PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9(PCSK9) DEFICIENCY IS ASSOCIATED WITH ALTERED GLUCOSE METABOLISM, PANCREATIC FUNCTION AND INSULIN RELEASE

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Background and aim: PCSK9genetic polymorphisms are associated with lower LDL-Cholesterol levels but also with higher plasma glucose levels and increased risk of developing T2D while therapy against PCSK9did not show any correlation on increased risk of New onset diabetes. We investigated the molecular mechanisms beyond this association.

Methods: Pcsk9KO, WT, albumin (Alb)Cre+/Pcsk9$^{LoxP/LoxP}$ (liver selective Pcsk9-KO mice) and Pdx1(Pdx1)Cre+/Pcsk9$^{LoxP/LoxP}$ (pancreas selective Pcsk9-KO mice) were used and fed for 20 week with chow diet and Standard Fed Diet. GTT, ITT, insulin and C-peptide plasma levels, pancreas morphology and cholesterol and triglycerides accumulation in pancreatic islets were studied in all different animal models.

Results: Glucose clearance was impaired in PCSK9KO mice compare to WT and in (Pdx1)Cre+/PCSK9fl/fl compare to (Pdx1) Cre-/PCSK9fl/fl while no difference were observed in insulin tolerance. Glucose tolerance was not impaired in (Alb)Cre+ mice fed with standard fat diet compared to WT animals; insulin sensitivity was not affected; both animal models showed a similar decrease in plasma glucose levels during ITT. A detailed analysis on (Alb)Cre+ pancreas morphology revealed no difference in islets. (Pdx1)Cre+ presented a similar phenotype observed in full PCSK9KO mice.

Conclusion an discussion: The PCSK9/LDLr axis affects beta cell function and insulin secretion. Our current findings confirm our previous observation that this effect is related to local PCSK9and support the observations available that anti-PCSK9antibodies or liver specific therapies, such as siRNAs, have a limited impact on glucose metabolism as opposed to statins.