The Biochemistry of Diabetes Complications Laboratory addresses important mechanistic questions across the spectrum of diabetic complications. This work is directed towards the development of novel preventive, diagnostic and therapeutic strategies through multidisciplinary approaches combining basic bench-top research with human physiology and clinical studies. Our work directly impacts on patient care and has been published in major journals including Circulation Research, Diabetes, Diabetes Care and Diabetologia.

Research Brief

Diabetic complications and the renin angiotensin system (RAS). Activating the RAS makes diabetic complications much worse, while inhibiting the RAS is able to prevent diabetic complications independent to blood pressure lowering. We have demonstrated the importance of ACE2 in regulating the RAS and atherogenesis, kidney and heart disease in diabetes. We are actively working on new ways to use this data to prevent diabetes-associated complications. We are also exploring the impact of salt intake in the diet in the development and progression of diabetic complications through modulation of the RAS.

Metabolic memory - previous exposure to metabolic perturbations can have long-lasting physiological effects. We have shown in animal models of diabetes, that restoration of healthy glucose control does not reduce atherosclerosis and the pro-inflammatory impact of hyperglycaemia when compared to that seen in mice with persistent hyperglycaemia. It is also apparent that even transient elevations in blood glucose may be sufficient to initiate a range of pathogenic pathways associated with an increased risk of microvascular and macrovascular damage, even while mean glycaemic control may be maintained within normal range. The physiological mechanism(s) responsible for metabolic memory are still poorly defined. But we are working on it.

Advanced Glycation End-products (AGEs) - AGEs are thought to act through receptor independent and dependent mechanisms to promote vascular damage, fibrosis and inflammation. Their long-lasting actions have also been implicated in the persistence of metabolic memory and the utility of optimal glycaemic control early in the course of diabetes. We are currently g at ways to block the receptor for AGEs (RAGE).

Kidney disease and diabetes – our work in collaboration with the Finnish Diabetic Nephropathy (FinnDiane) Study have clearly linked the presence and severity of renal damage, as both a key prognostic marker as well as potential mediator of adverse outcomes. However, those with nephropathy lead full and healthy lives. The reason why some people are protected is one of the key focuses of our research.

Methodologies
- Mouse models of accelerated atherosclerosis and diabetic nephropathy
- Assessment of vascular inflammation by dynamic flow adhesion
- Quantitation of AGEs, dicarbonyls and renal function in mice by HPLC

Selected Publications
Activation of the Renin-Angiotensin system mediates the effects of dietary salt intake on atherogenesis in the apoE knockout mouse (Tikellis et al. Hypertension, 2012)

Figure 1. Atherosclerotic plaque accumulation in the aortic arch of apoE KO mice fed a low salt (LS), normal chow (NS) or high salt diet (HS) or low salt with perindopril (LS+P).

Angiotensin Converting Enzyme 2 deficiency accelerates diabetes-associated renal damage not via changes in BP (Tikellis et al. Diabetes, 2007)

The expression of ACE2 is reduced in the diabetic kidney (right)

Increased SBP in ACE2 KO mice (upper panel) is prevented in the presence of diabetes (yellow, lower panel)

Genetic ACE2 deficiency accentuates vascular inflammation & atherosclerosis in the apoE knockout mouse (Thomas et al. Circ Research, 2010)