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Prevention and current onset delay approaches of type 2 diabetes mellitus (T2DM)

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Abstract

The demanding need of treating type 2 diabetes mellitus (T2DM), currently reaching epidemic dimensions, has been the major aim of healthcare systems and policy makers worldwide. Pharmacological treatment associated with lifestyle interventions, in addition to controlling of cardiovascular risk factors, are the main strategies to prevent or delay the onset of T2DM. The present review discusses the state of the art knowledge of effective therapeutic approaches (metformin, thiazolidinediones, nateglinides, α -glucosidase inhibitors, incretin and angiotensin based therapies, weight reducers, statins, fibric acid derivatives), including surgery and identifying the major lifestyle changes requested for specific target groups.

Key-words: impaired glucose tolerance; pre-diabetes; prevention; type 2 diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder worldwide and its prevalence nowadays has an unprecedented growth in developed and developing countries [1, 2]. The World Health Organization (WHO) estimates a size over 180 million people suffering from diabetes, and this number is projected to more than double by 2030 [3]. These epidemic proportions have been related to sedentary lifestyles, overweight and obesity, and an older population [4, 5]. According to the Centres for Disease Control and Prevention, cardiovascular disease (CVD) is the leading cause of death in diabetic patients, accounting for up to 80% of increased mortality. Furthermore, diabetes is followed by other long-term complications causing increased number of blindness, kidney failure and non-traumatic amputations in adults [3].

Obesity and insulin resistance are considered the major contributors for T2DM [6]. Before diagnosis, patients may have significant hyperglycemia for years, sometimes more than a decade. These patients have insulin resistance in varying degrees and β -cell dysfunction. In the majority of diabetic population, there is a slow progression from normal or impaired glucose tolerance (IGT) to overt diabetes. This depends on the interaction between genetic and environmental factors that regulate insulin-sensitivity or the ability of β -cell to secrete insulin. When a patient reveals higher insulin resistance, the peptide secretion increases; these two parameters are therefore interrelated (i.e., insulin secretion and sensitivity). A failure to compensate by increasing the insulin secretion, firstly results in IGT and secondly in T2DM. Interventions that decrease insulin resistance, and preserve or improve β -cell function are likely to be effective in slowing progression from IGT to diabetes, or even allowing reversion to normal glucose tolerance [7].

The economic impact associated with T2DM and its complications makes this disease an appropriate target for prevention or delay onset. Several studies have demonstrated that the disease can be prevented/delayed in patients with IGT by improving lifestyle quality, usage of pharmacological agents and/or surgery.

The risk factors for T2DM include modifiable causes, such as sedentary lifestyle (e.g. physical inactivity, high-caloric and high-fat intake, cigarette smoking, urbanization), overweight and obesity, pre-diabetes, dislipidemia and hypertension [5]. Non-modifiable causes include age (> 45 years), family history (parents or siblings), ethnicity (e.g. Native Americans, Hispanic Americans, African Americans, Asian Americans, and Pacific Islanders), and gestational diabetes [5]. With respect to the protective effects, coffee consumption has been reported to be inversely associated with risk of T2DM and similar associations have been noted for

decaffeinated coffee and tea [8]. Moreover, moderate alcohol consumption was shown to be protective against T2DM in both genders [9]. Nevertheless, these data require further investigation in randomized trials. In this review, an overview of the different approaches for T2DM prevention is given addressing the demanding lifestyle interventions of the patients and discussing the state of the art knowledge of therapeutic strategies.

2. Lifestyle changes

Several randomized clinical trials have studied the hypothesis that changes in lifestyle, such as diet improvement, increased activity or exercise, and weight loss, were shown effective in decreasing the incidence of T2DM in high-risk individuals [10]. The Finnish Diabetes Prevention Study (DPS) enrolled 522 adults overweight with IGT [11, 12]. In the Finnish study, the lifestyle intervention included weight reduction, diet, and exercise. From the study conducted during 4 years, the authors found a cumulative incidence of diabetes of 11% in the intervention group and 23% in control group. The intervention group lost an average of 4.2 kg in the first year and, compared with the control group revealed 58% reduction of incidence of T2DM. The study also revealed that after cessation of the intervention, the reduction in diabetes risk persisted over 7 years of follow-up, the intervention group had an overall reduction of 43% compared with control group. During the post intervention period, the risk reduction was 36% in the subset of participants who were free from diabetes in the end of the intervention period despite modest weight regain in the intervention group (1.3 kg regained of the original 3.1 kg lost by this subgroup) [13]. The patients that adopted the lifestyle changes during the extended follow-up revealed the greatest risk of T2DM reduction, i.e. about 46%. In a multivariate analysis that considered the success of achieving all lifestyle goals, only weight reduction remained a significant determinant of diabetes risk.

Another trial, conducted by the Diabetes Prevention Program (DPP) Research Group, enrolled 3234 overweight adults with pre-diabetes [14-16]. Participants were randomized following a lifestyle modification program aiming to achieve a 7% weight loss, taking metformin 850 mg twice a day, or matching placebo [17]. A group of 585 participants was randomly using troglitazone, but finished earlier due to hepatotoxic effects [14]. The DPP preferentially enrolled participants with high risk of T2DM, 45% were from high-risk ethnic groups, and 20% were aged between 60 and 85 years old at baseline. The study showed evident superiority of lifestyle changes in diabetes prevention. The 3-years incidence T2DM at was 28.9%, 21.7%, and 14.4% in the placebo, metformin, and lifestyle intervention groups, respectively. Lifestyle changes

reduced the cumulative incidence of diabetes by 58% and metformin by 31% compared with placebo. The authors found that lifestyle changes were significantly more effective than metformin itself. For each kilogram of weight loss, there was a 16% risk reduction of T2DM, adjusted to changes in diet and activity, revealing that weight loss was the predominant predictor of reduced diabetes incidence [18].

An older study conducted in China, also demonstrated the protective effect of lifestyle intervention in 577 individuals with IGT [19, 20]. Participants were randomized to dietary changes, exercise, or both, and were followed up for 6 years. The 6-year cumulative incidence of T2DM was 48%, 41%, 46% and 68% in the diet-only, exercise-only, diet plus exercise and control groups, respectively. The relationship between the amount of weight lost and T2DM incidence was inconsistent and all interventions were similarly effective in preventing diabetes.

3. Pharmacological interventions

3.1. Metformin

Metformin is one of the most studied drugs for T2DM prevention. It is an insulin-sensitizing agent that acts by reducing hepatic gluconeogenesis. By inhibiting free fatty acid (FFA) production and oxidation, reduces FFA-induced insulin resistance and promotes peripheral glucose uptake [21]. It may also exert protective effects on pancreatic islet cells and it is not related to body weight gain. Moreover, metformin is not associated with risk of hypoglycaemia and has a neutral to positive effect on lipid profile and blood pressure.

In the DPP study [17], described above, after 3 years of metformin 850 mg twice daily, the incidence of T2DM in patients with IGT reduced by 31% compared with placebo (22% in the metformin group vs 29% in the placebo group developed diabetes). Metformin was more effective in participants with higher fasting glucose levels and with body mass index (BMI) above 35 kg/m² at baseline, in whom it reduced T2DM incidence approximately 50%.

The recently published results of the CANadian Normoglycemia Outcomes Evaluation (CANOE) trial, showed that a low dose combination therapy with metformin and rosiglitazone was highly effective in prevention of T2DM in patients with IGT, with little effect on the clinical adverse events of the two drugs [22]. In this double-blind, randomized controlled trial, 207 patients with IGT were randomly assigned to receive combination of rosiglitazone (2 mg) and metformin (500 mg) twice daily or matching placebo. The authors found that the incidence of T2DM was lower in the intervention group than in the placebo group (14% versus 39%). The relative risk

reduction was 66% and the absolute risk reduction was 26%. In the intervention group, 80% of the patients returned to normal glucose tolerance (53% in placebo group).

Fontbonne et al. compared the changes in cardiometabolic risk factors between treatment groups (metformin versus placebo) in two subsets of trial subjects, namely with impaired fasting glucose (IFG) or with IGT (n=101), and those fulfilling the inclusion criteria of DPP [23]. In the IFG/IGT subset, significant differences in 1-year changes were observed for systolic blood pressure, which markedly decreased in the metformin group in a higher extent than in the placebo group ($p<0.003$), and for fasting plasma glucose, and total and LDL cholesterol, which slightly decreased in the metformin group, but increased in the placebo group ($p<0.04$). The authors concluded that in high risk subjects, metformin may have beneficial and no untoward effects on cardiometabolic risk factors.

3.2. Thiazolidinediones

Thiazolidinediones (TZDs) or glitazones are insulin-sensitizing agents that also have been shown to prevent T2DM. These drugs act by stimulation of peroxisome proliferator-activated receptor- γ (PPAR- γ), which increases hepatic and peripheral insulin sensitivity by stimulating conversion of pre-adipocytes to adipocytes [24]. Adipocytes increase adiponectin, increasing insulin sensitivity. Accumulating evidence also indicates that TZDs are associated with β -cell preservation [25], and some studies supports that they provide several other beneficial metabolic and vascular effects, e.g. improvement in lipid profile and blood pressure, peripheral redistribution of body fat and anti-inflammatory [24]. Their side effects, such as fluid retention and increased incidence of bone fractures, might indicate an unacceptable risk-to-benefit ratio in T2DM prevention.

The first study demonstrating diabetes prevention with TZDs was published in 2002 and involved troglitazone [25]. The Troglitazone in Prevention of Diabetes (TRIPOD) study randomized 266 Hispanic women with previous gestational diabetes to troglitazone or placebo [16, 25]. The authors showed a reduction greater than 50% of T2DM incidence after 1.5 years of follow-up in troglitazone group. This reduction was attributed to increased insulin sensitivity and reduction of endogenous insulin requirement, which was evident 3 months after starting drug therapy. Furthermore, the diabetes protection effect persisted for 8 months after drug discontinuation, which was attributed to the maintenance of β -cell function. In the DPP trial [20, 26], although troglitazone has been discontinued due to hepatotoxic effects, during the 0.9 years of therapy it was shown that T2DM incidence reduced by 75%.

In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, 5269 individuals with IFG and/or IGT were randomized to receive rosiglitazone, ramipril, and placebo [27]. Rosiglitazone group decreased the incidence of T2DM by 62% and reverted to normoglycemia by 70% to 80% compared with placebo. Like metformin, rosiglitazone seems to be most effective in participants with higher BMI (risk reduction of 40% for BMI < 28 and 68% for BMI > 33 kg/m²). It has also been reported a mean weight gain of 2.2 kg in rosiglitazone group and increased frequency of congestive heart failure.

Another trial using a TZD is the ongoing Actos Now for Prevention of Diabetes (ACT NOW) trial, with the purpose of examining whether pioglitazone can prevent/delay progression to T2DM in high risk patients, and to define the its mechanisms (improved insulin sensitivity and/or enhanced beta cell function) [28]. In this study 602 IGT participants were randomized. IGT subjects were required to have fasting plasma glucose (FPG) of about 95-125 mg/dl and at least bearing a second high risk characteristic. Subjects were randomized to receive pioglitazone (45 mg/day) or placebo, and returned every 2-3 months for FPG analysis and annually for oral glucose tolerance test (OGTT). Primary endpoint was the conversion of IGT to T2DM based on the FPG values at or above 126 mg/dl or on the 2-hour PG values at or above 200 mg/dl, and the secondary endpoints included evaluating whether pioglitazone could: (i) improve glycemic control (ii) enhance insulin sensitivity, (iii) improve beta cell function, (iv) improve risk factors for cardiovascular disease, (v) cause regression/slow progression of carotid IMT, (vi) revert newly diagnosed diabetes to normal glucose tolerance.

From the study carried out by Durbin, rosiglitazone and pioglitazone, were effective in reducing glycosylated haemoglobin levels in patients with diabetes and C-peptide levels in patients with IGT/insulin resistance [29]. Furthermore, progression of this condition to T2DM appeared to be significantly delayed or prevented with early TZD treatment.

3.3. Nateglinides

Nateglinide is a D-phenylalanine analogue that acts directly on the β cells to stimulate rapid short-duration secretion of insulin [30]. The ongoing Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study is a multinational, randomized, double-blind trial in subjects with IGT, with or older than 50 years old with known CVD or with or older than 55 years old with CVD risk factor of or above 1 [16, 31]. This study was designed to evaluate whether reducing postprandial hyperglycemia, blockade of the renin-angiotensin-aldosterone system, or both interventions reduced the risk of T2DM or cardiovascular events in

patients with IGT. The aim of the study was to examine the effect of nateglinide, 30 to 60 mg, three times daily and valsartan, 80 to 160 mg/day for 3 years on the prevention of diabetes in over 9000 subjects with IGT and increased risk of cardiovascular events.

3.4. α -Glucosidase inhibitors

The α -glucosidase inhibitors are antidiabetic agents that decrease postprandial hyperglycemia reducing the toxic effect of glucose on pancreatic β cells and have been shown to improve insulin sensitivity in individuals with IGT [32]. An example of this class of drugs is acarbose, which has been tested in a number of clinical trials. A multicenter randomized trial, the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) examined the efficacy of this drug in reducing the occurrence of diabetes in a population with IGT [33]. The authors reported that acarbose 100 mg, three times/day, was associated with a 25% reduction in the incidence of T2DM in a cohort of 1429 individuals with IGT and significantly increased the reversion of IGT to normal glucose. However, approximately 25% of the cohort (including 31% of the acarbose group) has not completed the study, with the consequence that the estimated acarbose effect on diabetes incidence might be unreliable. The high drop-out rate was attributed to gastrointestinal side effects. Therefore, in general practice, acarbose might have limited value for diabetes prevention. From the Cochrane Library search carried out by Van de Laar et al. the authors confirmed the evidence that acarbose is able to reduce the incidence of type 2 diabetes in patients with IGT, and may also prevent the occurrence of cardiovascular events [32].

3.5. Incretin-based therapies

In T2DM, beyond the known defects of insulin resistance and β -cell insufficiency, derangement of incretin hormones usually produced from the gut wall in response to food intake play an important role. In recent years, 'incretin-based' therapies (IBT) have been developed to address hyperglycemia through either mimicking the action of the endogenous incretin glucagon-like polypeptide (GLP-1) (GLP-1 receptor agonists) or by inhibiting the activity of the enzyme that degrades GLP-1 (the dipeptyl peptidase-4 inhibitors (DPP-4 inhibitors)) [34]. In addition to their glucose-lowering and weight-neutral or weight-reducing actions, decrease systolic BP, improve fasting and postprandial lipid parameters, reduce high-sensitivity C-reactive protein levels and improve endothelial dysfunction. IBT have several beneficial effects on cardiovascular risk factors and, for this reason, it has been recently suggested to extend the use of these drugs in

diabetic patients with cardiovascular complications. Yet, the long-term effects of IBT on subclinical or clinical atherosclerosis remain to be established by future studies.

A double-blind, randomized study was conducted in 179 subjects with IGT during 12 weeks, to determine the effects of vildagliptin (50 mg q.d.) on incretin hormone levels, islet function, and postprandial glucose [35]. The authors found that the known effects of vildagliptin on incretin levels and islet function in T2DM were reproduced in subjects with IGT, with a 32% reduction in postprandial glucose excursions and no evidence of hypoglycemia or weight gain.

Other study showed that the DPP-4 inhibitor vildagliptin improves insulin sensitivity and β -cell function, leading to improved postprandial glycemia in subjects with IFG, who are known to have β -cell dysfunction [36]. Thus, vildagliptin may prevent progression to T2DM in high-risk subjects. In this study, a total of 22 subjects with IFG were treated orally with 100 mg vildagliptin once daily in a single-blind study. Subjects received placebo for 2 weeks (run-in) followed by vildagliptin for 6 weeks (treatment) and then placebo for 2 weeks (washout). A frequently sampled intravenous glucose tolerance test (FSIGT), followed by a 2-hour meal tolerance test (MTT), was performed for 2, 8, and 10 weeks. From the FSIGT, the acute insulin response to glucose (AIRg) and insulin sensitivity index (SI) were determined and used to compute the disposition index (AIRg_{SI}) as a measure of β -cell function. The authors found that fasting plasma glucose did not change after 6 weeks of vildagliptin treatment. With treatment, mean_{SD} (standard deviation) AIRg increased from 224 \pm 44 up to 286 \pm 52 pmol/l, and SI improved from 2.8 \pm 0.5 up to 3.5 \pm 0.5 \times 10⁻⁵ min⁻¹.pmol⁻¹.l, resulting in an increase in the disposition index from 688 \pm 180 up to 1.164 \pm 318 \times 10⁻⁵/min. These effects were not sustained after washout. During the MTT, the incremental area under the glucose curve was significantly decreased after treatment (240 \pm 15 vs. 191 \pm 14 mmol.l⁻¹.min⁻¹), but this effect was not sustained after washout.

The Homeostasis Model Assessment (HOMA) index of insulin resistance (HOMA-IR), in addition to quantitative insulin-sensitivity check index (QUICKI) , are widely used indices to measure insulin sensitivity [37]. These are based on the concept that the product insulin versus glucose is a measurement of insulin resistance, with both insulin and glucose increasing when SI decreases. Recently these have been tested for their robustness in assessing insulin sensitivity [38]. A total of 191 obese children and adolescents, who had undergone a FSIVGTT were analyzed for the receiver operating characteristic curve (ROC) to compare indices in detecting insulin resistance and Bland-Altman plots. ROC analysis showed that the diagnostic accuracy was identical for QUICKI and HOMA-IR, and insulin revealed no significant improvement in lowering AUC. Glucose did not perform better than chance as a diagnostic test. Indices varied

with consecutive sampling, mainly attributable to fasting insulin variations. The authors concluded these indices function equally well as predictors of the FSIVGTT sensitivity index.

3.6. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Large randomized clinical trials have demonstrated that the inhibition of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockers (ARBs) can reduce the incidence of T2DM.

The HOPE (Heart Outcomes Prevention Evaluation) study showed that ramipril, 10 mg daily for 4.5 years, reduced the incidence of T2DM by 34% in non-diabetic individuals with CVD compared with placebo [16, 39]. Similar glycemic protective effects were found with captopril (in the Captopril Prevention Project, CAPPP), lisinopril (in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ALLHAT) and losartan (in the Losartan Intervention For Endpoint reduction in hypertension study, LIFE) [40-42]. However, in these studies, diabetes prevention was not the primary outcome.

In the DREAM trial, the primary outcome was the effect of ramipril and rosiglitazone on the development of diabetes [43]. The study consisted of evaluating 5269 participants with IGT and/or IFG. The authors found that ramipril, 15 mg/day for 3.5 years, did not prevent diabetes, however, there was a 9% non-significant decrease in new-onset diabetes, and a 16% significant increase in regression of IFG and IGT to normoglycemia, as well as a significant decrease in plasma glucose level 2 hours after oral load of glucose.

The discrepancy in findings between the DREAM trial and previous reports may be related to the difference in the study design and study population [16]. In the DREAM trial, diabetes prevention was a primary outcome and ramipril was compared with placebo. On the other hand, on previous trials ACEIs or ARBs were compared with antihypertensive medications, such as diuretics and β blockers, which are known to have adverse effects on glucose metabolism. In previous studies, the population was characterized by high cardiovascular risk profile, and was therefore more likely to have RAS system activated, in comparison to the low-risk DREAM population.

The ongoing trial, Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) is a study that takes the incidence of diabetes as a secondary end point in 22400 cardiovascular high-risk patients assigned for three distinct treatment groups: ramipril, telmisartan, and telmisartan plus ramipril [44]. This is the first trial with the purpose to demonstrate that the ARB, telmisartan, is as effective as the ACE-inhibitor, ramipril, in

cardiovascular protection in a high-risk, ACE-tolerant population. Whether all ARBs are equally cardioprotective is uncertain. Data indicate that the beneficial effects of telmisartan may be drug specific rather than a specific effect of a certain pharmacological class of drugs.

It is known that the effects of ACEIs or ARBs on glucose metabolism is related to different mechanisms, such as, (i) inhibition of the post-receptor insulin signalling abnormalities, (ii) increased blood flow to the skeletal muscle facilitating insulin action, (iii) enhanced differentiation of pre-adipocytes into mature adipocytes, (iv) increased pancreatic islet blood perfusion leading to appropriate insulin release, and (v) possible partial PPAR- γ activity [45-47].

3.7. Weight-reducing agents

Weight-reducing agents have been studied in small numbers of individuals with IFG, IGT, or both. Orlistat, an intestinal lipase inhibitor, reduced the development of T2DM by 40–52% in obese people with IGT [48, 49]. The effect of this drug on diabetes might be attributed to weight loss, which was greater than that achieved with lifestyle change regimen. However, the drop-out rate reached about 50%, which suggests that this therapy has limited acceptability, and potentially turns less reliable estimating the dimension of the effects of such treatment.

3.8. Statins

Statins are lipid-lowering agents that also confer protective cardiovascular and metabolic effects, such as, anti-inflammatory, anti-atherosclerotic, blood pressure-lowering and glucose-lowering effects [50, 51]. It seems to affect substrate delivery to insulin-sensitive tissues by increasing capillary recruitment and enhance insulin-activated signalling cascades that mediate glucose uptake. The anti-inflammatory effect leads to decreased cytokines interleukin-6 and tumour necrosis factor- α , which causes inhibition of lipoprotein lipase activity and stimulates lipolysis producing the metabolic syndrome with insulin resistance. Finally, dyslipidemia impairs endothelial function adversely affecting vasodilatation and resulting in diminished capillary recruitment and increased insulin resistance. The restoration of endothelial function through the lipid-lowering effect of statins improves selective tissue perfusion and beneficially affects glucose insulin transport.

Analyzing the results of the West of Scotland Coronary Prevention (WOSCOPS) study, with 5974 participants who had normal glucose on enrolment, the authors found that 139 subjects developed T2DM [16, 52]. After adjustment for risk factors, pravastatin therapy was found to

result in a 30% reduction in the development of diabetes, an effect that was independent of the triglyceride-lowering effect of pravastatin.

3.9. Fibric acid derivatives

Bezafibrate is a non-selective ligand for PPAR- α with comparable activation of other PPAR subtypes, such as γ and δ . PPAR- α primarily regulates gene expression involved in lipid metabolism stimulating the increase of high-density lipoprotein and the decrease of triglyceride levels [53]. Bezafibrate was also found to decrease fasting plasma glucose levels in T2DM patients with hyperlipidemia [16, 54]. This glucose-lowering potential is attributed to the non-selective activation of PPAR. Activation of PPAR- γ improves insulin sensitivity and enhances glucose disposal in adipose tissue and skeletal muscles [53]. The use of bezafibrate was also shown to reduce the incidence of T2DM in patients with IFG and in non-diabetic obese patients with normal glycemic levels [55, 56].

In the Bezafibrate Infarction Prevention (BIP) study, 303 patients with IFG received either placebo or 400 mg of bezafibrate daily [16, 56]. The authors found that over a mean of 6.2 years, development of T2DM was less prevalent and more delayed in the bezafibrate group. Multivariate analysis identified bezafibrate as an independent predictor of decreased risk of new diabetes development, regardless of BMI and lipid profile.

4. Surgery

Some studies demonstrate that bariatric surgery can effectively reverse or prevent T2DM. In a prospective study of individuals with IGT and severe obesity, diabetes incidence rates were 4.7 cases per 100 person*years of follow-up in the untreated group, compared with 0.15 cases per 100 person*years in patients who underwent bariatric surgery [20, 57]. Pories *et al.* also reported a marked effect of weight-reduction surgery on T2DM incidence, with an annual T2DM incidence of 4.5% in the control group, compared with only 1.0% in the surgically group [20, 58-60].

The Swedish Obese Subjects (SOS) study was a prospective trial of more than 2000 individuals who underwent a variety of surgical procedures (most commonly, vertical banded gastroplasty) and matched controls who received standard care [20, 61]. The odds ratio for diabetes in the surgically treated group was 0.14 (95% CI 0.08-0.24) at 2 years and 0.25 (95% CI 0.17-0.38) at 10 years of follow-up. As expected, the incidence of diabetes was related to the amount of

weight lost. None of the participants losing more than 12% of their initial body weight developed diabetes, in contrast to a 2-year diabetes incidence of 7% in those with a 2% weight loss, and 9% in those gaining weight [20].

Other studies reported that laparoscopic adjustable gastric banding in patients with established diabetes resulted in remission of diabetes in 64% and major improvements in glycemic control in 26% [62]. This suggests that this surgery could also successfully prevent diabetes. In a randomized, controlled trial of gastric banding, diabetes remission was reported in 73% of the surgically treated patients, compared with 13% of recipients of conventional therapy [63]. Biliopancreatic diversion has also been reported to normalize glucose tolerance in obese patients with either impaired glucose tolerance or established diabetes [64]. Glucose tolerance was shown to improve rapidly after bariatric surgery, even before much weight has been lost; neurohormonal mechanisms were reported to be involved [65].

5. Conclusions

Convincing evidence demonstrates that a multifactorial approach is required to deal T2DM on a daily basis. Patients are advised to adopt risk-reducing lifestyle behaviors, in addition to personalized therapeutic schemes, aiming at reducing the epidemic level of the disease. The current review suggests that personalized programs need to be implemented. Interventions that decrease insulin resistance, and preserve or improve β -cell function are effective in slowing progression to T2DM. The intervention in lifestyle changes, such as increasing activity or exercise, and reducing weight, is the most important prevention therapy. Regarding pharmacological therapy, metformin and TZDs are effective drugs in reducing the risk of T2DM in patients with IGT and higher BMI. Incretins are also promising drugs in patients with IGT, due to the reduction in postprandial glucose excursions demonstrated in studies with vildagliptin. Acarbose have limited value for diabetes prevention, because of the high drop-out rate due to gastrointestinal side effects. Therapy with ACE inhibition or ARBs can also reduce the incidence of T2DM; however, from studies conducted with these drugs, diabetes prevention was not the primary outcome. Therefore, ARBs are not recommended as therapeutic approach to reduce risk of T2DM. Orlistat can reduce the risk of development of T2DM in obese people with IGT, probably due to weight loss. However, the drop-out rate is high, suggesting that this drug has limited acceptability. Statins and bezafibrate have also beneficial effects in glucose metabolism in patients with hyperlipidemia. Apart from the pharmacological treatment, approaches to delay the T2DM onset and identify high-risk patients include performing pre-diabetes testing, by blood

measuring fasting glucose values or, more appropriately, an oral glucose tolerance test to define impaired glucose tolerance. Lifestyle changes require an implementing disciplinary programme supervised by the physicians on a daily based training of patients. Ultimately, bariatric surgery is recommended for obese patients to improve glycemic control.

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