Plasma CTSD activity: a non-invasive biomarker for hepatic insulin sensitivity

Due to the obesity epidemic, the incidence and prevalence of type 2 diabetes mellitus continues to rise globally. Type 2 diabetes is characterised by a relative insulin deficiency and an impaired insulin sensitivity in certain specific target organs. Insulin sensitivity can be subdivided into whole-body and tissue-specific insulin sensitivity, including peripheral (or muscle) and hepatic insulin sensitivity. Impaired peripheral insulin sensitivity reduces insulin-mediated glucose uptake from blood into peripheral tissues, while impaired hepatic insulin sensitivity manifests as the inability of insulin to suppress hepatic glucose production (gluconeogenesis).

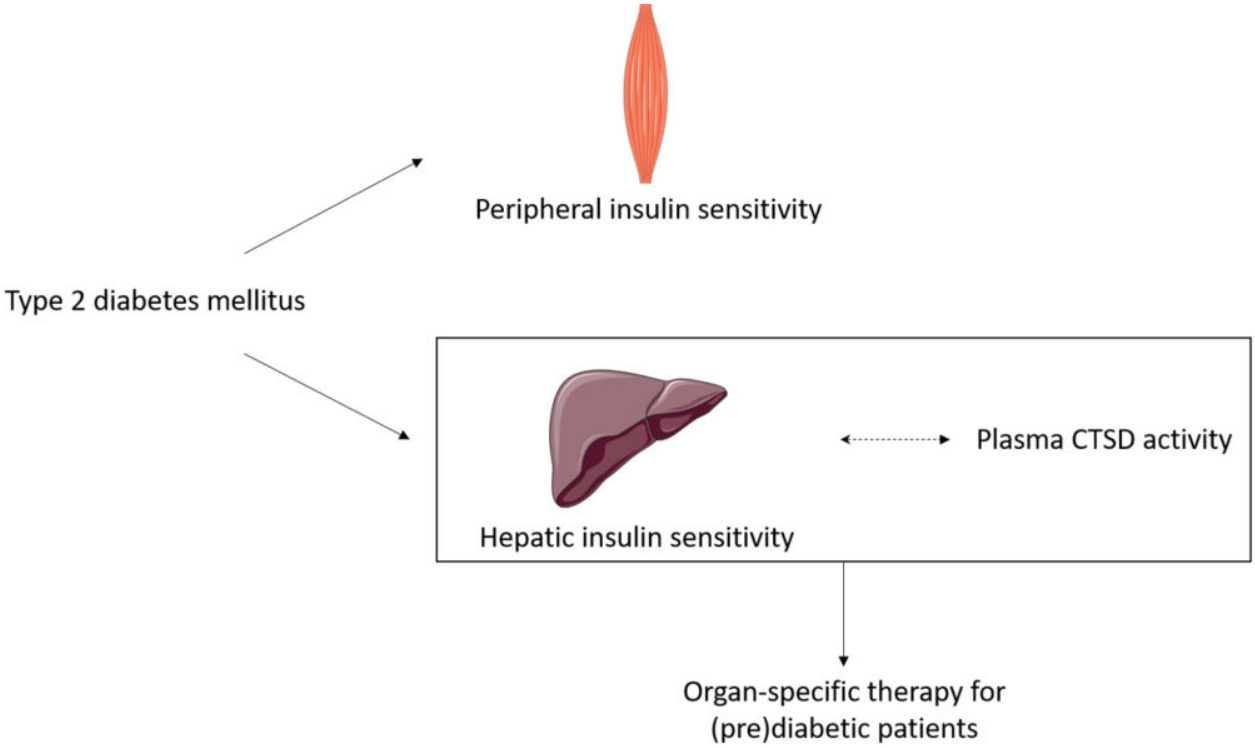

Fig. 1. In type 2 diabetes, insulin sensitivity may involve two aspects: peripheral (muscle) insulin senstivity and hepatic insulin senstivity. In this study, our data showed that plasma CTSD activity only associates with hepatic insulin sensitivity, suggesting that plasma CTSD activity may help in determining a organ-specific intervention for pre(diabetic) patients.

Interventions that improve insulin sensitivity may be organ-specific. Individuals with impaired peripheral insulin sensitivity are most likely to respond to interventions that improve skeletal muscle insulin sensitivity, including pharmacological treatment with a peroxisome proliferator-activated receptor-? agonist, exercise or a specific diet composition. On the other hand, individuals with

impaired hepatic insulin sensitivity most likely benefit from interventions that specifically improve hepatic insulin sensitivity, such as metformin treatment. Thus, determination of peripheral and hepatic insulin sensitivity is essential in the decision for a targeted therapeutic regimen for individuals. Currently, the two-step hyperinsulinaemic–euglycaemic clamp, in conjunction with the use of a glucose tracer, is considered the gold-standard approach to assessing peripheral and hepatic insulin sensitivity; yet, this is a difficult, labour-intensive and costly procedure. Therefore, there is a need for easier, cost-effective ways to assess hepatic and peripheral insulin sensitivity.

Recently, it has been demonstrated that plasma cathepsin D (CTSD) is negatively associated with insulin sensitivity, suggesting a link between plasma CTSD and insulin sensitivity. Previous findings from our group showed that plasma CTSD also had predictive value for the level of hepatic inflammation in individuals with non-alcoholic fatty liver disease (NAFLD), linking plasma CTSD to alterations in the liver. Furthermore, specific inhibition of the activity of plasma CTSD resulted in reduced plasma insulin levels and improved fatty liver features in a rat model for hepatic steatosis. However, it remains to be elucidated whether plasma CTSD is linked to hepatic insulin sensitivity.

To enable organ-specific interventions for each (pre)diabetic individual, it is of critical importance to determine hepatic and peripheral insulin sensitivity. Considering the association between plasma CTSD and whole-body insulin sensitivity, on one hand, and the link between plasma CTSD and hepatic inflammation on the other hand, our study investigated whether plasma CTSD is correlated with hepatic insulin sensitivity in humans. For this purpose, we analyzed the association between plasma CTSD and peripheral/hepatic insulin sensitivity as well as inflammatory markers by linear regression. We demonstrated for the first time that plasma CTSD activity inversely associated with hepatic insulin sensitivity in overweight/obese humans, suggesting a potential involvement of plasma CTSD in mechanisms leading to the impairment of hepatic insulin sensitivity. Our findings imply that plasma CTSD activity may be used as a non-invasive marker for hepatic insulin sensitivity in humans with advantages over the current golden standard being easier, faster and more cost-effective.

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