

Diabetes epidemics - classification and prevalence

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Classification of diabetes

Diabetes mellitus is a chronic metabolic disease characterized by the presence of hyperglycaemia that occurs due to defective insulin production and secretion by the pancreas, defective insulin action resulting from no response of the cells to insulin or both. High blood glucose leads to typical clinical symptoms: weight loss, polyuria, increased thirst, weakness. According to the American Diabetes Association (ADA) there are four main types of diabetes mellitus: type 1, type 2, gestational diabetes mellitus and other specific types.

Type 1 diabetes (T1D), named immune-mediated diabetes, account for 5-10% of all diabetic cases, occurs more commonly in the younger persons and results from an immune-mediated depletion of pancreatic beta-cells with very sudden onset, especially in infants and children, that causes lifelong dependence on exogenous insulin (1). This form of diabetes was previously referred to as "insulin-dependent juvenile diabetes mellitus" due to more frequent diagnosis in children. However, according to recent ADA position statement the majority of individuals with T1D are adults (1). T1D is traditionally diagnosed based on clinical symptoms suggestive of insulin deficiency: polyuria, increased thirst, tiredness, constant hunger, sudden decrease of weight, slow-healing wounds, recurrent infections, blurred vision and hyperglycemia resistant to oral hypoglycemic agents. Severe insulinopenia predisposes patients with T1D to diabetic ketoacidosis which may be the first manifestation of the disease. The characteristic of T1D are five different pancreatic autoantibodies: anti-glutamic acid decarboxylase antibodies (GADA or GAD65), islet cell antibodies (ICA), insulin autoantibodies (IAA), protein tyrosine phosphatases anti-

bodies (IA-2A and IA-2 β) and zinc transporter protein (ZnT8) (1,2). In 85-90% of individuals one or more type of these antibodies are present at diagnosis of fasting hyperglycemia. This type of diabetes has multiple genetic predispositions and is related to not yet defined environmental factors. Individuals with T1D are also prone to other disorders of autoimmune background. Some forms of T1D may be idiopathic without autoimmune background.

Individuals with type 2 diabetes are characterized by a spectrum of disturbances from „predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance" (2). There are several important risk factors associated with the development of type 2 diabetes (T2D) including obesity, poor diet, low physical activity, advancing age, family history of diabetes, ethnicity, prior high blood glucose in pregnancy, dyslipidemia and hypertension. Most cases with T2D have insulin resistance (with concomitant hypertriglyceridemia and low HDL-cholesterol) and concurrent insulin deficiency and glucagon excess. T2D can go unnoticed and undiagnosed for years. Those affected by T2D are unaware of the long-term damage being caused by the disease. As a result up to 25% of patients with T2D have already developed one or more microvascular complications by the time of diagnosis. T2D accounts for approx. 90-95% of all diabetic cases. There are more than sixty distinct genetic disorders associated with glucose intolerance or diabetes but substantial complex genetic factors which contribute to risk of type 2 diabetes are not defined yet. In spite of that routine genetic testing in T2D is not recommended.

In the recent observational study the long-term outcomes were compared in type 1 and 2 diabetic patients in Australia who had disease onset between 15 and 30 years of age (2). The two groups differed significantly on important characteristics such as age at onset, diabetes duration, and ethnicity. In the type 2 diabetes cohort significantly higher concentrations of serum triglycerides, lower HDL-cholesterol and higher blood pressure were found which may support the notion that T2D is by nature a cardiovascular condition. Macrovascular complications were much more common in the T2D cohort (ischemic heart disease and stroke), but there

was no difference in retinopathy or nephropathy. Death was also more common in patients with T2D and occurred after shorter disease duration (3).

Third main type is gestational diabetes (GDM) which occurs around the 24th week of pregnancy when women without a previous diagnosis of diabetes develop insulin-resistance and subsequent hyperglycaemia or glucose intolerance. This can lead to serious risks to the mothers and their infants (macrosomia, neonatal hypoglycemia, increased risk of perinatal mortality) and increase the risk for developing T2D 5-10 years later. In 50-60% of cases, however, glucose metabolism returns to normal after delivery. The risk to babies is more severe for those whose mother had type 1 or type 2 diabetes before pregnancy, a condition named diabetes in pregnancy, which is substantially distinct from GDM. GDM accounts for up to 4% of diabetic cases.

The other specific types of diabetes include genetic defects of pancreatic β -cell function, endocrinopathies, drug induced and infection related. Maturity onset diabetes of the young (MODY) has a genetic background with mutations in HNF-1A-hepatic nuclear transcription factor (MODY 3), HNF-4B (MODY 1) or glucokinase genes (MODY 2) as well as transient or permanent neonatal diabetes diagnosed in infants before 6 months of life. In the latter the diagnosis of genetic mutations may be valuable. Other genetic defects may lead to disturbed insulin action. Diabetes may also occur due to point mutations in mitochondrial DNA (2).

Pancreatitis, trauma, infection or cancer that can damage the pancreas can also cause diabetes.

Other factors which may cause the development of diabetes are endocrinopathies (Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma and hyperthyroidism), pharmacotherapy (nicotinic acid, glucocorticoids, thyroid hormones, thiazides) or toxic chemicals and infections (Rubella, cytomegalovirus).

Among uncommon forms of immune-mediated diabetes the presence of anti-insulin receptor antibodies which block insulin binding to the cell receptors or act as insulin agonists should be noted. These antibodies occur in individuals with other autoimmune diseases (2).

All types of diabetes should be treated in order to prevent long-term micro- and macrovascular complications such as: retinopathy, nephropathy, neuropathy and cardiovascular diseases (ischemic heart disease, stroke) to prevent or limit mortality.

Prediabetes is the term used to describe people with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Subjects with IGT are at increased risk of developing T2D but evidence supports the effectiveness of lifestyle changes to prevent diabetes (4).

Prevalence of diabetes

Diabetes is one of the fastest-growing health problem in the world, reaching epidemic proportion in some regions, as a consequence of life-style, lack of exercise, unhealthy diet, obesity and overweight. The estimated health costs are enormous reaching in 2013 almost 11% of the total worldwide health budget. The global prevalence of diabetes in adult population (20-79 years old) in 2013 is estimated as 8.3% (382 million people) [5]. According to these estimates the region with the higher prevalence of 11% is North America and the Caribbean followed by the Middle East and North Africa with the prevalence of 9.2% and Western Pacific regions with 8.6% that is close to the world prevalence.

There are three countries with the estimated prevalence of diabetes over 30% : Tokelau (37.5%), Federated States of Micronesia (35%) and Marshall Islands (34.9%) followed by at least seven countries with the estimated prevalence of diabetes over 20% including Saudi Arabia (23.9%), Kuwait (23.1%) and Qatar (22.9%). Of the total 219 countries 16%, located mainly in Western Pacific, Middle East and North Africa regions have very high prevalence of diabetes, over 12% (4).

In spite of the fact, that North Africa and three other African countries have high diabetes prevalence over 10%, this is the region with the lower estimated prevalence (4.9%). Mali, a small Middle-West African country with a population of 15 millions, has the lowest prevalence of diabetes of 1.6%. These numbers indicate that geographic distribution of the prevalence of diabetes mellitus is very heterogeneous.

Europe has the 8.5% prevalence, similar to the global, having Turkey in upper extreme with 14.9%, Montenegro with 10.1%, Serbia 9.9% and Bosnia Hercegovina with 9.7% of prevalence. The lowest prevalence of diabetes in Europe is in Norway, Sweden, United Kingdom (4-5%) followed by Croatia, Finland, France, Greece and Poland (5-6%). According to newly released data from the UK National Diabetes Audit (July 2014), each day 738 people are being diagnosed with type 2 diabetes, among them 30 people with T1DM.

The North America and Caribbean region not only show the highest average prevalence of diabetes but also the highest prevalence of impaired glucose tolerance (IGT) with a median of 12%. Globally, countries with high prevalence of diabetes tend to have higher IGT prevalence.

The new estimates show an increasing and worrisome trend towards younger generations developing diabetes and possible ~50% increase in its prevalence within next generation (5). The burden of diabetes is reflected in the growing number of premature deaths due to diabetes. In 2013 almost 50% of all deaths due to diabetes were noted in people under the age of 60. The greatest unfavourable changes are expected in the developing countries due to increasing life expectancy and rapid life style changes.

Trends in the prevalence of type 2 and type 1 diabetes in the United States.

The prevalence of diabetes in the United States has increased substantially over the last two decades, paralleling an increase in the prevalence of obesity (6). The prevalence of confirmed diabetes in US increased from 6.2% in 1988 to 9.9% in 2010 but simultaneously from 1994 to 2005 the prevalence of undiagnosed diabetes, defined by either HbA1c or fasting glucose, decreased from 16% to 11%.

The prevalence of type 2 diabetes in all major racial/ethnic groups of American teenagers, has enormously increased by 35% over an 8-year period (7). The greatest change in T2D were found in Hispanic children, on the contrary no significant changes were observed among Asian Pacific Islanders or American Indians. This trend in T2D reflects the current obesity epidemic and has also the long-term

impact of higher gestational diabetes rates. It was emphasized that some young people with type 2 diabetes have a more aggressive form of the disease than is seen in adults, with a high risk for complications such as early nephropathy leading to chronic kidney disease and cardiovascular disease.

The global prevalence of T1D is not known but in the US reaches approx. 9% (up to 3,3 mlns in youths aged 0-19 years). The prevalence of paediatric type 1 diabetes in US increased by 30% from 2001 to 2009 and this was mostly seen in white youth however, the increasing burden of type 1 diabetes is experienced by youth of minority racial/ethnic groups as well (7). The potential causes may be „lack of certain viral or bacterial triggers at an early age, changes in early diet that might negatively affect the developing gut microenvironment, and increased rates of obesity in the general population“ (7). The incidence of T1DM varies considerably among countries: East Asia and American Indians have the lowest incidence rates compared to Finland with the highest incidence rate (>64.2/100.000 per year, 8-fold higher) (1). Worldwide prevalence of T1D increases due to the rising number of new-onset cases of T1D diagnosed in adults, including those diagnosed with LADA (latent autoimmune diabetes of adults), as well as to longer lifetime of subjects with childhood-onset diabetes as a consequence of better care (1).

Recent study from Sweden showed that the incidence of type 1 diabetes among 0-34 years old was two to three times higher than previously reported (8). Contrary to this, new findings from Finland, which has the highest incidence of T1D in the world, suggest that it appears to be levelling off [9]. Since 2006 the overall incidence rate of T1D which was before 3.6% per year has not increased. In 2011 the incidence increased only in boys but continued to decline among girls. Interestingly, among the factors which might be behind these changes increased vitamin-D consumption is mentioned and the possibility that the T1D onset may have shifted to an older age group.

Trends in incidence of diabetes in pregnancy

The incidence of diabetes in pregnancy (named pre-GDM) and gestational diabetes is the rapidly-

growing concern. Recent large population-based study performed in Ontario, Canada compared several aspects of this issue including the trends in rates of diabetes in pregnancy over the past 14 years [10]. It was found that the age-adjusted rate doubled from 1996 to 2010 for GDM (2.7–5.6%, $p < 0.001$) and for pre-GDM (0.7–1.5%, $p < 0.001$). Among factors responsible for the increasing rates of GDM, obesity, decreased physical activity, diet and increasing prevalence of type 2 diabetes were listed. The rise of diabetes in pregnancy has also been found in German and UK studies. Presented data indicated that in pregnant women >30 years of age almost 10% had diabetes with the prevalence of GDM of 7.4% and pre-GDM of 1.9%.

In the United States the prevalence of GDM seems to be even higher, up to 9.2%, based on the study performed between 2007 and 2010 (11).

Hidden diabetes

Recent data published by the Danish authors have shown that increasing severity of heart failure in

Danish patients with a mean age of about 75 yrs was associated with an increasing risk of type 2 diabetes [12]. During a 10-year follow-up, patients with the most severe heart failure were three times more likely to develop diabetes than patients with the least severe heart failure. Type 2 diabetes is also a common co morbidity in patients hospitalized with an acute myocardial infarction and sometimes this hospitalization represents the first opportunity to recognize the disease.

Conclusion

The enormous increase in the prevalence of diabetes worldwide should shift the focus from improving treatment to much better diabetes prevention strategies in the next decades and reducing the human and health care costs associated with this condition. More efforts should be put on screening and earlier diagnosis of diabetes to limit high risk for heart attack, stroke, blindness, kidney disease and amputation.

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