diet-induced weight gain and cardiovascular pathophysiology in glutaredoxin-1 (Grx1Tg/+). overexpressing male and female mice.

Grx1Tg/+ (TG) and wild-type (WT) littermates (Female and Male, 8-12 weeks) were exposed to a normal chow (NC) or HFHS diet for 10 weeks. Bodyweights were taken weekly and EchoMRI was conducted before and after diet exposure. After 10 weeks, LV pressure-volume loop and blood pressure were obtained by inserting a catheter into the LV under anaesthesia.

In male and female WT mice, HFHS-diet increased bodyweight over 10-weeks. Interestingly, HFHS induced weight gain was attenuated in TG mice, accompanied with a decrease in% fat mass. HFHS-diet increased diastolic and mean blood pressure (BP). However, no significant increase in BP was observed in TG mice. In female TG mice, HFHS-diet reduced end diastolic volume stroke-volume and cardiac output compared to WT hearts. Heart-rates remained the same between all groups.

Overexpression of Grx1 attenuated weight-gain and% fat mass in male and female TG and hypertension in female TG. Additionally, it induced HFHS-diet induced cardiac remodelling in female TG.

**EFFECT OF MYELOID PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) INHIBITION ON DIABETIC WOUND HEALING**

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Diabetes and its associated vascular complications e.g., cardiovascular disease and chronic wounds is a leading healthcare concern. Protein tyrosine phosphatase 1B (PTP1B) is a key regulator of whole-body glucose and energy metabolism. Our recent research suggests that myeloid-specific PTP1B deletion protects against atherosclerosis. We hypothesised that inhibiting myeloid-specific (macrophage) PTP1B would improve the efficacy of wound healing that is hampered by the diabetic environment.

In vivo, wound healing was assessed under physiological, normoglycemic conditions in control wildtype (PTP1Bfl/fl) and myeloid-PTP1B deficient (LysM PTP1B-/-) littermate. Experiments were conducted in streptozotocin-induced diabetic mice. Wound closure was quantified over a period of 10 days. Two circular wounds were made horizontally in the dorsal region. The wounds were assessed using tracing and ruler methods.

In vitro, wound healing was assessed using wound healing assays, under hyper-glycaemic conditions. The keratinocyte cell line (HaCaT) was cultured with bone marrow-derived macrophages (BMDM) from diabetic C57Bl6 mice. Wound healing was also assessed in presence/absence of the PTP1B inhibitor, MSI-1436.

Under physiological conditions, there was a significant improvement in wound healing in LysM PTP1B-/- mice 4 days post-surgery. Under diabetic conditions, LysM PTP1B-/- mice had a significantly faster wound closure compared to PTP1Bfl/fl on day 8 post-surgery. Wound healing assays revealed more efficient wound closure in HaCaT cells co-cultured with BMDM from diabetic C57Bl6 mice, in the presence of MSI-1436. Thus, inhibiting myeloid-PTP1B improves wound healing rate under normoglycaemic and hyperglycaemic conditions, suggesting that PTP1B inhibition as a novel therapy for treatment of non-healing wounds in diabetes and CVD.

**MONOCYTE CHEMOATTRACTANT PROTEIN-1 AS A BIOMARKER OF VASCULAR DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES**

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Endothelial dysfunction has been shown to be strongly associated with cardiovascular disease (CVD) outcomes. CVD risk in diabetes shows heterogeneity and new biomarkers are required to stratify CVD risk in these patients. This study analysed the association of Monocyte Chemoattractant Protein-1 (MCP-1) with measures of vascular function in 509 patients with type 2 diabetes mellitus (T2DM). Endothelial function was measured using laser Doppler imaging (LDI) and peripheral artery tonometry (PAT) (EndoPat). Arterial stiffness was measured using carotid to femoral pulse wave velocity (PWV) (Sphygmocor).

Firstly, the study showed the negative association of MCP-1 with endothelium-dependent vasodilator responses to acetylcholine (R2=0.240, p=5.02*10^-10) as measured by LDI. Secondly, the study showed the negative association of MCP-1 with reactive hyperaemia index (RHI) (R2=0.0716, p=0.0109) and Framingham RHI (R2=0.0987, p=0.0294) as measured by PAT. Thirdly, the study showed the positive association of MCP-1 with PWV (R2=0.387, p=0.0088). Framingham risk factors, diabetes duration, HbA1c and eGFR were controlled for. The study also showed the independent association of MCP-1 with CVD death (odds ratio (OR)=18.2, 95% confidence interval (CI) [1.46 - 631.0], p=0.0487) and all-cause mortality (OR=4.51, 95% CI [1.07 - 21.8], p=0.0462) in a three-year follow-up period. There was no significant improvement to area under receiver operating characteristic curve (AUROC) when MCP-1 was added into risk models.

This study shows MCP-1 to be a good candidate as a biomarker of vascular dysfunction in T2DM. Further research in larger cohorts with longer follow-up periods should be conducted to determine its usefulness in improvement of risk models.

**GLUTAREDOXIN-1 OVEREXPRESSION INDUCES HYPERTENSIVE PREGNANCY AND MATERNAL CARDIOFIBROSIS**

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Elevation of oxidative stress is explicitly linked to hypertensive pregnancies with high levels measurable in the maternal circulation. Hypertensive pregnancies lead to life-long risk of cardiac dysfunction, yet the underpinning molecular pathway are unknown. Oxidative stress modify proteins via oxidative post-