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PREVENTION OF DIABETES MELLITUS TYPE 2

Butaboev M.T.
Candidate of Medical Sciences, Associate Professor,
Tyan.D.L.
Department of Rehabilitation, Sports Medicine and Traditional Medicine,assistant
Andijan State Medical Institute.

Abstract: The current global epidemic of diabetes mellitus type 2 (T2DM) is primarily a consequence of overweight/ obesity and a sedentary lifestyle. The prevention or modification of progressive insulin resistance is the key to preventing the development of diabetes. Along with lifestyle modification, pharmacological treatment methods (metformin, weight loss drugs – sibutramine) reduce the risk of progression of prediabetes in T2DM.

Key words: Prevention, obesity, prediabetes, diabetes mellitus.

The current global diabetes epidemic type 2 (T2DM) is primarily a consequence overweight/obesity and sedentary lifestyle. Obesity is widespread even in countries with developing economies [1]. By according to the World Health Organization (WHO), in 2016, more than 1.9 billion adults over 18 years of age had excess body weight. Of these, over 650 million suffered obesity. These data indicate that 39% adults over 18 years of age (39% men and 40% women) were overweight and about 13% of adults of the world's population (11% of men and 15% of women) suffered obesity [2]. According to the International Diabetes federation, in the world in 2015 there were 415 million adults had diabetes, another 318 million people had a disorder glucose tolerance (IGT), which significantly increases risk of developing diabetes [3]. The transition from prediabetes to diabetes occurs at a rate of 5–10% per year [4]. The threat to T2DM and its complications to the health and quality of life of patients is enormous. In December 2006 at the 61st UN General Assembly a resolution on T2DM was adopted. UN in its message recognizes the fact that diabetes is a chronic disabling disease leading to the development of severe complications and requiring significant economic costs. The adoption of this UN resolution indicates that the problem of diabetes in all countries of the world has long been has outgrown the framework of a purely medical focus and has become a socio-economic problem of global character. Diabetes is one of the leading causes of death. High blood glucose level was identified as 3rd most important risk factor for premature death ENDOCRINOLOGY: news, opinions, training No. 4 2017 15sti all over the world, after arterial hypertension and smoking. Approximately 5 million deaths were associated with diabetes in 2015 – more than from HIV/AIDS, tuberculosis and malaria [3, 5]. Chronic intake of excess energy can lead to the development of T2DM. Still at the stage of normoglycemia and IGT There is compensatory hypersecretion of insulin β-cells of the pancreas against the background of the development of insulin resistance (IR). However, over time, when it is not possible to compensate for hyperglycemia with adequate an increase in insulin levels [6–8] results in a decrease functions and/or mass of β-cells, which provokes the onset clinical manifestations of T2DM and disease progression as a result of metabolic disorders associated with impaired sensitivity of peripheral tissues to circulating insulin – in the liver, muscle and adipose tissues [6, 8, 9]. Loss of pulsatile insulin secretion is one of the the earliest detectable defects in individuals predisposed to developing T2DM [10–12]. Relative hyperinsulinemia increases body weight gain, promotes β-cell depletion or worsens desensitization insulin receptor (i.e. IR), characterized by a decrease in the number and affinity of receptors for insulin and pathology of glucose transporters. IR helps to reduce glycogen synthesis in the liver, activate gluconeogenesis and glycolysis.

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Obesity is often associated with peripheral IR and hyperinsulinemia. IR develops against the background of the accumulation of large amounts of lipids in adipocytes and their increase sizes. Research has proven that stimulated insulin uptake of glucose decreases as obesity progresses. Using the clamp method, a direct relationship was also revealed between the degree of development of abdominal-visceral adipose tissue and the severity of IR. In recent years, it has been proven that adipose tissue has endocrine and paracrine functions, secretes substances that affect tissue sensitivity to insulin. Adipocytes secrete large amounts cytokines. For example, tumor necrosis factor α (TNFα) disrupts the interaction of insulin with the receptor, and also affects intracellular glucose transporters (GLUT-4) both in adipocytes and muscle tissue, and leptin in the liver inhibits the action of insulin and insulin-stimulated glucose transport. Lipolysis in adipocytes leads to excess entry of free fatty acids (FFA) into the portal vein system and liver, which disrupts the binding of insulin by hepatocytes and leads to the development of systemic hyperinsulinemia. Excess FFA stimulates gluconeogenesis, increasing roduction of glucose by the liver. However, it is difficult to conceptually or experimentally separate the manifestations of hyperinsulinemia and IR. The generally accepted paradigm suggests that the relationship between deterioration insulin-stimulated glucose uptake and insulin secretion means that hyperinsulinemia is compensatory response to prevent hyperglycemia when peripheral tissues cannot perceive excess glucose due to conditions caused by obesity [13]. However, the chronology of obesity, hyperinsulinemia and IR is not always clear [13]. Characteristics of obesity such as toxic accumulation of lipids in lean tissue and increased levels of proinflammatory cytokines may cause or worsen insulin resistance, and elevated blood glucose levels may stimulate increased insulin secretion [13]. At the same time, clinical and experimental data suggest that hyperinsulinemia may precede and stimulate the development of both obesity and IR or dysglycemia [13]. Considering the general pathogenetic mechanisms underlying at the basis of obesity and T2DM, it is important as early as possible timing to identify the initial manifestations of metabolic disorders and take measures to correct these as early as possible defects. Numerous studies have convincingly demonstrated that preventive strategies (i.e. lifestyle and various pharmacological interventions) can delay or prevent the development of T2DM in high-risk patients with IGT [14]. Different measures and approaches applied at different populations have provided almost unequivocal evidence that that lifestyle changes and pharmacotherapy are effective measures to prevent the development of T2DM in individuals with high risks (see table) [14]. Pioneering Da Qing Study on IGT and Diabetes [14] became the first large-scale preventive study to test the effectiveness of lifestyle modification. The study compared the effects changes in diet, exercise, or and another with a control group without interventions in adults with IGT. After 6 years, the incidence of diabetes was significantly reduced by 31–46% in all intervention groups. Evaluation studies including 94% of the original cohort with follow-up periods of 20 and 23 years [12] showed a stable reduction in the incidence of diabetes by 43%, severe diabetic retinopathy by 47% [12], and by the 23rdyear – a significant decrease in cardiovascular (41%) and overall (29%) mortality. In the Finnish Diabetes Prevention Study (DPS) [15] studied the effect of lifestyle modification in adult men with excess body weight and IGT. Participants were randomized to either receive ongoing individual counseling or targeted at weight loss, dietary changes and increased physical activity, or a control group receiving general nutritional advice exercises, but without individual counseling.

After 4 years, the risk of diabetes was reduced by 58% in the intervention group, and all parameters of metabolic syndrome also improved. Long-term follow-up revealed a consistent relative reduction in the risk of diabetes incidence by 43% after 7 years and 38% after 13 years, while absolute the risk difference between groups continued to increase even after 13 years [12].

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American Diabetes Prevention Program (DPP) [6] demonstrated that lifestyle changes and metformin therapy may reduce the incidence of diabetes in persons at high risk. Overweight adults and IGT were randomized to either intensive lifestyle changes aimed at reducing body weight and physical activity, metformin therapy or placebo. After 2.8 years in the image modification group life, there was a decrease in the incidence of diabetes by 58% (a decrease similar to that in the DPS study), and in the metformin group the reduction was 31% compared to placebo. Group 4 DPP study using troglitazone thiazolidinedione (TZD) was premature discontinued due to hepatotoxicity of the drug. After Therapy for 10.8 months in the troglitazone group, the incidence of diabetes was reduced by 75% compared to placebo. However, 3 years after troglitazone therapy, the level getting sick with diabetes. 2 Indian studies on diabetes prevention (IDPP-1 and IDPP-2) [5] focused on developing practical methods for lifestyle modification and provided important information about potential variations, based on ethnic characteristics in both the pathophysiology of DM and responses to lifestyle modification and pharmacological interventions. In the study IDPP-1 patients with IGT were younger and slimmer compared to patients in the Finnish and American studies [15]. Participants were randomized to a simple lifestyle group with dietary changes and increased physical activity, low metformin therapyse (500 mg/day), combination of lifestyle modification plus metformin or no intervention (control). After 3 years, the risk of developing diabetes decreased by 28.5; 26.4 and 28.2% in the lifestyle modification group, metformin therapy and combination groups, respectively. Both interventions also had a positive effect on low-density lipoprotein cholesterol, but not on blood pressure [3]. The IDPP-2 study [8] examined whether addition of pioglitazone TZD effectiveness in patients with lifestyle modification from the IDPP-1 study. In contrast to the 72% reduction in the risk of diabetes identified against the background therapy with pioglitazone in the US ACT NOW study [24], pioglitazone had no significant effect in the population IDPP-2.

Since one of the effects of TZD is a reduction IR, a series of studies have been conducted on this class of drugs. The TRIPOD (Troglitasone in Diabetes Prevention) study [12] showed that troglitazone reduced the risk development of diabetes by 55% in Hispanic women with a history of gestational diabetes. In the DREAM study (Evaluating the Reduction in Diabetes with Ramipril and Rosiglitazone) [8] assessed the preventive value of rosiglitazone, and the ACT trial NOW [6] – pioglitazone. In the DREAM study, patients with impaired fasting glucose (IFG) or IGG were randomized to rosiglitazone or placebo. Through 3 years of taking rosiglitazone significantly reduced the risk of developing diabetes by more than 60% compared to placebo. Was Rosligliatzone has also been shown to increase the likelihood of return to normal glucose tolerance [9]. In the ACT NOW study, pioglitazone therapy for 2.4 years resulted in a 72% reduction in the risk of diabetes compared with placebo. In addition, the CANOE study (Canadian normoglycemia study) [9] found that combination therapy with rosiglitazone and metformin reduced the relative risk of diabetes by 66% over 3.9 years therapy. Additional preventative studies have been conducted with other classes of glucose-lowering drugs. The international STOP-NIDDM (Study to Prevent Insulin-Dependent Diabetes Mellitus) [32] and the 2009 Japanese study [11] assessed preventive effect of α-glucosidase inhibitors in persons with IGT. In the STOP-NIDDM study, participants who received 100 mg acarbose three times daily for 3 years showed a reduction in the relative risk of developing SD by 25% compared to placebo. In a Japanese study, patients receiving 0.2 mg voglibose three times daily over 4 years, the relative risk of diabetes decreased by 40% compared with placebo [15]. The international SCALE study [11] assessed Effects of the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide on body weight and cardiometabolic risk factors in obese adults without diabetes. Treatment with liraglutide resulted in weight loss, level of glycated hemoglobin and fasting glycemia. IR and β-cell function also improved with therapy liraglutide. The prevalence of prediabetes at week

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56 of the study was significantly lower in the liraglutide group, and the development of T2DM was noted in fewer patients. treated with liraglutide than with placebo(4 vs. 14 cases).

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