Hyperglycemia is the main mediator of prediabetes- and type 2 diabetes-associated impairment of microvascular function: the Maastricht Study

Methods: People with (DM=210) and without (NoDM=117) Type 2 diabetes had GFR (Cockroft-Gault) and AER (overnight urine collection) measured. Plasma biomarkers [MMP1, MMP3, MMP7, MMP10 and MMP12] were measured on OLINK proteomics platform.

Results: MMP3, MMP7, MMP10 were associated with GFR in DM but not in NoDM [For DM, Adjusted Standardised Beta (StdBeta) -0.324($p<0.001$), -0.251($p<0.001$) and -0.178 ($p=0.002$) respectively], independently of potential confounders (age, sex, blood pressure, BMI, cholesterol and HbA_{1c}). There was an interaction between presence/absence of diabetes and MMP3 ($p=0.007$). AER was associated with MMP7, independently of confounders, in DM but not in NoDM [For DM Adjusted StdBeta 0.266($p<0.001$)]. All other biomarkers were not associate with GFR or AER.

Conclusion: Decreasing GFR is associated with increasing MMPs in DM but not in NoDM. Increasing AER is associated with increasing levels MMP7 in DM but not in NoDM. These results suggest MMPs may play a role in diabetic renal complications.

PoA-19

Hyperglycemia is the Main Mediator of Prediabetes- and Type 2 Diabetes-Associated Impairment of Microvascular Function: The Maastricht Study

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Introduction: Prediabetes- and type 2 diabetes-associated microvascular dysfunction may explain their increased risk of microvascular complications. Mechanisms underlying microvascular dysfunction in (pre)diabetes remain poorly understood. We investigated to what extent differences in retinal and skin microvascular function between individuals without and with (pre)diabetes are potentially attributable to hyperglycemia, insulin resistance, blood pressure, lipid profile and low-grade inflammation.

Methods: In The Maastricht Study, a type 2 diabetes-enriched population-based cohort study (n=1791, 51% men, aged 60±8 years), we determined flicker light-induced retinal arteriolar %-dilation (Dynamic Vessel Analyzer), heat-induced skin %-hyperemia (laser-Doppler flowmetry) and diabetes status (OGTT; normal glucose metabolism (NGM), (n=1040), prediabetes (n=276) or type 2 diabetes (n=475)). Composite indices were formed of hyperglycemia, insulin resistance, blood pressure, lipid profile, and low-grade inflammation. Mediating effects of composite indices on prediabetes- and type 2 diabetes-associated microvascular dysfunction were estimated by linear regression.

Results: Age- and sex-adjusted analyses showed lower retinal arteriolar %-dilation in prediabetes (B=-0.16, 95%CI [-0.53;0.21]), with further deterioration in type 2 diabetes (B=-0.83 [-1.15;-0.51]) versus NGM, p-trend<0.001. Skin %-hyperemia was lower in prediabetes (B=-80 [-198;38]), with further deterioration in type 2 diabetes (B=-210 [-309;-112]) versus NGM, p-trend<0.001. Type 2 diabetes-associated differences in microvascular function were explained mainly by hyperglycemia (mediating effect [bootstrapped 95%CI] 55.3% [20.4%;91.3%] and 64.8% [6.2%;122.4%], respectively). Other composite indices did not significantly contribute. Patterns of mediation were similar for prediabetes-associated microvascular dysfunction.

Conclusions: Our findings suggest early and intensive glycemic control in (pre)diabetes as a promising therapeutic target for the prevention of (pre)diabetes-associated microvascular complications.

PoA-20

Type 1 Diabetes Increases Retention of Low-Density Lipoprotein at Atherosclerosis-Susceptible Sites in the Mouse Vasculature.

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Introduction: Individuals with type 1 diabetes are at high risk of developing atherosclerotic cardiovascular disease. However, comprehensive knowledge of the underlying mechanism is lacking. Increased retention of low-density lipoprotein (LDL) at atherosclerosis-susceptible sites has been suggested to accelerate atherogenesis in type 1 diabetic individuals. The aim of the present study was to test this hypothesis by investigating whether retention of LDL is increased in atherosclerosis-susceptible sites in a mouse model of type 1 diabetes.

Methods: Fluorescently-labeled LDL from healthy non-diabetic human individuals was intravenously injected into type 1 diabetic Ins2(Akita) mice and non-diabetic wildtype littermates. The amount of retained LDL 24 hours post-injection was quantified by fluorescence microscopy of cryosections of the atherosclerosis-susceptible inner curvature of the aortic arch, and by scans of thoracic aorta en face preparations. Vascular gene expression in the inner curvature of the aortic arch was analyzed by microarray and quantitative polymerase chain reaction.

Results: LDL retention was detected at atherosclerosis-prone sites of the aortic arch and located in both intimal and medial layers. Quantitative microscopy revealed a 8.1-fold increase in retained LDL in Ins2(Akita) mice compared to wildtype littermates. These findings were confirmed in independent experiments using near-infrared scans of thoracic aorta en face preparations. However, diabetic status did not affect expression of genes known to be involved in LDL retention.

Conclusion: Experimental type 1 diabetes increases the ability of the vascular wall to retain LDL. This effect may contribute to the increase in atherosclerotic cardiovascular disease observed in type 1 diabetic patients.

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