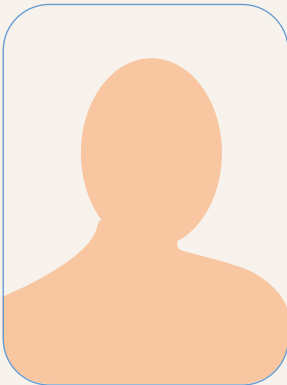


Expert Views in Diabetes

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Professor Allan Vaag heads a research group at the Steno Diabetes Center in Copenhagen, Denmark, focusing primarily on studies concerning the impact of the prenatal environment on the aetiology and pathophysiology of type 2

diabetes. Besides being a Chief Physician at the Steno Diabetes Center, Professor Vaag is Adjunct Professor of Metabolism and Clinical Diabetes Research at Lund University in Sweden. Professor Vaag graduated as an MD from the University of Southern Denmark in 1986 and since then he has been engaged in various aspects of diabetes research with an emphasis on the pathophysiology of type 2 diabetes. He wrote his PhD thesis on the glucose-fatty acid cycle in humans, including patients with type 2 diabetes. It was based on a series of studies that documented for the first time how acute inhibition of lipolysis with a nicotinic acid derivative significantly improves insulin action in patients with type 2 diabetes (Vaag et al. *JCI* 1991). As a continuation of his PhD thesis, Professor Vaag wrote and defended a Master of Science Thesis on the current state of art of the pathophysiology of type 2 diabetes in 1999. Based on a series of studies in prediabetic subjects including first degree relatives

(papers including Vaag et al. *JCI* 1992) and monozygotic twins discordant for type 2 diabetes (papers including Vaag et al. *JCI* 1995), Professor Vaag was among the first to describe early defects of insulin action – including impaired muscle glycogen synthesis and defective insulin secretion in prediabetic subjects. These findings contribute substantially to our present knowledge of how type 2 diabetes is not only a multifactorial disease, but is also a multiple organ disease involving muscle, beta-cells, liver, adipose tissue, gut and possibly causing a number of other organ defects. Professor Vaag has authored or co-authored more than 100 original papers in the area of diabetes research in leading international diabetes and medical journals including the *New England Journal of Medicine*, *The Lancet*, *Journal of Clinical Investigation*, *British Medical Journal*, *PNAS*, *PLoS Medicine*, *Diabetes* and *Diabetologia*. In addition he has authored a large number of national and international review papers and text book chapters. Professor Vaag is a past and present reviewer on more than 25 international journals including the *New England Journal of Medicine*. He is a member of the editorial boards of the *European Journal of Endocrinology* and *Journal of Physiology*, a member of The Danish Strategic Research Council, and serves on referee panels of various other national research councils including the Swedish and Finnish research councils.

Predisposition for type 2 diabetes – a matter of genes, foetal programming or both?

Professor Allan Vaag, Steno Diabetes Center

Overview

The prevalence and incidence of type 2 diabetes is increasing throughout the world and it has been forecast that the total number of patients with type 2 diabetes will be close to

300 million by the year 2025. Undoubtedly, this global 'diabetes epidemic' has been precipitated by a more sedentary lifestyle and increased intake of energy-dense food.

Nevertheless, type 2 diabetes predominantly develops in people who are predisposed to the disease: increased knowledge about the aetiological and molecular mechanisms

predisposing some people more than others to type 2 diabetes may eventually lead to more efficient and target-specific primary prevention and treatment of the disease. Our knowledge about the specific roles – and molecular mechanisms – of both major primary predisposing factors in type 2 diabetes, genetics and the prenatal environment, has increased substantially during recent years. In this commentary, a critical update is provided of the extent to which, and through which mechanisms, these two distinctly different primary predisposing factors contribute to type 2 diabetes.

Introduction

The development of type 2 diabetes results from a complicated interplay between several primary, secondary and tertiary aetiological predisposing factors on the one side and a number of distinct organ defects of glucose homeostasis on the other side. These include muscle insulin resistance, elevated hepatic glucose production, defective insulin secretion and defective gut incretin hormone secretion. Other predisposing factors are altered adipocyte fatty acid and adipokine metabolism

and secretion.¹ The primary predisposing factors include adverse intrauterine environment and genetics, and the secondary factors are obesity, low physical activity and age. Tertiary accelerating factors are represented by glucose and lipid toxicity (Table 1). This commentary aims to focus explicitly on current and recent advances in our understanding of the differential and quantitative aetiological as well as mechanistic pathophysiologic roles of genetics versus the prenatal environment in type 2 diabetes.

Genetics

The notion of a genetic component in type 2 diabetes has been supported by a number of epidemiological and metabolic family studies including studies in twins as well as in first degree relatives (FDR) of patients with type 2 diabetes.² Detailed metabolic studies of subjects with a genetic predisposition to type 2 diabetes, including both FDR and non-diabetic monozygotic co-twins of patients with type 2 diabetes, have shown that defects in both insulin secretion and action are present several decades before onset of overt type 2 diabetes.² Peripheral

insulin resistance has been demonstrated in non-diabetic FDR of patients with type 2 diabetes in all age groups from their early 20s,² whereas defects in insulin secretion have primarily been reported in somewhat elderly FDR and co-twins of monozygotic twins with overt type 2 diabetes from their 30s and upwards.² Thus, the majority of studies support the concept of an accelerated decline of beta-cell function that is initiated more than a decade before onset of overt type 2 diabetes, subsequently continuing with unaltered or even more accelerated rates of decline regardless of treatment after the onset of overt type 2 diabetes.

Many more or less rare gene polymorphisms have been reported to contribute to type 2 diabetes and distinct pre-diabetic defects of metabolism in some, but not all, populations, including polymorphisms of the PPAR-gamma, PGC-1 and Kir6.2 genes.³ Recently, the Icelandic Decode study identified the transcription factor 7-like 2 (TCF7L2) gene as a significant type 2 diabetes susceptibility gene.⁴ Using high density single nucleotide polymorphism (SNP) arrays, recent high impact scientific reports have added several interesting, but most probably minor, susceptibility genes to the list of genes involved in the development of type 2 diabetes. These include a non-synonymous polymorphism in the pancreatic beta-cell zinc transporter SLC30A8, the

Table 1. Aetiology of type 2 diabetes

Primary predisposing factors

- Genes
- Adverse intrauterine environment

Tertiary accelerating factors

- Glucose and lipid toxicity

Secondary precipitating factors

- Obesity
- Low physical activity
- Age
- Smoking
- Sleep disturbance

IDE-KIF11-HHEX and EXT2-ALX4 genes potentially involved in beta-cell development or function, and introns of the insulin-like growth factor binding protein two (IGF2BP2) and CDKAL1 genes.⁵⁻⁸

Furthermore, a genome-wide search for type 2 diabetes susceptibility genes has identified a common variant in the FTO (fat mass and obesity associated) gene that predisposes to diabetes through an effect on body mass index (BMI).⁹

However, it may be claimed, somewhat provocatively, that the polymorphism of the transcription factor TCF7L2 may be to date the most consistent type 2 diabetes susceptibility gene replicated across different populations. Nevertheless, even this polymorphism may still only explain a minor proportion of type 2 diabetes cases and having the predisposing geno- (or haplo-) type of the TCF7L2 gene is certainly not sufficient to guarantee development of overt type 2 diabetes.⁴ Thus, we still lack the expected major breakthrough in the search for the genetic origin of the common form of type 2 diabetes.

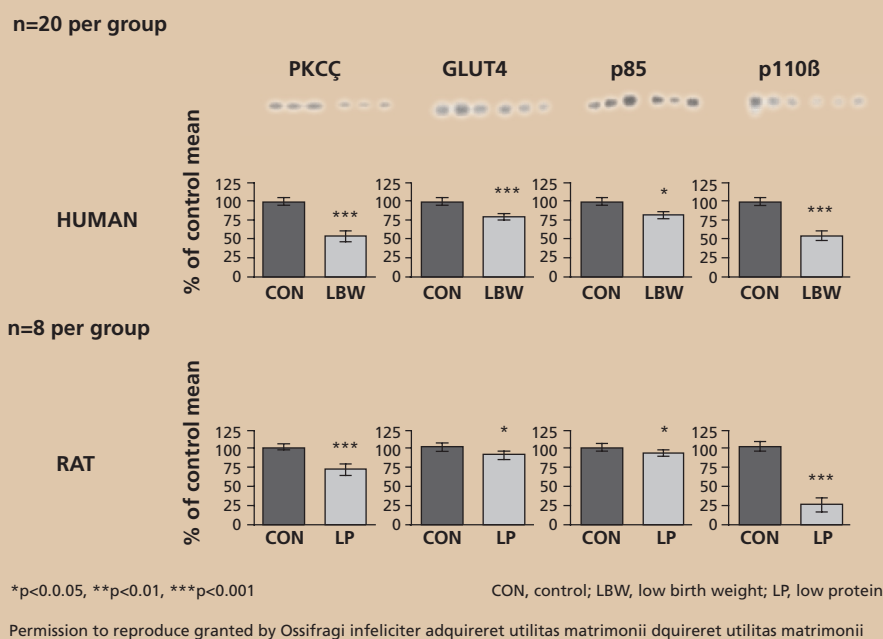
Admittedly, the reason for this may be a complicated scenario with many minor susceptibility genes adding together to form various different genetic mosaics in type 2 diabetes and further analyses and results of ongoing and recently published SNP-Chip studies may in the near future throw significant light on the putative genetics of type 2 diabetes.

The prenatal environment

The position of genetics as the major primary predisposing factor in type 2 diabetes has been seriously challenged by the concept of the so-called 'thrifty phenotype hypothesis', which proposes that altered programming *in utero* associated with low birth weight plays a significant role in predisposing to type 2 diabetes.^{10,11} It is likely, but still unproven, that this hypothesis may play a significant and predominant role in the current diabetes epidemic – in particular in the third world – where under-nutrition in general and during pregnancy has been, and still is, a major challenge for society, but also where over-nutrition, at least in the wealthiest sections of the population, has become more common with the propagation of a 'Western lifestyle'. The association between low birth weight and type 2 diabetes may explain and/or contribute to the slightly lower adult height as well as increased abdominal obesity in patients with type 2 diabetes. Studies in both Caucasian and Asian populations suggest that adverse intrauterine environment linked with low birth weight can contribute to increased adiposity regardless of BMI and, most interestingly, that people of Asian origin have a higher degree of adiposity for the same BMI compared with people of Caucasian origin.¹² Besides adiposity and abdominal obesity, low birth weight has been linked to other key components of the metabolic syndrome including hypertension, dyslipidaemia, low-grade inflammation and, most

importantly, premature risk for cardiovascular disease.¹³ Animal studies, as well as studies of Caucasian young, lean and otherwise healthy subjects, have documented the presence of many of the key defects associated with type 2 diabetes in subjects born with low birth weight several decades before they are supposed to be at risk for the disease.^{11,14,15} These defects include an age-dependent decline in insulin secretion, reduced muscle glucose uptake and insulin stimulated glycolysis (present before the onset of overt whole body insulin resistance), slightly elevated fasting plasma glucose concentrations within the normal range, abdominal obesity and lower fasting plasma glycerol levels indicating reduced lipolysis and increased risk of fat accumulation (adiposity).^{11,14,15} Recent analysis of skeletal muscle along with adipose tissue biopsies have shown reduced expression of several key proteins involved in insulin signalling and glucose transport, including the protein kinase C- ζ , the two subunits of the phosphoinositol-3-kinase (PI-3-kinase: P-85 α and P-110 β) and the insulin sensitive glucose transporter, GLUT-4, in young lean men born with low birth weight (Figure 1).^{14,15} The striking similarities of the full-blown range of metabolic abnormalities in this distinct young and lean prediabetic phenotype on one side, and in patients with overt type 2 diabetes on the other side, strongly support the significant role of the intrauterine environment in the aetiology and pathophysiology of type 2 diabetes.

Figure 1. Reduced expression of insulin signalling proteins in low birth weight human muscle and offspring of rats undernourished with protein *in utero*¹⁴



the idea that the prenatal environment and low birth weight contribute to the development of type 2 diabetes and the metabolic syndrome, including insulin resistance and hypertension, in a significant non-genetic manner. It is likely, but still not conclusively documented, that the prenatal contribution exceeds that of genetics as the most significant factor predisposing humans to type 2 diabetes and the metabolic syndrome.

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The fact that these abnormalities may be programmed by an adverse intrauterine environment is supported by animal studies showing that protein undernourishment *in utero* results in virtually similar quantitative, as well as qualitative, *in vivo* metabolic defects. Similar reduced tissue protein expression levels in rat offspring are also evident (Figure 1).¹⁴

The genetic identity of monozygotic twins provides a unique opportunity to study non-genetic factors of importance for the development of a certain phenotype or state of disease. In particular, any genetic contribution to a trait can be eliminated by studying differences among monozygotic twin pairs using either simple comparative tests or more elaborate correlation or regression analyses, with or without correcting for various additional non-genetic confounders. We used this approach to demonstrate that

the reported association between weight at birth and risk of developing type 2 diabetes is, at least partly, mediated by non-genetic mechanisms,¹⁵ a finding subsequently reproduced in various different twin populations with either type 2 diabetes *per se*, insulin resistance or the metabolic syndrome as the phenotypes in focus.¹⁶ In a recent large-scale twin study, this approach was used to provide conclusive evidence to show that the association between low birth weight and hypertension is at least partly determined by non-genetic factors.^{17,18}

Conclusion

Recent studies have provided conclusive evidence for the existence of several, although minor, true type 2 diabetes susceptibility genotypes, of which a polymorphism of the transcription factor TCF7L2 gene is the most significant. However, at the same time, overwhelming evidence has emerged to support

