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Effects of Telmisartan and Pioglitazone on High Fructose Induced Metabolic Syndrome in Rats

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Abstract

Metabolic syndrome (MS) is a cluster of hypertension, insulin resistance, dyslipidaemia and hyperuricemia. This study was designed to assess the effect of telmisartan and pioglitazone on high fructose induced metabolic syndrome. 35 Male albino rats were classified into 5 groups: A: Normal diet-fed; B: High Fructose-fed (HFD) subdivided into B1 (HFD only), B2 (telmisartan 5mg/kg), B3 (pioglitazone 10mg/kg) and B4 (telmisartan + pioglitazone). Drugs started 4 weeks after starting HFD & lasts for 4 weeks. Body weight (BW), blood pressure (BP) measurement, estimation of the level of fasting glucose, fasting insulin, uric acid (UA), total cholesterol, triglycerides (TG), high density lipoprotein (HDL-c), low density lipoprotein (LDL-c), blood urea nitrogen (BUN), creatinine and (nitric oxide) NO were done. Compared to group-B1: Telmisartan sig decrease BP, BW, serum glucose, insulin, UA, urea, cholesterol, TGA, LDL and sig increase HDL; pioglitazone sig decrease BP, serum glucose, insulin, UA, urea, creat., cholesterol, TGA, LDL and sig increase HDL. Co-administration of Pioglitazone + telmisartan sig decrease insulin, urea and creat compared to telmisartan alone. Combined telmisartan plus pioglitazone allow better control of BP, hyperglycaemia, insulin resistance and the amelioration of BW increase that may be associated with pioglitazone treatment.

Keywords: Metabolic syndrome, Telmisartan, Pioglitazone, Body weight, Blood pressure, dyslipidaemia, uric acid, insulin resistance

Introduction:

Metabolic syndrome (MS) is a worldwide problem that is currently receiving much exploration, both in experimental animals and in the clinic (Alam et al. 2016; Liu et al. 2016; Rabie et al. 2015; Vu et al. 2016). MS is a combination of medical disorders which increases the risk of cardiovascular disease and diabetes (Benson et al. 2004). MS includes hypertension, insulin resistance (IR), dyslipidaemia and hyperuricemia which is strongly associated with risk of impaired glucose metabolism and diabetes (Puig and Martinez 2008).

The renin-angiotensin system (RAS) plays an important role in the pathophysiological consequences of MS and many researchers in clinical trials showed the significant benefits of RAS blockade for end-organ protection in MS (Galle et al. 2008). Either inhibition of RAS or Block of angiotensin receptors is thought to ameliorate MS criteria (Rabie et al. 2015), may be through improvement of insulin sensitivity independent of changes in blood pressure (Mori et al. 2007), prevention of weight gain in addition (de Kloet et al. 2010), reduction in liver injury, attenuation of oxidative stress parameters and hepatic expressions of inflammatory and fibrotic markers (Rabie et al. 2015)

Telmisartan is an orally active antagonist of angiotensin II type I receptors (AT₁), it has the highest affinity for the AT₁ receptors among the available AT₁ antagonists (Kakuta et al. 2004).

Pioglitazone is thiazolidinedione agent that improve glucose homeostasis in type 2 diabetes by decreasing insulin resistance (Olefsky 2000) especially in adipose tissue and muscles (Finelli and Tarantino 2012a). In addition, it significantly decreases the risks of the dangerous cardiovascular side effects and strokes that are common in patients with high-risk type 2 diabetes (Dormandy et al. 2005). The Pioglitazone has agonistic activity of nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR- γ) which is expressed in endothelium, vascular smooth muscle cells and is thought to be responsible for atherosclerosis (Little et al. 2008).

The aim of the present work is to study the effect of telmisartan on HFD induced MS in rats in comparison to anti-diabetic drug pioglitazone.

Materials and Methods

Drugs and Chemicals:

Telmisartan: (*Bohringer Ingelheim, Germany*), Allopurinol: (*GSK, Egypt*), Pioglitazone: (*Takeda, Egypt*) to be dissolved in distilled water to a concentration of 1mg/ml. Fructose: *Uni fructose powder (Universal Industrial Pharmaceutical Co. (UNIPHARMA – Egypt).*

Animals:

35 adult male Sprage Dawley rats weighing (190-200 g) were handled according to the guidelines of local ethical committee that it adhere to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). The rats were housed in metal cages under ordinary room temperature, exposed to natural daily light-dark cycles. They were fed a standard chow diet composed. They were allowed free access of water. Animals were divided into 2 main groups.

Group A: (7 rats) (Non-fructose-fed) received vehicle (distilled water, 1 ml/kg), served as negative control group

Group B: (28 rats) Fructose-fed rats were fed high fructose diet (HFD) for 8 weeks (60% HFD consists of fructose mixed with normal diet in a ratio of 6:4 (Nagi et al. 1995) and further subdivided into 4 groups, 7 rats each:

Group B1: HFD diet only + (water, 1 ml/kg) served as positive control.

Group B2: HFD + Telmisartan (5 mg/kg) (Zanchi et al. 2007).

Group B3: HFD + Pioglitazone (10 mg/kg) (Suzuki et al. 1997) .

Group B4: HFD + Telmisartan + Pioglitazone in the above mentioned doses.

All drugs were given daily orally by gavage starting 4 weeks from HFD feeding and last for 4 weeks:-

- Body weight (BW) of each rat was recorded at the start and at the end of the 8th week of the experiment.

- Measurement of Systolic (SBP), diastolic (DBP) and mean blood pressure (MBP) digitally were done in conscious rats using a tail-cuff sphygmomanometer a non-invasive blood pressure measurement system (*Biosynthesis Biotechnology TSE-system, Homburg, Germany*), at the start and at the end of the 8th week of the experiment. The mean value of three consecutive measurements was obtained. All animals were preconditioned daily for BP measurements one week before the experiment.

- Biochemical examination

After 6-8 fasting hours, retro-orbital 5 ml blood sample was drawn under inhalation anaesthesia, centrifuged at 3000 round/minute for 20 minutes, the serum was transferred into clean vials and stored at -20°C.

Using commercially available-ready to use kits for estimation of the level of glucose, insulin (*Monobind Inc, USA*), UA, total cholesterol, TG, HDL-c, LDL-c, BUN, creatinine (*Biodiagnostic, Egypt*) and NO (*IBL International GmbH, Germany*) according to the manufacturer guidelines.

Homeostasis assessment of insulin resistance (HOMA-IR) (IR index)

Insulin resistance (IR) was determined using (The Homeostasis assessment of insulin resistance (HOMA-IR) (IR index)). It was calculated by using the fasting serum glucose and insulin levels according to Matthews et al. The equation: $\text{HOMA-IR} = \text{fasting glucose (mg/dl)} \times \text{fasting insulin } (\mu\text{U/L}) / 450$ (Matthews et al. 1985).

Histopathological examination of rat knee joints

At the end of experiment, animals were sacrificed. Right/left rats knee joints of each animal were removed into 10% neutral buffered formalin, processed for complete decalcification in EDTA, embedded in paraffin, sectioned longitudinally at 5 μm and stained with hematoxylin and eosin for histopathology study

Statistical analysis

Results were expressed as Mean $\pm$ Standard Deviation (SD) and analysed for statistically significant differences using one way analysis of variance

(ANOVA) followed by the LSD (Least Significant Difference) post analysis test to compare the means from different groups. P value < 0.05 was considered significant. SPSS 17 for windows was used for statistical calculations (San Diego, CA, USA).

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Results

HFD for eight weeks resulted in appearance of classic symptoms of MS in the form of significant increase in BW, SBP, DBP, MBP, serum glucose and insulin, IR, UA, urea and creatinine, serum TG, total cholesterol, LDL and significant decrease in serum NO level and HDL-c levels compared to normal non medicated group-A.

Body Weight:

Telmisartan (group B2) and combined telmisartan with pioglitazone (group B3) significantly decreased mean BW; while, pioglitazone treatment (group B4) didn't result in significant difference in rats BW compared to group B1. On the other hand, adding telmisartan to pioglitazone in group B4 result in significant reduction of BW compared to that produced by pioglitazone alone (B2).

In all situations, there was significant higher mean BW in all groups compared to normal control group i.e. the tested drugs ameliorated but not normalized the BW effects of HFD (Table 1).

Blood Pressure:

Telmisartan (group B2), pioglitazone (group B 3) significantly decreased mean BP compared to group B1. Combined therapy with

pioglitazone and telmisartan didn't show additive synergistic or potentiating action over using each drug alone.

On the other hand, there was significantly higher blood pressure in all groups compared to normal control non medicated group A i.e. the currently used drugs alone or in combination couldn't normalize BP but ameliorate it (Table 2).

Glucose and insulin

Telmisartan (group B2), pioglitazone (group B 3) or combined telmisartan with pioglitazone (group B4) significantly decreased mean serum glucose and insulin levels compared to group B1. Furthermore, serum glucose was normalized by pioglitazone and combined telmisartan plus pioglitazone.

On the other hand, serum insulin levels were normalized by pioglitazone only. In addition, pioglitazone resulted in significantly lower mean insulin level compared to telmisartan.

While adding telmisartan to pioglitazone resulted in insignificant changes compared to those produced by pioglitazone alone in mean serum glucose and insulin levels (Table 3).

Insulin Resistance (IR):

Telmisartan, pioglitazone and combined telmisartan with pioglitazone significantly decreased IR compared to group B1. In

addition, pioglitazone significantly decreased IR compared to telmisartan. Furthermore, addition of telmisartan to pioglitazone didn't result in further decrease in IR compared to telmisartan alone. Neither telmisartan, pioglitazone nor their combination could normalize the IR (Figure 1).

Nitric Oxide

Telmisartan and pioglitazone resulted in insignificant increase in serum NO level compared to that of group-B1. Combined telmisartan with pioglitazone resulted in significant increase in NO level compared to that in group-B1. Adding pioglitazone to telmisartan resulted in insignificant changes in NO level compared to the effect of each drug alone (Table 3).

Uric Acid

Telmisartan, pioglitazone and combined telmisartan with pioglitazone significantly decreased the mean serum UA levels compared to group-B1. Combined pioglitazone to telmisartan in group B 4 resulted in insignificant differences compared to the effect of each drug alone (Table 4).

Urea & Creatinine

Pioglitazone and combined telmisartan with pioglitazone significantly decreased mean serum urea and creatinine levels compared to group B1 with insignificant differences from that in normal control non

medicated group A i.e. they normalized these parameters compared to B1 non treated group.

While telmisartan in group B2 significantly decreased mean serum urea with insignificant change in mean creatinine level. Pioglitazone treatments significantly decreased mean creatinine and urea levels compared to telmisartan.

Co-administration of pioglitazone and telmisartan resulted in no more significant reduction in neither mean serum creatinine nor urea levels, than those produced by pioglitazone alone (Table 4).

Dyslipidaemia:

Telmisartan, pioglitazone or combined telmisartan with pioglitazone significantly decreased TG, total cholesterol and LDL-c; whereas significantly increased HDL level compared to group-B1.

Pioglitazone normalized serum TG, LDL-c or HDL-c and total cholesterol levels, whereas telmisartan normalized only total cholesterol but can't normalize serum TG, LDL-c or HDL-c.

On the other hand, addition of telmisartan to pioglitazone abolished its ability to normalize serum LDL-c and HDL-c but not TG or cholesterol. Telmisartan decreasing effect of LDL-c levels is less significant than pioglitazone effect (Table 5).

- Histopathological examination of rat knee joints:

In the group B1, histopathological study of the knee of rats, demonstrated features of acute gouty arthritis in only two animals of the examined rat knee joints in the form of edema, moderate to mild infiltrate of neutrophils and mast cells within the periarticular soft tissues (Fig. 3) compared to that of the control group-A that showed no gouty arthritis lesions within the articular and periarticular soft tissues with normal histological structure (Fig. 2).

Histopathological study of the 7 animals in the groups B2, B 3 and B 4 showed no lesions of gouty arthritis within the articular and periarticular soft tissues (Fig. 4) (Fig. 5) and (Fig. 6) respectively.

Discussion:

Fructose is a commonly used sweetener associated with diets (Finelli and Tarantino 2012*b*). The increase in fructose consumption in high fructose sweetener represents an important contributor to the epidemic MS world wide (Rabie et al. 2015). The HFD induce a deranged lipid profile that is associated with adipose tissue hypertrophy, increased ratios of visceral and epididymal fats to body weight and fatty liver (Finelli and Tarantino 2012*b*)

The results of the present study showed that administration of HFD to rats for 8 weeks induced signs of MS, in the form of significant increase in BW, Bp, blood glucose, serum insulin, IR, serum triglycerides level, serum cholesterol, serum LDL and decrease serum HDL level with insignificantly decrease in serum NO compared to control rats that didn't receive HFD which is in agreement with previous report (Kelishadi et al. 2014).

Telmisartan significantly ameliorated the increased BW produced by HFD, this is in agreement with (Khan et al. 2011), which may be due to affection of adipocyte biology and stimulation of efficient adipocytes

formation (Sharma et al. 2002), thus may leads to increase in energy expenditure and decrease in dietary-induced increases in BW and accumulation of visceral fat. It may also be mediated via PPAR γ partial agonistic activity that leads to improved glucose and lipid metabolism and prevention of the increase in BW induced by diet as a result of adipocyte hypertrophy.

While pioglitazone results in insignificant difference in mean BW compared to normal rats which run with results of (Collino et al. 2010) and (Kong et al. 2014) in experimental MS in rats, but against (Haque 2012) in MS patients. The weight gain associated with pioglitazone may be due to increase in fat mass and redistribution of fat from visceral to subcutaneous adipose depot or due to fluid retention (Endo et al. 2011).

The beneficial effect of adding telmisartan to pioglitazone in amelioration of BW in the present study is in agreement with (Zanchi et al. 2007) and (Miyazaki and DeFronzo 2008).

The explanation of this beneficial effect may be a result of prevention of fluid and sodium retention induced by pioglitazone (Endo et al. 2011).

The antihypertensive effect of telmisartan is a well-known and established therapeutic indication (Xu and Liu 2013), which is due to AT $_1$ receptor block that results in a fall of peripheral resistance (Werner et al. 2008) or may be through a PPAR γ -dependent increase in eNOS

expression and activity (Yuen et al. 2011). This is apparently obvious via insignificant difference in BP effects between telmisartan and pioglitazone (which is also a PPAR - γ modifying drug) and when concurrently administered; such observation is in accordance with (Knorr et al. 2011).

Telmisartan could enhance NO release and reduce oxidative stress (Xu and Liu 2013). Anti-oxidant activities didn't investigated in the present study; Alternatively NO results showed insignificant increase in telmisartan or pioglitazone treated groups compared to non-treated group; such a result confirms the observation of (BARUTÇUOĞLU et al. 2010) who stated that telmisartan didn't improve serum NO either in essential hypertensive or diabetic hypertensive patients although it normalization of Bp.

Another explanation of MS pathogenesis is hyperuricemia that may induce a primary afferent arteriopathy which may explain hypertension pathogenesis (Mazzali et al. 2001), induce vascular wall thickening leading to severe vasoconstriction. The resulting decrease in renal plasma flow, GFR, and per tubular capillaries (Sanchez-Lozada et al. 2005) leading to ischemia which is a potent stimulus to arterial hypertension. Development of salt-sensitive hypertension in normal rats

that could be imitated by mild hyperuricemia (Watanabe et al. 2002) supported this explanation.

Pioglitazone significantly decreased BP in fructose-induced (Suzuki et al. 1997), in insulin resistance model in rats (Zanchi et al. 2007), these results are in agreement with our results. Whereas in opposite to results published by (Haque 2012).

The antihypertensive effects of pioglitazone could be due to improving insulin sensitivity, decreasing peripheral vascular resistance and improving endothelial dysfunction (Sung et al. 1999), through stimulation of the production of endothelium-derived vasodilator substances (Goke and German Pioglitazone Study 2002), with their inhibiting effects on various cytokines and the pro-inflammatory transcription factors (Diamant and Heine 2003); however anti-inflammatory parameters weren't assessed in the present study.

In the present result, co-administration of both pioglitazone and telmisartan resulted in insignificant change in diastolic, systolic and mean BP compared to telmisartan alone.

In agreement to (Kong et al. 2014), the present results showed absence of additive effect of combined pioglitazone and telmisartan in controlling BP compared to either drug alone. In contrast was the clinical

studies carried by (Suzuki et al. 2013), who suggested that addition of pioglitazone to candesartan might be a good therapeutic strategy for treating hypertensive-patients with type-2 diabetes.

In the present study, the antihypertensive effect of pioglitazone isn't related to NO levels that run with results of (Shokouh et al. 2013) who found insignificant change in Asymmetric Dimethylarginine (ADMA), the principal endogenous NOS inhibitor, in non-diabetic MS patients treated by pioglitazone.

Telmisartan significantly decreased mean serum glucose and insulin levels compared to non-treated group, such result is in agreement with (Haque 2012), but in contrast to results of (Bahr et al. 2011) in MS patients.

The insulin sensitizing effect of telmisartan has been revealed by (Schupp et al. 2004), through a partial PPAR γ agonistic activity, a central regulator of insulin sensitivity. Telmisartan caused a dose-dependent insulin-sensitizing activity via PPAR γ activation, leading to augmented GLUT4 protein expression and 2-deoxy glucose uptake, both in basal and insulin-stimulated states of adipocytes and induced adiponectin (Fujimoto et al. 2004).

Moreover, (Lardizabal and Deedwania 2010) demonstrated the improvement in insulin-stimulated glucose uptake in muscle, hepatic cells and adipose tissue induced by telmisartan is related to PPAR γ activation, or may be through its anti-inflammatory processes, free fatty acid concentration and/or metabolism alteration.

Pioglitazone showed significant decrease in mean serum glucose and insulin levels, possibly through stimulation of the expression of genes involved in lipid metabolism such as the insulin-responsive GLUT, acid synthase and phosphoenol pyruvate carboxykinase genes, and inhibition of the expression of the “*ob*” gene, which encodes for leptin in MS rats (Collino et al. 2010) or in patients with MS (Haque 2012), by modulation of plasma high-molecular-weight adiponectin concentrations (Vu et al. 2016) or by up-regulation of maternally expressed 3 expression that protect endothelial progenitor cells (Liu et al. 2016).

Adding telmisartan to pioglitazone resulted in insignificant changes in mean serum glucose and insulin levels from those produced by pioglitazone alone, indicating that both of them regulate blood glucose and insulin level through PPAR γ partial agonistic activity.

Although Telmisartan attenuated the pioglitazone-induced increase in fat mass, it doesn't interfere with its insulin-sensitizing properties (Zanchi et al. 2007) which is in agreement with the present results.

In the present study, telmisartan significantly decreased uric acid level that is in agreement with (Sato et al. 2008) but opposite to (Burgess and Buckley 2000) in hypertensive patients. Pioglitazone significantly decrease the uric acid that run with study of (Kutoh and Hori 2013) and (WU et al. 2011) possibly by relieving insulin resistance or may be centrally through upregulation of beta cell related factors especially in early stage type-2 diabetes (Kimura et al. 2015), this is in agreement with our results as regard IR which is significantly reduced by pioglitazone, telmisartan or their combination compared to MS non-treated group.

Telmisartan significantly decrease mean serum urea with insignificant change in mean creatinine level, this result run with *Mandarim-de-Lacerda and Pereira*, in diabetic and non-diabetic hypertensive patients (Mandarim-de-Lacerda and Pereira 2004).

On the other hand, a renoprotective effect of telmisartan is approved in streptozotocin induced diabetes (Zhang et al. 2012). Telmisartan through PPAR- γ partial agonist activity has the ability to improve glycemic and lipid status in a high fat, high carbohydrate diet (Kakuta et al. 2004), anti-inflammatory, antioxidative and anti-

proliferative effects on vasculature (Knight et al. 2008) that is consequently decrease glomerular damage .

The differences between these results and our results may be due to differences in drug doses used, animal models or duration of treatment.

Pioglitazone ameliorate HFD increase in serum urea and creatinine. Many evidences support the use of TZDs as renoprotective beyond their glycemic control and hypertension effects (WU et al. 2011).

Although TGF- β 1 is fundamentally released by hepatic stellate cells during chronic liver injury and plays a critical role in liver apoptosis and fibrogenesis in non-alcoholic fatty liver disease or hepatic steatosis (Tarantino et al. 2008); Weigert et al., approved the benefits of PPAR γ agonists activity of pioglitazone in reduction of TGF- β 1 transcription induced by high glucose (Weigert et al. 2003), pioglitazone also may induce arrest of cell growth and mesangial cell differentiation (Guan et al. 2001), inhibit platelet-derived growth factor (PDGF) induced mesangial growth (Ghosh et al. 2003) and suppress of proinflammatory cytokine expression in mesangial cells (Xiong et al. 2004).

In the present study, telmisartan significantly decreased TG, total cholesterol and LDL-c and significantly increased HDL-c compared to

non-treated group. This is in agreement with (Ono et al. 2009) but in contrast to observation of (De Luis et al. 2010).

The improvement in lipid profile with telmisartan may be due to its PPAR γ -modulating effect (Derosa et al. 2004), with potent induction of hepatic PPAR α -target genes involved in fatty acids catabolism (Jayapriya et al. 2013).

There is positive correlation between hyperuricemia and components of metabolic syndrome (Lin et al. 2007). Moreover, a correlation between UA and total cholesterol, TG and LDL-C and an inverse correlation with HDL-C was observed in 66 adult patients (Heimbach et al. 2012).

The mechanism by which UA may regulate lipids is unclear, may be due to decrease lipid peroxidase (Struthers et al. 2002), decrease in lipase activity (Nakagawa et al. 2006) that results in a decrease in oxidative stress harmful effect (Kanbay et al. 2007). Hyperuricemia may impair endothelium dependent vasodilatation via lipid oxidation (Osgood et al. 2003). Furthermore (Balasubramanian 2003), reported a significant direct relationship between UA and total cholesterol levels in animal models.

The ameliorative effect of pioglitazone on HFD induced dyslipidaemia is in agreement with (Collino et al. 2010) while opposite to (Haque 2012).

Pioglitazone is “dual PPAR γ -PPAR α agonist (Bailey 2001), the activation to PPAR α has been linked to lowering TG levels (Duez et al. 2002) or as a result of PPAR γ agonistic activity that results in hepatic inflammatory response reduction, modulation of the expression of numerous genes in adipocytes that results in improved insulin sensitivity, increased fatty acid uptake and decreased lipolysis (Bailey 2001). Hence the restoration of insulin sensitivity that contribute to dyslipidaemia improvement (Gastaldelli et al. 2009).

The hyperuricemia associated with MS affected the knee joint of two rats of the examined animals in the positive control group (B1) that showed features of acute gouty arthritis in the form of edema, moderate to mild neutrophils and mast cells infiltration within the periarticular soft tissues compared to animals of the negative control group (A) that showed normal structure of the examined knee joints with no detection of any lesion.

The hypouricemic effect of both telmisartan and pioglitazone was supported by histopathological study of all animals in the remaining

groups (B2, B4, and B6) where no lesions of gouty arthritis were detected within the articular and periarticular soft tissues.

This could be explained partly by hypouricemic activity of both pioglitazone and telmisartan together with their anti-inflammatory effects.

Similarly, (Al-Hejjaj et al. 2011) showed anti-inflammatory effect of telmisartan and suggested that telmisartan may possess anti-proliferative and anti-arthritic activities in rat models of chronic inflammation induced by formaldehyde- and cotton pellet.

The antioxidant and anti-inflammatory effects of telmisartan are related to its ability to prevent the activation of NF- κ B signalling pathway which promotes the transcription of NADPH oxidase, TNF- α and inducible nitric oxide synthase genes (Morishima et al. 2009), resulting in induction of gene expression, decrease oxidative stress and amelioration of pro-inflammatory responses as a results of a partial agonistic activity of the PPAR- γ (Blessing et al. 2008) as a result of a PPAR- γ partial agonistic activity (Benson et al. 2004)

Pioglitazone produced a significant improvement of serum oxidative stress parameters and inflammatory cytokines in treatment of collagen induced rheumatoid arthritis in rats (Shahin et al. 2011). Pioglitazone act

as ligands for the PPAR- γ which is important immunomodulator that suppresses the production of inflammatory cytokines (Larsen et al. 2003), reactive oxygen species (Hwang et al. 2005) and inhibits pro-inflammatory gene expression (Verrier et al. 2004).

In summary; both of telmisartan and pioglitazone ameliorated MS and the associated hypertension induced by HFR in rats. The protective effect of either drug was accompanied by significant amelioration in glucose, insulin, IR, dyslipidaemia. Pioglitazone is more superior to telmisartan in controlling levels of blood glucose and insulin, IR reduction and in renal protection, whereas telmisartan is more effective than pioglitazone in controlling BP and BW, combined drugs showed better control of BW and hypertension compared to pioglitazone alone and better renoprotective compared to telmisartan alone.

From this work we can conclude that combined telmisartan plus pioglitazone allow better control of MS manifestations as BP, hyperglycaemia, insulin resistance and the amelioration of increase in BW that may be associated with pioglitazone treatment alone

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Table (1): Body Weight of the Studied Groups

	Group A1	Group B1	Group B2	Group B3	Group B4
BW (gm)1 st week	194.6± 2.9	196.2±6.3	200.1±3.1	199.1±5.1	197.9±7.3
BW(gm) 8 th Week	271± 5.8	328.6±13.7 *	298.6±7 *†	334.1± 9 *‡	300.7±9.2 *†

- Each group = 7 rats, data expressed as Mean ± SD.

* Significant compared to group A1 (P value < 0.05).

† Significant compared to group B1 (P value < 0.05).

‡ Significant compared to group B2 (P value < 0.05).

Table (2): Blood Pressure of the Studied Groups.

	Group A1	Group B1	Group B2	Group B3	Group B4
Systolic (mmHg)	119.3±1.5	173.4±9. 6 *	135.3±5. 5 *†	138.3 ±8.2 *†	132.3±5 *†
Diastolic (mmHg)	72.1±6.4	103.6±1 3 *	89.6±3.9 * †	92.1 ±3.4 *†	91.8±2. 4 *†
Mean BP (mmHg)	87.2±4.9	124±4.6 *	104.9±3. 7 *†	108 ±4.6 *†	105.3 ±3.2 *†

- Each group = 7 rats, data presented as Mean ± SD

* Significant compared to group A1 (*P* value < 0.05).

† Significant compared to group B1 (*P* value < 0.05).

Table (3): Serum Glucose, Insulin and Nitric Oxide Levels

	Group A1	Group B1	Group B2	Group B3	Group B4
Glucose (mg/dl)	90.4±10.1	190.7±32.1*	112.1±16*†	96 ± 6.7 †§	98.9±9.8 †
Insulin (μIU/ml)	1.34±0.58	15.9±3.11*	7.11±3.53 *†‡	3.04±1.2 †§	4.03±2.41 *†§
NO (μU/ml)	2.46±0.94	1.9 ± 0.38	2.5 ± 0.96	2.7 ± 1.3	3.6±1.9 †

- Each group = 7 rats, data presented as Mean ± SD

*Significant compared to group A1 (P value < 0.05).

†: Significant compared to group B1 (P value < 0.05).

‡: Significant compared to group B4 (P value < 0.05).

§: Significant compared to group B2 (P value < 0.05).

Table (4): Serum Uric Acid, Creatinine and Urea Levels in the Studied Groups

	Group A1	Group B1	Group B2	Group B3	Group B4
Uric acid (mg/dl)	1.41±0.33	4.2±1.2 *	2.96±1.9 *†	2.3±0.9 *†	2.1±0.6 †
Creatinine (mg/dl)	0.75±0.06	2.3±0.6 *	2.4±0.8 *‡	1±0.3 †¥	0.7±0.1 †§
Urea (mg/dl)	22.1±3.3	100.3±16.03 *	64.6 ±21.5 *†‡	36.1±8.2 †§	35±4.1 †§

- Each group = 7 rats, data presented as Mean ± SD

Each group = 7 rats, data presented as Mean ± SD

*Significant compared to group A1 (*P* value < 0.05).

†: Significant compared to group B1 (*P* value < 0.05).

‡: Significant compared to group B4 (*P* value < 0.05).

§: Significant compared to group B2 (*P* value < 0.05).

Table (5): Serum Triglycerides, Cholesterol, HDL and LDL levels in the Studied Groups.

	Group A1	Group B1	Group B2	Group B3	Group B4
Triglycerides (mg/dl)	65.3±12.6	137.3±25.3 *	84.4±21.1 *†	71.7±7.7 †	72.1±9.9 †
Cholesterol (mg/dl)	78.6±6.2	95.1±11.3 *	70.3±10.7 †	69.7±4.4 †	77.4±7.8 †
HDL (mg/dl)	30.1±3.5	20.3± 1.8 * †	25.9± 3.3 *†	26.3± 2.7 †	24.7± 3.8 *†
LDL (mg/dl)	25± 2.71	40 ± 4.6* †	33.9± 3.6 *†‡	28.9±4.6 †§	31.1± 3.5 *†

- Each group = 7 rats, data presented as Mean ± SD

*Significant compared to group A1 (P value < 0.05).

†: Significant compared to group B1 (P value < 0.05).

‡: Significant compared to group B4 (P value < 0.05).

§: Significant compared to group B2 (P value < 0.05).

Figure legends:

Figure (1): Insulin resistance of The Studied Groups

- Each group = 7 rats, data presented as Mean $\pm$ SD

*Significant compared to group A1 (P value < 0.05).

† Significant compared to group B1 (P value < 0.05).

Figure (2) Microscopic Picture of Rat Knee Joint of The Normal Control

Group (A): Normal histological structure (A-joint cavity, B-synovial membrane, C- articular cartilage, D- periarticular soft tissue) (H&E X200).

Figure (3): Microscopic Picture of Rat Knee Joint of Group B1 (HFD): showed features of acute gouty arthritis in the form of edema (stare), moderate to mild infiltrate of neutrophils (arrow) (H&E X200).

Figure (4) Microscopic picture of rat knee joint of group B2 (Telmisartan treated group): Normal histological structure (A-joint cavity, B-synovial membrane, C- articular cartilage, D- periarticular soft tissue) (H&E X200).

Figure (5): Microscopic Picture of Rat Knee Joint of Group B3 (pioglitazone): Normal histological structure (A-joint cavity, B-synovial membrane, C- articular cartilage, D- periarticular soft tissue) (H&E X200).

Figure (6): Microscopic Picture of Rat Knee Joint of Group B4 (Telmisartan + Pioglitazone): Normal histological structure (A-joint cavity, B-synovial membrane, C- articular cartilage, D- periarticular soft tissue) (H&E X200).

Draft

Figure 1
124x92mm (300 x 300 DPI)

Figure 2
130x114mm (300 x 300 DPI)

Figure 3
98x87mm (300 x 300 DPI)

Figure 4
99x90mm (300 x 300 DPI)

Figure 5
97x90mm (300 x 300 DPI)

Figure 6
102x90mm (300 x 300 DPI)