Soluble E-Selectin is a liver-derived endothelial marker that is associated with nonalcoholic fatty liver disease

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INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) is a risk factor for cardiovascular disease (CVD)¹.
- The development of atherosclerosis is initiated by retention of plasma lipids in the arterial wall and endothelial dysfunction.
- Epidemiological studies have shown that NAFLD is a significant contributor to plasma biomarkers of endothelial dysfunction, particularly sE-selectin^{2,3}.
- However, experimental studies suggest a causal role for E-selectin in the development of AFLD⁴, which shares histologically and genetically similarities with NAFLD.

AIM

- This study aims to explore the contribution of the liver to plasma sE-selectin levels, in the context of NAFLD.

METHODS

- Hepatic expression of E-Selectin was determined in C57BL/6J LDLR^{-/-} mice on a high cholesterol diet. This mouse model allows disentanglement of inflammation from steatosis⁵.
- Hepatic expression of E-Selectin and plasma sE-Selectin levels were determined in severely obese subjects with various degrees of NAFLD (n=74).
- The association between NAFLD susceptibility genes (i.e. *PNPLA3* and *GCKR*) and plasma sE-selectin was determined in the combined CODAM and Hoorn studies (n=1266).

RESULTS

Mice

In LDLR^{-/-} mice fed a high-cholesterol diet, hepatic steatosis (A) appeared after hepatic inflammation (B). Hepatic E-selectin mRNA expression pattern (C) paralleled hepatic inflammation, not hepatic steatosis.

Humans

NAFLD histological stage was associated with hepatic E-selectin mRNA expression and plasma sE-selectin levels in severely obese individuals (D, E). Hepatic E-selectin mRNA expression was associated with plasma sE-selectin levels (F).

Population

In the CODAM and Hoorn populations, the NAFLD susceptibility genes rs738409 (*PNPLA3*) and rs1260326 (*GCKR*) had similar effects on plasma ALT levels (G, H), but opposing effects on plasma triglycerides (I, J). Both variants were positively associated with plasma sE-selectin levels (K, L).

CONCLUSION

These findings suggest that E-selectin plays a role in the pathogenesis of NAFLD and that plasma sE-selectin is a marker of *hepatic* endothelial dysfunction.