REVIEW ARTICLE

Diabetes Mellitus Type 2: Possibilities of Prevention

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ABSTRACT

The prevalence of type 2 diabetes mellitus (DM2) is increasing rapidly worldwide. It is assumed that the onset of the disease is preceded by a phase of impaired glucose tolerance (IGT) or impaired fasting glycaemia (IFG). Confirmed IFG or IGT are strong predictors of DM2 manifestation and are associated (especially IGT) with increased cardiovascular risk. Other significant risk factors (RF) of DM2 are obesity and the metabolic syndrome. Clinical trials performed in recent years have shown that certain metabolic abnormalities preceding the onset of DM2 may be managed favourably by effective lifestyle modifications, i. e. by adjustment of the diet or increased energy expenditure, and that such interventions may lead to the prevention of the onset, or at least to the delay of manifestation of type 2 diabetes mellitus, and thus of cardiovascular disease. A beneficial effect is also achieved by certain types of pharmacological agents that have either already been tested or are currently being tested in clinical trials, namely glitazones, metformin, and also ACE inhibitors, sartans and other.

Key words: type 2 diabetes mellitus, impaired glucose tolerance, metabolic syndrome, obesity, lifestyle changes, prevention of diabetes.

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INTRODUCTION

The incidence of type 2 diabetes mellitus (DM2) has increased significantly worldwide in the last 40 years and its prevalence is tracing a continuously rising curve. In 1985 there were approximately 30 million diabetics in the world, and the estimate is that at least 150 million people are currently suffering from diabetes and that this number will double over the next 25 years (1, 2). According to the International Diabetes Federation (IDF), the Czech Republic ranks among the countries with the highest prevalence of DM2 (1) (Fig. 1). The life expectancy of diabetics is considerably shorter than that of the general population, with 75 per cent of their deaths being caused by cardiovascular disease (CVD), especially by ischaemic heart disease (IHD) (3). Type 2 diabetes mellitus and CVD have a number of risk factors (RF), often operating simultaneously. This has led to the formulation of the "common soil" hypothesis (4). The risk factors (e. g. dyslipidaemia, hyperuricaemia, visceral obesity) are generally components of the metabolic syndrome (MS), or insulin resistance syndrome (5). The metabolic syndrome is a significant independent RF of DM2 (6). MS components are also associated with elevated concentrations of inflammatory markers, as has been proven by the IRAS trial (7), and it is generally accepted that obesity, MS and DM2 are connected with a chronic inflammatory status (8-11). The onset of DM2 is conditioned both by genetic and environmental factors, some of which can be controlled. The American Diabetes Association lists the following risk factors of DM2: age over 45, overweight and obesity (BMI $\geq$ 25 kg/m^2), decreased energy expenditure, impaired glucose tolerance (IGT) or impaired fasting glycaemia (fasting plasma glucose levels $\geq$ 6.1 mmol/l), next of kin history of diabetes, history of gestational diabetes or of high birth weight, dyslipidaemia [hypertriglyceridaemia (HTG) and/or hypoalphacholesterolaemia], arterial hypertension, being a member of a high risk population (e. g. African Americans, Latinos, Pacific Islanders) or current cardiovascular disease (12).

Micro- as well as macrovascular complications are often present prior to the diagnosis of DM2 (13). Cardiovascular disease develops long before manifestation of DM2 (3) and is apparently present as early as in the IGT phase (14, 15). It is evident from these findings that the most effective prevention of micro- and macrovascular complications of diabetes is the prevention of diabetes itself, with even a minor delay in DM2 manifestation being important for the patient. In recent years the results have been published of a number of clinical studies concerning the possibility of DM2 prevention by managing the most significant risk factors, such as obesity or IGT. The basic means in the possible prevention or delay of DM2 are non-pharmacological approaches, including low calorie and low saturated fat diet and increased physical activity. Interesting results, indicating a possibility to delay or prevent DM2 by pharmacological treatment, were presented recently by trials monitoring the effects of thiazolidinediones, alpha-glycosidase inhibitors, angiotensin converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (sartans) or hypolipidemics (statins and fibrates).

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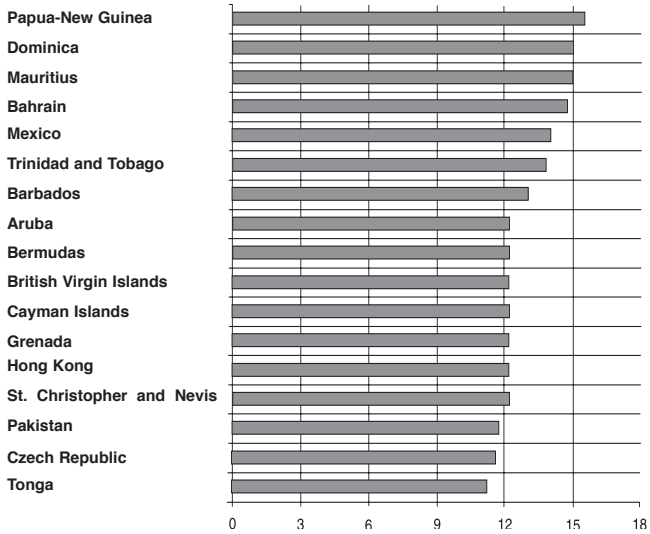

Fig. 1. Countries with the highest prevalence of type 2 diabetes mellitus (1)

IMPAIRED GLUCOSE TOLERANCE, IMPAIRED FASTING GLYCAEMIA

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG; i. e. fasting glycaemia within the range of 6.1 to 6.9 mmol/l) occurs on the border-line between normal glucose tolerance and DM2 (Tab. 1) (16). Both states are strong predictors of the onset of DM2 and are also connected with higher cardiovascular risk. Epidemiological data show that IFG is more common in men, while IGT is more common in women. IGT prevalence increases with age, while IFG prevalence peaks in middle age and later, especially in European men, declines (17). IGT is a more significant predictor of CVD than IFG, apparently due to the fact that it is a better indicator of insulin resistance (18). Impaired glucose tolerance is defined as a blood glucose concentration in the range of 7.8 - 11.0 mmol/l two hours after the administration of a 75 g glucose load, and it reflects both the degree of liver gluconeogenesis and the retarded postprandial uptake of glucose by the skeletal muscles and adipose tissue. The results of the studies show that persons with IGT face a significantly higher risk of death and myocardial infarction, cerebrovascular disease and of peripheral arterial atherosclerotic disease; they also, however, face a higher risk of microvascular complications of diabetes (diabetic retinopathy, nephropathy and neuropathy). A role in the pathophysiology of development of micro- and macrovascular complications is played by oxidative stress, endothelial dysfunction and elevated serum non-esterified fatty acids, and also by changes in the spectrum of adipocytokines, secreted by the adipose tissue, especially adiponectin and TNFα (18).

NON-PHARMACOLOGICAL MEANS OF DIABETES PREVENTION

An extraordinarily significant risk factor in the development of DM2 is obesity; approx. 90 per cent of patients with DM2 are either obese or at least overweight (19). During the sixteen years of monitoring in the Nurses Health Study a gradual increase in the manifestations of DM2 has been observed to trace growing BMI; in individuals with a BMI of 30-35 the risk was 20x higher than in individuals with a BMI ≤ 23 (20). The basic measure in the prevention or delay of DM2 manifestation is lifestyle modification consisting of diet adjustment (reduction of caloric intake and content of saturated fat) and exercise. The importance of such interventions has been documented by the results of several controlled clinical trials which have been published recently.

Tab. 1. American Diabetes Association (ADA) criteria for diagnosis of type 2 diabetes mellitus, IGT and IFG (1997)

Status	Fasting glycaemia (mmol/l)	Glycaemia after 2 hours during oGTT
Normal GT	<6.1	<7.8
IFG	6.1–6.9	–
IGT	–	7.8–11.0
Type 2 DM	≥7.0	≥11.1

In the Chinese Da Qing Impaired Glucose Tolerance and Diabetes Study (21), IGT patients were randomized into groups in which intervention consisted of diet, or exercise, or diet combined with exercise. The annual risk of DM onset was thus reduced from 15.7 per cent to 8 per cent. During the six-year-long study, the risk of DM2 onset dropped by almost 50 per cent.

The Finnish Diabetes Prevention Study (22), which included 523 persons aged 40-65 who were overweight (BMI ≥ 25 kg/m^2) and had IGT, was carried out over an average period of 3.2 years. The intervened group received individualized counselling aimed at a weight reduction by 5 per cent (diet measures were recommended, consisting of reduction of the amount of total and saturated fat in food and increase of its fibre content, and of aerobic exercises and resistance training based on regular individual consultations). The oral glucose tolerance test (oGTT) was performed once a year and in positive findings the diabetes was confirmed by a repeated oGTT. After four years, the cumulative DM incidence was 11 per cent in the intervened and 23 per cent in the control group; the risk of onset of DM2 was reduced in the intervened group by 58 per cent ($P < 0.001$).

A large U.S. randomized multi-centric study (Diabetes Prevention Project, DPP) (23) monitored 3,234 obese persons with IGT and IFG, divided into three groups (group subjected to intensive diet instruction, exercise and behavioural techniques intervention; group receiving 2 x 850 mg metformin; and placebo group). Originally, a troglitazone group was planned, but this was abolished soon after the launch of the study due to a description of hepatotoxicity of troglitazone. Compared to the Finnish study, DPP included slightly younger and more obese patients; 68 per cent were women. The annual DM2 incidence in the control group was 11 per cent, in the metformin group 7.8 per cent (reduction by 31 per cent), and in the group managed by intervention in the form of exercise and dietary counselling 4.8 per cent (reduction by 58 per cent).

PHARMACOLOGICAL MEANS OF PREVENTION OF DIABETES

Glitazones

Glitazones (thiazolidinediones) are pharmacological agents that enhance the sensitivity of muscular cells, adipose tissue and apparently also hepatic cells to insulin without affecting insulin secretion. The TRIPOD (Troglitazone in Prevention of Diabetes) randomized prospective study carried out in the U.S. and involving 236 Hispanic women with gestational diabetes in their history, recorded an annual growth of DM2 incidence of 12.3 per cent in the placebo group, while the growth in the troglitazone group was only 5.4 per cent, i. e. the relative risk of progression to DM was reduced by 56 per cent (24). An interesting finding was the

observation of the preventive effect for as long as eight months after the discontinuation of therapy; it is possible therefore that troglitazone affects DM2 etiopathogenesis more than just by delaying its onset. Troglitazone has been withdrawn because of its adverse side effects (liver toxicity), but there are other glitazones available which do not cause hepatic lesions and have a similar effect on glucose homeostasis as troglitazone. A small prospective study tested the possibilities of DM2 prevention or delay by second generation glitazones (rosiglitazone and pioglitazone) in patients with IGT and insulin resistance. After three years of monitoring, DM2 incidence was 88.9 per cent lower in the group treated with glitazones than in the control group (25). An extensive (4,000 patients) prospective, international, randomized study, DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial), is currently underway and investigating whether ramipril (angiotensin converting enzyme inhibitor) and/or rosiglitazone treatment reduces the risk of development of DM2 (2).

Metformin

Due to its effect, metformin represents another possible means of pharmacological prevention of DM2 onset in vulnerable individuals (26-28). Metformin enhances peripheral tissue sensitivity to insulin, reduces liver glucose output, probably also affects intestinal absorption of glucose and leads to weight reduction in obese diabetics. The BIGPRO trial compared the effect of metformin against placebo in middle-aged individuals with the visceral type of obesity. During the one-year long monitoring, metformin caused a considerable reduction of weight, serum cholesterol levels and fasting insulinaemia (26). In a small study of patients with IGT the administration of metformin compared to placebo resulted in a significant delay in the progression of IGT to DM2 (28). The results of metformin administration in the earlier mentioned DPP study were even more significant in this regard (23).

Acarbose

Acarbose, the alpha-glucosidase inhibitor, was tested in the STOP-NIDDM trial (29) as possible means of DM2 prevention. 1,429 patients with IGT were randomized into groups given either placebo or acarbose. The trial took 3.3 years on average and the administration of acarbose resulted in an approx. 25 per cent reduction in the incidence of DM2 diagnosed by oGTT.

Orlistat

The anti-obesity drug orlistat is a pancreatic lipase inhibitor which prevents the absorption of about 30 per cent of the digested fat by the gastro-intestinal tract. In several trials, especially with type 2 DM patients, orlistat had an effect on considerable weight loss and glycaemia reduction. The results of another randomized study, XENDOS (XENical in the Prevention of Diabetes in Obese Subjects), have been published recently. This trial tested the effect of orlistat on weight reduction in obese patients with the aim of preventing DM2. The trial was a four-year long prospective study of a cohort of 3,305 patients with BMI $\geq$ 30 kg/m^2 and normal (79 per cent) or impaired (21 per cent) glucose tolerance, randomized into a group treated by lifestyle intervention and, simultaneously, by orlistat 3 x 120 mg, and a placebo group (30). After four years, the cumulative incidence of diabetes was 9 per cent in the placebo group and 6.2 per cent in the orlistat group, which meant a significant reduction of DM2 risk by 37.3 per cent. The orlistat group also recorded rather significant decreases in systolic and diastolic blood pressure, serum cholesterol levels and insulinaemia (30).

ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS (SARTANS)

Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers can also play an important role in the prevention of diabetes. A reduction of the risk of development of DM2 in hypertonic patients was documented in CAPP (Captopril Prevention Project), in which the effect on cardiovascular disease of captopril was compared with beta-blockers and diuretics (31). The number of newly diagnosed diabetics in the group randomized for captopril was about 14 per cent smaller than in the second group. In HOPE Study (9,297 patients in all, of this number 3,577 diabetics), where the primary objective was the monitoring of the effect of the administration of the ACE antagonist ramipril on the incidence of cardiovascular events, over an average period of five years ramipril caused a significant drop in the incidence of all cardiovascular events, myocardial infarction (MI), cerebrovascular events, as well as of the number of revascularizations and DM complications (32). Moreover, a drop in the number of new DM cases was observed (by 35 per cent). The results of LIFE Study (Losartan Intervention For Endpoint reduction in hypertension study) have been published recently (33). A 25 per cent lower incidence of DM2 has been observed in hypertonic patients treated with the angiotensin receptor 2 blocker losartan against atenolol. In addition to the already mentioned DREAM trial, in a large international multicenter, randomized, controlled trial, NAVIGATOR, the effects of the angiotensin receptor II blocker valsartan and insulin secretagogue nateglinide on DM2 prevention are currently being evaluated (2). The mechanisms by which ACE-I and sartans improve sensitivity to insulin and delay DM manifestation are not quite clear. Maybe the effect is due to an adjustment of microcirculation in adipose and muscle tissue and/or improvement of the effect of insulin at cell level (by interfering with the unfavourable effect of angiotensin II on the insulin signalling function) (34).

STATINS AND FIBRATES

The possible importance of statins in DM2 prevention was shown in the results of the *post hoc* analysis of possible predictors of the onset of diabetes in the cohort of patients in the WOSCOPS (West of Scotland Coronary Prevention Study) trial (35), where treatment with pravastatin resulted in 5,974 patients in a drop of plasma cholesterol levels by 20 per cent with a simultaneous reduction in the incidence of ischaemic heart disease by 31 per cent. At the same time pravastatin treatment reduced the risk of development of DM2 by 30 per cent. The multivariation analysis showed that significant diabetes development predictors are BMI, log TG, fasting glycaemia and pravastatin treatment. The currently prevailing view is that the cause of this finding is the proven anti-inflammatory effect of statins (36, 37).

It has been proven recently that fibrates, used in HTG management, also have an anti-inflammatory effect besides their hypolipidaemic one (38, 39). The administration of fibrates led to a drop in IL-6; the results of individual studies monitoring the effect of fibrates on glucose tolerance are not consistent. It is possible, however, that fibrate therapy might delay the development of IGT and onset of DM2 in hyperlipidaemics (40).

CONCLUSION

Type 2 diabetes mellitus is a disease affecting a considerable proportion of the world population and having an increasing

incidence. It is a phenomenon which presents a special problem for the health care systems of all countries - amongst other things due to the fact that by the time diabetes becomes manifest, macrovascular and microvascular complications of the disease are already present, and diabetes is commonly linked to other risk factors of atherosclerosis and its complications, especially arterial hypertension and dyslipidaemia. The most significant risk factors of diabetes (obesity, insulin resistance, impaired glucose tolerance) are associated, significantly, with an enhanced risk of cardiovascular disease. Studies carried out in recent years have shown that certain metabolic abnormalities preceding the onset of type 2 diabetes mellitus may be influenced favourably by effective lifestyle modifications, i. e. by adjusting the diet and by increased exercise, and that these means may result in the prevention, or at least delay of the manifestation of type 2 diabetes mellitus. This should be reflected in changes in the management of patients with diagnosed impaired glucose tolerance, which should focus on the active screening and treatment of hypertension and dyslipidaemia and, appropriately, perform screening of already manifest cardiovascular disease. Certain pharmacological agents, already tested or currently being tested in clinical trials, namely glitazones, metformin, and ACE inhibitors, sartans and others, evidently also have a favourable effect.

Abbreviations

ACE	angiotensin converting enzyme
ACE-I	angiotensin converting enzyme inhibitors
BIGPRO	Biguanides and the Prevention of the Risk of Obesity
BMI	body mass index
CAPP	Captopril Prevention Project
CVD	cardiovascular disease
DM2	type 2 diabetes mellitus
DPP	Diabetes Prevention Project
DREAM	Diabetes REduction Approaches with ramipril and rosiglitazone Medications
HOPE	Heart Outcomes Prevention Evaluation
IDF	International Diabetes Federation
IFG	impaired fasting glycaemia
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
IL-6	interleukin 6
LIFE	Losartan Intervention For Endpoint reduction in hypertension study
MI	myocardial infarction
NAVIGATOR	Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research
oGTT	oral glucose tolerance test
RF	risk factors
STOP-NIDDM	Study of Preventing Non-Insulin Dependent Diabetes Mellitus
TNFα	tumor necrosis factor alpha
TRIPOD	Troglitazone in Prevention of Diabetes
WOSCOPS	West of Scotland Coronary Prevention Study
XENDOS	XENical in the Prevention of Diabetes in Obese Subjects

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