LES JOURNÉES SCIENTIFIQUES
DE L'INSTITUT SERVIER

HETEROGENEITY IN DIABETES AND BETA CELLS

20e COLLOQUE 2021

Subphenotypes of prediabetes: the role of brain insulin resistance

Martin HENI[1,2,3], **Robert WAGNER**[1,2,3], **Stephanie KULLMANN**[1,2,3], **Hubert PREISSL**[1,2,3], **Norbert STEFAN**[1,2,3], **Andreas FRITSCHE**[1,2,3], **Hans-Ulrich HÄRING**[1,2,3]

[1]Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany; [2]German Center for Diabetes Research (DZD), Tübingen, Germany; [3]Department of Internal Medicine, Division of Diabetology, Endocrinology, and Nephrology, Eberhard Karls University Tübingen, Tübingen, Germany

L'INSTITUT SERVIER

Springer Healthcare Communications

Abstract

The progression from prediabetes to clinical type 2 diabetes (T2D) is generally a gradual process, related to insulin resistance, along with a loss of compensatory insulin hypersecretion. Amongst individuals with prediabetes, there is marked heterogeneity in disease progression and response to lifestyle intervention, and defining prediabetes subtypes may aid individualized prevention or treatment. Different fat distribution patterns can influence whether an individual progresses to T2D, and their response to lifestyle intervention. There is accumulating evidence that these fat distribution phenotypes may be related to insulin action in the brain; in brain insulin resistant individuals, insulin signaling is impaired, leading to insufficient suppression of endogenous glucose production, and, ultimately, resulting in fatty liver and high visceral adipose tissue. It is possible that brain insulin resistance begins *in utero*. Using variables including genetic risk, insulin resistance, fat distribution and liver fat content, we identified six clusters of prediabetic individuals. Two clusters had very high risk of developing T2D (one with very high liver fat content). One cluster had a moderate T2D risk, but a higher risk of nephropathy. The other three clusters had low risk of developing T2D. Initial trials into reducing liver fat and improving brain insulin sensitivity have shown promising results.

Key words: brain insulin resistance, cluster analysis, fat distribution, fatty liver, prediabetes

Introduction

As the prevalence of type 2 diabetes (T2D) continues to rise, so too does interest in finding different phenotypes, with the aim of predicting disease trajectory and individualizing treatment and care. T2D develops gradually, and prior to overt clinical T2D, patients are in a phase of prediabetes; that is, at increased risk of developing T2D.[1,2] This stepwise progression to T2D relates to an increase in insulin resistance, along with a loss of compensatory insulin hypersecretion. In individuals with prediabetes, the primary method aimed at preventing T2D is lifestyle intervention. Although alterations in diet and exercise have shown some efficacy in T2D prevention, a substantial portion of patients with prediabetes do not respond to this lifestyle intervention. Conversely, some patients with prediabetes never progress to T2D, even without intervention. This has led researchers to question: why do some people progress when others do not? With a view to answering this and other questions, globally, several prediabetes cohorts have been initiated. Together, these cohorts provide many years of data on the progression from prediabetes to clinical T2D.[1] One such cohort has been extensively studied by our group at the University of Tübingen. This cohort was initiated in 1998, and we now have insulin sensitivity and secretion data for over several thousand individuals. This paper briefly outlines some of our findings, along with some potential clinical implications of these findings. It should be noted that, for many of our findings, other groups have made similar discoveries in parallel to us.

Body-fat distribution phenotypes

In a subgroup of our cohort, in which we studied the effects of lifestyle intervention on numerous parameters, we found that, while baseline insulin secretion was a predictor of progression to T2D, the most important predictor was liver fat.[1,3] In prediabetic individuals who were involved in a 24-month lifestyle intervention program and then followed up for over 8 years, those with fatty liver at baseline were significantly more likely to progress to overt T2D than those without fatty liver.[3] In these earlier studies, using whole-body magnetic resonance imaging (MRI) to analyze patterns of fat distribution, two major phenotypes of obesity were identified. At one extreme, there are individuals with metabolically healthy obesity.[4] These people, in spite of being overweight, have a fat distribution pattern which is not associated with insulin resistance. On the other hand, the majority of obese individuals are classified as having metabolically unhealthy obesity. Compared with the healthy phenotype, a higher percentage of these people display insulin resistance, fatty liver, high levels of visceral fat,[4] and, as we now know, fat accumulation in the pancreas.[5]

This led us to investigate fat distribution patterns in lean people, and we found similar phenotypes in this population. A portion of normal weight people have a similar fat distribution pattern to metabolically unhealthy obese people.[4] In particular, these lean people have fatty liver, all the signs of cardiovascular disease, and fatty pancreas.[4,5] They are also more likely to develop T2D than metabolically healthy lean individuals. Of concern, this normal weight metabolically unhealthy fat distribution pattern is, for obvious reasons, generally overlooked.

What determines the fat distribution pattern?

Our discovery that different fat distribution patterns can affect an individual's risk of developing T2D led us to question: what determines these distribution patterns? Why are some obese people metabolically healthy, when others are not? We investigated the role of genetics, by testing all of the obesity genes, and, at least in our database, we could not find a major genetic impact. Accumulating evidence suggests that these phenotypes may be related to insulin action in the brain. Using magnetoencephalography, we determined the baseline insulin sensitivity of prediabetic individuals before lifestyle intervention.[6] Within the first 9 months of intervention, the individuals with brain insulin resistance showed only minimal reductions in body weight, visceral adipose tissue, and total adipose tissue, whereas those with a good brain insulin sensitivity had significantly greater reductions in these parameters. By the end of the 24-month intervention, the brain insulin resistant individuals had already regained weight, and total and visceral adipose tissue, while, in the sensitive group, mean reductions continued. After follow-up for close to 10 years, the brain insulin sensitive individuals regained less body weight and total and visceral adipose tissue, compared with brain insulin resistant individuals. When we analyzed the fat distribution pattern at this timepoint, we found that the brain insulin sensitive individuals had less visceral adipose tissue and, relatively, more subcutaneous fat.

We have performed numerous studies in an attempt to better understand the different effects of insulin action in the brains of resistant and sensitive individuals. Based on these studies, our current hypothesis is that, after food intake in a brain insulin sensitive individual, the resulting secreted insulin acts not only in the periphery, but also travels to the brain via the bloodstream.[7,8] Insulin signaling in the hypothalamus connects to many centers in the brain and, in addition to this crosstalk within the brain, it appears there is feedback to the body which causes peripheral effects, most likely through the autonomic nervous system. Peripheral effects include signaling to the liver to suppress endogenous glucose production. This brain signaling also increases uptake of energy in the periphery and the subcutaneous tissue.[8] In our opinion, the biological purpose of this system is that when there is an acute uptake of food/energy, insulin directs it towards the correct organs; however, this system may not be effective when there is a chronic surplus supply of food.

In brain insulin resistant individuals, this insulin signaling to the brain is either reduced or does not work at all.[8] This means signaling to the periphery is also impaired, causing insufficient suppression of endogenous glucose production, and minimal increased energy uptake in subcutaneous tissue. This results in a phenotype with fatty liver and a lot of visceral adipose tissue.[8] Thus, we believe that brain insulin resistance is an important additive mechanism to peripheral insulin resistance in the development of T2D.

When does brain insulin resistance start?

We have performed pregnancy studies in an attempt to elucidate whether brain insulin resistance develops *in utero*. In fetal imaging studies, we found that fetal brain activity was influenced by maternal glucose ingestion.[8,9] When the mother was brain insulin resistant, the fetus showed reduced responsiveness to glucose ingestion, which might indicate brain insulin resistance.[8,9] This suggests the possibility that propensity towards brain insulin resistance and the resulting unhealthy metabolic phenotype may develop, or at least begin to develop, *in utero*. We are following up over 100 young children in whom we assessed brain activity *in utero*, and the hypothesis is that this may be linked to the development of obesity later in life. However, we will need to wait some years before we can assess the accuracy of this hypothesis.

Phenotyping using cluster analysis

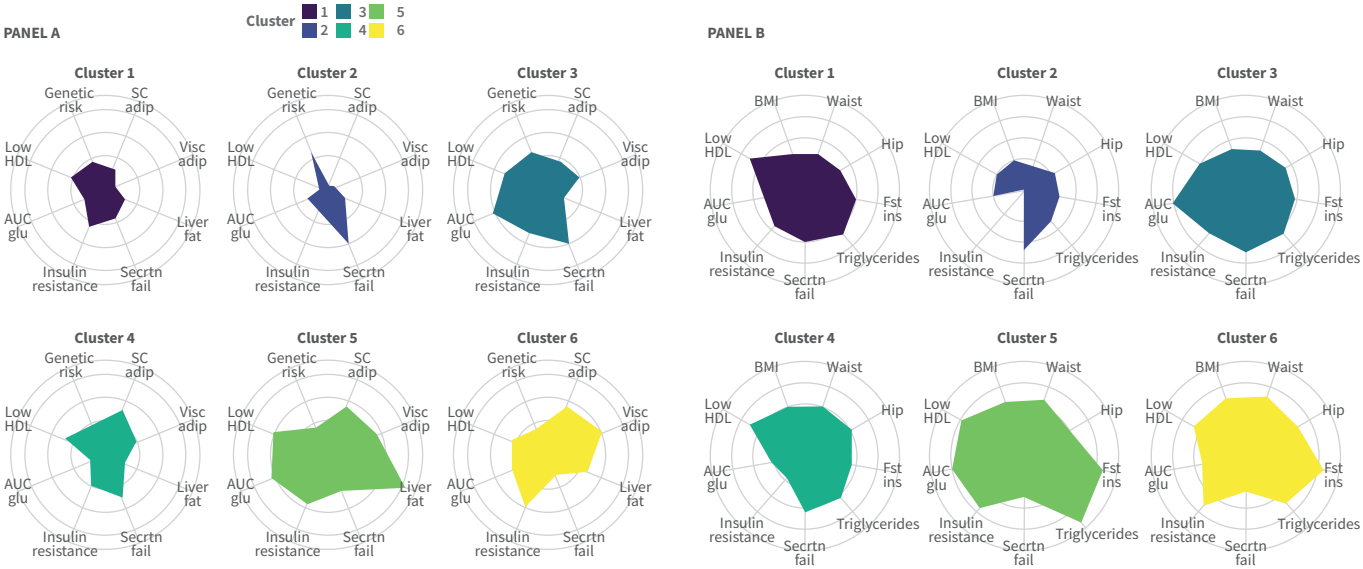
As outlined above, our hypothesis is that brain insulin resistance contributes to the pathogenesis of T2D, probably by determining fat distribution patterns and the development of a metabolically healthy or unhealthy phenotype, with the unhealthy phenotype characterized by fatty liver, and fatty pancreas. To assess the validity of this hypothesis, we used several variables to perform a cluster analysis in individuals at increased risk of developing T2D.[10] Variables used included genetic risk of T2D, insulin resistance, fat distribution pattern, liver fat content, and glucose tolerance. We identified six clusters (**Figure 1**). Individuals in clusters 3 and 5 had a high probability of developing T2D; in cluster 5, after around 10 years, almost all individuals had developed overt clinical T2D. In contrast, the risk of developing T2D within 10 years was very low in the other four clusters. Although individuals in cluster 6 mostly only had dysglycemia and a low short-term risk of T2D, they were at increased risk of nephropathy and all-cause death; longer-term (>10 years), these individuals also had an increased risk of developing T2D, whereas the risk remained low in clusters 1, 2 and 4.

In cluster 5, the cluster at highest risk for T2D, vascular and renal diseases, and all-cause death, the phenotypic characteristics included insulin resistance and minimal insulin secretion, extreme liver fat and obesity, but only moderate levels of visceral adipose tissue.[10] Cluster 3, which had the second-highest risk of T2D, was characterized by increased genetic risk, and moderate levels of visceral adipose tissue and fatty liver. Phenotypic characteristics of cluster 6 included insulin resistance and high visceral adipose tissue, but, compared with cluster 5, higher levels of insulin secretion, and somewhat lower liver fat content.

Our hypothesis is that organ cross talk is important in the progression from prediabetes to T2D. Although pancreatic fat does not necessarily predispose an individual to T2D, in certain situations, including prediabetes, increased pancreatic fat can lead to reduced insulin secretion.[5] Experiments that simulated fatty liver *in vitro* (high levels of palmitic acid, fetuin, and other hepatokines) found that this can cause pancreatic adipocytes to release pro-inflammatory cytokines and chemokines, which may result in impaired β cell function and therefore reduced insulin secretion.[5] Our aim is to test the hypothesis that it is the brain that initiates this process, determining fat distribution patterns and thus influencing the organ cross talk and, ultimately, impacting insulin secretion.

Figure 1: *Distribution of the cluster feature variables identified in the TUEF/TULIP study (N=899, panel A) and replicated in the Whitehall II cohort (N=6,810, panel B). The figures show the medoids or the medians of each cluster with the corresponding standardized level (z scores) of the feature variables. Reprinted by permission from Springer Nature: Nat Med. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. Wagner R, Heni M, Tabák AG, et al. 2021;27(1):49-57. © 2021.*

AUC glu, area under the glucose curve during oral glucose tolerance test; BMI, body mass index; fst ins, fasting insulin; HDL, high-density lipoprotein; hip, hip circumference; SC adip, subcutaneous adipose tissue; secrtn fail, insulin secretion failure; visc adip, visceral adipose tissue; waist, waist circumference.



Possible clinical utility of our findings

The ultimate goal of subtyping patients with prediabetes is to individualize care in order to prevent progression to T2D, or improve treatment after progression. We performed a randomized controlled lifestyle intervention study in individuals with prediabetes who were classified as either high or low risk for developing T2D, based on liver fat content and insulin secretion and sensitivity.[2] For 12 months, low-risk participants received either no intervention or standard lifestyle intervention, while high-risk individuals received either standard or intensified lifestyle intervention. Compared with standard intervention, those receiving intensified intervention had more counselling sessions (16 vs 8 sessions over 12 months), and were asked to perform more exercise each week (6 vs 3 hours/week). The study was completed by 908 individuals, of whom 707 were high-risk. In high-risk participants, compared with normal intervention, intensification resulted in significantly greater reductions in liver fat and cardiovascular risk, and improved glucose metabolism and insulin sensitivity, but had no impact on insulin secretion capacity. In low-risk participants, there was no between-group difference in glucose metabolism; however, this may possibly be explained by the smaller sample size in this group.

Taken together with our cluster analysis, these results suggest that in prediabetic individuals with high liver fat, such as cluster 5, intensified lifestyle intervention is likely to reduce liver fat and improve insulin sensitivity, and therefore reduce the risk of T2D development. Other possible therapies that lend themselves to further investigation include incretin analogs for the prevention of T2D in individuals with fatty liver, early insulin therapy in individuals with cluster 3 characteristics (minimal liver fat), and sodium-glucose transport protein 2 (SGLT2) inhibitors to prevent nephropathy in individuals with cluster 6 characteristics. In an 8-week, double-blind trial in 40 individuals with prediabetes, compared with placebo, empagliflozin significantly increased hypothalamic insulin responsiveness (as assessed by MRI), resulting in decreased fasting glucose levels and liver fat.[11] In contrast to brain sensitivity, there was no significant between-group difference in whole-body insulin sensitivity. Larger, longer-term trials are required to confirm these results.

Conclusions

The question of why some people with prediabetes progress to T2D, while others do not, has been the subject of extensive investigation, and, globally, several prediabetes cohorts have been initiated. There is accumulating evidence that brain insulin resistance may play an important role in determining fat distribution patterns and, thus, the progression from prediabetes to T2D. The ability to identify subtypes of prediabetes may enable individualized care, with the goal of preventing progression and diabetes complications. Using several variables, including liver fat, insulin resistance, and genetic risk, our group has identified six prediabetes clusters with different long-term outcomes. Two clusters (3 and 5) have a significantly higher risk of progressing to T2D, and individuals in cluster 6 have persistent dysglycemia with increased risk of nephropathy. These results suggest the possibilities of different treatment approaches depending on cluster characteristics, and we have seen promising results with intensified lifestyle intervention for reducing fatty liver, and SGLT2 inhibition for improving brain insulin sensitivity.

Medical writing assistance was provided by Toni Dando, on behalf of Springer Healthcare Communications, and funded by L'Institut Servier.

References

1. Häring HU. Novel phenotypes of prediabetes? *Diabetologia*. 2016;59(9):1806-1818.
2. Fritsche A, Wagner R, Heni M, et al. Different effects of lifestyle intervention in high- and low-risk prediabetes: results of the randomized controlled Prediabetes Lifestyle Intervention Study (PLIS). *Diabetes*. 2021;70(12):2785-2795.
3. Schmid V, Wagner R, Sailer C, et al. Non-alcoholic fatty liver disease and impaired proinsulin conversion as newly identified predictors of the long-term non-response to a lifestyle intervention for diabetes prevention: results from the TULIP study. *Diabetologia.* 2017;60(12):2341-2351.
4. Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. *Cell Metab*. 2017;26(2):292-300.
5. Wagner R, Eckstein SS, Yamazaki H, et al. Metabolic implications of pancreatic fat accumulation. *Nat Rev Endocrinol.* 2022;18(1):43-54.
6. Kullmann S, Valenta V, Wagner R, et al. Brain insulin sensitivity is linked to adiposity and body fat distribution. *Nat Commun.* 2020;11(1):1841.
7. Heni M, Kullmann S, Preissl H et al. Impaired insulin action in the human brain: causes and metabolic consequences. *Nat Rev Endocrinol.* 2015;11(12):701-711.
8. Kullmann S, Kleinridders A, Small DM, et al. Central nervous pathways of insulin action in the control of metabolism and food intake. *Lancet Diabetes Endocrinol.* 2020;8(6):524-534.
9. Linder K, Schleger F, Ketterer C, et al. Maternal insulin sensitivity is associated with oral glucose-induced changes in fetal brain activity. *Diabetologia*. 2014;57(6):1192-1198.
10. Wagner R, Heni M, Tabák AG, et al. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. *Nat Med.* 2021;27(1):49-57.
11. Kullmann S, Hummel J, Wagner R, et al. Empagliflozin improves insulin sensitivity of the hypothalamus in humans with prediabetes: a randomized, double-blind, placebo-controlled, phase 2 trial. *Diabetes Care*. 2022;45(2):398-406.