Diabetes mellitus is a large and growing public health problem, and has emerged as a major worldwide epidemic. Type 2 diabetes mellitus is increasingly recognized as a cardiovascular disorder due to its contributory role to the development of atheroscleropathy. It is now widely considered a component of a group of disorders called the metabolic syndrome – a cluster of metabolic and cardiovascular abnormalities characterized by abdominal obesity, atherogenic dyslipidaemia, elevated blood pressure, insulin resistance (impaired glucose tolerance [IGT] and/or type 2 diabetes), as well as a prothrombotic and proinflammatory state, all of which – either individually or collectively – predispose to the development of atherosclerosis and an increased risk of cardiovascular morbidity and mortality.

Prediabetes - The New Target for Primary Prevention of Cardiovascular Metabolic Dysfunction

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It is estimated that more than 20% of overweight adults have prediabetes.
It is now increasingly recognized that some features of the metabolic syndrome are prevalent in the “prediabetic state” - an intermediate phase of altered glucose metabolism preceding the development of type 2 diabetes mellitus, which is characterized by the presence of IGT and/or impaired fasting glucose (IFG). Insulin resistance and central obesity are regarded as important risk factors for cardiovascular diseases in the prediabetic population. An elevated level of circulating free fatty acids (FFA), which is highly prevalent in the insulin-resistant state and obesity, causes further progression of hyperglycaemia, increases the formation of smaller, denser, more atherogenic low-density lipoprotein (LDL) particles and impairs insulin secretion, thereby contributing to the accelerated prevalence of type 2 diabetes and cardiovascular diseases in susceptible prediabetic patients. In addition, cytokines produced by central adipocytes such as interleukin-6 (IL-6), tumour necrosis factor (TNF)-α and plasminogen activator inhibitor-1 (PAI-1) are proinflammatory mediators for atherosclerosis. Early detection of prediabetes and intervention have therefore been a focus of recent research for the prevention of cardiovascular diseases in addition to type 2 diabetes mellitus. This article aims to provide an overview of the prediabetic state and the significance of early detection and intervention in this patient population. The benefits of lifestyle modification and pharmacological intervention, including oral hypoglycaemic agents, insulin sensitizing agents and lipid-lowering agents in the prediabetic population are also discussed.

The unremitting medical and socioeconomic burden of type 2 diabetes and its complications has become one of the major public health challenges of the 21st century. The number of type 2 diabetics worldwide is projected to rise from the current estimate of 125 million to 221 million by 2010, and to 300 million by 2025. This rising prevalence of type 2 diabetes mellitus is seen not only in adults, but now also more frequently in children and adolescents. The major contributors to the early development of type 2 diabetes appear to be obesity and a rise in insulin resistance, preceding the onset of the metabolic disorder. Progression from normal glucose homeostasis to overt type 2 diabetic hyperglycaemia in adults involves an intermediate phase of altered glucose metabolism referred to as “prediabetes”, or the glucose-intolerant state. Increased insulin resistance and decreased insulin secretion both contribute to the abnormal glucose homoeostasis (dysglycaemia) in the prediabetic condition. However, insulin resistance, rather than impaired pancreatic β-cell function, is believed to account for most of the pathologic conditions that may be present in prediabetes. Several studies have suggested that dysglycaemia is a continuous risk factor for cardiovascular disease. In the Rancho Bernado study involving 3,458 non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L. A recent systematic review and meta-regression analysis of published cohort studies on non-diabetic subjects, the age-adjusted mortality rates for ischaemic heart disease were increased by approximately two-fold in men as their fasting glucose level increased from 5 to 7 mmol/L.
It has therefore been suggested that glucose levels within the nondiabetic range may still be associated with increased risks of macrovascular diseases, and that the risk of cardiovascular diseases sets in at the prediabetic state. An epidemiological study using data from the US Third National Health and Nutrition Examination Survey (NHANES III) estimated that in 2000, 22.6% of overweight adults aged 45 to 74 years had prediabetes. It was established from the survey that the prevalence of cardiovascular risk factors was high among prediabetic individuals: 94.9% had dyslipidaemia, 56.5% had hypertension, 13.9% had microalbuminuria and 16.6% were current smokers. Prediabetic individuals, particularly the insulin-resistant subjects, have also been shown to have elevated proinflammatory profiles, in addition to other conventional cardiovascular risk factors such as obesity, hypertension and dyslipidaemia. The prediabetic population has thus emerged as a potential target for the prevention of cardiovascular diseases in addition to type 2 diabetes mellitus.

The Prediabetic State

The prediabetic condition is characterized by an impaired glucose regulation in the body, reflected by plasma glucose concentrations that are clearly above normal but fall short of the diagnostic values for diabetes. Impairment in glucose homeostasis can be classified into three subcategories: (1) IFG; (2) IGT; and (3) combined IFG and IGT. Isolated IFG, defined as a fasting plasma glucose level of 6.1 to 6.9 mmol/L (110-126 mg/dL), occurs either due to the inability of the body to maintain adequate basal insulin secretion, or a decreased insulin sensitivity in the liver, leading to an elevated hepatic glucose output. On the other hand, IGT, diagnosed when the plasma glucose reaches a level between 7.8 and 11.0 mmol/L (140-200 mg/dL) 2 hours postigestion of a 75 g glucose load, is primarily associated with peripheral insulin resistance, particularly at the level of skeletal muscle, the primary depot for postprandial glucose disposal. Insulin resistance is a physiologic state in which the normal amount of insulin produces a subnormal physiologic response. It is believed to be the first metabolic derangement to appear in terms of time. The pancreatic β cells normally compensate for the insulin-resistant state by increasing basal and postprandial insulin secretion. However, over a period of time, the pancreas fails to sustain the compensatory hyperinsulinaemia, leading to deterioration in glucose homeostasis and the development of glucose intolerance or early diabetes.

Insulin resistance is regarded as one of the important factors associated with cardiovascular diseases, in concert with other metabolic and cardiovascular abnormalities such as abdominal obesity, dyslipidaemia, elevated blood pressure as well as the prothrombotic and proinflammatory state, jointly referred to as the “metabolic syndrome”.

Insulin resistance contributes to the process of atherogenesis in a number of ways. Hyperinsulinaemia induced by insulin resistance causes elevated levels of circulating FFA, which are involved in the synthesis of very low-density lipoprotein (VLDL). Increased levels of VLDL particles accentuate cholesterol delivery to the atherosclerotic plaques. In addition, insulin resistance induces chronic hyperglycaemia, leading to the formation of advanced glycation end-products (AGEs), which in turn modify apolipoprotein B, a component of LDL cholesterol. This leads to a reduction in the affinity of LDL particles for their receptors in the liver. The subsequently prolonged half-life of the modified LDL particles (smaller and denser) makes them more likely to undergo oxidation and be taken up by scavenger receptors on macrophages in the vascular wall, contributing to the formation of atherosclerotic plaques.

Insulin resistance at the level of adipose tissues results in an elevated lipolysis rate and thus an increased level of circulating nonesterified free fatty acids (NEFAs), the latter of which lead to further progression of hyperglycaemia (via reduction in hepatic and skeletal muscle glucose uptake, and increased gluconeogenesis), and increased formation of triglyceriderich VLDL. In addition, NEFAs are toxic to the pancreas, and chronic excessive delivery of NEFAs to the pancreatic β cells impairs insulin secretion, contributing to the development of type 2 diabetes in susceptible prediabetic individuals.

Obesity is also known to induce and exacerbate insulin resistance. Body fat accumulation has recently been identified as an important factor that increases cardiovascular risks. Several studies have recently demonstrated that visceral fat accumulation is more strongly linked to the development of diabetes and coronary artery diseases compared with peripheral fat depots (gluteal/subcutaneous). In a recent study involving 271 Japanese men (IGT, n=123; controls, n=148), increased visceral fat was related to an
increase in blood pressure and serum triglyceride, as well as worsening of insulin resistance. Central adipocytes are believed to be a major source of cytokines such as IL-6, TNF-α and PAI-1, which are proinflammatory mediators of atherosclerosis.15-18

Another important factor mediating the atherosclerosis process is the activation of subclinical inflammatory response in relation to insulin resistance. The Insulin Resistance Atherosclerosis Study (IRAS) found that insulin resistance, as determined by the frequent sampled intravenous glucose tolerance test (FSIGT), was significantly correlated with high levels of inflammatory markers, including C-reactive protein (CRP), fibrinogen and PAI-1. Potential mechanisms that may explain the relationship between chronic inflammation and insulin resistance include hypersecretion of proinflammatory cytokines (e.g. IL-6, TNF-α) from adipose tissues, as well as the unopposed augmentation of hepatic inflammatory proteins as a result of decreased insulin sensitivity in the liver.22

Insulin resistance arises from a defect in the insulin signal transduction process. Inhibition of insulin signalling can occur at the insulin receptor level, or downstream at the postreceptor site. The various abnormalities in signal transduction mechanisms that have been implicated in the pathogenesis of insulin resistance include alterations in insulin-receptor autophosphorylation, decreased tyrosine kinase activities, marked reduction in the expression of insulin receptor substrate (IRS-1) (docking proteins regulating the insulin signal) and defects in the expression and/or activation of glucose transport molecules (GLUT4) in skeletal muscles.25

Insulin resistance is also strongly linked to obesity. Adipocytes express and secrete various peptide hormones and cytokines including TNF-α and leptin. Elevated levels of TNF-α in obese individuals inhibit lipogenesis and increase lipolysis, leading to an increased level of circulating FFA. Elevated FFA levels impair the ability of insulin to suppress hepatic glucose output, cause a defect at the level of muscle glucose uptake, and induce apoptosis of the pancreatic β-cells, leading to an accelerated progression to overt diabetes. TNF-α signalling and elevated FFA levels also directly block the cellular insulin signalling mechanism, in part through serine phosphorylation of IRS-1, resulting in decreased expression of GLUT4 molecules and, subsequently, reduced peripheral glucose uptake.26

Leptin deficiency is another contributory factor for the development of insulin resistance. Leptin, an adipocyte-derived peptide hormone, has a central and peripheral insulin sensitizing effect. A recent study has shown that Q223R polymorphism at the leptin receptor gene is associated with insulin resistance in normotensive nondiabetic subjects.27

Another important factor mediating insulin resistance is the peroxisome proliferator-activated receptor gamma (PPAR-γ), an adipocyte-predominant transcription factor that regulates genes involved in glucose and lipid homoeostasis. Patients with a dominant-negative mutation in the PPAR-γ gene exhibit severe insulin resistance and hyperglycaemia. Much of the evidence relating this transcription factor to insulin resistance has been inferred from indirect observation of the effect of the PPAR-γ agonists in improving glycaemic profiles and other features of the metabolic syndrome among type 2 diabetic patients. The PPAR-γ synthetic agonists (thiazolidinediones [TZDs]) improve glucose homoeostasis by directly activating genes of the glucose-sensing apparatus in the liver and pancreatic β-cells, as well as reducing circulating FFA levels in the plasma.29

Apart from cellular factors, insulin resistance is also associated with ageing and sedentary lifestyle. In addition, the susceptibility to insulin resistance is itself the result of a complex pattern of inheritance. In this era of preventive medicine, the population at high risk of developing diabetes and associated cardiovascular complications has become an emerging area of research. Among the high-risk groups are individuals genetically...
predisposed to type 2 diabetes mellitus, i.e. first-degree relatives of type 2 diabetic patients (FDRs). FDRs have a 40% lifetime risk of developing diabetes, and an increased cardiovascular risk compared with individuals without a family history of type 2 diabetes. They are characterized by being insulin-resistant, having impaired first-phase insulin secretion, visceral obesity, elevated systolic blood pressure, dyslipidaemia (low levels of high-density-lipoprotein [HDL]-cholesterol, high levels of triglycerides and LDL-cholesterol levels), reduced aerobic fitness, and impaired endothelial function, all of which could individually or collectively contribute to an accelerated rate of atherosclerosis. In addition, glucose-tolerant subjects with genetic predisposition to type 2 diabetes have also been shown to have an increased intima-media thickness of the common carotid artery, a surrogate marker for coronary atherosclerosis.

Considering the substantial risk for developing diabetes and cardiovascular diseases, great emphasis is being placed on the holistic management of prediabetic patients and those genetically predisposed to type 2 diabetes mellitus, in order to reduce the economic and medical burden associated with these conditions.

**Therapeutic Interventions in the Prediabetic Population**

Emerging data suggest that insulin resistance and other components of the metabolic syndrome may be inter-related. Collectively, they contribute to an accelerated development of atherosclerosis and vascular complications. Therefore, any interventions in the prediabetic population that ameliorate insulin resistance, protect the pancreatic β cells and improve other components of the metabolic syndrome will ultimately reduce the risk of developing diabetes and cardiovascular diseases. There is now strong evidence suggesting that the onset of diabetes in IGT individuals can be delayed or prevented by both lifestyle and pharmacological interventions. Current management guidelines for individual components of the insulin resistance syndrome emphasize lifestyle modification (weight loss and physical activity) as first-line therapy. However, adjunct drug therapy may be necessary in many prediabetic patients to achieve and maintain their recommended therapeutic goals.

**Benefits of Lifestyle Interventions in the Prediabetic Population**

Physical exercise confers both immediate and long-term benefits in regulating plasma glucose in the body. The immediate effect of exercise in regulating plasma glucose is likely to be due to the contractile activities of the skeletal muscles, which enhance peripheral glucose uptake through activation of the glucose transport protein GLUT4. A recent study has shown that immediately after a single bout of exercise, plasma levels of membrane GLUT4 protein in vastus lateralis muscles of type 2 diabetics have increased by 74% ± 20% from baseline, similar to the postexercise increment seen in nondiabetic individuals (71% ± 18%). Hughes et al demonstrated a 24% increase in skeletal muscle glycogen and a 60% increment of GLUT4 concentration in IGT subjects after 12 weeks of exercise training at 70% of the subjects' heart rate reserve. In addition, 24 hours after a single session of exercise in type 2 diabetics, a significant enhancement of the insulin receptor's tyrosine phosphorylation and IRS-1 protein was observed in the skeletal muscles. This may also contribute to an increased translocation...
and activation of GLUT4 proteins, leading to a more efficient peripheral glucose uptake.

Apart from altering the insulin-signalling pathway, regular physical activity also promotes other physiological benefits, including greater cardiac output, better blood pressure regulation and endothelial function, as well as normalization of lipid profile. Exercise conditioning may also have antithrombotic effects by reducing plasma fibrinogen and fibronectin in type 2 diabetes. The indication of exercise prescription in diabetics is strengthened by the fact that low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause mortality in men with type 2 diabetes mellitus. It has been shown that diabetic men with low fitness have a 2.1-fold increase in all-cause mortality compared with the aerobically fit diabetics. Since many cardiovascular risk factors may already be prevalent in prediabetic patients, simple and appropriate lifestyle modifications should be strongly advocated in this subgroup of population, as part of the strategies to prevent or delay the onset of type 2 diabetes mellitus and its metabolic consequences.

There are three large randomized, controlled trials on intensive lifestyle intervention in the prediabetic populations that are worth referring to: the Chinese Da Qing IGT and Diabetes Study, the Finnish Diabetes Prevention Study (FDPS) and the American Diabetes Prevention Program (DPP). In the Da Qing study conducted in 1996, a total of 530 Chinese subjects with IGT were successfully followed up over a 6-year period for progression to type 2 diabetes. Subjects were randomized to either the control group or one of three lifestyle intervention groups: diet, exercise, and diet plus exercise. The cumulative incidence of diabetes at 6 years was 67.7% in the control group, compared with 43.8% in the diet group, 41.1% in the exercise group and 46% in the diet-plus-exercise group. In this series, diet, exercise and diet-plus-exercise interventions were associated with a 31%, 46% and 42% risk reduction in developing diabetes, respectively.

The benefits of physical activity and weight loss programme in preventing diabetes were further elucidated by the other two large prospective studies. The FDPS revealed a 58% reduction in the cumulative incidence of diabetes in the intervention group (comprehensive dietary plan aimed towards ≥5% weight loss, and endurance exercise programme), compared with the control group after an average follow-up of 3.2 years. The more recent, larger randomized DPP clinical trial compared the efficacy of lifestyle modification with basic pharmacological interventions in 3,234 prediabetic US populations. Subjects were randomized to one of three intervention arms: placebo; metformin (850 mg twice daily); and intensive lifestyle modification programme with goals of at least 7% weight loss and 150 minutes of physical activity per week. Participants were followed up for an average of 2.8 years. The data showed a similarly effective diabetes prevention rate in the lifestyle intervention group and the metformin group, with a 58% and 31% lower incidence of diabetes, respectively, compared with the placebo group.

Since obesity has been proven to be closely linked to insulin resistance and type 2 diabetes, it has been hypothesized that adding a weight-reduction agent on top of lifestyle changes may lead to an even greater decrease in body weight, and thus in the incidence of type 2 diabetes in obese patients. This has been explored by a double-blind, randomized, placebo-controlled, prospective study involving 3,305 Swedish patients – the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study. Patients were randomized to lifestyle changes plus either orlistat (a gastrointestinal lipase inhibitor, at a dose of 120 mg) or placebo three times daily. Primary endpoints were time to onset of type 2 diabetes and change in body weight. After 4 years of treatment,
the cumulative incidence of diabetes was 9% with placebo and 6.2% with orlistat, corresponding to a significant risk reduction of 37.3%. Mean weight loss after 4 years was also greater with orlistat (5.8 kg vs. 3 kg with placebo).

These prospective, large-scale studies demonstrated that adherence to intensive, controlled lifestyle modification programmes renders a range of benefits in the primary prevention of type 2 diabetes. The addition of pharmacological agents to facilitate weight loss has also been proven to significantly delay or prevent the onset of diabetes, particularly in high-risk obese individuals.

**Role of Pharmacological Agents in the Primary Prevention of Type 2 Diabetes**

Metabolic syndrome is a multifaceted disorder, which requires an integrated therapeutic approach targeted at the collective components of the syndrome to reduce the risk of developing type 2 diabetes and cardiovascular diseases. Whilst behavioural interventions (diet and exercise) have been proven to be reasonably effective in achieving this goal, adherence to drastic lifestyle changes can be difficult, and many prediabetic patients require additional pharmacological therapy as part of the multifactorial intervention. Pharmacological management of the traditional cardiovascular risk factors such as hypertension, obesity, dyslipidaemia and insulin resistance, which are integral components of the metabolic syndrome, is of paramount importance in preventing stroke or coronary artery disease in prediabetic individuals. Previous studies on the role of pharmacological therapy in the prediabetic population have primarily focused on three aspects: (1) the effect of glycaemic management in the primary prevention of type 2 diabetes; (2) the effect of insulin-sensitization on various atherogenic and metabolic profiles; and (3) the effect of lipid-lowering therapy in slowing down the progression of atherosclerosis.

**Oral Hypoglycaemic Agents in Diabetes Prevention**

It has been shown that adequate glycaemic control with metformin, a novel oral hypoglycaemic agent, in the prediabetic state resulted in a 31% risk reduction of developing type 2 diabetes compared with placebo.45

Insulin resistance is often reflected by postprandial hyperglycaemia resulting from the loss of early insulin secretion.46 Effective meal-time glucose regulators have been proven beneficial in preventing overt hyperglycaemia in the prediabetic population. The STOP-NIDDM trial48 has shown that acarbose, an α-glucosidase inhibitor for reducing postprandial hyperglycaemia, contributed to a 36% risk reduction of diabetes in IGT subjects (n=1429). The study was later extended to evaluate the risk of developing cardiovascular disease. It was found that treatment with acarbose in the prediabetic stage also resulted in a 49% relative risk reduction and a 2.5% absolute risk reduction in the development of cardiovascular disease.49 It was projected that 40 IGT patients need to be treated for 3.3 years to prevent one cardiovascular event. Furthermore, acarbose treatment also resulted in a significant decrease in blood pressure, with a 34% relative risk reduction and a 5.3% absolute risk reduction in the incidence of new cases of hypertension.

Another class of drugs that selectively enhance early meal-induced insulin secretion is insulin secretagogues (e.g. nateglinide). The beneficial effect of intensive postprandial glycaemic control with insulin secretagogues in preventing type 2 diabetes and ameliorating cardiovascular risks is being evaluated in the ongoing Nateglinide And Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) trial.50 This will be the largest diabetes prevention trial to date, involving 7,500 IGT subjects, randomized into four treatment arms: nateglinide (60 mg before main meals), valsartan (160 mg daily), a combination of both or placebo. The study will be carried out in two phases over an estimated period of nearly 6 years, and the results are to be announced by 2007. The first phase of the study is designed to evaluate the effect of nateglinide and valsartan on progression to type 2 diabetes over a 3-year period after recruitment of the last subject, and the second phase will evaluate the effects of the drugs on the incidence of cardiovascular events. The NAVIGATOR trial will determine whether restoration of early-phase insulin secretion and improvements in insulin sensitivity slow down progression to type 2 diabetes and prevent cardiovascular disease in the high-risk prediabetic population.

Insulin-sensitizing Agents in Diabetes Prevention

Since insulin resistance appears to be one of the important mechanisms in the pathogenesis of atherosclerotic disease, there has been a growing research interest in the effect of insulin sensitization on atherogenic profiles. The recent focus is on
TZDs, as their insulin-sensitizing property is believed to exert many potential benefits on a range of atherosclerotic mechanisms. Data from preclinical and clinical studies have been promising, demonstrating the cardioprotective effect of the drugs. TZDs (only rosiglitazone and pioglitazone are currently on the market) are a class of oral anti-diabetic agents that controls hyperglycaemia by directly targeting insulin resistance. The TZDs directly decrease insulin resistance by binding to and activating the PPAR-γ in insulin-sensitive tissues, including adipocytes, skeletal muscle and liver. Apart from established evidence on their effectiveness in lowering glucose, emerging data suggest TZDs also ameliorate a number of cardiovascular risk factors. Rosiglitazone therapy has been shown to increase HDL-cholesterol and decrease the proportion of small, dense LDL particles relative to the larger, less atherogenic ones.TZDs may provide supplementary antihypertensive effects when used as an adjunct to conventional antihypertensive medications. Both rosiglitazone and troglitazone have been reported to reduce ambulatory diastolic blood pressure significantly in patients with type 2 diabetes. In addition, treatment with rosiglitazone reduced urinary albumin excretion in type 2 diabetic subjects, demonstrating its microvascular protective effect. The antiatherogenic properties of TZDs were further elucidated by preclinical findings suggesting that they suppress nuclear factor kappa B (NFκB), a molecule that induces inflammatory cytokines such as monocyte chemoattractant protein-1, TNF, adhesion molecules and reactive oxygen species. Clinically, rosiglitazone has been shown to be effective in decreasing plasma concentration of CRP in diabetics. Additionally, diabetic patients treated with pioglitazone had significant reductions in carotid artery intima-media thickness. In another preclinical study, troglitazone inhibited matrix-degrading metalloproteinase-9 (MMP-9) activity in human monocytes and macrophages, thus aiding the stabilization of atherosclerotic plaques. In patients with type 2 diabetes, the addition of rosiglitazone to sulfonylurea therapy has led to a 34% reduction in PAI-1 activity as compared with sulfonylurea treatment alone. TZDs also inhibit oxidized LDL-induced expression of adhesion molecules, including intercellular adhesion molecule 1 (ICAM-1), E-selectin and vascular cell adhesion molecule 1 (VCAM-1), thus minimizing leukocyte penetration into the endothelial layer and reducing atherosclerotic plaque formation. TZDs may also address the problem of central obesity, an integral characteristic of the metabolic syndrome. Several studies have indicated that TZDs induce the redistribution of fat from the central compartment to the periphery, reducing the atherogenicity caused by visceral fat accumulation in the body.In summary, research data have so far suggested TZDs are a valuable group of drugs for improving atherogenic profiles and one of the treatment approaches in type 2 diabetes. However, there is still insufficient evidence from prospective clinical studies on their effects on reducing cardiovascular risk in the prediabetic state. Thus, the indication of these drugs in prediabetic patients for the prevention of atherogenesis and diabetes remains unclear, and needs to be further supported by long-term outcome studies. An ongoing prospective clinical study that addresses this issue is the Diabetes Reduction Approaches with ramipril and rosiglitazone Medications (DREAM) trial. This 3-year project will involve 4,000 IGT patients. The primary objectives of the study are to evaluate the efficacy of rosiglitazone in improving insulin sensitivity, as well as to determine whether rosiglitazone or ramipril, as monotherapy or in combination, can delay or prevent the progression to type 2 diabetes in high-risk patients. The secondary endpoints are microvascular endpoints and a multitude of adjudicated cardiovascular endpoints, including the incidence of myocardial infarction (Q-wave MI, non-Q wave MI and silent MI), cardiovascular death or revascularization and congestive heart failure. The study results are expected to be presented by 2006. Results from such large studies may dramatically alter the treatment approach in the prediabetic population.

Lipid-lowering Therapy for Prevention of Diabetes and Atherosclerosis

Prediabetic patients with insulin resistance syndrome exhibit a characteristic dyslipidaemia, which includes smaller and more atherogenic LDL particles, high triglyceride levels and low HDL-cholesterol levels. There are well established data demonstrating the beneficial effects of lipid-lowering therapy in preventing coronary events in type 2 diabetes. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are a group of lipid-lowering agents well studied for their cardioprotective effects. The beneficial effects of statins can be ascribed not only to...
their ability to lower cholesterol level that improves lipid profiles, but also to their vascular modulatory and anti-inflammatory actions independent of their cholesterol-lowering effect. Treatments with statins have been shown to improve endothelial function, reduce proinflammatory cytokines and inhibit platelet aggregation and adhesion.68 The Heart Protection Study (HPS) revealed a 26% reduction in first major vascular event in diabetics without history of coronary disease after 5 years of daily treatment with 40 mg simvastatin.67 Recently, interest has focused on the beneficial effects of statins well before the onset of type 2 diabetes mellitus. A recent study by Economides et al has shown that short-term (12 weeks) daily treatment with 20 mg atorvastatin improved endothelial function (increased flow-mediated dilation from 6.6% to 7.2%, p<0.05) and decreased levels of vascular inflammatory markers such as CRP (from 0.24 to 0.12 mg/dL) and TNF-α (from 4.4 to 2.6 pg/mL) in subjects at risk of developing type 2 diabetes.69 Our group has also observed similar findings: we have demonstrated a significant improvement in endothelial-dependent vasodilatation in a much younger, normotensive, normoglycaemic FDR population after only 4 weeks of treatment with atorvastatin (80 mg).70 These findings add support to the use of statins in the prediabetic population beyond their lipid-lowering benefits.

**Conclusion**

Prediabetes signifies an intermediate stage between normal glucose homoeostasis and overt type 2 diabetes. The prediabetic population represents a new target group for primary prevention of type 2 diabetes and its associated constellation of cardiometabolic abnormalities known as the metabolic syndrome. Insulin resistance, an integral part of this syndrome, has been regarded as an important mechanism in the genesis of various metabolic and vascular abnormalities, mediating the process of atherosclerosis and other cardiovascular dysfunction. Early screening for prediabetes, followed by appropriate therapeutic interventions, may have considerable benefits in preventing type 2 diabetes and cardiovascular diseases. Lifestyle intervention is currently recommended as first-line therapy in the management of insulin-resistant prediabetic individuals, based on a large body of evidence generated by prospective clinical trials. In addition, intensive glycaemic control with conventional oral hypoglycaemic drugs or newer insulin-sensitizing agents may have benefits in the primary prevention of type 2 diabetes and its cardiovascular complications. There are also promising data indicating a cardioprotective effect of lipid-lowering agents such as statins, and this may form the basis for future indication in prediabetic individuals. Results from many ongoing large prospective studies may alter current management approach for individuals at high risk of developing type 2 diabetes.

**References**

Practice Points

- IFG is defined as a fasting plasma glucose level of 6.1 to 6.9 mmol/L (110-126 mg/dL); IGT is diagnosed when the plasma glucose reaches a level between 7.8 and 11.0 mmol/L (140-200 mg/dL) 2 hours postigestion of a 75 g glucose load.

- Lifestyle intervention remains the current first-line therapy in prediabetic individuals. Simple and appropriate lifestyle modifications should be strongly advocated for these patients.

- In high-risk obese patients, lifestyle changes plus a weight-reduction agent may delay or prevent the onset of diabetes.

- Effective meal-time glucose regulators have been proven beneficial in preventing overt hyperglycaemia in the prediabetic population.

- Data from preclinical and clinical trials suggest TZDs are effective in improving atherogenic profiles; however, their use in prediabetic patients needs further elucidation.

- Recent studies support the use of statins in the prediabetic population beyond their lipid-lowering benefits.


