The entero-insular axis and genetic variation in disease progression during the first year after diagnosis of childhood onset type 1 diabetes

With focus on residual beta cell function and glycaemic control

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ABSTRACT

This PhD dissertation is the result of work performed at the Pediatric Department, Glostrup University Hospital, and at Novo Nordisk A/S as part of the industrial PhD programme at the Ministry of Science, Technology and Innovation. The aim of the study was to define the time window and biomarkers for optimal pharmaceutical rescue of residual beta-cell function in new onset type 1 diabetes (T1D). The dissertation describes how the dynamic changes within the entero-insular axis, genetic variation, and autoantibody status influence disease progression; 275 children were followed for 12 months after onset of T1D.

Beta-cell response to endogenous GLP-1 seems to be lost somewhere within six months after disease onset, indicating that this time window is critical for achieving a maximal effect of pharmaceutical intervention. Blood glucose and GLP-1 were positively associated with glucagon release after six and 12 months, and postprandial glucagon levels did not influence glycaemic control. Variation within the *PPAR gamma (PPARG)* gene associated with an impaired residual beta-cell function and poorer glycaemic control, indicating that PPARG may play an active role in T1D disease pathogenesis and progression.

A total of 22 patients negative for diabetes associated autoantibodies had a slower decline in residual beta-cell function and glycaemic control.

Our study indicates that early intervention and testing for relevant biomarkers (genes and autoantibodies) may be critical for successful pharmaceutical beta-cell rescue.