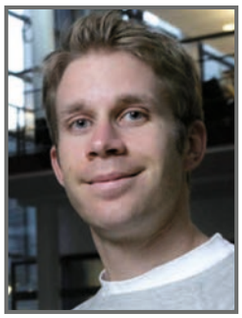
What implications do biomarkers have for the prediction and treatment of Type 2 diabetes?



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"A major problem with Type 2 diabetes research is that the pathophysiological components are typically studied in isolation. A more integrated view ... will be necessary to better understand the causal relationships and dynamics..."

Type 2 diabetes (T2D) is an escalating health problem of enormous proportions. Current treatment is insufficient, as evidenced by the devastating complications that many patients encounter. In this editorial, I present my views on how we may obtain a more integrated view of the disease to facilitate more effective interventions using a combination of biomarkers. This article begins with a background about what is currently known about the pathophysiology.

T2D is characterized by chronic hyperglycemia. Despite extensive research, the molecular causes and the sequence of pathophysiological events leading to the disease are largely unknown. Reduced insulin sensitivity in target tissues is a key feature; however, only 20% of insulin-resistant individuals develop T2D [1], as the β-cells manage to compensate for the increased insulin demands in the majority of individuals.

Consequently, a key issue is to elucidate why the β-cells fail to compensate and increase the insulin output. Several hypotheses have been proposed, involving both a reduction in β-cell mass and functional failure [2–4]. Whether there is a specific tipping point, in analogy to the Starling curve for heart failure, leading to incompensation of the insulin secretion capacity is not known. An equally interesting topic would perhaps be to study why some individuals in fact manage to compensate for severe insulin resistance with adequate insulin output.

In addition to β-cell failure, the most commonly studied components in the pathophysiology of T2D include but are not limited to: low-grade inflammation in metabolically active tissues; ER stress; impaired glucose uptake in muscle and fat; elevated hepatic glucose production; increased lipolysis; impaired response to the incretin hormones GLP-1 and

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GIP; defects in hypothalamic homeostatic functions; and exaggerated glucagon secretion.

Current biomarkers for T2D

T2D is highly heterogeneous and it is likely that different disease processes are prevalent to a different extent in different individuals. It has for example, been shown that islet pathology differs considerably between lean and obese T2D patients [4]. Biomarkers for different disease processes would be of great importance to guide more specific treatment, but only a few exist today. C-peptide is a marker for insulin secretion capacity, and a low level strengthens the indication for using insulin secretagogues, such as sulfonylureas. Detailed metabolic measures can be obtained by euglycemic hyperinsulinemic clamps, but this is not feasible in the routine clinical setting. A major problem with T2D research is that the pathophysiological components are typically studied in isolation. A more integrated view, including prospective data, will be necessary to better understand the causal relationships and dynamics of these components during disease progression in different individuals.

Hopes have been raised for using genetic variants as biomarkers for T2D. Close to 50 genetic loci have been consistently associated with T2D [5–7]. However, the odds ratio of each variant is small (<1.5). Moreover, it was shown that a panel of 11 of the strongest genetic risk variants had only a small effect in addition to traditional clinical risk factors such as family history and high BMI in predicting T2D [8].

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The disease mechanisms coupled to the genetic risk variants are unknown in most cases, making it difficult to use individual genotypes as markers of pathophysiological states. One exception is a variant in the *ADRA2A* (α_{2A}-adrenergic receptor) gene, which has been shown to confer overexpression of the receptor, impaired insulin release and increased T2D risk [9]. Studies are currently ongoing to investigate whether ADRA2A antagonists could be used to block the exaggerated adrenergic signaling in risk allele carriers [Rosengren A et al., Unpublished Data].

Another interesting avenue is to use combinations of serum biomarkers and traditional clinical markers. In this vein, a diabetes risk score including the serum markers adiponectin, CRP, ferritin and IL2RA was recently shown to perform better than fasting glucose and glucose tolerance alone in predicting T2D [10].

An advantage of serum biomarkers compared with genetic variants is that they can inform about the current pathophysiological state. From a bioinformatics approach we have recently identified SFRP4 as one of the first serum biomarkers for T2D that is linked with a specific disease process [11]. Functional studies showed that SFRP4 is induced by IL-1β and reduces insulin secretion. It thus constitutes the first molecular link between inflammation and reduced insulin secretion. We also found that the protein is elevated in T2D patients up to 10 years before clinical diagnosis. Individuals with SFRP4 above median had a fivefold elevated risk of developing T2D. SFRP4 is an interesting potential biomarker since it would be a specific marker for low-grade islet inflammation and defective insulin secretion, and as a secreted protein it may also be a therapeutic target. The study shows the potential of using a global unbiased approach combined with detailed functional studies to identify previously unrecognized biomarkers.

The road ahead: predictive, prognostic & pathophysiological biomarkers

What could new biomarkers add and how could they be identified? Disease prevention is of course more effective than any treatment, but it is still an open question as to how useful new predictive biomarkers would be in clinical practice. Would, for example, an individual with high BMI and slightly elevated fasting glucose (but below the threshold for T2D, so-called 'prediabetes') be more motivated to lifestyle changes if a panel of genetic variants and serum biomarkers was also added to the risk prediction? It has been suggested that individualized risk assessments and lifestyle advice have a larger effect than general information, so if the risk prediction could be combined with some tailored intervention it might have higher chance of being successful.

T2D leads to devastating complications in the kidneys, eyes, nerves and cardiovascular system. However, some patients with apparently perfect metabolic control become severely affected. Finding prognostic biomarkers for complication risk would therefore be of great clinical value. This would require both extensive molecular data and prospective phenotypic information.

Finding biomarkers for drug metabolism and side effects would also be of great value. To effectively find such markers, it is important to have clinical registries with treatment effects and adverse reactions combined with the ability to analyze stored patient samples for genetic and serum biomarkers. Patient data from Phase III trials conducted by pharmaceutical companies would also be valuable for this purpose.

The greatest potential, in my view, lies in finding biomarkers for different pathophysiological processes that could be used to generate individual and time-dependent 'disease signatures'. The disease signature could include traditional clinical features, genotype and serum proteins but also serum metabolites, mRNA and miRNA profiles, and expression profiles from exosomes, among others. I outline a few points that I believe are critical to obtaining such signatures:

- With recent technical advances it has become possible to obtain large-scale molecular data including genotype, transcription and metabolite profiles. However, these profiles have so far mainly been correlated with gross clinical phenotypes such as fasting glucose or HbA1c. Only if combined with detailed *in vivo* physiological data can these profiles be used to inform about disease processes. Therefore, there have to be new initiatives both from researchers and funders for classic *in vivo* physiology, which will constitute a critical intermediate layer to better utilize the enormous amounts of molecular data being generated;

- It may sound like a paradox, but to enable specific and individualized treatment we first need a more integrated view of T2D. To achieve this, patients should be comprehensively profiled in a longitudinal manner. The readouts should be selected to cover broad aspects of metabolism and may include glucose tolerance tests, euglycemic hyperinsulinemic clamps, GLP-1 infusions and calorimetry, as well as lifestyle questionnaires. These investigations should be combined with concomitant molecular profiling. Longitudinal data will greatly facilitate the identification of biomarkers for the different pathophysiological components of T2D as compared with the single snapshots that are currently most common;

- The physiological data and corresponding molecular profiles would then guide in-depth cellular and mechanistic studies. This is a top-down approach where we start by profiling the disease in an unbiased manner to form hypotheses that can later be tested with our classic cell biological and biochemical techniques. There is a widespread skepticism towards all kinds of 'fishing expeditions' among traditional cell biological researchers. Since I am myself a cell physiologist by training I have a certain understanding for the negative attitude and fully agree on the need for mechanistic understanding. However, I see great potential in using a global unbiased approach to center mechanistic studies on the pathways that seem most relevant for the disease rather than going the other way and trying to squeeze your favorite protein into a disease context. After all, rather than spending yet another decade studying the finest details of salmon in a reservoir, it seems more efficient to first make a trip to the ocean and see which fish is most relevant in the larger context and then initiate the dissections.

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Taken together, pathophysiological biomarkers, or disease signatures, for T2D could potentially be very useful as surrogate markers of the individual disease state, particularly since extensive metabolic profiling is too time-consuming to be feasible in routine clinical care. The signatures could provide a guide to more specific treatment using a cocktail of drugs targeted to the metabolic pathways that are most severely perturbed in the individual patient. This could enable more effective use of current and future anti-diabetic compounds and, hopefully, improved management of this rapidly growing disease.

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