ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LVII, N 1, 76 SECTIO D 2002

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Type 2 diabetes mellitus – a multifactorial disease

AETIOLOGY

Recent proposals by the American Diabetes Association (ADA) (3) and the World Health Organization (WHO) (1) have attempted to reclassify diabetes on both clinical stages and aetiological grounds. The clinical staging reflects that diabetes, regardless of its aetiology, progresses through several clinical stages during its natural history. Moreover, individual subjects may move from stage to stage in either direction. Persons who have, or who are developing diabetes mellitus can be categorized by stage according to the clinical characteristics, even in the absence of information concerning the underlying aetiology. The classification by aetiological type results from improved understanding of the causes of diabetes mellitus.

It has recently been recognized that an appreciable minority of type 2 diabetes patients also share serological and genetic features, with autoimmune diabetes usually presenting in children. Although it is possible that such serological markers are secondary to islet β-cell damage from some other cause, it seems likely that a primary autoimmune aetiology may account for about 10% of type 2 diabetes (11). A further subset of type 2 diabetes has been identified for a substantial proportion of cases of maturity-onset diabetes of the young (MODY) (6), but together with mitochondrial mutations, which are typically associated with maternally inherited diabetes and deafness, these account for only a small percentage of idiopathic type 2 diabetes. Furthermore, rare genetic defects affecting insulin action have been identified. Most of the remaining patients with type 2 diabetes present with a heterogenous disease, which is often characterized by insulin resistance and relative (rather than absolute) insulin deficiency.

GENES

Type 2 diabetes is a familial disease and there are convincing arguments to support its partial genetic determination. The lifetime risk of a first-degree relative of a patient with type 2 diabetes has been estimated at about 35% with the relative risk of diabetes compared with the general population of between three- and fourfold. Furthermore, twin studies have shown much higher concordance among homozygotic compared with dizygotic twins. The more common form of late onset type 2 diabetes shows a complex mode of inheritance and segregation studies have supported an oligo-polygenic inheritance. Genome-wide scannings have provided evidence for linkage to type 2 diabetes on chromosome 1, 2, 3, 10, 11, 12 and 20, respectively, and recently genetic variation in the gene encoding calpain-10 was shown to be associated with type 2 diabetes. This finding suggests a new biochemical pathway involved in the regulation of blood glucose that might contribute to the development of type 2 diabetes (8). Studies of candidate genes for type 2 diabetes have resulted in many reports of findings of gene variants associated with type 2 diabetes or intermediary prediabetic phenotypes, but only a few have been confirmed in multiple samples. Among these are variations in the insulin receptor substrate-1 gene (IRS-1, Gly972Arg) (5) and in the peroxisome proliferator-activated receptor-γ gene (PPARγ, Pro12Ala) (2).

Despite the known inherited susceptibility to this disorder only a few percent of type 2 diabetes has a known genetic background. The most frequent known genetic cause of type 2 diabetes is maturity-onset diabetes of the young (MODY) (6). This subtype of type 2 diabetes is characterized by an early onset, usually under 25 years, autosomal dominant inheritance and β-cell dysfunction. If defined by strict criteria it is a monogenic condition, i.e. the inheritance of a mutation in a single gene will cause type 2 diabetes. MODY is genetically heterogeneous because it can result from mutations in five different genes: the pancreatic "glucose-sensing" enzyme glucokinase (MODY2), and the transcription factors hepatic nuclear factor 4α (HNF-4α) (MODY1), HNF-1α (MODY2), insulin promoter factor-1 (IPF1) (MODY4) and HNF-1β (MODY5). Mutations in known MODY genes do only explain about 80% of all MODY in Europe, so there must be at least one more MODY gene (MODYX). The most common form of known MODY is MODY3, which is caused by mutations in the HNF-1α gene. Mutations are highly penetrant, with only a few percent of individuals with mutations over the age of 25 years not being diabetic. There is, however, a great variation in the severity at presentation. About 10% of families originally classified as atypical 1 diabetic families (families who do not carry any high-risk HLA-haplotypes, i.e. DR3 or DR4) might actually be MODY3 families. In other families treatment of the disease can be managed by diet or tablets for years. Patients with a long duration of diabetes frequently suffer from complications, particularly retinopathy and nephropathy. Therefore, it is important to aim at as tight a glycemic control as possible.

ENVIRONMENT

Type 2 diabetes is a multifactorial disease with both a genetic component and an important non-genetic component(s) which undoubtly interacts in order to precipitate the diabetic phenotype (4). Secular changes in prevalence within populations, differing prevalence in urban and rural communities within the same ethnic groups and migration studies showing increased prevalence in populations moving from relatively underdeveloped to "westernized" societies all support the hypothesis that changes in diet and physical activity have marked influence on the development of the condition. Within populations, obesity, particularly if centrally distributed, and the habitual level of exercise and physical fitness, are strong determinants of risk. A specific environmental effect that has received considerable attention recently is the relationship of intrauterine growth to the subsequent development of diabetes, obesity and several cardiovascular risk factors (7). Babies who are small or thin at birth have a relative impairment of glucose tolerance and an increased prevalence of type 2 diabetes in later life. This effect of birthweight has been confirmed in several populations, but the relative contribution of small birthweight to the pathogenesis of diabetes remains to be estimated.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Three important abnormalities have been demonstrated to contribute to hyperglycemia in subjects with type 2 diabetes mellitus: 1) impaired basal and stimulated insulin secretion, 2) an increased rate of endogenous hepatic glucose release, and 3) impaired insulin stimulated peripheral tissue glucose utilization primarily in muscle and adipose tissue (=insulin resistance) (4). Hyperglycemia *per se* can further impair insulin sensitivity and b-cell function (glucose toxicity), and the degree of hepatic glucose production is positively correlated with the degree of fasting glycemia. Similarly, increased levels of free fatty acids in obese type 2 diabetic subjects cause impairments both of insulin secretion and insulin sensitivity (lipotoxicity). The relative role of the mentioned metabolic abnormalities in the causation of type 2 diabetes has been illuminated both by cross-sectional studies of subjects at high risk for type 2 diabetes and in prospective studies. Hepatic glucose production was found to be normal in normoglycemic first degree relatives to patients with type 2 diabetes. Available data suggest that insulin resistance represents a major primary defect in the pathogenesis of type 2 diabetes (9, 10). A low acute insulin response to glucose is an additional but relatively weaker risk factor. The following model for the development of type 2 diabetes has been proposed: at least 2 genetic defects are required most likely including defects in both insulin action and insulin secretion. Although both defects act jointly to cause diabetes, insulin resistance is the trigger, which increases the insulin demands thereby unmasking the defect in the β-cell.

ASSOCIATED FEATURES

Type 2 diabetes is associated with a two/fivefold increased cardiovascular risk and, at diagnosis, is often characterized by hypertension and several adverse biochemical risk factors. These factors comprising hypertriglyceridemia, low high-density lipoprotein and abnormalities of the coagulation and lipolytic systems, also characterize pre-diabetic hyperglycemia and the normoglycemic siblings and children of patients with type 2 diabetes, and the offspring of subjects with IGT. The clustering of abnormal glucose tolerance and/or insulin resistance together with 2 or more of the cardiovascular risk factors, raised blood pressure, dyslipidemia, central obesity and microalbuminuria are the features of the metabolic syndrome (1).

CONCLUSIONS

Type 2 diabetes mellitus is a multifactorial disease with both a genetic component which in most cases is oligo-polygenic and a non-genetic component characterized by an imbalance between energy intake and output as well as other lifestyle factors. Most of the genes and the gene products responsible, and the interaction between these and the environment, at the molecular, cellular, tissue and whole body levels, remain to be discovered. The fundamental understanding of the pathogenesis of the condition will be essential for the development of novel treatments and strategies for effective prevention of this common disease.

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2001.12.01

SUMMARY

Type 2 diabetes is a multifactorial disease caused by both oligo- and polygenic genetic factors as well as non-genetic factors that result from a lack of balance between the energy intake and output and other life style related factors. ADA and WHO have recently reclassified diabetes on both clinical stages and aetiological grounds. There is a lot of data releated to the genetics of type 2 diabetes. However, many genes and gene products as well as their interactions with the environment at the molecular, cellular, tissue, and the whole organism levels are still unknown. Changes in the frequency of diabetes occurrence in various urban and rural populations and ethnic groups prove the relationship with the transition to the 'western' life style. Understanding of diabetes pathogenesis is essential to the development of new methods of treatment and strategies of effective prevention of this disease.

Cukrzyca typu 2 – choroba wieloczynnikowa

Cukrzyca typu 2 jest chorobą wieloczynnikową, u której podłoża leżą zarówno oligo- i poligeniczne czynniki genetyczne, jak i czynniki niegenetyczne, będące wypadkową braku równowagi między poborem i zużyciem energii oraz innych czynników związanych ze stylem życia. Ostatnie ustalenia ADA i WHO dokonały reklasyfikacji cukrzycy zarówno pod względem stadiów klinicznych, jak i etiologii. Istnieje już wiele danych dotyczących genetyki cukrzycy typu 2. Jednak wiele genów i związanych z nimi metabolitów oraz interakcje między nimi a środowiskiem na poziomie molekularnym, komórkowym, tkankowym i całego organizmu pozostają nadal nieznane. Zmiany w częstości występowania cukrzycy w różnych miejskich i wiejskich populacjach i grupach etnicznych wykazują związek z przechodzeniem na zachodni styl życia. Zrozumienie patogenezy cukrzycy jest niezbędne w rozwoju nowych metod leczenia i strategii skutecznej prewencji tej choroby.