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My name is Leontine Sandforth and I am a Clinician Scientist at the IDM and the Clinic for Diabetology, Endocrinology and Nephrology at the University Clinic Tübingen. I am interested in the underlying mechanisms of diabetes development and prevention and try to answer the emerging questions both in basic and in clinical research. My project “Impact of human Kallistatin on the metabolic phenotype of diet induced obese mice” aimed at understanding the role of Kallistatin (KST) on the pathogenesis of type 2 diabetes.

Kallistatin is a circulating plasma protein which is involved in multiple anti-inflammatory, anti-angiogenic and other pathways including Wnt/β-catenin signaling. In humans, we observed an increase in KST expression in subcutaneous white adipose tissue after weight loss and an association with insulin sensitivity. Therefore, we hypothesized that KST may mediate the effect of weight loss on insulin sensitivity, at least in part. To study the so far unexplored role of KST in insulin resistance, I compared high fat diet fed mice with a transgenic overexpression of human KST (hKST-Tg) to littermate control wildtype mice (wt). I observed that hKST-TG and wt mice gained similar amounts of body weight and fat and had comparable measures of energy homeostasis. Intriguingly, in the face of similar body weights, hKST-TG mice were clearly more insulin sensitive as indicated by an increased glucose infusion rate in the hyperinsulinemic-euglycemic clamp experiment. This was due to an augmented overall glucose uptake and improved suppression of endogenous glucose production in hKST-TG mice. To better understand how the improved hepatic insulin sensitivity was mediated on the molecular level, we excluded inflammatory and lipotoxic mechanisms, but observed a beneficial effect on the hepatic Wnt/ß-catenin signaling cascade.

From these findings, we conclude that KST improves hepatic insulin sensitivity in high fat diet induced obese mice via an interaction with the Wnt/ß-catenin pathway. Potentially, this could contribute to the improvement in insulin sensitivity observed during weight loss. We will determine in the future if Kallistatin may be applicable to therapeutic interventions in insulin resistance and T2D.