR-gamma knockout mice.

Finally it was concluded that Telmisartan prevents adipogenesis and weight gain through activation of PPAR-gamma dependent liolytic pathways and energy uncoupling in several tissues.

Effect of Telmisartan on selected adipokines, insulin sensitivity and substrate utilization during insulin-stimulated conditions in patients with metabolic syndrome and impaired fasting glucose was studied by PETER WOHL *et al* [13] with the objective of evaluating the effect of Telmisartan on the above parameters. In the end, they observed that Telmisartan increased the plasma leptin as well as adiponectin levels and it could be beneficial in metabolic syndrome.

In the study conducted by KANA ARAKI *et al* [14] it was seen that hyperglycemia, hyperinsulinemia and hypertriglyceredemia in diet-induced obese mice, all improved with Telmisartan treatment.

DE LUIS DA *et al* [15] studied the effects of Telmisartan versus Olmesartan on metabolic parameters, insulin resistance and adipocytokines in obese hypertensive patients. The results of the above study showed that patients treated with Telmisartan had a significant decrease of glucose, insulin and HOMA-IR.

MAKITA-S *et al* [16] designed a prospective, randomized study to compare a PPAR gamma activating ARB with a non-activating ARB to delineate the effects of metabolic factors associated with cardiovascular disease. This study was conducted for 6 months with 2 drugs Telmisartan and Candesartan. At the end of the study it was observed that Telmisartan decreased body weight and increased serum adiponectin levels whereas Candesartan has not shown such effects on body weight and other parameters.

JM NAGEL *et al* [17] studied the effects of Telmisartan on glucose and insulin resistance in non-diabetic insulin resistant subjects and found out that Telmisartan treatment compared to placebo resulted in an improvement in the beta cell function as evidenced by an increase in the insulinogenic index. This study indicates that improvement in glucose metabolism is due to activation of PPAR gamma. KHAN AH *et al* (2011) [18] through their study showed that Telmisartan provides better renal protection than Valsartan in a rat model of metabolic syndrome. In an open-label prospective randomized study, patients with metabolic syndrome with waist circumference >90 cm in women and >85 cm in men were treated either with Amlodipine or Telmisartan for 24 weeks. At the end of the treatment fat distribution and insulin sensitivity were determined.[19]

In the abdominal fat depot intervention programme of Okayama (ADIPO), the effects of Telmisartan treatment on the abdominal fat in patients with essential hypertension and metabolic syndrome were studied. In that study it was concluded that Telmisartan had beneficial effect in the reduction of visceral fat in comparison to Valsartan.[20]

To summarize all the results showed that Telmisartan is effective in the management of hypertension as well as having additive benefits in reducing body weight, waist circumference and body mass index in obese subjects. With regard to the antihypertensive effect, both the drugs Telmisartan and Losartan showed similar effects.

CONCLUSION

Telmisartan is superior to Losartan and other angiotensin receptor blockers in good control of 24 hour hypertension as well as in reducing body weight, body mass index and waist circumference in obese subjects. This drug can also bring about good glycemic control through its effect on PPAR gamma modulation.

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