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The role of urinary carnosinase 1 in diabetic kidney disease

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Serum carnosinase(known as carnosinase 1(CN1)) hydrolyzes a small subset of histidine containing dipeptides, i.e. carnosine, homocarnosine and anserine. Although the physiological relevance of these substrates is not well understood, it is believed that they may have protective properties in the setting of hyperglycemia and/or oxidative stress. CN1 is mainly produced in the liver from where it is secreted into the blood. Also in the kidney CN1 is expressed in distal tubules, albeit to a lesser extent than in liver. Interestingly, renal CN1 is more expressed on proximal tubules in patients with proteinuria including those with diabetic kidney disease (DKD). This study sought to delineate the role of urinary CN1 with respect to hyperglycemia and renal function in the development of DKD. To this end, an hCN1 transgenic model and a cohort of 3000 type 2 diabetic mellitus (T2DM) patients were studied.
The main findings of this study are as follows: 1) the hCN1 transgenic mice model demonstrates that carnosinasuria is more prevalent in non-diabetic BTBR mice, that male BTBR ob/ob mice develop more severe diabetes and DKD than female mice and that only in female ob/ob mice the *CNDP1* gene significantly aggravates hyperglycemia and DKD. 2) Urinary CN1 and urinary CN1 creatinine ratio (CCR) are significantly increased in T2DM patients with micro- and macro- albuminuria. However, in nomo-albuminuric T2DM patients the prevalence to detect urinary CN1 was significantly lower as compared to healthy controls (n=18). 3) CCR significantly correlated with albuminuria creatinine ratio (ACR), age, duration of diabetes, body mass index (BMI), hemoglobin A1C (HbA1C), triglycerides (TG), systolic blood pressure (SBP) and reverse correlated with eGFR. 4) ACR, eGFR, and SBP were independent factors for CCR as revealed by stepwise multiple regression analysis. This study is the first to demonstrate the existence of carnosinasuria and the influence of diabetes hereon. However it remains to be assessed if hyperglycemia truly decreases the prevelance of carnosinauria and if this is a consequence of an increased diuresis. Further studies are also warranted to delineate if carnosinasuria contributes to renal pathology.