EFFECT OF MYELOID PROTEIN TYROSINE PHOSPHATASE GLUTAREDOXIN-1 OVEREXPRESSION INDUCES MONOCYTE CHEMOTACTANT PROTEIN-1 AS A HEART WOUND HEALING RATE UNDER NORMOGLYCÆMIC AND HYPERGLYCAEMIC ENVIRONMENT.

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Diabetes and its associated vascular complications e.g., cardiovascular disease and chronic wounds is a leading healthcare concern. Protein tyrosine phosphatase1B (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 healing 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.

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 CHEMOTACTANT 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 Chemotactic 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 CARDIAC FIBROSIS

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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-
translational modifications (ox-PTMs) which can regulate intracellular signalling by either potentiating or inhibiting protein activity. One of these, S-glutathionylation is a common oxPTM reversed by glutaredoxin (Glrx). We aimed to investigate the role of Glrx in a murine model of pregnancy combining physiological in vivo cardiac dynamics with histological assessment of maternal organs, to identify how perturbation of redox signalling can lead to cause pregnancy-induced cardiovascular complications.

Mice overexpressing Glrx (Glrx-TG) and littermate controls (WT) underwent timed pregnancy. Left-ventricle (LV) pressure-volume (PV) loops was measured on day 18.5 by catheter inserted into LV. Pregnancy outcome and maternal organ pathology was conducted.

At day 18.5 of pregnancy Glrx-TG mice had higher aortic blood pressure, with more incidents of fetal reabsorptions compared to WT. End-systolic pressure assessed from PV-loops showed a trend for increase in TG vs WT, although there was no overall effect on cardiac ejection fraction or stroke-volume. Interestingly, TG LV appeared to have higher contractility (End-systolic PV relationship), TG mice had an increase in cardiomyocyte size with no change in capillary density. Moreover, there was a significant increase in cardiac and renal fibrosis in Glrx-TG mothers.

Further studies will be needed to identify the redox sensitive molecular pathways, that are altered by Glrx overexpression in the maternal cardiovascular system.

Elevated blood cobalt secondary to metal-on-metal (MoM) hip arthroplasties has been shown to be a risk factor for developing cardiovascular complications including cardiomyopathy. Published case reports document cardiomyopathy in patients with blood cobalt levels as low as 13 μg/l. Clinical studies have found conflicting evidence of cobalt-induced cardiomyopathy in patients with MoM hips. The extent of cardiovascular injury, measured by global longitudinal strain (GLS), in patients with elevated blood cobalt levels has not previously been examined.

Sixteen patients with documented blood cobalt ion levels above 13 μg/l were identified and matched with eight patients awaiting hip arthroplasty with no history of cobalt implants. Patients underwent echocardiogram assessment including GLS.

Patients with MoM hip arthroplasties had a mean blood cobalt level of 29 μg/l compared to 0.01 μg/l in the control group. There was no difference or correlation in EF, left ventricular (LV) end systolic dimension, LV end diastolic dimension, fractional shortening, ventricular wall thickness or E/e ratio. However, GLS was significantly reduced in patients with MoM hip arthroplasties compared to those without (-15.2% v -18%, (MoM v control) p = 0.0125). Pearson correlation demonstrated that GLS is significantly correlated with blood cobalt level (r = 0.8742, p = 0.0009).

This study has demonstrated reduced cardiac function in the presence of normal EF as assessed by GLS in patients with elevated cobalt above 13 μg/l. As GLS is a more sensitive measure of systolic function than EF, routine echocardiogram assessment including GLS should be performed in all patients with MoM hip arthroplasties and elevated blood cobalt.

**Abstracts**

**11** CARDIAC FUNCTION IS COMPROMISED IN PATIENTS WITH ELEVATED BLOOD COBALT LEVELS SECONDARY TO METAL-ON-METAL HIP IMPLANTS

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Angiotensin-II (AngII) induces hypertension and cardiac hypertrophy and is a potent inductor of oxidative stress, which causes oxidative post-translational modifications (ox-PTMs). Glutaredoxin-1 (Glrx) catalyses the removal of an oxPTM, S-glutathionylation, and has been shown to be important in peripheral artery disease. Therefore, we investigated the effect of Glrx overexpression on AngII-pressure overload.

Glrx transgenic (TG) and wild-type (WT) littermates were implanted with osmotic pumps (Alzet) containing either saline or AngII (1.1mg/kg/day; s.c). After 2 weeks, mice were anaesthetised (2% isoflurane) and a pressure-volume (PV) catheter was inserted retrogradely into the left ventricle (LV).

In WT mice, AngII increased systolic and diastolic BP. However, no significant increase in SBP and DBP were observed in TG mice. Heart rates remained similar between all 4 groups. Although AngII increased BP in WT mice, LV end-diastolic/systolic pressure (EDP/ESP) and end systolic volume (ESV) remained unchanged between the four groups. However, AngII significantly lowered end diastolic volume (EDV) in TG compared to WT. Hence, stroke volume (SV) was also lowered in TG compared to WT. Yet, these changes had no overall effect on LV cardiac output or stroke work. Interestingly, AngII significantly lowered LV contractile state (Powermax) in response to AngII in TG compared to WT mice.

In summary, chronic AngII infusion did not increase blood pressure in mice overexpressing Glrx, but lowered pre-load with subsequent lower stroke volume and cardiac contractility. Future studies will investigate which redox sensitive proteins undergo pre-load oxPTM to elicit these functional changes.

**12** GLUTAREDOXIN-OVEREXPRESSSION ATTENUATES CHRONIC ANGIOTENSIN-II INDUCED HYPERTENSION AND CHANGES CARDIAC DYNAMICS

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Jagged1 (Jag1) has essential roles in angiogenesis and development. Altered function of this transmembrane protein results in congenital birth defects and cancer progression. Redox signalling regulates cardiovascular physiology through Endotelial cells (EC). Proteins sense redox signals through cysteine thiols.