Internist Cees Tack reflects on diabetes and the role of the BDC in internal medicine

There is a rapidly increasing global prevalence of obesity, which originates from chronic overnutrition and physical inactivity. Obesity can lead to metabolic disturbances, such as dyslipidemia, hypertension, hyperglycemia and insulin resistance, the underlying cause of Type 2 Diabetes (T2D). T2D is the most common form of diabetes; it is estimated that 90% of the currently 350 million diabetes patients suffer from T2D. Diabetes is associated with many complications like nephropathy, atherosclerosis, fibrosis and non-alcoholic steatohepatitis (NASH).

Not all obese subjects, however, develop metabolic complications in a comparable rate and manner and following similar mechanisms. Some are considered as “metabolically healthy obese”, whereas others have a greater risk to develop T2D. Similarly, the heterogeneous population of diabetes patients highly varies regarding their risk to develop (cardiovascular) complications. Despite these observations, the currently used evidence-based therapy uses guidelines without options for further refinement of T2D classification. A biomarker-driven early stratification of diabetes patients could help to direct the intensities of diabetes therapies, avoid over-treatment and drive more personalized and efficient diabetes care.

There is overwhelming evidence that chronic inflammation plays a driving role in the development of insulin resistance and T2D. In general, an increase in adipose tissue mass causes chemokines to be released from adipocytes, which is thought to attract macrophages that in turn release pro-inflammatory cytokines and concomitantly lead to pre-diabetes. Therefore, we will focus on protein en metabolite biomarkers for inflamed adipose tissue processes. The interleukin-1 family is an important component within this metabolically evoked chronic inflammation[1]. While pro-inflammatory cytokines (e.g. IL-1β) are known to exert potent inflammatory effects, anti-inflammatory cytokines (e.g. Il-1ra) are designed to counterbalance an excessive inflammatory response. A disturbed balance between pro- and anti-inflammatory cytokines may contribute to the chronic inflammation arising from expanding adipose tissue[2].

As obesity progresses, the inflammatory response at the level of adipose tissue expands to a more systemic inflammatory response, for example at the level of the liver and vascular wall, thereby contributing to insulin resistance, NASH and the development of atherosclerosis and

cardiovascular diseases[3]. Inflammatory responses thus seem to determine whether excess fat leads to detrimental metabolic consequences and may thereby serve as biomarkers to discriminate between “healthy obese” versus “unhealthy obese” people. With the development of biomarkers that can diagnose the prevalence of those inflammatory changes at an early stage, we may be able to stratify risk, guide therapeutic interventions by nutritional or pharmaceutical therapies, and improve success rates.

The Biomarker Development Center (BDC) is a unique collaboration to clinically validate protein and metabolite biomarkers that relate to inflammatory changes in the onset of T2D. This can help to identify patients that have a low risk to develop complications and should not be treated with additional therapies, versus those that have a high risk and should be treated more intensively. Potentially, this may even be applied to pre-diabetic obese subjects to timely direct preventive strategies. Such early and personalized diagnosis will avoid over-treatment and will be a breakthrough in the management of the disease. The challenges will be to develop robust assays to monitor low levels of inflammation-related proteins and metabolites in the healthy state and at an early stage of diabetes development; to use this data to select and define the clinically validated biomarkers; and to translate biomarker data to clinical guidelines, either in prevention of disease or to guide therapeutic interventions.

1. Tack CJ, et al., (2012) Immunological Reviews 249:239-252.
2. Sun S, et al., (2012) Annual Review of Nutrition 32: 261-286.
3. Gustafson B (2010) Journal of Atherosclerosis and Thrombosis 17:332-341.

Cees Tack has been working as an internist since 1990 and received his PhD in 1997. He was appointed Full Professor in 2007. He is currently working as head of the diabetes section at the Department of Internal Medicine of the Radboudumc and is involved in the BDC as Principal Investigator of the “Diabetes Demonstrator Project”. His ambition in research focuses on metabolic syndrome, insulin resistance in relation to the sympathetic nervous system, chronic fatigue and atherosclerosis. In this article, Cees Tack reflects on diabetes and the role of the BDC in internal medicine.