

# Can nerve growth factor gene therapy prevent diabetic heart disease?

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Diabetes is a major risk factor for cardiovascular disease and can reduce blood supply to the heart tissue and damage cardiac cells, resulting in heart failure. New research has investigated if nerve growth factor (NGF) gene therapy can prevent diabetic heart failure and small vascular disease in mice.

The study by Professor Costanza Emanuelli, British [Heart](#) Foundation Senior Research Fellow and colleagues of the Bristol Heart Institute in the [Regenerative Medicine](#) Section of the School of Clinical Sciences at the University of Bristol is published online in *Diabetes*, which is the journal of the [American Diabetes Association](#).

Scientists believe that NGF has a protective effect on the cardiovascular system but the possibility that cardiac NGF [gene therapy](#) could prevent diabetes-induced heart failure has not been previously studied.

The team investigated whether increasing the myocardial level of NGF by using adeno-associated viral (AAV) vectors could prevent the diabetic heart from failure. AAVs are small non-enveloped, single-stranded DNA viruses that can potentially infect all cell types. They exist in different forms, allowing to better target different cells for gene therapy, including after AAV injection in a vein. Importantly, at variance from more popular [viral vectors](#), AAVs allow for virtually permanent increased level of a therapeutic protein.

Professor Emanuelli said: "Our study represents a major advance in tackling heart disease in diabetics, a leading cause of death in the western world. It also represents one important step forward in our goal for translating NGF-based therapies in cardiovascular patients.

"The critical scientific finding from our research is that diabetes reduces cardiac level of NGF. Most importantly, engineering the diabetic heart with

AAVs to make it produce NGF can prevent heart failure."

Professor Jeremy Pearson, Associate Medical Director at the BHF, added: "Targeted gene therapy is now becoming a realistic prospect for several human diseases. This study suggests that there is real promise for NGF gene therapy in future to alleviate [heart failure](#) in diabetic patients - a major and often fatal complication of their disease."

Type 1 diabetes mellitus was induced in mice by damaging their insulin producing pancreatic cells with streptozotocin. Non-diabetic age-matched control mice were studied for reference.

Murine NGF mRNA expression in the heart was measured by real-time RT-PCR in mice at 12 weeks of diabetes or controls. In separate experiments, at two weeks of diabetes, cardiac expression of human NGF or the AAV control  $\gamma$ -Gal genes was induced by either intra-myocardial injection of adeno-associated virus vectors serotype 2 (AAV2) or systemic injection of AAV9, which is especially able to target [cardiac cells](#). Non-diabetic mice received AAV2- $\gamma$ -Gal or AAV9- $\gamma$ -Gal.

The researchers found diabetes lowered the cardiac expression of endogenous NGF mRNA. A progressive deterioration of cardiac function and left ventricular chamber dilatation appeared in  $\gamma$ -Gal - treated diabetic mice. At 12 weeks of diabetes,  $\gamma$ -Gal - treated mice showed myocardial microvascular rarefaction, hypoperfusion, more interstitial fibrosis and increased apoptosis of endothelial cells and cardiomyocytes. NGF gene therapy using either AAV2 or AAV9 prevented diabetes-induced cardiac dysfunction, reduced cardiac apoptosis and preserved cardiac microvasculature and blood flow.

The research results suggest that NGF gene therapy might have a tremendous therapeutic potential for the treatment of diabetic

cardiomyopathy and encourage further translational efforts for the final benefit of diabetic patients.

However, before this gene therapy approach can be trialled in patients, additional pre-clinical studies need to be performed in order to verify not only the efficiency and the safety of AAVs-mediated NGF in type 1 [diabetes](#), but also to find the most efficient AAV serotype, as well as the optimal dose and delivery route to be used.

Provided by University of Bristol

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