SUMMARY AND CONCLUSION

The metabolic syndrome is strongly associated with insulin resistance and consists of a constellation of factors such as hypertension and hyperlipidemia that raise the risk for cardiovascular disease and diabetes mellitus.

Since insulin resistance is the core malfunction that leads eventually to development of type-2 diabetes, improving insulin sensitivity can be beneficial and contribute to lower the risk for developing diabetes .

The optimal anti-hypertensive approach to target organ protection in these insulin resistant patients is interruption of RAS for end organ protection with ACE inhibitors or ARBs. This approach has wide spread agreement recently.

Telmisartan is a promising" cardiometabolic sartan " that act on AT_1 receptor so block the risk of RAS and also PPAR-γ activity. PPAR-γ influences the gene expression involved in carbohydrate, lipid metabolism and also it exert anti inflammatory, anti oxidant, anti proliferative effects on vascular wall cells.

This study was carried out to study the therapeutics implication of telmisartan in cardiometabolic disorders in metabolic syndrome-induced rats and possible mechanisms of telmisartan against the atherosclerosis in a model of hypertension hypercholesterolemic- induced rats. Also vitro studies were done to investigate the effects and site of action of this drugs on the isolated perfused rabbit's heart and on isolated rabbit's aorta.

Concerning the cardiometabolic effects of telmisartan 32 rats were used and divided into four equal groups: Normal control group (group

I),Vehicle group (group II), Metabolic syndrome-induced group (group III), Metabolic syndrome-induced group treated with telmisartan (group IV) which suspended in 0.5% carboxymethyl cellulose and administrated orally at a dose of (5mg/kg/day) during last 2 weeks of the study period. The induction of metabolic syndrome was done by 10%L-fructose in drinking water for 5weeks. At the end of the study period and after overnight fasting the rats were subjected to measuring blood pressure, plasma insulin level, blood glucose , HOMA-IR levels, triglyceride level.

Telmisartan was found to reverse fructose induced hypertension, hyperinsulinemia and hypertriglyceridemia in this model. Telmisartan significantly reduced SBP ,DBP and MBP and improved the hyperinsulinemia through decreasing plasma insulin level, decreasing fasting blood glucose ,decreasing HOMA-IR level which are all index for improving the insulin resistance, finally telmisartan showed to decrease the triglyceride level.

Concerning the mechanism of telmisartan against the atherosclerosis another 32rats were used and divided into three equal groups: Normal control group (group I),Vehicle group(group II), hypertensive hypercholesterolemic group (group III), hypertensive hypercholesterolemic group treated with telmisartan which suspended in 0.5% carboxymethyl cellulose and administrated orally at a dose of (5mg/kg/day) during last 2 weeks of the study period (group IV).

The induction of hypertension was done by given a suspension of deoxycorticosterone acetate (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg)subcutaneously for a period of 6 weeks and the induction of hypercholesterolemia was done by adding 2% cholesterol powder with rat chow to make a homogenous mixture for a period of 6

weeks. At the end of the study period, the rats were subjected to measuring blood pressure, total cholesterol, TG, LDL, HDL levels and histopathology of aortic strip was done.

It was found that telmisartan significantly reduced SBP, DBP and MBP. As regard the lipid profiles telmisartan significantly reduced total cholesterol, TG and LDL , finally telmisartan significantly increased HDL in comparison to non treated group and it showed significant reduction of atherosclerotic changes that occurred in aortic sections.

Regarding the vitro results, telmisartan was dissolved in 1% methanol which produce no effect on the isolated heart in an increasing dose (1,3, 10,30,100,300,1000 μg) also It was observed that preincubation of gradually increasing doses of methanol in a dose of (1,3,10, 30,100μg/ml) for 5 minutes before the addition of Ang II in a submaximal dose (5 ng/ml) and norepinephrine in a submaximal dose (2 μg/ml) had no effect in the aortic strip response to Ang II and norepinephrine respectively.

Telmisartan produced significant dose- related positive inotropic effect starts at a dose of (30μg/ml) this effect was still present after blocking of β adrenergic receptor by using propranolol (10μg/ml).

This study also revealed that telmisartan in gradually increasing doses (1μg to 30 μg/ml bath) produced significant dose dependent reduction of the (Ang II) – induced contractions of isolated rabbit's aortic spiral strip. As regards interaction of telmisartan with noreponephrine, it was observed that preincubation of gradually increasing doses of telmisartan (1, 3, 10, 30 and 100 μg/ml) for 5 minutes before the addition of norepinephrine in a submaximal doses (2 μg/ml) it was noticed

telmisartan produced no change in the aortic strip response to norepinephrine.

In conclusion, since activation of telmisartan "the isoform of PPAR-gamma" improved insulin sensitivity &improvement the endothelial function & decreased inflammation, plasma lipids, and blood pressure all that lead to inhibition of atherogenesis and reduction of cardiovascular events.

telmisartan had simultaneous beneficial effect on blood pressure, metabolic parameters and act as anti atherosclerotic agent. This multifactorial effect may provide synergistic benefits in patients with hypertension and other cardiovascular risk factors such as glucose intolerance and atherosclerosis.

However, chronic experiment and clinical studies are needed for confirming effectiveness and safety.