PHENOTYPES OF PREDIABETES: PATHOGENESIS AND CONSEQUENCES FOR PREDICTION AND PREVENTION OF TYPE 2 DIABETES AND CARDIOVASCULAR DISEASES

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The prevalence of type 2 diabetes is increasing world-wide. Thus, it is necessary to better understand its pathogenesis, the risk of diabetes-associated complications and effective treatment strategies. Because type 2 diabetes is a very heterogenous disease, both, related to its pathogenesis and risk of complications, phenotyping strategies in diabetes may help to tailor the preventive strategies based on the individual's risk. As the the hyperglycemic state of prediabetes is already associated with an increased risk of cardiometabolic diseases it is necessary to investigate the impact of phenotypes for predictive and preventive outcomes already in this early state of hyperglycemia. In this review artice I discuss how important phenotypes of prediabetes, such as nonalcoholic fatty liver disease, visceral obesity, insulin secretion defect and insulin resistance can be used to improve the prediction and prevention of type 2 diabetes and cardiovascular disease.

KEYWORDS: prediabetes, diabetes mellitus type 2; profilactic; cardiovascular diseases

ФЕНОТИПЫ ПРЕДИАБЕТА: ПАТОГЕНЕЗ И ПОСЛЕДСТВИЯ В РАМКАХ ПРОГНОЗИРОВАНИЯ И ПРОФИЛАКТИКИ САХАРНОГО ДИАБЕТА 2 ТИПА И СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

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Распространенность сахарного диабета 2-го типа (СД2) растет во всем мире. В связи с этим необходимо лучше понимать его патогенез, риск развития осложнений, ассоциированных с СД, и эффективные подходы к лечению. Поскольку СД2 представляет собой очень гетерогенное заболевание, обе стратегии фенотипирования, связанные с его патогенезом и риском осложнений, могут помочь разработать способы профилактики на основе индивидуального риска. Поскольку уже показано, что гипергликемическое состояние при предиабете ассоциировано с повышенным риском метаболического синдрома, необходимо исследовать влияние фенотипов на предсказательные и превентивные исходы уже в этом раннем состоянии гипергликемии. В этой обзорной статье обсуждается, как можно использовать важные фенотипы предиабета, такие как неалкогольная жировая болезнь печени, висцеральное ожирение, нарушение секреции инсулина и инсулинорезистентность, для улучшения прогнозирования и профилактики СД2 и сердечно-сосудистых заболеваний.

КЛЮЧЕВЫЕ СЛОВА: предиабет; сахарный диабет 2 типа; профилактика; сердечно-сосудистые заболевания

The prevalence of diabetes and prediabetes is increasing world-wide. While in the United States and in China the prevalence of diabetes in adults amounted to 14% and 11%, respectively, the prevalence of prediabetes is thought to be as high as 38% and 36% (1,2).

Type 2 diabetes is associated with 2 to 4 times higher risks of death and cardiovascular events than the general population (3). Particularly the age-standardized incidence rate of first coronary heart disease is significantly higher in patients with than in patients without type 2 diabetes (4). Furthermore, in patients with type 1 diabetes the risk of death from any cause or from cardiovascular causes is twice as high as the risk for matched controls (5). Also in type 1 diabetes cardiovascular disease is the leading cause of mortality. Similar to type 2 diabetes the strongest risk factors for cardiovascular disease and mortality for patients with type 1 diabetes are hyperglycaemia, hypertension, dyslipidaemia, diabetic kidney disease, insulin resistance and obesity (6). Thus, early, safe and effective treatment of these risk factors helps to reduce mortality and cardiovascular disease (CVD) in diabetes (7,8).

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Presently there is critical discussion to what extent the hyperglycemic state of prediabetes represents a condition that already puts subjects at an increased risk of CVD (9). However, the epidemiological data clearly point to a high risk of cardiometabolic complications in prediabetes, that almost reached the level of complications presently observed in manifest diabetes (10,11). Prediabetes is a very heterogeneous metabolic state, both in respect to its pathogenesis and prediction of diseases. Therefore, it is necessary to better understand its pathophysiology and stratify the risk of prediabetes-associated diseases. In this respect applying precise anthropometric and metabolic phenotyping strategies in prediabetes may help to achieve this goal.

PHENOTYPES OF PREDIABETES AND THE RISK OF TYPE 2 DIABETES AND CVD

To investigate the role of the major parameters, not only predicting the incidence of diabetes and CVD in prediabetes, first they have to be identified among several risk parameters that were proposed during the last decades. Elegant studies performed in the Pima Indian population, which has the highest risk of type 2 diabetes on a population level, provided evidence that low insulin secretion and high insulin resistance independenty of each other predict increased risk of type 2 diabetes (12,13). Furthermore, increased visceral fat mass and increased liver fat content are associated with an elevated risk of diabetes and CVD (14,15).

The next question is: to what extent are these parameters independently of each other associated with the risk of type 2 diabetes and CVD? My colleagues and I could show in 2008 that NAFLD [determined by ^{1}H-magnetic resonance (MR) spectroscopy] stronger than visceral obesity [determined by MR tomography (16)] associates with insulin resistance (17), a finding that was replicated by another group in 2009 (18). We also found that high liver fat content, but not high visceral fat mass, may explain the insulin resistance that is a ssociated with short adult stature (19). Furthermore, my collegues and I could show in 2011 that a higher liver fat content stronger than a high visceral fat mass, associates with the severity of prediabetes, determined as isolated impaired fasting glycemia (iIFG), isolated impaired glucose tolerance (iIGT) and IFG+IGT (20).

We also investigated the relationships of these phenotypes with the risk of CVD. We found that NAFLD, stronger than visceral obesity, and independently of insulin resistance, insulin secretion failure and the status prediabetes, associates with increased carotid intima-media thickness (21), an early marker of atherosclerosis. In addition, we investigated the relationship of NAFLD and visceral obesity with metabolically healthy obesity (22). We found that high liver fat content, stronger than high visceral fat mass, predicts the regression from a metabolically unhealthy obese to a metabolically healthy condition during lifestyle intervention-mediated weight-loss (23). In respect to metabolically unhealthy normal weight we found that low leg fat mass determines this condition stronger that NAFLD and visceral obesity in normal weight subjects and that NAFLD and visceral obesity become more relevant in metabolically unhealthy overweight and obesity (24).

PHENOTYPES OF PREDIABETES AND MECHANISMS INVOLVED IN THEIR CONTRIBUTION OF TYPE 2 DIAVBETES AND CVD

Increased visceral fat mass has extensively been studied regarding its contribution to the pathogenesis of type 2 diabetes and CVD. In this respect particularly the concept of dysregulated adipokine and cytokine secretion from expanded visceral adipose tissue is well established (25-27). Regarding the contribution of NAFLD to the pathogenesis of type 2 diabetes and CVD we have proposed the novel concept of dysregulated hepatokine secretion (Figure 1) (28). Among the most extensively studied hepatokines fetuin-A is increasingly released from NAFLD and is considered to promote insulin resistance, insulin secretion failure and subclinical inflammation and fetuin-A levels were found to predict incident type 2 diabetes and CVD (29-35).

IMPLEMENTATION OF PHENOTYPES OF PREDIABETES IN CLINICAL PRACTICE

In the Tübingen Lifestyle Intervention Program (TULIP) study, we investigated whether phenotypes of prediabetes can help to identify in subjects with prediabetes unique at-risk phenotypes that associate with the nonresponse to a 9 months structured lifestyle intervention in respect to restoration of normal glucose regulation (NGR). First, we found a large variability in the change of glycemia among the subjects that underwent the lifestyle intervention. Second, among baseline parameters that may predict reversal from prediabetes to NGR such as sex and the continuous baseline variables age, BMI, waist circumference, liver fat content, insulin sensitivity, 2hr glucose levels, fasting glucose levels and insulin secretion only impaired insulin secretion and insulin resistant NAFLD predicted a low chance for the restoration of NGR (Figure 2) (36). During the same lifestyle intervention we also found that NAFLD predicted a lower chance of subjects to revert from a metabolically unhealthy to a healthy phenotype, independently of the amount of weight loss.

CONCLUSION

There is growing evidence that major phenotypes of prediabetes can be identified. They may not only be used to improve cardiometabolic risk stratification, but also to identify drug targets for pharmacological intervention and to tailor lifestyle intervention programs to prevent type 2 diabetes and CVD.

ADDITIONAL INFORMATION

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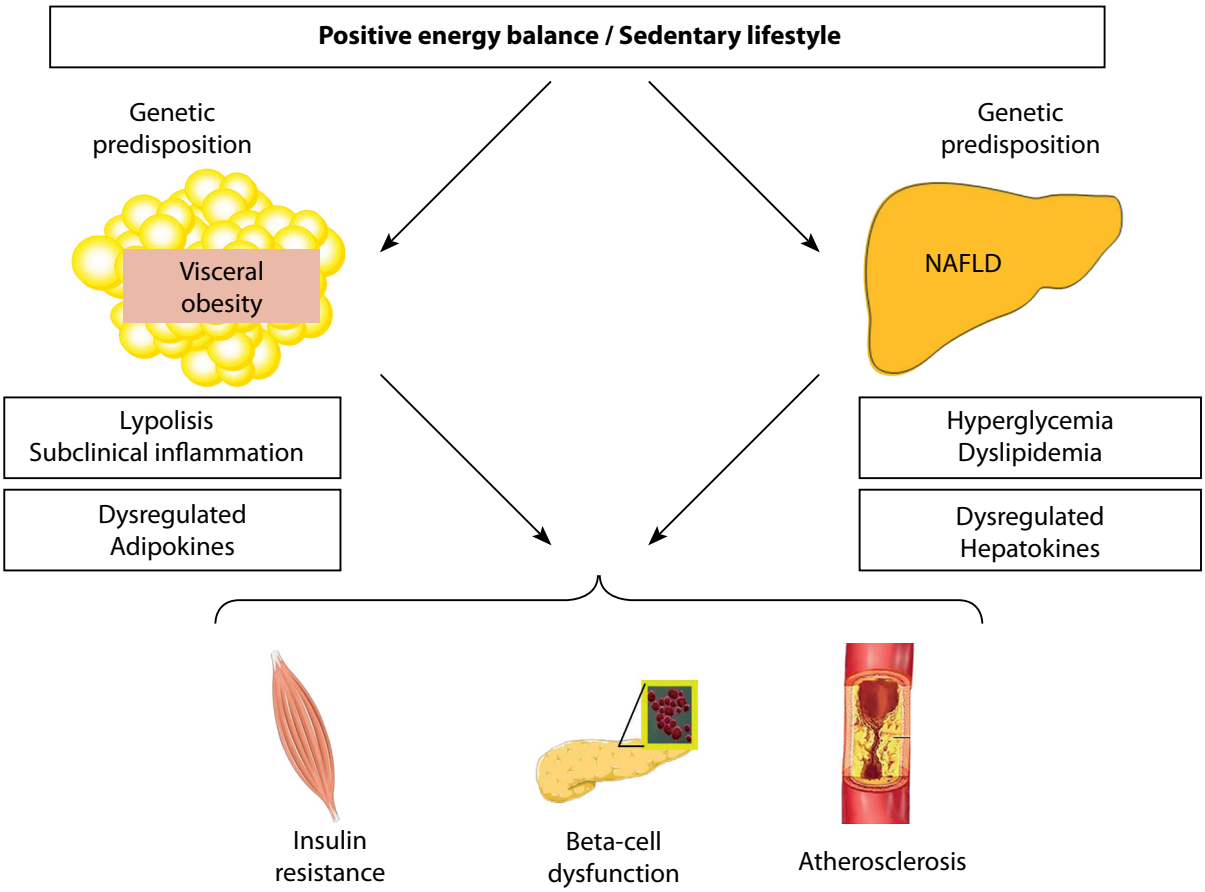

Figure 1. If a positive energy balance and a sedentary lifestyle converge with a genetic risk, visceral obesity and nonalcoholic fatty liver disease (NAFLD) develop. Visceral obesity via increased lipolysis, subclinical inflammation and dysregulated release of adipokines and NAFLD via hyperglycemia, dyslipidemia and dysregulated release of hepatokines induce insulin resistance, beta-cell dysfunction and atherosclerosis.

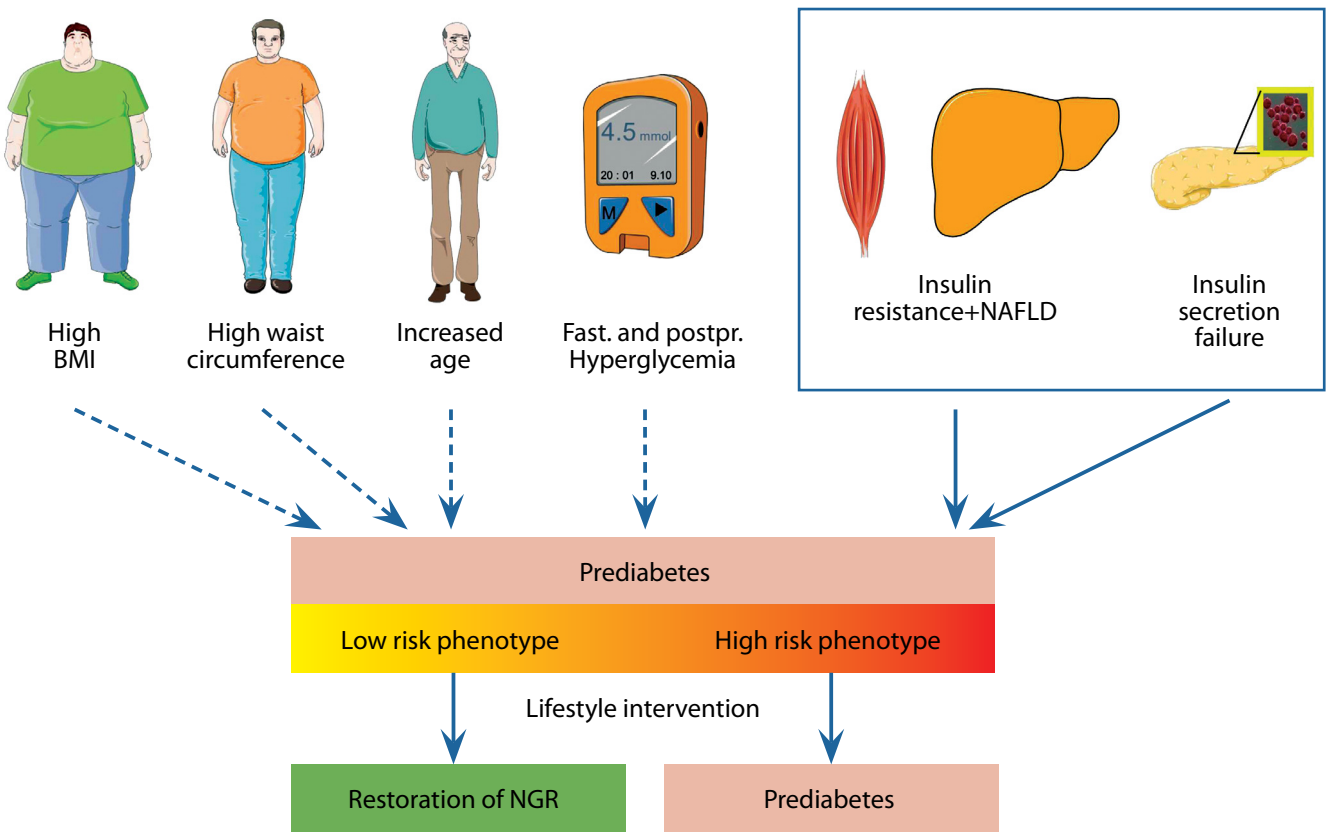

Figure 2. Among the risk factors high body-mass index (BMI), high waist circumference, increased age, fasting and postprandial hyperglycemia, insulin resistance+NAFLD and insulin secretion failure, only the latter two predicted a low chance for a regression to normal glucose regulation in 120 subjects with prediabetes, who underwent a lifestyle intervention (36).

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