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Adiponectin signalling as a therapeutic target for diabetic cardiomyopathy and heart failure

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The global prevalence of diabetes is estimated to increase to 700 million by 2045, significantly impacting global health and expenditure. Diabetes substantially increases the risk of developing diabetic complications, including cardiovascular diseases and heart failure (HF). This is commonly termed diabetic cardiomyopathy and is often characterised by increased cardiac fibrosis, pathological cardiomyocyte hypertrophy, inflammation, lipotoxicity, increased oxidative and endoplasmic reticulum stress, leading to diastolic dysfunction and HF. In fact, epidemiological studies suggested that diabetic patients are at 2-3 fold increased risk of developing heart failure than non-diabetics. Currently, diabetic cardiomyopathy lacks effective treatment options.

Clinical and experimental studies have long suggested that the adipokine adiponectin and its receptors play a major role in preventing cardiovascular dysfunction and remodelling of the heart. More recently, it was revealed that the heart has a local adiponectin signalling system, which is downregulated in the diabetic heart of animal models and in patients. This reduction in cardiac expression of the cardioprotective adipokine, adiponectin, its receptors (AdipoR1 and AdipoR2) and its downstream signalling molecules, AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor α (PPARα), have been associated with diabetes and the pathological features of diabetic cardiomyopathy.

In this presentation, I will summarise the current evidence for links between the suppressed adiponectin signalling pathway in the heart and diastolic dysfunction, in animal models of diabetes and in patients with diabetes and heart failure. I will also present data where we have targeted this pathway with adeno-associated viral (AAV) gene therapy in a mouse model of T2D *in vivo,* as a possible intervention for diabetic cardiomyopathy.