Effects of Evolocumab, Tocilizumab and Canagliflizon on Cardiac Dysfunction, Proprotein Convertase Subtilisin / Kexin Type 9 and Cardiac Nucleotide Like Receptor 3 in Rats with Metabolic Syndrome.

Thesis to fulfill MD degree in Clinical Pharmacology

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SUMMARY

Metabolic syndrome is a group of conditions that occur together and increasing the risk of heart disease, stroke and T2DM. These conditions include IR, high blood glucose, increased blood pressure, abnormal cholesterol or triglyceride levels and proinflammatory properties. Fructose-induced MetS can be created experimentally either with a high-fructose diet (20 - 66%) or by adding fructose (10 - 20%) to drinking water.

The aim of this work was to investigate and compare the potential protective effect of evolocumab, tocilizumab and canagliflozin on fructose induced metabolic syndrome.

In this work, 48 adult male albino rats were studied, 24 rats were given drinking water with 10% fructose in the first 39 days then the concentration was modified to 25% in the last 10 days.

Rats were divided into 8 groups as follows:

Group 1 (Control group): The rats received normal food and drink for 7 weeks.

Group 2 (Evolocumab group): The rats were injected evolocumab subcutaneously in a dose of (15mg/ kg) once weekly for 7 weeks.

Group 3 (Tocilizumab group): The rats were injected tocilizumab intraperitoneally in a dose of (8mg/kg) once weekly for 7 weeks.

Group 4 (Canagliflozin group): The rats were given oral canagliflozin in a dose of (10 mg/kg) daily for 7 weeks.

Group 5 (Fructose group): The rats were given FDW (10%) in the first 39, then FDW (25%) in the last 10 days.

Group 6 (Fructose + Evolocumab group): The rats were given FDW and subcutaneous evolocumab for 7 weeks.

Group 7 (Fructose + Tocilizumab group): The rats were given FDW and intraperitoneal tocilizumab for 7 weeks.

Group 8 (Fructose + Canagliflozin group): The rats were given FDW and oral canagliflozin for 7 weeks.

At the end of 7 weeks SBP and HR were measured for all groups. Blood was then collected from retro-orbital veins of fasting rats then serum was separated for determination of the following parameters: glucose, insulin, IL6 and lipids (TG, TC, HDL and LDL) levels.

Immediately after collection of blood, rats were sacrificed by cervical dislocation, hearts were excised and washed with ice-cold saline, then each heart was sectioned into two parts, one part was preserved in formalin (10%) for histopathological examination and the other part preserved in deep freezer at -20^{o}C up to measure PCSK9, NLRP3 and TIMP1 concentrations by using ELISA kits.

Results revealed that the serum glucose and insulin levels were increased significantly with fructose feeding. With taking evolocumab, tocilizumab and canagliflozin serum glucose and insulin levels were significantly lower than that in untreated fructose fed group. IR was higher with fructose feeding and significantly improved in fructose groups taking evolocumab, tocilizumab or canagliflozin. Similarly, serum IL6 level was significantly higher with fructose feeding and improved with evolocumab, tocilizumab and canagliflozin.

As regards lipids profile, serum levels of TG, TC and LDL were significantly increased and the serum level of HDL was significantly decreased in fructose fed groups. With taking either evolocumab, tocilizumab or canagliflozin the levels of TG, TC and LDL were lower and the level of HDL was higher than untreated fructose fed group.

PCSK9 and NLRP3 cardiac levels were significantly increased with fructose feeding and the levels were decreased with the three drugs as compared to untreated fructose fed group. On the other hand TIMP1 cardiac levels were significantly lower in fructose group and was increased in fructose groups taking either evolocumab, tocilizumab or canagliflozin.

Systolic blood pressure was measured and it was noticed that it was significantly increased with fructose feeding and was improved with evolocumab and canagliflozin but not with tocilizumab as it was high as untreated fructose fed group. Heart rate was significantly higher in fructose group and improved with the three drugs.

Histopathological examination of cardiac tissues revealed abnormal degenerative changes in fructose fed groups, congestion, inflammatory cell infiltration and fibrosis. These changes were improved with evolocumab, tocilizumab and canagliflozin.

In our study there was significant positive correlation between the serum glucose levels and both SBP, serum IL6 levels, cardiac PCSK9 levels and cardiac NLRP3 levels. In contrast there was significant negative correlation between the serum glucose levels and cardiac TIMP1 levels in the 48 rats.

There was also significant positive correlation between IR and both SBP, serum IL6 levels, cardiac PCSK9 levels and cardiac NLRP3 levels. In contrast there was significant negative correlation between the insulin resistance and cardiac TIMP1 levels in the 48 rats.

There was significant positive correlation between SBP and serum IL6 levels, cardiac PCSK9 levels and cardiac NLRP3levels. In contrast there was significant negative correlation between SBP and cardiac TIMP1 levels.