Present recommendations in type 2 diabetes treatment

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Recommendations for the treatment of type 2 diabetes have been made by many organizations and expert committees. The so-called "ADA/EASD Consensus Algorithm on the Treatment of Type 2 Diabetes" after several revisions shows two tiers of treatment: Tier 1 based on a "well validated core therapy" and Tier 2 "less well validated therapies"[1]. Tier 1 uses lifestyle, metformin, sulfonylureas, and basal or intensive insulin therapy all of which were in use during 1970s through the 1990s and were neither supported by large, well controlled clinical trials nor shown to result in long-term glycated hemoglobine (A1C) < 7 %[2]. Tier 2 allows the use of pioglitazone but not rosiglitazone; glucagon-like peptide 1 (GLP-1) agonist but not dipeptidyl peptidase 4 (DPP-4) inhibitors; no glitinides and no alpha-glucosidase inhibitors. An algorithm proposed for Korea suggests testing patients with type 2 diabetes for insulin resistance by a short insulin tolerance test and insulin secretion by plasma C-peptide levels[3]. Patients with predominately insulin deficiency are recommended for treatment with lifestyle + insulin producing regimens and patients with predominately insulin resistant with lifestyle + insulin-sensitizing regimens. The Canadian Guidelines for Diabetes Management recommend treatment based on A1C < 9.0 %; ≥ 9.0 %; and symptomatic hyperglycemia with metabolic decompensation[4]. First step therapy is lifestyle + metformin; lifestyle + metformin + another agent; lifestyle + metformin + insulin respectively. If step 1 does not achieve target A1C then any other pharmacologic agents can be added depending on the advantages and disadvantages for the individual patient. The American Association of Clinical Endocrinologist have created three roadmaps depending on whether the patient has prediabetes, newly diagnosed diabetes or established diabetes[5]. Within each roadmap, the specific treatment recommendations are based on presenting A1C, and the degree of fasting and postprandial glucose excursions.

It is obvious that all of the algorithms proposed are based on the expert opinions of the members of the various panels making the recommendations. When the literature is carefully examined it becomes apparent that there are relatively few long-term, randomized, controlled comparative trials of the treatment of patients with type 2 diabetes. An additional complication which has recently been identified is that the clinical benefits of therapy are dissociated from surrogate markers of benefits such as A1C by duration of known diabetes[6,7], previous clinical vascular complications[8] and history of previous glycemic control[8-10].

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Thus, it would appear that a treatment scheme based on matching the patient's pathophysiology with the pharmacology of the various therapeutic agents might provide a better guide to the treatment of type 2 diabetes than the various expert committee's opinions.

Figure 1 illustrates that type 2 diabetes is a disease of the beta cell. The underlying abnormalities appear to be genetically-mediated and are likely to involve combinations of multiple predisposing genes that influence fundamental cellular processes of the beta cell. The result is an increase in beta cell apoptosis without a compensatory increase in beta cell replication leading to a decrease in beta cell mass. Additionally, there appear to be defects in insulin biosynthesis and secretion from the remaining beta cells. This overall decrease in beta cell function results in fasting and postprandial hyperglycemia. Long standing hyperglycemia causes microvascular disease. Poor glycemic control and the development of diabetic nephropathy increase cardiovascular risk factors and the development of macrovascular disease late in the course of the disease. Such a sequence occurs in type 2 diabetes in which there is no primary insulin resistance. A similar sequence of events occurs in another primary beta cell disease, type 1 diabetes.

Another independent metabolic abnormality which has assumed epidemic characteristics in our society is the metabolic syndrome (fig. 1). It is due to an increase in ectopic fat in such organs as the visceral fat depot, liver, pericardium, muscle, etc. The metabolic consequence of this ectopic fat is the development of insulin resistance, activation of the inflammatory cascade, dyslipidemia, endothelial dysfunction, and a procoagulant state. The aggregate of these associated abnormalities comprise the metabolic syndrome. The metabolic syndrome is a cardiovascular risk syndrome and is associated with an increase in macrovascular disease. When the metabolic syndrome occurs in the individual with the genetic predisposition to beta cell functional loss, the insulin resistant component markedly accelerates the decreasing beta cell function and will bring about the expression of clinical diabetes at an earlier age and in persons who ordinarily would not express the disease in a normal life span.

Thus, we can look upon type 2 diabetes as two entities, one relatively uncommon with only a beta cell problem and one increasingly more common with both insulin resistance and a beta cell defect. Obviously, the management of the two different types requires different therapeutic strategies[11]; an insulin providing strategy and an insulin sensitization strategy which may at some stage also require endogenous or exogenous insulin supplementation (fig. 2).

Insulin providing therapies[11] include drugs that can directly close the beta cell ATP-dependent potassium channel and stimulate insulin secretion independent of glucose-mediated ATP production and agents that activate the GLP-1 beta cell receptor and modulate hyperglycemia-mediated insulin secretion through a cyclic AMP-mediated pathway (fig. 2). The former agents include the sulfonylureas and meglitinides and the later the GLP-1 receptor agonists and the DPP-4 inhibitors. In the absence of adequate numbers of functioning beta cells, insulin provision can be provided by the various insulin and insulin analogs available. The major side

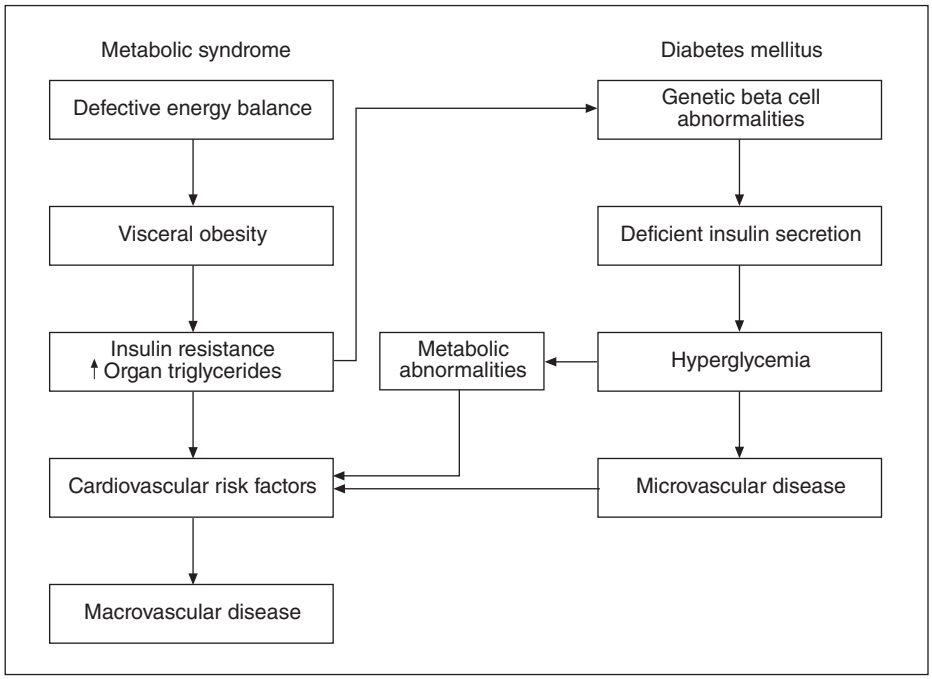

Fig. 1. Pathogenesis of insulin-resistant type 2 diabetes. Beta cell mass and function decrease at an increased rate because of pre-disposing genetic abnormalities. In the absence of insulin resistance the number of individuals who will lose sufficient beta cell mass to cause hyperglycemia is rather small (1 to 2% of the adult population). The metabolic syndrome is a cardiovascular risk syndrome due to an increase in visceral and ectopic fat. This leads to insulin resistance in muscle, liver, adipose tissue and endothelial cells. When the metabolic syndrome occurs in individuals with the genetic predisposition to lose beta cell mass and function, the loss is greatly accelerated and a much larger percentaage of the adult population (10-30%) will develop hyperglycemia within the normal lifespan.

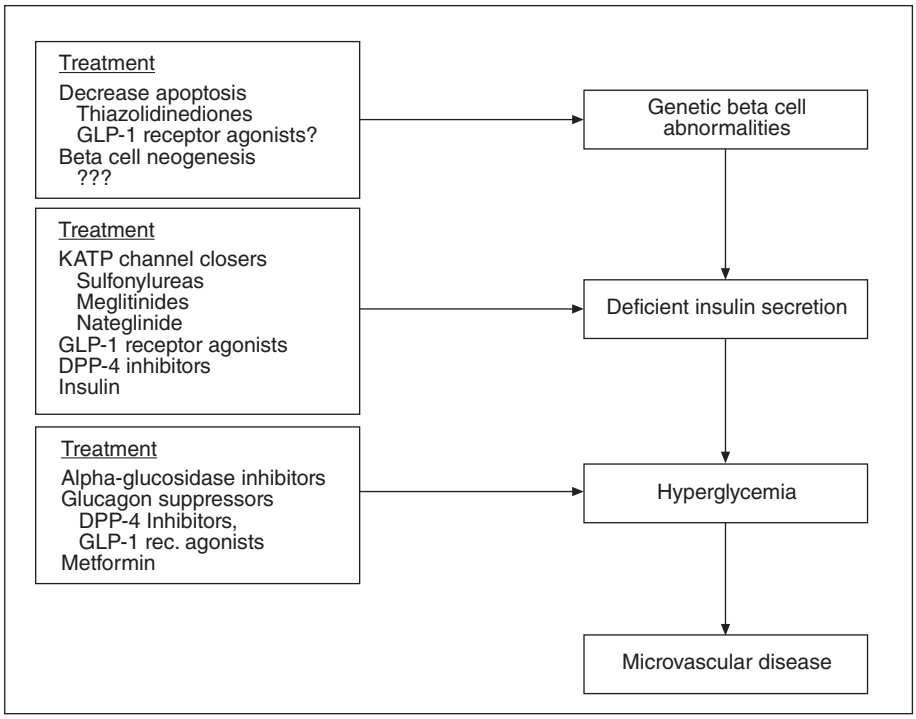

Fig. 2. Treatment options for the consequences of the beta cell abnormalities. These include decreasing the rate of beta cell apoptosis, increasing insulin secretion and directly decreasing hyperglycemia. DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1.

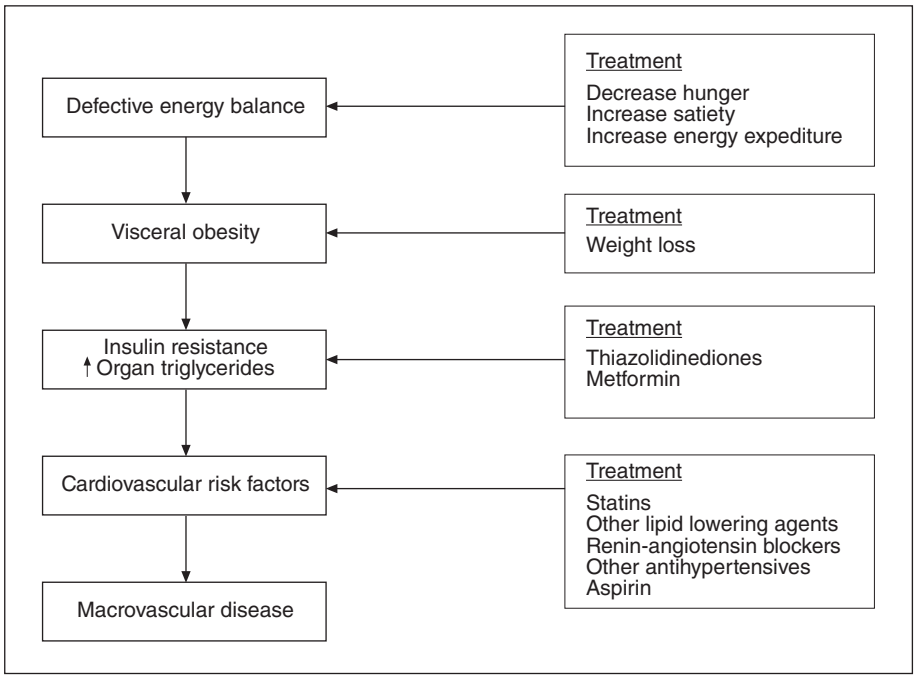

Fig. 3. Treatment options for the metabolic syndrome. Correcting energy balance and decreasing visceral obesity would be ideal but not readily effective at the present time. Insulin resistence is decreased by metformin and thiazolidinediones. The specific cardiovascular risk factors (hypertension, dyslipidemia, procoagulant state) are managed by the appropriate pharmacologic agents.

effects of sulfonylureas and particularly intensive insulin therapy are hypoglycemia and weight gain[11]. The DPP-4 inhibitors are weight neutral and are not prone to significant hypoglycemia[11]. The GLP-1 receptor agonists cause weight loss and are also not prone to significant hypoglycemia[11]. The meglitinides are given prior to each meal and have a major action in reducing meal-mediated hyperglycemia[11].

Insulin sensitizing therapies include metformin (biguanide class) and thiazolidinediones (peroxisome proliferator-activated receptor-gamma (PPARγ) agonists) (fig. 3). Metformin reduces hepatic insulin resistance. Its

mechanism is unclear though several involving intracellular metabolism have been proposed. The thiazolidinediones reduce both hepatic and peripheral insulin resistance[11]. Their mechanism appears to be in reducing the metabolic effects of the ectopic fat deposits, i.e. decreasing plasma free fatty acids, decreasing tumor necrosis factor alpha and interleukin 6 production, increasing adiponectin production and reducing hepatic steatosis[11]. The choice of insulin sensitizers depends on the degree and site of the insulin resistance to be treated. Metformin therapy is associated with a small weight loss, cannot be used in the presence of decreased renal function and is associated with gastrointestinal discomfort, diarrhea and decreased vitamin B_{12} levels[11]. Thiazolidinediones are associated with weight gain, fluid retention (infrequently precipitating heart failure) and bone fractures involving peripheral extremities and mostly occurring in women[11]. Thiazolidinediones appear to decrease the rate of loss of beta cell function (fig. 2).

Several studies have demonstrated that the greatest reduction in vascular complications in type 2 diabetic patients is achieved by a multifactorial approach to treating all of the metabolic abnormalities including hyperglycemia, obesity, hypertension, hyperlipidemia and the pro-coagulant state[7,12]. A proposed strategy is depicted in figure 3.

Conflict of interest

Advisory Boards: Amylin, Biocon, Glaxo SmithKline, Novo-Nordisk, Sanofi-Aventis. Speaker: Glaxo SmithKline, Lilly. Shareholder: Amylin, Merck.

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