Serum metabolomic profiles associated with subclinical and clinical cardiovascular phenotypes in people with type 2 diabetes

The Edinburgh Type 2 Diabetes Study (ET2DS)

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Background

- Atherosclerotic cardiovascular diseases (CVD) is the **leading cause of death in diabetes**, and its **subclinical stage** usually keeps '**silent**' for decades[1,2].
- The full range of **biomarkers reflecting atherosclerotic burden and CVD risk** in people with diabetes is **unknown**.
- **Metabolomics** provides a high-definition snapshot of numerous metabolites and may therefore **facilitate identification of novel biomarkers** potentially involved in development and/or progression of atherosclerosis.[3]
- **Previous studies** which have explored the association between metabolomics and CVD in diabetes tend to be **small-scale cross-sectional studies**, and **few** have included the metabolomic profile of **subclinical atherosclerosis**.[4,5]

Aim: To describe the serum metabolomic profile for subclinical atherosclerosis, measured using ankle brachial index (ABI), in people with type 2 diabetes, compared with the profile for clinical cardiovascular disease (CVD) in the same population.

Methods

- ☐ **ET2DS** is a prospective cohort of 1,066 individuals with type 2 diabetes, aged over 60 years at baseline and **followed up for 10 years**.
- ☐ A panel of **158** serum **metabolites** were measured at baseline through a targeted nucleic magnetic resonance platform (Nightingale, Finland).
- ☐ Traditional **univariate regression models** and least absolute shrinkage and selection operator (**LASSO**) were applied to explore the association of metabolites with baseline ABI and with prevalent CVD.
- ☐ Metabolites associated with baseline ABI were further explored in terms of association with **follow-up ABI** and **incident CVD**.
- ☐ **Bonferroni** correction was applied to take account of multiple comparisons.

Results

➢ **Descriptive analysis**

1025 available participants with mean age of 67.8 years and 50.7% male formed the study population. Mean ABI at baseline was 0.97 and prevalence of CVD was 35.02%. During 10-year follow-up, mean change in ABI was +0.006 (n=436), and there were 257 incident CVD events.

➢ **Metabolomic profile associated with ABI**

- Lactate, glycerol, creatinine and glycoprotein acetyls levels were associated with baseline ABI in both univariate regression (*β*s: -0.025 to -0.023, all $p<0.0003$, Model 1 in Figure 1A) and LASSO analyses.
- Only lactate showed nominally significant association with ABI measured at year 4 (Figure 1B) and year 10 (Figure 1C) following adjustment for baseline ABI.

➢ **Metabolomic profile associated with clinical CVD**

- All the four baseline ABI-associated metabolites were also risk factors for prevalent CVD (ORs per 1-SD increase in metabolites: 1.29, 1.34, 1.49 and 1.31 respectively, all $p<0.0003$).
- The four metabolites also showed nominally positive association with overall incidence of CVD in 10 years (ORs: 1.19 to 1.35).
- Several components of medium and small high-density lipoprotein (HDL) showed negative associations with prevalent CVD in both univariate regression models (ORs:0.58 to 0.73, all $p<0.0003$) and LASSO analyses.

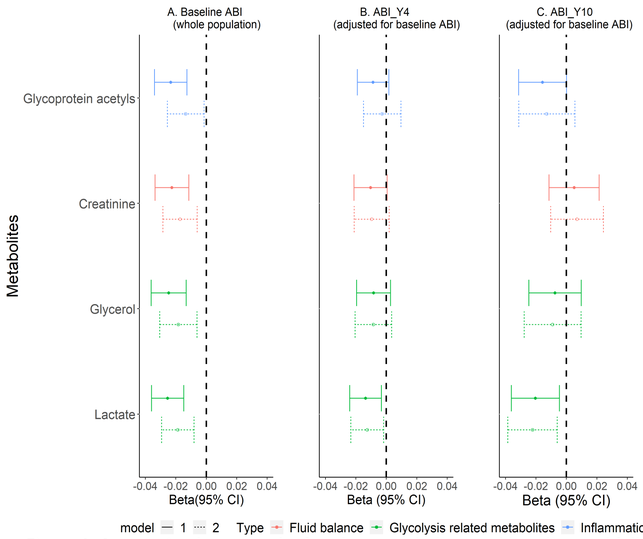

Figure 1. Association between the four key metabolites and baseline and follow-up ABI. A: Baseline ABI (whole population, N=1025), B: ABI at Year 4 (adjusted for baseline ABI, n=731), C: ABI at Year 10 (adjusted for baseline ABI, n=436). The solid lines represent Model 1 (adjusted for age and gender), and the dotted lines represent Model 2 (model 1 plus SBP, smoking, HDL-cholesterol, total cholesterol, BMI and HbA1c).

Conclusions

Serum metabolites relating to glycolysis, fluid balance and inflammation were independently associated with both a marker of subclinical atherosclerosis and with symptomatic CVD in people with type 2 diabetes. Additional investigation is warranted to determine their roles as possible etiological and/or predictive biomarkers for atherosclerotic CVD.

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