Proposed hypothesis: calpain-10 (*CAPN10*) gene stimulation in the management of dual disease model of diabetic liver injury

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Hypercholesterolemia and hyperglycemia can be considered as major contributing factors of type-II diabetes mellitus and liver-related complications. CAPN10, ENPP1, IRS1 and GLUT4 genes are known to play a significant role in the metabolism of fat and glucose. Any mutation in these genes can lead to the pathological condition of dual disease model of diabetic liver injury. The in vitro scientific literature revealed that CAPN10 plays an important role in stimulating the breakdown of fat. It is emphasized that the proposed molecular CAPN10 signalling pathway is associated with lipid metabolism and insulin activity for maintaining balance of fat levels in body cells to minimize the metabolic complications.

Abnormal *de novo* lipogenesis (DNL) and fat accumulation cause insulin resistance and increase in the synthesis of free fatty acid which leads to the progression of type-II diabetes mellitus (T2DM) and related metabolic complications like non-alcoholic fatty liver disorder (NAFLD) and liver-related disorders[1,2]. There are numerous key players involved in the cellular metabolism of glucose and fat in the body cells (like adipocytes)[3] which are calpain-10 (*CAPN10*), ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*), insulin receptor substrate 1 (*IRS1*) and glucose transporter (*GLUT4*)[4]. Excessive intake of high-fat diet and carbohydrates creates an imbalance of glucose metabolism due to the condition of hypercholesterolemia and hyperglycemia[2]. Another reason for hypercholesterolemia and hyperglycemia is the mutation in the above-mentioned key genes that are directly involved in fat and glucose metabolism. Simultaneous intake of fat-rich diet and mutation in the *CAPN10* gene lead to the dysregulation of fat metabolism in body cells. This gene is responsible for fat breakdown and its mutation causes unregulated calpain proteolysis leading to β-cell damage[5,6]. In lieu of the same, abnormality in the *CAPN10* gene increases the levels of free fat in the blood, which is translocated towards the outer periphery of the body cells (Figure 1). As a result, a fatty layer gets deposited over the cell membranes, inhibiting the interaction of insulin with *ENPP1*, leading to insulin resistance. Consequently, the *ENPP1*-assisted insulin interaction with *IRS1* for the activation of *GLUT4* transporter is inhibited. The hindered *CAPN10* activity can be considered as a major contributing factor in the pathogenesis of dual disease model of diabetic liver injury. The upregulation and stimulation of *CAPN10* gene with the help of novel pharmacological interventions will enhance fat metabolism in the condition of hypercholesterolemia. So the *CAPN10* gene can serve as a novel target for the management of devastating condition of diabetic liver injury.

Prolonged consumption of high fat and high sugar diet causes pathogenesis of dual disease model of diabetic liver injury. Hyperlipidemia is the key player in insulin resistance, inflammation and oxidative stress, resulting in diabetes and liver-related complication. The upregulation and stimulation of the *CAPN10* gene for enhancing fat metabolism in the condition of metabolic complications serve as novel target for the management of devastating condition of diabetic liver injury.

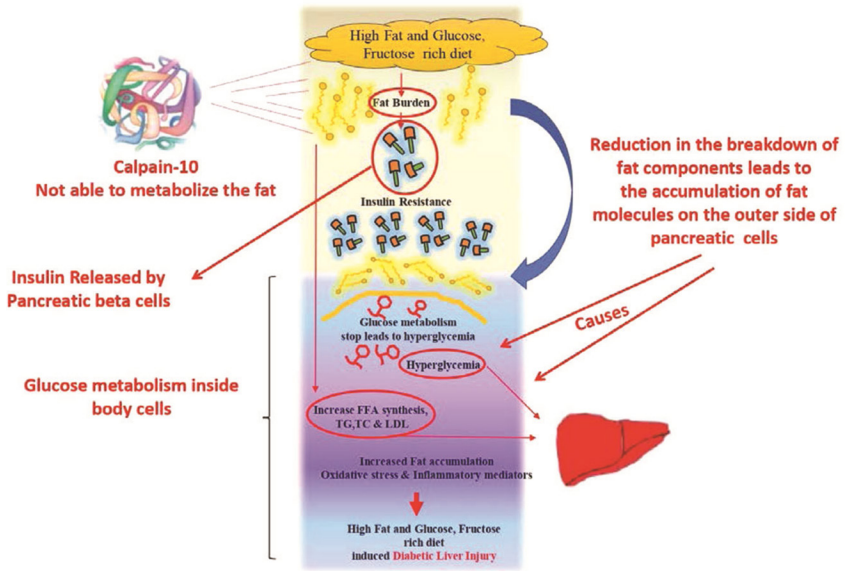

Figure 1. Illustrated role of *CAPN10* gene in the metabolism of fat and glucose which is directly related with the condition of hypercholesterolemia and hyperglycemia.

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