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Influence of non-diabetic agent as "losartan" on serum glucose levels in healthy volunteers. A preliminary study

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ABSTRACT

Background: To investigate the potential effect of losartan, angiotensin II receptor antagonist, on the serum glucose levels, was studied in healthy volunteers. ***Method:*** Losartan was studied at a dose of 100 mg single dose at the morning with breakfast in 10 healthy volunteers. The blood samples were collected at fasting and postprandial 2 hours of breakfast and measured for glucose levels using a glucometer in control and test groups. ***Results:*** Losartan 100 mg single oral dose was administered in the test group versus that in control group. The results showed that the two groups at the start were identical and no significant difference between them in age, BMI, weight, height and fasting serum glucose levels, and their means were 28.20 ± 2.57; 27.70 ± 2.75 year (P-value =0.69), 23.33 ± 1.60 K/m^2 (P-value=0.06), 74.15 ± 8.87; 67.50± 8.31 kg (P-value=0.102), 1.78 ± 0.09; 1.75 ± 0.09 m; (P-value=0.44), 83.80 ± 8.98; 79.90 ± 4.80 mg/dL; (P-value=0.15). The results showed that the mean serum levels of glucose postprandial in mg/dL.in test group versus control group 134.50 ± 5.38; and 94.00 ± 6.81 mg/dL; its P-value =0.000$^{***.}$ ***Conclusions:*** The study indicates that single dose of losartan decreases the glucose level in healthy subjects. The study also suggests that caution may be recommended concerning combined use of losartan and an oral hypoglycemic agent.

Key words: losartan,serum glucose levels

Introduction

Influence of losartan on the hypoglycemic activity of glimepiride in normal and diabetic rats was studied before, but the question of our study "does the losartan have an effect on serum glucose levels in healthy volunteers?

Angiotensin receptor blockers (ARBs) reduce the rate of diabetic kidney disease progression in hypertensive azotemic patients with type 2 diabetes (Brenner *et al.,* 2001; Levey *et al.,* 2009). Their efficacy in slowing progression of early kidney disease, however, is less certain, and surrogate end points, such as albuminuria progression, complicate interpretation of most studies (Parving *et al.,* 2001).

In the Irbesartan in Patients with Type 2 Diabetes and Micro-albuminuria (IRMA 2) study(Gomis *et al.,* 2001), frequency of progression to macro-albuminuria was reduced by the study drug, but decline in glomerular filtration rate (GFR), as estimated by creatinine clearance, was not. Similarly, in the Steno-2 study (Gaede *et al.,* 2003), intensive multifactorial intervention in patients with type 2 diabetes and microalbuminuria significantly reduced progression to proteinuria but did not alter the rate of GFR decline. Microalbuminuria significantly reduced progression to proteinuria but did not alter the rate of GFR decline.

Diabetes mellitus is described as a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin production or action or both (Murthy *et al.,* 2008; Bastaki, 2005).

The literature reveals that diabetes and hypertension are interrelated and strongly predispose an individual to atherosclerotic vascular disease (James and Epstein, 1995).

Diabetes is the leading cause of peripheral neuropathy globally. Duration of diabetes, glycemic control, and preexisting cardiovascular risk factors independently correlate with the development and progression of diabetic peripheral neuropathy as well as cardiovascular autonomic neuropathy.

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Diabetic neuropathies are a family of nerve disorders caused by diabetes. Many trials have shown that intensive glucose control in patients with type 2 diabetes mellitus reduces the progression of microvascular disease (Tesfaye *et al.,* 1993; Eaton *et al.,* 2003).

Losartan is a non-peptide angiotensin II receptor antagonist with high affinity and selectivity for the AT 1 receptor (Foote and Halstenson, 1993; Goldberg *et al.,* 1995; Eberhardt *et al.,* 1993; Brunner *et al.,* 1994; Burnier *et al.,* 1994; Chiu *et al.,* 1991). Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT 1 receptor (Goldberg *et al.,* 1995; Brunner *et al.,* 1994; Burnier *et al.,* 1994).

Losartan undergoes substantial first-pass metabolism by the cytochrome P450 system (Eberhardt *et al.,* 1993; Chiu *et al.,* 1991). Biotransformation results in a major active carboxylic acid metabolite that is 10 to 40 times more potent than the parent compound and is responsible for most of the pharmacologic activity(Munafo *et al.,* 1992; Cody, 1994; Kang *et al.,* 1994), In addition, there are 5 minor metabolites that are much less active than the parent compound.

The half-life of losartan is approximately 2 hours, and the time needed to reach cpmax (maximum plasma concentration) is about 1 hour (Munafo *et al.,* 1992; Ohtawa *et al.,* 1993) (17, 23). Losartan is a substrate of CYP2C9, which is metabolized by CYP3A4 (Iwamura *et al.,* 2011). The influence of losartan on the hypoglycemic effect of glimepiride was studied in normal and diabetic rats, and they concluded that chronic losartan pretreatment elevates the hypoglycemic effect of glimepiride by a possible rise in insulin sensitivity and improving insulin homeostasis or may be due to the inhibition of CYP2C9 (Murthy *et al.,* 2013).

Subjects and Method:

Drug product used:

Amosar^{R} (losartan potassium) *100 mg* 30 Scored Film Coated Tablets from Amoun Pharmaceutical Co. S.A.E Cairo, Egypt.

A glucometer for blood glucose estimation was obtained from Bionime USA Corporation.

Subjects:

Twenty healthy volunteers were enrolled in this study; their age is among 24-32 year. The volunteers were informed about the objectives of the study and all the procedures were explained to them. A written consent form was signed by each agreement to participate in this study.

a) Inclusion criteria

Twenty healthy male adult volunteers with age ranging from 24 up to 32 years, and their weight ranging from 60 to 85 kg were enrolled (non-obese). Physical examination showed that all the volunteers had no clinical evidences of chronic diseases.

b) Exclusion criteria

Volunteers with liver diseases, smokers, regular prescription medication, chronic diseases (hypertension, diabetes, kidney disease, ischemic heart diseases), were excluded.

Study design:

Ten volunteers in group I were treated with the vehicle (120 ml water) considered as control, and group II administered with losartan 100 mg for each one, considered as test group.

Group I: All volunteers in this group (control group), their blood glucose levels were measured by glucometer (Bionime) fasting and post prandial (2 hour) after breakfast with drinking 120 ml water.

Group II: All volunteers in this group (test group), their blood glucose levels were measured by glucometer (Bionime) fasting and post prandial (2 hour) after 2 hours of breakfast and administration of 100 mg losartan (amosar^{R}), as a single oral dose.

Statistical analysis

All values are presented as the mean ± standard deviation (±SD) and were analyzed by Statistical Package for Social Science (SPSS) version 20. The analysis of variance (ANOVA) test was used to compare between the means of the two different treatment groups and paired t-test was used to

compare two mean parameter values for the same group. The level of significance was set at P value of 0.05 or less. Data were also presented as figures using Microsoft Excel 2016 software.

Results

Ten healthy volunteers served as Control Group was treated with the vehicle (120 ml water) and test group was administered 100 mg of losartan orally as a single dose.

Losartan at the dose of 100 mg orally once daily after breakfast was studied in 10 healthy volunteers compared with control group to assess its effects on serum levels of glucose after 2 hours of losartan administration.

The results of our study showed that the mean of age by year in volunteers in control group was 28.2 ± 2.57 years, and that in the test group was 27.70 ± 2.75 years. The P-value was non-significant (P=0.689). It means there is no statistical difference in both groups in their age Tablet (1).

Table 1: Demographic characteristics of healthy volunteers enrolled in the control and test groups.

Characteristic	Control group	Test group	P-value
Age, in years mean ± (SD)	28.20 ± 2.57	27.70 ± 2.75	0.69 (NS)
BMI, in Kg/m^2 mean ± (SD)	23.33 ± 1.60	21.90 ± 1.46	0.06 (NS)
Weight in kg	74.15 ± 8.87	67.50± 8.31	0.102 (NS)
Height in meter	1.78 ± 0.09	1.75 ± 0.09	0.440
Gender	Male (10/10)	Male (10/10)	
Serum levels of glucose fasting in mg/dL mean ± (SD)	83.80 ± 8.98	79.90 ± 4.80	0.15 (NS)

All data are means ±SD (standard deviation), Statistical analyses were performed by using SPSS paired t-test, and when P-value is NS, it means non-significant

We calculated the BMI (body mass index) for both groups, the BMI for control group and test group were 23.34 ± 1.6, 21.91 ± 1.42 kg/m^2 respectively, and by using SPSS paired t-test the P-value was non-significant (0.06). It means that both groups are identical in BMI as there was no significant difference between the means of their BMI. Table (1).

The used equation to calculate BMI is the following:

$$\text{BMI} = \frac{weight\ in\ Kg}{(height\ in\ meter)^2} = \text{kg}/m^2$$

In control group the means for their weight was 74.15 ± 8.87 Kg., and that for test group was 67.50± 8.31 Kg., P-value between their means was equal to 0.102, so there was no significant difference between the two groups in their weights.

In control group, the means for their height was 1.78 ± 0.09 meter, and that for the test group was 1.75 ± 0.09 meter, P-value between their means was equal to 0.44, so there was no significant difference between two groups in their heights. Table (1), figure (1)

In control group, the mean serum glucose levels fasting in control group was 83.8 ± 8.97 mg/dL, in test group, the mean serum glucose levels fasting was 79.9 ± 4.79 mg/dL., and the P-value was insignificant (0.47). Table (2).

According to analysis of the data in the demographic characteristics of healthy volunteers enrolled in this study, the control and test groups were started at base line with no significant difference in age, BMI, weight, height, and fasting serum glucose levels. Table (1)

The results showed that, in table (2), figure (2, 3), the mean serum levels of glucose postprandial (2 hours) in control group was 134.5 ± 5.38 mg/dL, and the mean serum levels of glucose postprandial (2 hours) in test group was 94 ± 6.81 mg/dL., the P-value was highly significant (0.00).

The results of the study found that, there was an increased in mean serum levels of glucose, in the control group about 61.85 ± 15.28 %, after 2 hours of their breakfast, whereas in the test group, the mean serum glucose levels were increased only by 24.59 ± 6.29 % after 2 hours of their breakfast and administration of 100 mg losartan orally, the P-value was highly significant (0.00).

We calculated the percentage decrease in serum glucose levels due to administration of losartan using the following equation:

$$\%\ decrease\ in\ serum\ glucose\ level = \frac{a-b}{a} \times 100$$

a= post-prandial glucose level for control group (expected)
b= post-prandial glucose level for test group (actual)
We found that the mean % decrease in serum glucose levels in test group after losartan administration by 2 hours was - 30.03 ± 5.46 %. Table (2), and figure (4).

Table 2: Changes in mean of serum glucose levels after administration of 100 mg tablet single oral dose to healthy volunteers enrolled in this study versus the control group**.**

Parameters	Control group	Test group	P-value
The mean serum levels of glucose fasting in mg/dL (mean ± SD)	83.80 ± 8.98	79.90 ± 4.79	0.15 ^{ns}
The mean serum levels of glucose postprandial in mg/dL (mean ± SD)	134.50 ± 5.38	94.00 ± 6.81	0.000***

All data are means ±SD (standard deviation), Statistical analyses were performed by using SPSS paired t-test, and when P-value is below 0.05, significant.
*** = highly significant.
ns=non-significant.

Our results showed that there was percentage increased in serum glucose levels about 61.85± 15.28% in control group when measured 2 hours postprandial; whereas, in test group the percentage increase was significantly reduced when compared with control group, where P-value was (0.000). on the other hand, the percentage decrease in serum levels of glucose postprandial in test group due to the action of losartan was 30.03± 5.46% as in Table (3), and figure (3)

Table 3: Changes in mean percentage increase or decrease in serum glucose levels as a result of administration of 100 mg tablet single oral dose to healthy volunteers enrolled in this study versus the control group.

Parameters	Control group	Test group	P-value
The mean percentage increase in serum levels of glucose postprandial %	61.85 ± 15.28	24.59 ± 6.29	0.000***
The mean percentage decrease in serum levels of glucose postprandial and after administration of losartan in %		-30.03% ± 5.46	

All data are means ±SD (standard deviation), Statistical analyses were performed by using SPSS paired t-test, and when P-value is below 0.05, significant.
*** = highly significant.

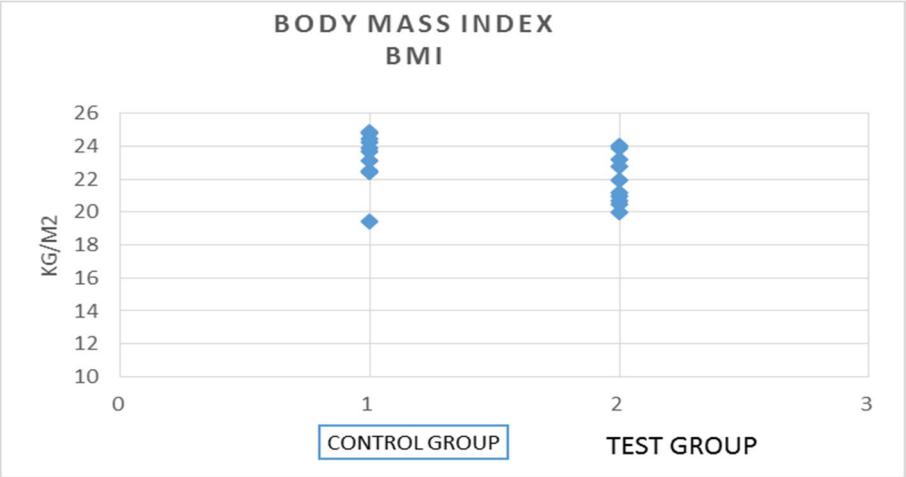

Fig. 1: The baseline of healthy volunteers in control group (taken no drug), and test group (taken losartan 100 mg tablet), showing no significant difference between the two groups in their body mass index by Kg/m^2 (BMI).

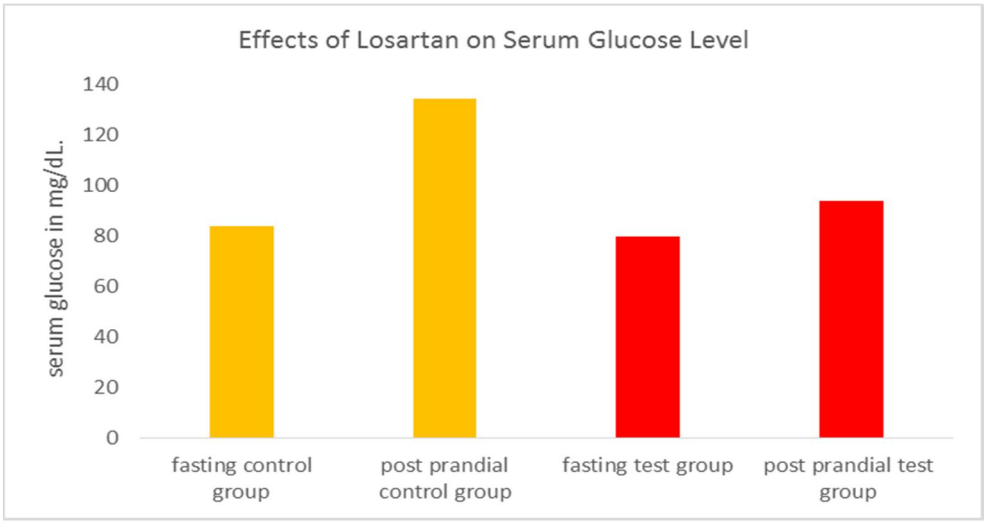

Fig. 2: Ten healthy volunteers (served as test group) showed a significant effect on serum glucose levels post prandial 2 hours of administration of 100 mg tablet orally as single dose and their breakfast, versus 10 healthy volunteers (served as control group) postprandial 2 hours of their breakfast

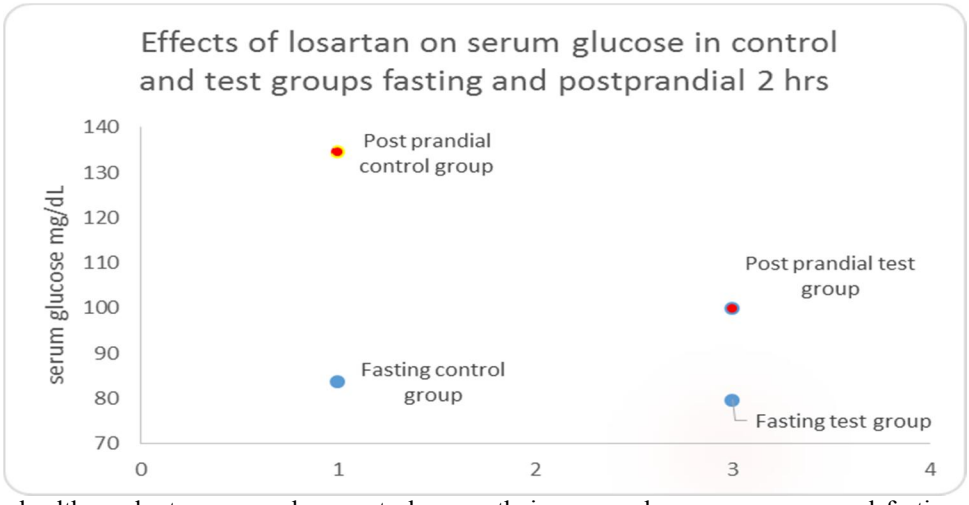

Fig. 3: Ten healthy volunteers served as control group their serum glucose was measured fasting and after 2 hours after their breakfast in mg/dL., versus 10 healthy volunteers served as test group their serum glucose was measured after 2 hours (in mg/dL.) of their breakfast and administration of 100 mg losartan tablet taken orally.

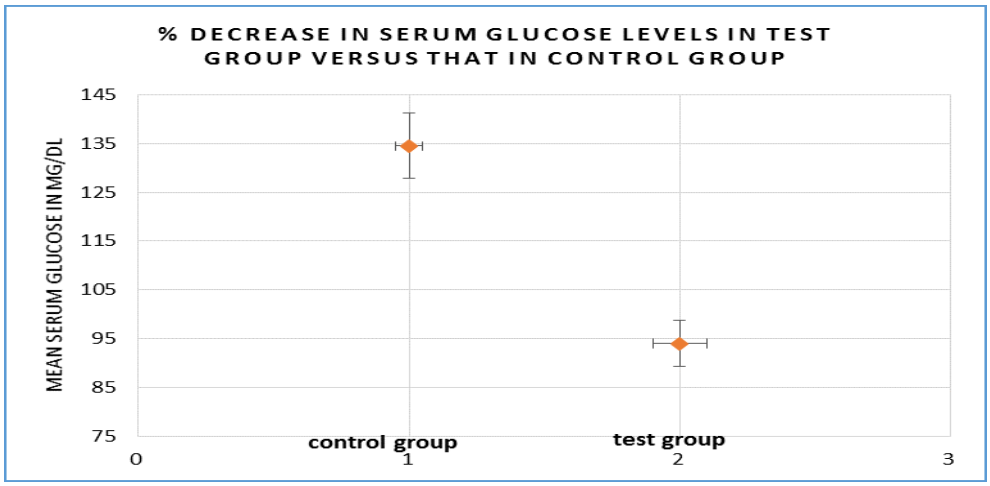

Fig. 4: Twenty healthy volunteers in two groups, 10 in each; representing the degree of decrease in serum glucose levels after 2 hours from administration of 100 mg of losartan and their breakfast in test group from that in control group (serum glucose levels were measured after 2 hours from their breakfast).

Discussion

Influence of losartan on the hypoglycemic activity of glimepiride in normal and diabetic rats as add in therapy had been studied before, but the question of our study "does the losartan have an effect on serum glucose levels in healthy volunteers?

In our study losartan decrease serum glucose levels and this result is consistent with Schupp et al. reported that ARBs induce activation of PPAR γ (*Peroxisome proliferator-activated receptor-gamma*) in cultured adipose cell lines of mice, which partially removes insulin resistance(Ran et al., 2006). The effects of ARBs on glucose metabolism have been reported in several experiments on animals and cell lines.

Furthermore, Furuhashi *et al.* (2014) showed that blocking of the renin-angiotensin system by an ARB increased the plasma adiponectin level. This hypothesized is to be the mechanism by which ARBs reduce blood glucose, and explained our results about hypoglycemic effect of single dose of losartan on serum glucose level after 2 hours postprandial.

Limitations:

Further study on whether the blood glucose-lowering effect by suppression of the renin-angiotensin system was direct or through some other factor are needed.

In addition, the use of losartan on glucose metabolism abnormalities as additive therapy for patients with diabetic type 2, this was not examined in the present study. We are looking into these issues as future subjects of research.

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