Review Article

# Preventive pharmacotherapy in type 2 diabetes mellitus

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## ABSTRACT

Over the last few decades certain demographic changes have been observed worldwide, which have led to an increase in the prevalence of chronic non-communicable diseases. Type 2 diabetes mellitus and associated cardiovascular disease are major contributors to this disease burden leading to rising morbidity and mortality. It is worrisome to see that type 2 diabetes with its micro- and macrovascular complications is occurring in younger populations where it was hitherto unseen. Prevention appears to be an important strategy to reduce the burden of disease. Along with inculcating healthy lifestyle habits across populations, it may be suitable to use preventive pharmacotherapy in those with pre-diabetes and / or other risk factors like obesity, hypertension, and on the like. Metformin, alpha glucosidase inhibitors like acarbose, miglitol, and voglibose, and pioglitazone have all been used with success. The issues of compliance and adverse effects during long-term use have tempered the use of these drugs. The best approach would be to motivate the patient for effective lifestyle changes, and pharmacological management if the lifestyle changes are not successful in achieving their goals.

**Key words:** Acarbose, metformin, pharmacotherapy, pioglitazone, prevention, type 2 diabetes mellitus, voglibose

## Introduction

The last few decades have witnessed significant demographic changes around the globe, especially in the developing nations.[1] Economic improvements, increasing urbanization, and changing lifestyle patterns along with increased longevity have led to a shift in the pattern of disease occurence.[2] There has been a gradual increase in the prevalence of chronic non-communicable diseases, across populations and continents.

Type 2 diabetes mellitus and its associated chronic complications such as diabetic nephropathy, hypertension, and coronary heart disease are major contributors to the global burden of chronic diseases, leading to a rise in morbidity and mortality.[3,4] Till a decade or so ago, type 2 diabetes was considered a disease predominantly affecting the middle-aged and the elderly, but it is now increasingly seen in subjects of a younger age group, including children and adolescents. This changing trend is not restricted to isolated geographical areas, but is being seen across geographic distributions and boundaries.[5] This is worrisome with the knowledge that type 2 diabetes is associated with a huge burden of micro- and-macrovascular complications, and these concerns are even greater in the younger diabetic population as they are exposed to hyperglycemia for longer durations in comparison to adult diabetics. If these trends are not reversed, the physician, over the next couple of decades, will face the challenge of managing these complications in younger patients, in whom there is a limited understanding of the disease-course and the time-gap between the occurrence of complications; a scenario where they come across individuals in their late 20s or 30s presenting with coronary artery disease, or chronic kidney disease, or stroke.

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## Etiopathogenesis of Type 2 Diabetes

The pathophysiology of diabetes includes defects in the action or secretion of insulin, which leads to the development of glucose intolerance[6] and an eventual progression to the full-blown disease. There is a progressive increase in tissue resistance to insulin, which in turn causes the pancreatic beta cells to progressively increase the insulin secretion, in order to overcome the tissue resistance. This process continues till the beta cells can compensate for insulin resistance, but eventually, the beta cells get progressively exhausted leading to corresponding increments in the glucose levels. De Fronzo labeled the combination of insulin resistance in the muscle and liver and the eventual beta-cell failure as 'the triumvirate'.[7] Insulin resistance in the muscle and liver results in hyperglycemia, poor metabolic control, and a further decline in insulin sensitivity, however, disease progression is determined by the progressive beta-cell failure.

The natural course thereby progresses from impaired fasting glucose (IFG) / impaired glucose tolerance (IGT) and the consequent postprandial hyperglycemia to type 2 diabetes.[8] Individuals with IGT have an increased risk of progression to type 2 diabetes as well as an increased risk for cardiovascular disease (CVD) and death, compared to those without IGT.[9]

The development of insulin resistance is predominantly determined by the presence of obesity and / or lack of physical activity.[10] It is considered that a comparatively higher amount of abdominal fat in diabetics than their non-diabetic counterparts may have a direct effect on the development of insulin resistance and chronic disease.[11] Adiposity is also often associated with pro-inflammatory adipokines. Adiposity results in the increased release of proinflammatory adipokines like TNF-alpha, monocyte chemoattractant protein (MCP-1), and interleukin 6 and 8, which will worsen insulin resistance.[12,13]

Genetic predisposition is another factor in the development of type 2 diabetes. Even as there is a wide variation in the prevalence of type 2 diabetes among different ethnic groups, specific populations also have varying environmental and cultural influences that can independently affect the risk of developing diabetes. A positive family history of diabetes is also a pointer of genetic influences.[14]

Over the years we have learned that apart from the established culprits, other factors also contribute to the complex pathogenesis of type 2 diabetes. Along with fat cells, gastrointestinal tissues and the incretins, pancreatic alpha-cells, kidneys that absorb up to 90% of the filtered loss of glucose, and not to be left behind, the brain, all form a cohort, labeled as the 'ominous octet' by Defronzo.[15]

## Prevention of Type 2 Diabetes

Identification of individuals with pre-diabetes provides an opportunity to identify those who are at high risk for developing overt type 2 diabetes and at increased risk for CVD. Treating pre-diabetes to prevent progression to overt diabetes could be beneficial in several ways [Table 1].

These interventions may be classified as primordial, primary, secondary, or tertiary level strategies, depending on the pathophysiological stage at which they are being targeted. Primordial interventions will be targeted on entire populations and include dietary and lifestyle modifications like reduction of fat or salt intake, increased physical activity, and weight loss.

A primary intervention would be focused at the stage of IFG / IGT, where it is possible to prevent the progression to type 2 diabetes. This would include the use of pharmacological agents and lifestyle modification. Prevention of the occurrence of diabetic complications would come under secondary prevention, and tertiary prevention would encompass the treatment of specific diabetic complications, to prevent excess morbidity and mortality.

The American Diabetes Association (ADA) recommends the use of interventions in individuals at high risk for developing diabetes (those with IFG, IGT, or both) [Table 2].[16]

### Metabolic modulation in type 2 diabetes

It is now understood that diabetes is the result of a combination of genetic susceptibility, external influences, and increased calorie consumption of which fat is the most important element. The elevated plasma glucose is a constituent of a more general dysregulation of 'fuel utilization,' such as metabolism of glucose and lipids.[17]

**Table 1: Benefits of prevention of progression from pre-diabetes to overt type 2 diabetes**

| | |
|---|---|
| Altering the natural course | Improvement of islet cell function |
| | Simplifying treatment |
| Prevention of microvascular complications | Nephropathy |
| | Retinopathy |
| | Neuropathy |
| | Diabetic foot disease / amputations |
| Prevention of macrovascular complications | Myocardial infarction |
| | Stroke |
| | Peripheral vascular disease |

**Table 2: American Diabetes Association recommendations to prevent / delay type 2 diabetes[16]**

- An effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 minutes/ week of moderate activity, such as walking, is recommended for patients with IGT, IFG, or an HbA1C of 5.7 – 6.4%
- These patients should receive follow-up counseling for successful implementation
- Metformin therapy for prevention of type 2 diabetes may be considered in those at the highest risk for developing diabetes, such as those with multiple risk factors, especially if they demonstrate progression of hyperglycemia, despite lifestyle interventions
- Monitoring the development of diabetes in those with pre-diabetes should be performed every year.

There is a profound disturbance in lipid metabolism, with the elevation of plasma-free fatty acids (FFA), reflecting the impaired anti-lipolytic activity of insulin in the fat tissue and of the increased amounts of fat tissue.[17] This eventually results in the development of a diabetic dyslipidemic lipoprotein profile, with elevated levels of small dense LDL particles and a decreased concentration of HDL cholesterol.

In recent times, many novel agent-classes have been identified, which act through different mechanisms, to target the underlying metabolic disturbances in type 2 diabetes. Agents in this category would include thiazolidinediones like pioglitazone, certain statins and fibrates, and agents blocking the renin angiotensin system (RAS). Certain other agents are now being identified, which have novel mechanisms through which they produce their beneficial effects in type 2 diabetics.

## Diabetes: Economic Burden

Diabetes is the second among the four leading chronic diseases in India, as measured by their prevalence, the top position being occupied by cardiovascular diseases.[18] With the current demographic trends, diabetes is projected to continue to increase in prevalence in the near future, with the disease making inroads into the population subgroups where it was hitherto rare.[5] The International Diabetes Federation (IDF) reports a projected prevalence of 70 million patients in India by the year 2025,[19] and the World Health Organization (WHO) estimates that India will have 80 million cases of diabetes by 2030.[20]

The average cost of treating a diabetic in India has been estimated at USD 575 annually in terms of direct costs, while, indirect costs like lost work-time, would account for another USD 100 annually. It should be highlighted that a majority of these expenses are made directly by the patient or the family, and when translated into overall costs for the entire population, they assume enormous proportions.[18]

## Pharmacotherapy for Prevention of Type 2 Diabetes

Even as lifestyle interventions in IGT have a status similar to their status in the management of type 2 diabetes, it remains to be seen whether the intensive lifestyle interventions employed in clinical trials can be transferred successfully from the highly structured and disciplined environment of a trial to the more routine, day-to-day management in a primary care set-up. It would therefore seem prudent to introduce pharmacological interventions to prevent type 2 diabetes in the 'at-risk' population. The history of pharmacological interventions for prevention goes a long way back to a small trial published in 1980, with 49 subjects, which demonstrated that the sulfonylurea tolbutamide was effective in blocking the progression of IGT to type 2 diabetes over a 10-year follow-up period, compared to a 29% incidence among control patients.[21]

Since then we have come a long way in terms of understanding the disease process and the interventions that may block it at various levels.

Keeping in view the multimodal pathophysiological basis for type 2 diabetes, it is not necessary that these interventions be targeted at hyperglycemia alone. Other agents that do not primarily target hyperglycemia may also reduce the risk of type 2 diabetes. The use of orlistat for use of orlistat for managing obesity, RAS blockade with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBS), and recently the use of vitamin D and bromocriptine are all different approaches toward the common goal.

### Metformin

Metformin has been found to be useful in the prevention of development of diabetes in many large, well-powered trials. It has been shown to lower fasting blood glucose in individuals at risk for type 2 diabetes, without causing hypoglycemia. In addition, it has a favorable action on cardiovascular risk factors, which are often present in these individuals. It helps in maintaining diet-induced weight loss and lowers fasting plasma insulin concentrations, total and low density lipoprotein-cholesterol, and free fatty acids. These effects make metformin a first-line agent for the prevention of type 2 diabetes as recommended by the ADA.[16]

The Diabetes Prevention Program (DPP) was a multicenter clinical trial, aimed at finding the effect of modest weight loss through dietary changes and increased physical activity or treatment with metformin for the prevention or delay

in the onset of type 2 diabetes in pre-diabetes, overweight subjects.[22] The trial found that both lifestyle interventions and metformin were effective in slowing the progression of IGT to diabetes. For participants in the lifestyle intervention group, the risk-reduction for type 2 diabetes was to the tune of 58%, while it was about 31% in the metformin group. In the lifestyle intervention group, around 5% developed diabetes / year, compared to 7.8% in the metformin group, and 11% in the placebo group.

On similar lines, the Indian Diabetes Prevention Program (IDPP) reported a 28.5% reduction in the incidence of type 2 diabetes with lifestyle modifications and 26.4% reduction with metformin in comparison to placebo, in subjects with IGT.[23]

The Chinese Diabetes Prevention Program (CDPP) evaluated the preventive effect of diet and exercise, acarbose, and metformin on the progression to diabetes mellitus in 321 subjects with IGT.[24] The subjects were divided into the control, diet plus exercise, acarbose, and metformin groups. The glycemic control deteriorated in the control group with elevations in both fasting and postprandial plasma glucose at the end of study period. In the diet and exercise groups, the fasting plasma glucose increased slightly and postprandial plasma glucose levels were reduced. The other two groups demonstrated significant reductions in the two glycemic indices. Annual diabetes incidence was 11.6, 8.2, 2.0, and 4.1% in the control, diet and exercise, acarbose, and metformin groups, respectively.

The Early Diabetes Intervention Trial (EDIT) gave insights into the use of therapeutic agents for the prevention of type 2 diabetes in 631 patients with IFG. At three years, there was an 8% risk reduction with acarbose and 37% with metformin, compared to placebo.[25] Although there was no difference in the relative risk for diabetes with acarbose or metformin at the six year follow-up, it was observed that for subjects with IGT at baseline the relative risk reduction was significant with acarbose (0.66), but not with metformin (1.09), implying that there could be differences in the ability of the therapies, to reduce the risk of diabetes in subjects with IGT or IFG.[26]

Metformin has also been found to be effective in pregnant females with gestational diabetes and polycystic ovarian syndrome (PCOS). In a study by Begum *et al*.,[27] the two main outcome measures in this trial were development of gestational diabetes and the fetal outcome. The occurrence of gestational diabetes was significantly lower in the metformin group with only one subject (3.44%) developing gestational diabetes. On the other hand, nine of 30 pregnant (30%) subjects developed diabetes in the control group. Of note was the observation that all the babies in the metformin group had an average birth weight, while four babies in the control group were large for date. Another study of GDM prevention in PCOS patients with the use of metformin by Gluek *et al*.,[28] yielded similar results.

Even as metformin has been found to be useful in preventing the progression to type 2 diabetes, the topic has also raised questions on certain issues. One of the more important issues is whether the effect of metformin to reduce the incidence of diabetes during DPP is true prevention or simply a masking of diabetes, as the post-trial washout period is very short for testing that distinction. It is suggested that the very rapid effect of metformin to increase insulin sensitivity can similarly dissipate rapidly as well. These effects of metformin on insulin sensitivity may disappear two weeks after stopping metformin. The available data does not provide direct measures of insulin sensitivity; it also remains uncertain whether the glucose levels are stabilized or still rise two weeks after discontinuing metformin. With the current understanding of the effects of metformin on carbohydrate metabolism, it is possible that only a part of the effects are due to beta-cell protection, while another part is simply a masking due to the acute glucose-lowering effects of metformin; it will probably be difficult to estimate the proportion of these two effects.

### Alpha-glucosidase inhibitors

The alpha-glucosidase inhibitors acarbose, miglitol, and voglibose act by competitively inhibiting the alpha-glucosidase enzymes present in the intestines and are involved in carbohydrate digestion. They decrease both postprandial hyperglycemia and hyperinsulinemia, and may improve insulin sensitivity and diminish the stress on pancreatic beta-cells.[29] These compounds have a good safety profile and do not cause hypoglycemia, although gastrointestinal side effects are commonly observed and may lead to a reduced long-term compliance.

The Study TO Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) was a multicenter, international, double-blind, placebo-controlled study to evaluate the effects of acarbose in delaying the progression of IGT to type 2 diabetes in 1418 subjects with IGT.[30] The primary endpoint was the development of type 2 diabetes, based on an oral glucose tolerance test. There was a 25% relative risk reduction of progression to type 2 diabetes in the acarbose group compared to the placebo group. Acarbose significantly increased the reversion of IGT to normal glucose tolerance.

Voglibose has also been found to be useful in the prevention

progression of IGT to type 2 diabetes. In a clinical trial by Ryuzo Kawamori *et al*.,[31] voglibose was seen to improve glycemic parameters in 1780 Japanese subjects with IGT. The patients treated with voglibose had a significantly lower risk of progression to type 2 diabetes compared to the placebo group. A significantly higher number of subjects in the voglibose group achieved normoglycemia than those in the placebo group. Voglibose was approved by the Japanese Ministry of Health, Labor, and Welfare, in the year 2009, for the prevention of new-onset type 2 diabetes, in patients with impaired glucose tolerance.

### Thiazolidinediones

Pioglitazone, a PPAR-gamma agonist, is a member of the thiazolidinedione class (which also includes troglitazone and rosiglitazone). Pioglitazone is primarily expressed in the adipose tissue and has a favorable influence on systemic insulin resistance.[32]

Troglitazone in Prevention of Diabetes (TRIPOD)[33] was a randomized, placebo-controlled trial of 266 women with recent gestational diabetes, with 126 completing the treatment of 3.6 years, with an eight-month, post-drug washout period. A 55% reduction in the incidence of diabetes was observed, with persistent protection from diabetes for eight months post the drug, and stable glucose and beta-cell function for 4.5 years, in women who did not get diabetes during the troglitazone treatment. The study was terminated prematurely when troglitazone was withdrawn from the market.[33]

The Pioglitazone in Prevention of Diabetes (PIPOD)[34] study with pioglitazone was an open-label follow-up of 89 women from TRIPOD. The results were similar to the TRIPOD study, and a comparison of changes in beta-cell compensation for insulin resistance in both the studies showed that pioglitazone halted the decline in the beta-cell function that was seen with the placebo treatment in the TRIPOD study, and also maintained the stability of the beta-cell function that occurred in the TRIPOD with troglitazone treatment. Together, these two studies demonstrated that prevention of type 2 diabetes is possible with thiazolidinediones providing beta-cell rest.

The Actos Now for the prevention of diabetes (ACT NOW) study,[35] was a randomized, double-blind, placebo-controlled trial conducted to examine the effectiveness of pioglitazone in the prevention of type 2 diabetes in 602 subjects with IGT. The annual incidence rate of type 2 diabetes was 2.1% in the pioglitazone group compared to 7.6% in the placebo group. The hazard ratio of conversion of type 2 diabetes was 0.28 (95% CI 0.16 – 0.49 $p < 0.001$)

The diabetes reduction approaches with ramipril and rosiglitazone medications (DREAM)[36] study evaluated the efficacy of rosiglitazone in the prevention of type 2 diabetes. The trial randomized 5269 subjects with IGT and / or IFG to either rosiglitazone or ramipril versus placebo. More subjects regained normoglycemia on rosiglitazone (50.5%) than on placebo (30.3%). The ramipril therapy had no effect on the incidence of diabetes or death, but was more effective than placebo in achieving normoglycemia (42.5 vs. 38.2%, for ramipril vs. placebo). Importantly, rosiglitazone reduced the incidence of diabetes by 60% relative to the placebo and was effective in subjects with IFG and IGT.

Although each of these drugs has been found to be useful in preventing the progression from prediabetic to the diabetic stage, these drugs have been mired by issues of safety. Troglitazone was banned following its hepatotoxic effects. The United States Food and Drug Administration (USFDA) has restricted the use of Rosiglitazone, due to its increased risk for cardiac morbidity and mortality. USFDA recently (June 2011) issued a safety announcement on the use of pioglitazone, stating that taking pioglitazone for more than one year may be associated with an increased risk of bladder cancer. Although the Endocrine Society, the American Association of Clinical Endocrinologists, and the American Diabetes Association have appealed to patients to continue taking their prescribed medications, unless instructed otherwise by their healthcare provider, one must address the issue of pioglitazone-use in the light of the fact that the highest risk of bladder cancer was noted among patients who had been on pioglitazone for the longest durations and had received higher doses.[37]

### Orlistat

Orlistat, a specific inhibitor of gastrointestinal lipases (gastric and pancreatic), is responsible for the hydrolysis of ingested triglycerides into fatty acids and monoglycerides. Orlistat also increases postprandial glucagon-like peptide 1 (GLP-1) levels, thereby enhancing the insulin secretory response to a meal and blunting the postprandial glucose surge in obese diabetics. This probably leads to decreased food intake, and may also contribute to weight loss.[38] Orlistat has been shown to lower plasma insulin levels versus the placebo in clinical trials.[39,40] Heymsfield *et al*., conducted a post hoc analysis of orlistat therapy in 675 obese adults with IGT, from three randomized, placebo-controlled trials.[41] Orlistat was found to reduce the progression of IGT to diabetes versus placebo (3 vs. 7.6%). Seventy-two percent of the subjects on orlistat achieved fasting glucose values in the normal range, compared to 49%, in the placebo group.

The XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study[42] led to the confirmation of results from previous studies.[41] This prospective multicenter, randomized, double-blind, placebo-controlled, parallel group study investigated the effectiveness of orlistat along with lifestyle changes compared with lifestyle modifications alone in 3305 subjects. Over four years of therapy, orlistat led to a risk reduction of 37.3% in the cumulative incidence of diabetes versus placebo. Despite intensive lifestyle modifications in both the groups, weight loss was greater in the orlistat group versus the placebo group (– 6.9 vs. – 5.8 kg, respectively). Orlistat treatment led to a significant reduction in visceral adipose tissue.

### Incretin-mimetics

The use of certain oral hypoglycemic agents has been known to cause weight gain and this constitutes an important risk factor for diabetes; there is an incremental risk of 9% for every kilogram increase in body weight.[43] Incretin-mimetics like exenatide have been shown to address this issue as their use has been found to be associated with significant weight loss. Exenatide acts through multiple mechanisms, the net result of which is improved glycemic control. The effects have been categorized as immediate effects — glucose dependent insulin secretion, suppression of post-prandial high glucagon levels, and delayed gastric emptying and delayed effects — with weight loss and improvement in beta cell mass and function.[44]

Exenatide plus lifestyle modification have been shown to reduce caloric intake, produce weight loss, and improve glucose tolerance in nondiabetic obese subjects with both IGT and IFG.[44,45] In a study of 152 obese subjects with and without pre-diabetes, IGT or IFG normalized in 77 and 56% of exenatide- and placebo-treated subjects, respectively, at the end of the study. Exenatide-treated subjects had a significantly higher weight loss of 5.1 kg versus 1.6 kg for placebo. Subjects on exenatide treatment also consumed a lower number of calories. In summary the data available so far suggests that exenatide produced beneficial effects on insulin sensitivity and islet function [Table 3].

### Statins

Statins are commonly prescribed for the prevention of cardiovascular disease in patients with diabetes and even pre-diabetes. As statins have variable and complex effects on glucose metabolism, the risk of diabetes remains an area of controversy. In experimental studies statin lipophilicity as well as the potential to inhibit 3-hydroxy-3-methylglutaryl-coenzyme-A reductase are considered prognostic factors of an adverse impact of statin treatment on carbohydrate metabolism. Other factors like hypotriglyceridemic capacity, increase in islet blood flow, anti-inflammatory properties, and the ability to alter circulating levels of several adipokines are known to affect glucose homeostasis. Among the various drugs in this class, pravastatin appears to possess beneficial effects on glucose metabolism and also reduces the risk of diabetes. In general, the hydrophilic statins pravastatin, rosuvastatin, and pitavastatin are preferable to the lipophilic agents atorvastatin and simvastatin.[46]

A large body of evidence has demonstrated that the risk of new-onset type 2 diabetes may be increased by certain agents and a list of some of the statin trials and their results are given in Table 4. The risk may also be related to the duration and the dose of the individual statin used. Having said this, it is also true that their benefits far outweigh any potential risk in populations where statin-use has proven benefits.

### Renin angiotensin system blockade

A large body of evidence suggests that RAS blockade may reduce the incidence of new-onset type 2 diabetes in the at-risk population, with or without hypertension.[54] The reduction in the incidence of new-onset diabetes by ACE inhibitors or ARBs can be explained by hemodynamic effects like improved delivery of insulin and glucose to the skeletal muscle, and by non-hemodynamic effects, including direct effects on glucose transport and insulin signaling pathways; factors that contribute to reducing insulin resistance. RAS blockers help in maintaining a critical beta cell mass by blocking the effect of angiotensin II. It has also been found that these drugs delay or prevent the development of insulin resistance through novel mechanisms. Table 5 provides the results from some of the trials where these agents have been found to be useful.

All these trials taken together involved a large number of non-diabetic subjects and demonstrated that ACE inhibitors or ARBs produced a significant 25% reduction in the incidence of new-onset diabetes. Although these trials differed in their methods and only few had the development of diabetes as a pre-specified end point,[62] it could be inferred that the interplay of hypertension, hyperglycemia, and dyslipidemia worked as a cardiovascular risk factors and the RAS blockade had a positive effect on the metabolic milieu. Clinically, the inhibition of RAS improved insulin sensitivity and decreased the incidence of type 2 diabetes.

### Vitamin D

Vitamin D has been receiving attention for its potential role in preventing cardiovascular disease and type 2 diabetes mellitus. Epidemiological studies have suggested that individuals with low blood levels of vitamin D have

**Table 3: Summary of clinical trials on the risk of new onset Type 2 diabetes with oral hypoglycemic agents**

| Trial / study | Drugs | Subjects | Results |
|---|---|---|---|
| DPP[22] | LSM vs. Metformin 850 mg BD vs. placebo | 3234 study participants, overweight and pre-diabetes | LSM group – reduced their risk of developing diabetes by 58% and metformin by 31% |
| IDPP[23] | LSM vs. Metformin vs. LSM + metformin vs. placebo | 531 subjects with IGT | Risk reduction for type 2 diabetes with LSM was 28.5%, metformin 26.4%, and combination 28.2% compared to placebo |
| CDPP[24] | LSM vs. Acarbose 50 mg TID vs. metformin 250 mg TID vs. placebo | 321 subjects with IGT | Annual incidence of type 2 diabetes was 11.6, 8.2, 2, and 4.1% in control, LSM, acarbose, and metformin, respectively |
| EDIT[25,26] | Acarbose 50 mg TID vs. metformin 500 mg TID vs. placebo | 631 patients with IFG | 8% risk reduction with acarbose and 37% with metformin, compared to placebo |
| Begum MR *et al*.[27] | Metformin 2 – 2.5 g per day vs. controls | 29 PCOS patients on metformin compared with 30 controls with PCOS | GDM developed in 3.44% of patients on metformin compared to 30% in controls |
| Glueck *et al*.[28] | Metformin 850 mg TID vs. controls | 33 PCOS patients on metformin compared with 39 controls with PCOS | Use of metformin is associated with a 10-fold reduction in gestational diabetes (31 to 3%) |
| STOP NIDDM[30] | Acarbose 100 mg TID vs. placebo | 1418 subjects with IGT | 25% relative risk reduction on acarbose compared to placebo. Absolute risk reduction after 3.3 years was 9.1%. |
| Ryuzo Kawamori *et al*.[31] | Voglibose 0.2 mg TID vs. placebo | 1780 subjects with IGT | Lower risk of progression to type 2 diabetes in patients treated with voglibose compared to placebo, hazard ratio 0·595 (interim analysis) |
| TRIPOD[33] | Troglitazone 400 mg / day vs. placebo | 266 women with recent GDM | 55% reduction in the incidence of type 2 diabetes in troglitazone arm |
| PIPOD[34] | Pioglitazone 45 mg / day | Open label study on 89 women without diabetes in TRIPOD | Annual diabetes incidence was 4.6% |
| ACT NOW[35] | Pioglitazone 45 mg / day vs. placebo | 602 patients with IGT | Annual incidence rates for type 2 diabetes mellitus were 2.1% in the pioglitazone group and 7.6% in the placebo group, and the hazard ratio for conversion to diabetes in the pioglitazone group was 0.28 |
| DREAM[36] | Rosiglitazone 8 mg / day vs. placebo and Ramipril 15 mg / day vs. placebo | 5269 subjects with IGT and / or IFG | 60% relative risk reduction in new onset type 2 diabetes or death with rosiglitazone and 9% with ramipril |
| Rosenstock *et al*.[45] | Exenatide 10 ug BD vs. placebo | 152 obese subjects with or without IFG or IGT | IGT or IFG normalized at end point in 77 and 56% of exenatide and placebo subjects, respectively. |

DPP: Diabetes Prevention Program, IDPP: Indian Diabetes Prevention Program, CDPP: Chinese Diabetes Prevention Program, EDIT: Early Diabetes Intervention Trial, STOP NIDDM: Study to prevent non-insulin dependent diabetes, TRIPOD: Troglitazone in Prevention of Diabetes, PIPOD: Pioglitazone in Prevention of Diabetes, ACT NOW: Actos Now for the prevention of diabete, DREAM: Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications, LSM: Lifestyle modifications, IGT: Impaired glucose tolerance, IFG: Impaired fasting glucose, GDM: Gestational diabetes mellitus, BD: Twice daily, TID: Thrice daily

**Table 4: Summary of clinical trials on the risk of new-onset type 2 diabetes with statin therapy**

| Study | Study-drugs | Objective | Results |
|---|---|---|---|
| Ridker *et al*.[47] | Rosuvastatin vs. placebo | Effect on vascular events in 18,000 subjects with no evidence of diabetes | New-onset type 2 diabetes - 3 vs. 2.4%, rosuvastatin vs. placebo, respectively ($P$ = 0.01) |
| Freeman *et al*.[48] | Pravastatin vs. placebo | 3000 males in West of Scotland Coronary Prevention Study (WOSCOPS) | Pravastatin-treatment associated with a 30% risk-reduction for new-onset diabetes vs. placebo, respectively ($P$ = 0.042) |
| Keech *et al*.[49] | Pravastatin vs. placebo | Sub-study of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial | New-onset type 2 diabetes in those who were normoglycemic at study-onset: 4.0 vs. 4.5%, pravastatin vs. placebo, respectively<br>New-onset type 2 diabetes in those in the IFG group: 9.7 vs. 9.2%, pravastatin vs. placebo, respectively |
| Heart Protection Study Collaborators[50] | Simvastatin vs. placebo | Sub-analysis of the Heart Protection Study (HPS) | New-onset type 2 diabetes: 4.6 vs. 4.0%, simvastatin vs. placebo, respectively ($P$ = 0.10) |
| Sever *et al*.[51] | Atorvastatin vs. placebo | Sub-analysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) | New-onset type 2 diabetes: 3.0% vs. 2.6%, atorvastatin vs. placebo, respectively ($P$ = not significant). |
| Sattar *et al*.[52] | Statin vs. placebo | Review of 13 statin trials | Nine percent increased risk for developing diabetes while on a statin. Rates of developing diabetes were highest in trials involving older subjects. No differences in statin selection. |
| Preiss *et al*.[53] | Statins vs. placebo | Review of five statin trials | New-onset type 2 diabetes – 4.4 vs. 4%, intensive vs. moderate-dose therapy, respectively (OR 1.12). |

**Table 5: Summary of clinical trials on the risk of new-onset type 2 diabetes with Renin Angiotensin System blocking drugs**

| Trial | Agents / drugs | Result (New-onset diabetes) | Risk ratio |
|---|---|---|---|
| CAPPP[55] | Captopril vs. conventional antihypertensive treatment (diuretics, beta-blockers) | 6.5 vs. 7.3%, Captopril vs. diuretic / beta-blocker, respectively | 0.79 |
| HOPE[56] | Ramipril vs. placebo | 3.6 vs. 5.4%, Ramipril vs. placebo, respectively | 0.66 |
| LIFE[57] | Losartan vs. atenolol | 6 vs. 8%, Losartan vs. atenolol, respectively | 0.75 |
| ALLHAT[58] | Lisinopril vs. chlorthalidone | 8.1 vs. 11.6%, Lisinopril vs. chlorthalidone, respectively | 0.70 |
| SCOPE[59] | Candesartan vs. placebo | 4.3 vs. 5.3%, Candesartan vs. placebo, respectively | 0.81 |
| CHARM[60] | Candesartan vs. placebo | 6 vs. 7%, Candesartan vs. placebo, respectively | 0.78 |
| SOLVD[61] | Enalapril vs. placebo | 5.9 vs. 22.4%, Enalapril vs. placebo, respectively | 0.26 |
| VALUE[62] | Valsartan vs. amlodipine | 13.1 vs. 16.4%, respectively | 0.77 |
| PRoFESS[63] | Telmisartan vs. placebo | - | 0.82 |

CAPPP: Captopril Prevention Project, HOPE: Heart Outcome Prevention Study, LIFE: Losartan Intervention for Endpoint reduction in hypertension study, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, SCOPE: Study on Cognition and Prognosis in the Elderly, CHARM: Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity, SOLVD: Studies of Left Ventricular Dysfunction, VALUE: Valsartan Antihypertensive Long-Term Use Evaluation Trial, PRoFESS: Prevention Regimen for Effectively Avoiding Second Strokes

increased risks of heart disease, stroke, hypertension, and diabetes. Vitamin D receptors are present in most cells and tissues where they stimulate the nuclear transcription of various genes to alter cellular function. Vitamin D, appears to have an effect on numerous disease states and disorders, including osteoporosis, chronic musculoskeletal pain, diabetes (types 1 and 2), multiple sclerosis, cardiovascular disease, and various cancers.[64]

As calcium is necessary for insulin secretion, it has been suggested that vitamin D may contribute to maintaining insulin secretion. Many mechanisms are known, whereby, hypovitaminosis D may be involved in the causation of hyperglycemia, type 2 diabetes, and metabolic disorders like an increase in insulin resistance, reduction in insulin secretion, and an increase in damage to pancreatic islets.

In a recent trial of 12,719 non-diabetic participants, lower serum levels were associated with pre-diabetes after adjusting for a variety of factors such as age, sex, and race.[65]

### Pre-and-probiotics

This is another group of agents that has been recently postulated to be involved in the development of insulin resistance and a variety of other deleterious effects. It is being increasingly recognized that there is interplay between the gut flora, energy homeostasis, and inflammation, and that these have a role in the pathogenesis of obesity-related disorders. Several mechanisms have been considered to play a role in this interplay: increased energy from diet, altered fatty acid metabolism, and composition of the adipose tissue and liver are some of them.[66] Chronic low-grade endotoxemia, has also been postulated as a link between gut microbial flora and obesity. This low-grade endotoxemia further induces chronic inflammation. In summation, endotoxemia may play a key role in the pathogenesis of an obesity-associated inflammatory state and the type of food may affect the endotoxin levels.[66]

There is evidence to suggest that there may be quantitative and qualitative differences in the gut microbial flora among lean and obese, and between diabetic and non-diabetic subjects.[67] Modification of the gut flora and / or its biochemical capacity by dietary or pharmacological interventions may favorably affect host metabolism. Short-term clinical trials have shown the benefit of prebiotics and probiotics on insulin sensitivity, inflammatory markers, postprandial incretins, and glucose tolerance.

The fascinating role of gut flora on metabolic disease opens new avenues in the treatment of obesity, insulin resistance, and type 2 diabetes.

### Concerns of safety

Even as the preventive aspect of diabetes may appear as a tremendous opportunity at all levels including those of the population, physician, and planners, in clinical practice, it is limited by the occurrence of a variety of therapy-related side effects, which limit the usefulness. Certain agents are also known to cause serious adverse effects during long-term use.

Another problem area is of long-term adherence to these pharmacological interventions. While a majority of clinical trials demonstrate the benefits of appropriate therapy, they also highlight the issue of non-compliance. In the STOP-NIDDM[30] and XENical in the prevention of Diabetes in Obese Subjects (XENDOS)[42] trials, 30 and 48% of subjects, respectively, did not complete the active intervention. Adherence to therapy has been around 70% in the DPP[24] and DREAM[36] trials. This is probably explained by the lack of tangible benefits for an asymptomatic subject with pre-diabetes, who has to constantly live with obvious adverse effects and the fear of developing frank diabetes.

**Table 6: Medications causing hyperglycemia**

| | |
|---|---|
| Aminophylline | Alpha-interferon |
| Beta-agonists | Caffeine |
| Chlorpromazine | Calcitonin |
| Corticosteroids | Cyclophosphamide |
| Diazoxide | Didanosine |
| Estrogens | Ethacrynic acid |
| Frusemide | Haloperidol |
| Indomethacin | Isoniazid |
| Levodopa | Lithium |
| Morphine | Methyldopa |
| Nicotine | Oral contraceptives |
| Phenothiazines | Phenytoin |
| Pentamidine | Sympathomimetics |
| Theophylline | Thiazides |

### Drugs causing hyperglycemia

Even when focusing on the preventive aspects of diabetes with the use of drugs one should not forget that there are certain drugs that can cause alter the glucose-insulin homeostasis through a variety of mechanisms, some of which are not fully understood. As hyperglycemia is one component of the metabolic changes, it is often seen that a patient already taking some medication for another component like hypertension or dyslipidemia is subsequently found to have an impaired glucose tolerance or frank diabetes. Diuretics and beta-blockers used for the treatment of hypertension, certain statins like rosuvastatin, and many other agents can cause hyperglycemia. Other agents include corticosteroids, niacin, and pentamidine.[68] A list of drugs that commonly cause hyperglycemia is given in Table 6.

## Conclusion

The clinician is faced with many challenges in the prevention and management of type 2 diabetes. Undoubtedly, the first step in diabetes prevention was, is, and will be lifestyle changes, including dietary modifications and increased physical activity. It is also known that a majority of patients have difficulty in sustaining lifestyle changes. Any other intervention, such as the use of pharmacological agents, will therefore follow logically. Although it is easy to add a pharmacological agent, the risks must be balanced by the benefits. The upside is the possibility of delaying or preventing the devastating consequences of diabetes, but at the same time metabolic disturbances beginning at an early age will increase the use of preventive therapy for much longer durations, with issues of long-term compliance and adverse effects, some of them serious.

Currently, the best approach is that the physician devotes enough time to motivate the patient to make suitable and effective lifestyle changes and utilize all the available resources to achieve these goals. Pharmacological management may be indicated if the patient, despite adequate lifestyle changes, is still at a significant risk of developing diabetes and cardiovascular disease.

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