**MicroRNAs could increase the risk of amputation in diabetics**

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New research has found one of the smallest entities in the human genome, micro-RNA, could increase the risk of limb amputation in diabetic patients who have poor blood flow.

The study by Dr Andrea Caporali and colleagues in Professor Costanza Emanueli’s research group in the [Regenerative Medicine Section](http://www.bris.ac.uk/bhi/research/regeneration.html) of the [School of Clinical Sciences](http://www.bristol.ac.uk/fmd/) at the University of Bristol was funded by the Medical Research Council and the British Heart Foundation and is published online in [*Circulation*](http://circ.ahajournals.org/cgi/content/abstract/CIRCULATIONAHA.110.952325v1)*: Journal of the American Heart Association*.

The research group have shown in an experimental cell study that conditions mimicking diabetes and a lack of blood supply to a tissue increased a particular miRNA (miRNA-503) and impaired the ability of endothelial cells, which line the interior surface of blood vessels.

Micro-RNAs (miRNAs) are small sections of ribonucleic acid (RNA) that can inhibit many genes.

Alternatively, slowing down miRNA-503 improved the capability of endothelial cells to duplicate and form into networks of small blood vessels.

The researchers showed that microRNA-503 reduces cell growth and prevents the formation of blood vessels by direct binding and inhibition of cyclin E1 and Cdc25 mRNA.

Costanza Emanueli, Professorial Research Fellow in Vascular Pathology & Regeneration, said: “Because each miRNA can regulate many genes, they represent an exciting new target to correct diseases that have complex underlying mechanisms, like diabetes, rather than trying to target one specific gene.

Our study is the first to provide evidence for a role of miRNAs in diabetes-induced defects in reparative angiogenesis.”

The team subsequently investigated miR-503 and target gene expression in muscular specimens from the amputated ischaemic legs of diabetic patients.

As controls, calf biopsies of non-diabetic and non-ischemic patients undergoing saphenous vein stripping were used.

In diabetic muscles, miR-503 expression was remarkably higher, and plasma miR-503 levels were also elevated in the diabetic subjects.

Finally, using mouse models of diabetes and limb ischaemia, the researchers found that inhibition of the miRNA-503 (using a “decoy miRNA”) could restore-post-ischaemic blood flow recovery.

The findings of this study highlight important clinical implications of miR-503 in diabetes-associated vascular complications.

In early diabetes, high blood glucose levels damage blood vessels leading to lack of blood flow (ischaemia).

Such ischaemic complications are the leading cause of disease and death in diabetic patients.

In limbs, lack of blood flow can result in non-healing ulcers and, in diabetic patients, the ischaemic disease follows an unalterable course and limb amputation is too often the eventual remedy.

Tissues can recover from lack of blood flow by new blood vessel growth (angiogenesis), which restores blood supply to the tissue (reperfusion).

However, diabetes harms the restoration of the flow of blood to a previously ischemic tissue, by mechanisms that are not fully understood, and so a better understanding of the molecular mechanisms underpinning diabetes-associated vascular complications is urgently needed to improve therapeutic options.

**Paper**: [*Deregulation of microRNA-503 contributes to diabetes mellitus induced impairment of endothelial function and reparative angiogenesis after limb ischemia*](http://circ.ahajournals.org/cgi/content/abstract/CIRCULATIONAHA.110.952325v1), Andrea Caporali, Marco Meloni, Christine Völlenkle, Desiree Bonci, Graciela B Sala-Newby, Roberta Addis, Gaia Spinetti, Sergio Losa, Rachel Masson, Andrew H Baker, Reuven Agami, Carlos le Sage, Gianluigi Condorelli, Paolo Madeddu, Fabio Martelli, Costanza Emanueli, *Circulation*, published online before print January 10, 2011.

Please contact [Joanne Fryer](mailto:joanne.fryer@bristol.ac.uk) for further information.

**Further information:**

Costanza Emanueli is a British Heart Foundation Basic Science Senior Research Fellow and Professorial Research Fellow in Vascular Pathology & Regeneration in the School of Clinical Sciences, Section of Regenerative Medicine and Bristol Heart Institute at the University of Bristol.

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The [**Bristol Heart Institute**](http://www.bris.ac.uk/bhi) is made up of over 200 researchers and clinicians, from eight different departments in the University of Bristol, spanning three faculties, and from associated Bristol NHS Trusts. Research income is generated from grants, with the British Heart Foundation being the Institute’s main funder.

As well as improving collaboration between scientists and clinicians within the Institute, the aim is to communicate research findings to the public.

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The [**British Heart Foundation**](http://www.bhf.org.uk) (BHF) is the nation’s heart charity, dedicated to saving lives through pioneering research, patient care, campaigning for change and by providing vital information. But we urgently need help. We rely on donations of time and money to continue our life-saving work. Because together we can beat heart disease.