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The role of human serum carnosinase 1 in diabetic nephropathy

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Homozygosity for the *CNDP1* $(CTG)_5$ allele of serum carnosinase (CN-1) affords protection against diabetic nephropathy in type 2 diabetic (T2D) patients. While CN-1 is mainly expressed in liver in other organs low expression has been observed. This study assessed to what extent ectopically expressed CN-1 differs in conformation and if CN-1 concentration, activity and conformation in $(CTG)_5$ homozygous T2D patients with nephropathy (DN) differ from patients without nephropathy. The protective effect of carnosine on iron mediated toxicity in the presence of serum carnosinase was as well evaluated in this study.

The main findings of these studies are as follows: 1) It seems that ectopically expressed CN-1 have a higher proportion of the RYSK173 conformation. This might be related to differences in N-glycosylation and metal ion binding to CN-1. 2) *CNDP1* $(CTG)_5$ homozygous T2D patients with nephropathy had a significant lower CN-1 concentration (30.4 ± 18.3 vs 51.2 ± 17.6 µg/ml) and activity (1.25 ± 0.5 vs 2.53 ± 1.1 µmol/ml/h, $p<0.05$) as compared to those without nephropathy. The lower CN-1 concentration correlated with hemodialysis, renal function and body mass index. Carnosinasuria was found in patients with micro- or macro-albuminuria and correlated with albuminuria. In kidney biopsies from patients with DN and persistent proteinuria or from patients with membranous glomerulonephritis, CN-1 expression was increased in proximal tubules (0.014 ± 0.021 vs 0.102 ± 0.130) as compared to normal kidneys. 3) Carnosine prevents iron mediated toxicity in short term iron exposure experiments irrespective of the presence of CN-1, At longer exposure times the presence of CN-1 slightly compromised the protective effect of carnosine (i.e. cell viability on 3rd day: 108.3 ± 2% vs. 88.1 ± 3.4%). The protective effect of carnosine was not mediated via its anti-oxidant properties.

Since this is the first study on carnosinasuria ever, our data warrant further studies using large cohorts to underpin these initial findings and to delineate the relevance of carnosinasuria for renal function deterioration and the protective effect of carnosine in DN.