ABSTRACT

Type 2 diabetes (T2DM) is a chronic, debilitating disease characterized by insulin resistance, impaired insulin secretion, and hyperglycaemia. A pathophysiologic hallmark of T2DM is insulin resistance. In T2DM there is impairment of normal biologic response to insulin in the liver and peripheral tissues (insulin resistance), defects in glucagon regulation, and decreased β-cell mass. Glucose intolerance and hyperglycaemia supervene only when the pancreatic β cells are unable to maintain compensatory hyperinsulinemia to overcome tissue resistance to insulin action. It is desirable to maintain the β cell function in order to minimize the complications of hyperglycaemia. Several interventions like early initiation of insulin, use of metformin, incretin mimetics, thiazolidinediones etc. have been proposed to preserve the β cell function.

INTRODUCTION

In its early stages, T2DM takes the form of impaired glucose tolerance or impaired fasting glucose (prediabetes) or both. This is characteristically associated with insulin resistance coupled with a loss of β-cell sensitivity and responsiveness to glucose. The continual exposure of β-cells to hyperglycaemia causes damage that can lead to progressive cellular dysfunction, a process termed “glucotoxicity,” and may contribute to the increase in apoptosis. Most patients with T2DM are overweight, and their increased adiposity leads to dyslipidemia and long-term increases in plasma levels of free fatty acids (FFAs), which, in turn, stimulate gluconeogenesis, induce further insulin resistance in liver and muscle, and diminish insulin secretion. Obesity also causes increases in circulating leptin and inflammatory cytokines, which have been shown to affect β-cell function and survival adversely.

Considerable evidence now indicates that the formation of extracellular islet amyloid polypeptide (IAPP) within the pancreatic islets may be a major cause of increased β-cell apoptosis. At high concentrations, IAPP proteins aggregate and amyloid fibril formation occurs; thus, islet amyloidosis is promoted, results in further glucotoxicity as part of an ever-worsening cycle. The gradual deterioration of glycaemic control over time attributable to the progressive loss of β-cell function and mass remains a major challenge in the management of T2DM. The mechanisms underlying these defects include decreased insulin secretion, increased insulin resistance in muscle cells and the liver, and increased plasma glucose.

STRATEGIES TO PRESERVE BETA-CELL

Ultimate objective in the course of T2DM is to achieve proper metabolic control and minimize the risk for micro and macrovascular complications. Similarly strategies are needed to preserve beta cells (Table 1).

<table>
<thead>
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<th>Table 1: Strategies for preservation of β cells</th>
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<td><strong>Intensive glycaemic control</strong></td>
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<td>Multiple therapeutic strategies</td>
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<td>(diet and exercise; metformin and sulfonylurea)</td>
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<td><strong>Early initiation of insulin therapy</strong></td>
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<td>Continuous subcutaneous insulin infusion</td>
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<td>Low dose short- and long-acting insulin</td>
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<td><strong>Diabetes Prevention Program strategies</strong></td>
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<td>Diet and exercise and/or drugs</td>
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<td>Metformin</td>
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<td>DPP-IV inhibitors</td>
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Intensive glycaemic control:

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glycaemic control plays an important role in the prevention of progressive beta-cell dysfunction and loss. In the Diabetes Control and Complications Trial (DCCT), Epidemiology of Diabetes Interventions and Complications (EDIC) study, intensive therapy in patients with T2DM as shown to reduce the risk for associated complications. Subsequent analysis of the effect of intensive diabetes therapy on long-term reduction in CV risk in patients with type 1 diabetes showed a similar pattern. Thus, findings from these trials clearly show, improved glycaemic control can reduce the risk for, and slow the progression of, microvascular and macrovascular complications.
Whether it is due to preservation of beta cells or due to better control of T2DM is not clear.

Early Insulin Initiation:

Early insulin initiation is the most effective antidiabetic tool, with appropriate dose titration may protect against the progression of β-cell dysfunction in T2DM. Insulin may alleviate glucotoxicity and lipotoxicity, which are known to adversely affect β-cell function. In recent study, individuals who required less insulin therapy during the active treatment phase and who achieved a lower FPG on treatment were more likely to maintain glycaemic control after the cessation of therapy.

Clinical evidence demonstrates the benefit of early intensive insulin therapy in preventing T2DM progression and potentially improving outcomes by maintaining glycaemic control. In the Kumamoto trial, treatment with multiple insulin injections (short-acting prandial insulin and intermediate-acting insulin at bedtime) maintained an A1C of approximately 7.2% for 8 years and prevented the development and progression of microvascular complications.

Timing may be an important factor when initiating insulin to improve β-cell function: early initiation of intensive insulin therapy appears to delay the progression of β-cell dysfunction, while the impact of insulin on β-cell function in established T2DM is less certain. Consequently, there appears to be a window of opportunity for treatment during which intensive insulin therapy may slow or prevent further progression of T2DM.

TREATMENT APPROACH

Current treatment recommendations involve lifestyle changes and metformin treatment followed by additional oral antidiabetic drugs to further delay loss of insulin secretory function and, finally, therapeutic insulin. These, and newer agents, such as incretin analogs and dipeptidyl peptidase-IV (DPP-IV) inhibitors, have been evaluated for effects on β-cell function and insulin sensitivity.

Lifestyle Interventions:

Important therapeutic goal in the T2DM is to achieve and maintain normoglycaemia with initial treatment approach include lifestyle intervention and Metformin. Goals of the lifestyle-modification program included at least a 7% weight loss and at least 150 min of physical activity per week. Both the lifestyle-modification program and metformin delayed the onset of T2DM.

In a study by the Diabetes Prevention Program Research Group in US adults it is found that patients randomized to the lifestyle intervention experienced the greatest improvement in insulin sensitivity and the best preservation of β-cell function after 1 year, compared to placebo group. Similar results were also found in the Indian Diabetes Prevention Program Study.

Oral hypoglycaemic agents (OHAs) and β-Cell Function:

Antidiabetes therapy conventionally reduce the microvascular complications of T2DM, however effect of these therapy on macrovascular complication has not been unequivocally established. Oral therapy is effective early during the course of T2DM but most patients ultimately require insulin because of progressive β-cell failure. Most of these agents are effective at lowering glucose concentrations and lower A1C levels by about 1% to 2%, with greater improvements typically occurring with higher initial levels of A1C, but frequent adverse effects associated with these medications are hypoglycaemia (sulfonylurea, meglinides), gastrointestinal (GI) side effects (biguanides, α-glucosidase inhibitors), weight gain (sulfonylurea, thiazolidinediones), and fluid retention (thiazolidinediones).

Despite their efficacy, none of these agents has been shown to prevent the progression of the disease itself. Several published trials have suggested that some orally administered hypoglycaemic agents (OHAs) may slow the progression of pre-diabetes to overt diabetes, durability of glycaemic control with OHAs in patients with T2DM is limited, with a thiazolidinedione.

Novel agents and future trends:

The present unmet need is for more effective agents capable of not only treating the disease but also preventing its progression and associated complications with compliance and safety. One new approach to achieve long term efficacy focuses on the effects of GLP-1, which maintains the capacity of β-cells to synthesize and secrete insulin in response to glucose, increase β-cell mass, and suppresses glucagon secretion, all of which help to decrease glucose levels. Furthermore, there is evidence that GLP-1 analogues may additionally reduce systolic blood pressure and triglyceride levels.

Incretin-analogs: Insulin secretion associated with two gut hormones, GIP and GLP-1, that enter the circulation in response to the absorption of glucose and other nutrients, powerfully augment glucose induced insulin secretion and aid in the maintenance of glucose metabolism. GLP-1 is the incretin that has the greatest therapeutic relevance in T2DM, has a short circulating half-life because it is rapidly inactivated by the photolytic enzyme DPP-IV.

Incretin analogs, such as exenatide and liraglutide, and DPP-IV enzyme inhibitors, such as sitagliptin and vildagliptin, have the potential to improve and prevent the progression of β-cell dysfunction by restoring glucose–dependent insulin secretion and may improve associated risk factors and morbidities such as overweight and obesity. In long term studies found that, GLP-1 agonists have increased β-cell mass by stimulating β-cell proliferation, inducing islet neogenesis and inhibiting β-cell apoptosis.

DPP-IV Inhibitors: DPP-IV inhibitors, act by slowing the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose–dependent insulinotropic peptides (GIP), may promote β-cell proliferation and neogenesis and inhibit apoptosis. In patients with T2DM, DPP-IV inhibitors have provided incremental improvements in A1C, increased postprandial insulin secretion, C-peptide, β-cell responsiveness and HOMA-b. All of these agents appear to be effective in improving glycaemic control, but is unknown whether they will have an impact on
the course of the disease or associated micro and macrovascular complication. Recent preliminary clinical data support a role for DPP-IV inhibitors in improving β-cell function in T2DM patients, sitagliptin, vildagliptin have successfully developed for clinical use, liiraglutide and mitiglinide are likely to reach market next, although further clinical trials may be required.

ACE-Inhibitors: Meta-analysis and recent clinical study angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduced the incidence of diabetes by approximately 25% by improving delivery of insulin, glucose transport, insulin signaling and enhanced insulin secretion by β-cells. ACE inhibitors and ARBs may attenuate the harmful effect of angiotensin II on vasoconstriction, inflammation, fibrosis, apoptosis and β-cell death, thus preserving β-cell mass. Additional research is needed to clarify the mechanisms underlying the beneficial impact of inhibition of the renin-angiotensin system in reducing a diabetes risk.

Cytokine suppressors: IL-1b is a proinflammatory cytokine implicated in β-cell dysfunction and apoptosis. Elevated glucose concentrations stimulate production of IL-1b in pancreatic β-cells, resulting in impaired insulin secretion, decreased cellular proliferation and apoptosis. In a study by Larsen CM et al., it is found that anakinra (recombinant human IL-1ra; Amgen) 100 mg subcutaneously once daily significantly decrease in A1C, increase in C-peptide secretion and a reduction in the insulin-proinsulin ratio compared with the placebo.

K⁺ Channel activators: Activation of β-cell ATP-sensitive K⁺ (K⁺ATP) channel selectively using diazoxide and the new selective K⁺ATP channel opener NN414 has been shown to preserve insulin stores and insulin secretion, thereby protecting β-cells from chronic overstimulation and improving β-cell function. Preliminary data by Bjork E et al and Ortqvist E etal indicate that the beneficial effects of these agents may partly relate to their anti-apoptotic effects. By contrast, the closure of K⁺ATP channels by sulfonylurea may induce β-cell apoptosis.

These therapies are experimental and further clinical trials are needed to completely ascertain therapeutic benefits, risks and uses for these agents.

BARIATRIC SURGERY:

Bariatric surgery for weight loss is an emerging option for severely diabetic obese patients. Weight loss occurs with gastric volume reduction, intestinal malabsorption or a combination of the two. Obese patient has been shown to delay or prevent the onset of diabetes in those with prediabetes or IGT. Bariatric surgery prevents T2DM in 99-100% of patients with IGT, and resolved diabetes symptoms in 64-93% of patients. The benefits to β-cell function appear to be greatest when weight loss is achieved before β-cell function is completely impaired. Restoration of first-phase insulin release and normalization of insulin sensitivity was associated with a 46% reduction in body weight 1 year following bariatric surgery. Still it is not clear that weight loss is the sole reason for normalization of glucose concentrations.

CONCLUSIONS

The T2DM involve a progressive failure of β-cell function, often associated with insulin resistance and glucagon hypersecretion, difficult puzzle to those managing this disease is microvascular and macrovascular complications associated with it. Recently, trials have highlighted the importance of initiating therapy sooner and more aggressively, tight glycaemic control is strongly associated with the prevention of common complications of diabetes, including CVD. Professional associations have responded to such findings by issuing newer, more stringent guidelines to combat this perceived clinical inertia. Incretin hormones offer an expansion of therapeutic options that may help to regulate many aspect of glucose metabolism, contribute to improved glycaemic control, and preserved β-cell function.

GLP-1 analogues and DPP-4 inhibitors promises to provide important new strategies to improve therapy for diabetes, use of GLP-1-based therapies early in the course of type 2 diabetes may even delay disease progression by arresting the otherwise inevitable deterioration of β-cell function and mass. The enhanced understanding of the pathophysiologic aspects of T2DM that has evolved in recent years will be essential in the design of new pharmacologic agents that can help to achieve and maintain optimal glycaemic control in patients with T2DM and that may even be able to slow the progression or prevent the disease.

REFERENCES

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