

3. NEW DIAGNOSTIC CRITERIA, NEW CLASSIFICATION OF DM AND MODERN THERAPY APPROACH

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1.1 Introduction

The current classification of diabetes mellitus, proposed by the American Diabetic Association (ADA) in 1997 (1,2), and accepted in a slightly revised form as a working classification by World Health Organisation (WHO) (3), is an attempt of staging diabetes mellitus. This takes into account current knowledge on the aetiology and natural history of the disease and has therapeutic implications. Figure 1 shows the natural history of various types of diabetes regarding the need for insulin treatment. Since another speaker will discuss diagnostic criteria and classification in more details, this talk is more treatment-oriented.

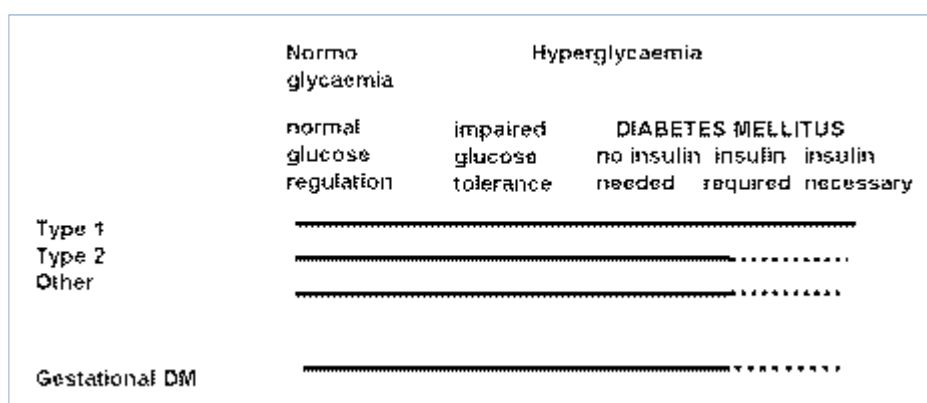


Figure 1. Types and stages of diabetes ((2) - modified)

1.2. Type 1 diabetes treatment

Type 1 diabetes is less common (less than 10% of total number of diabetics have this type of disease) and its basic characteristic is lack of insulin caused predominantly by autoimmune destruction of pancreatic b-cells. The younger the affected individual is the more rapid is the destruction. However, it is clear that before signs and symptoms develop each patient goes through glucose intolerance stages caused by relative lack of insulin. Finally, all type 1 diabetics inevitably require insulin for survival.

The essence of treatment of type 1 diabetes is adequate insulin supplementation. It is not possible without proper education, meal planning (diet) and exercise – cornerstones of diabetes regulation. A landmark study (Diabetes Control Complication Trial - DCCT) confirmed that basal – bolus insulin treatment is a treatment of choice for type 1 patients (3). Insulin is delivered by multiple injections: 1-3 doses of intermediate or long acting insulin or insulin analogue for basal requirement and a bolus of rapid acting insulin or ultrarapid insulin analogue before each meal; or by insulin pump with adaptation of infusion rate.

1.3. Type 2 diabetes treatment

Type 2 diabetes, much more common, has two different defects: insulin resistance and failure of b-cells to secrete insulin adequately (5-7). Not all patients reach the stage of requiring insulin for treatment. However, in some of type 2 patients the insulin defect may become so deep that they need insulin permanently. In principle, the longer the duration of diabetes, the more prominent the b-cell failure.

The first and most important line of treatment of type 2 diabetes is lifestyle modification including healthy eating, exercise and self-monitoring. Moreover, there is recent evidence that this type of intervention can prevent the onset of diabetes in high-risk individuals (8). If hyperglycaemia persists in spite of this basic treatment there are five groups of oral medication that can be added:

Insulin secretagogues: sulfonylureas and meglitinide analogues.

Sulphonylureas are the oldest and, until recently, the main oral agents for treatment of type 2 diabetes. There are number of agents in this group:

- first generation: tolbutamide, chlorpropamide, acetoxexamide, tolazamide,
- second and novel generations: glipizide, glibenclamide, gliclazide, gliquidone and glimepiride.

The level of HbA1c decreases by 1-2%, the same as with novel insulin secretagogues – meglitinide analogues (repaglinide and nateglinide), with a weight gain of 2-3 kg (9) Meglitinide analogues are aimed at controlling post-prandial glucose peaks. They have hypoglycaemia as the most common side effect, similarly to sulphonylurea.

The United Kingdom Prospective Diabetes Study (UKPDS) revealed that better blood glucose and blood pressure control correlates with better prognosis of diabetes regarding its long-term complications, irrespectively of type of treatment (10,11). In other words, there is still no evidence that either glibenclamide or insulin has advantage in the treatment of type 2 diabetics, with exclusion of obese treatment-naïve patients who benefited most from metformin (12). Regarding other sulphonylurea preparations, there is no evidence of difference, however there are no long-term studies comparing different sulphonylureas.

Metformin-a bigvanide.

Other drugs from the same group are fenformin and buformin, withdrawn from most markets due to unacceptable risk of lactic acidosis. Metformin acts primarily on suppression of hepatic glucose output. Additional effects are better muscle utilization of glucose, decreased free fatty acids oxidation and enhanced metabolism of glucose in the gut. It cannot cause hypoglycaemia. The reduction of glycosylated haemoglobin is similar to that with sulphonylurea, with less weight gain (9). As already mentioned, UKPDS revealed the advantage of metformin in obese treatment naïve type 2 patients.

Glucosidase inhibitors

Glucosidase inhibitors (acarbose and miglitol) act within the intestine. Through inhibition of luminal alpha-glucosidase, carbohydrate absorption is delayed and post-prandial glycaemia blunted. As monotherapy, the glucosidase inhibitors reduce glycosylated hemoglobin by 0.7-1.8% (9). There are no serious side effects reported. They can cause no hypoglycaemia. However, poor compliance due to flatulence and diarrhoea is relatively common.

Thiazolidinediones

Thiazolidinediones (glitazones) (rosiglitazone and pioglitazone) are synthetic agonists of the nuclear PPAR-gamma (peroxisome proliferator- activated receptor gamma) which act as insulin sensitizers. First agent from this group, troglitazone, has been withdrawn because of serious liver damages. With currently used agents a reduction of HbA1c is 0.9-1.5%, with weight gain of 0.7-1.9 kg not associated with hypoglycaemia (9).

1.3.1. Insulin in the treatment of type 2 diabetes

In many type 2 patients, insulin may be needed temporarily to correct glycaemia in acute situations: concomitant serious illnesses, surgery, etc. However, a number of patients reach a stage when metabolic control can no longer be maintained by oral agents and basic principles (secondary failure). There is still no evidence which approach to switching to insulin in these patients is the best. It seems that with proper self-monitoring and adequate meal plans, equal levels of glycaemia control can be achieved with any proposed insulin regimen. However, combination of bedtime intermediate acting insulin and metformin seems to be better for weight control in overweight individuals (13). It is important to note that from the UKPDS and other studies there is definitely no evidence that insulin treatment in type 2 diabetics increases the risk of atherosclerosis. On the contrary, for the long-term survival after acute myocardial infarction intensified insulin treatment in type 2 diabetics has been proved to be beneficial (14). It remains to be confirmed that intensified insulin treatment has same effect in all type 2 as type 1 diabetics (15).

1.4. Other specific types and gestational diabetes

Other specific types of disease are either like type 1 or type 2 diabetes. Thus, the principles of treatment are basically same: meal planning, exercise and pharmacological treatment aimed to overcome the defect that is identified as more prominent (insulin resistance or b-cell failure).

The aim of the treatment of gestational diabetes is normalization of glycaemia, which has been shown to reduce neonatal hypoglycaemia, macrosmia and neonatal morbidity. If it is not possible by basic principles only, multiple insulin injections are the treatment of choice (16).

1.5. Conclusion

Disregarding the type of diabetes, it is obvious that glycaemic control is the cornerstone in the prevention of late complications. In both types of disease, an inevitable part of treatment is continuing patient education with a goal of making patients capable of performing a

life-long programme of continuous self-control, meal planning and exercise. For type 1 patients, insulin supplementation is necessary in form of basal- bolus treatment. Most type 2 patients can, at least for some time, achieve and maintain good glycaemic control with basic treatment only: meal planning and exercise. When it is not possible any longer in overweight patients metformin is the first drug of choice (if there are no contraindications). Glucosidase inhibitors may additionally be used, or as monotherapy in patients whose major problem are postprandial glycaemic peaks. In patients whose major problem seems to be insulin resistance glitazones are an option. In non- obese type 2 diabetics, insulin secretagogues: sulphonylureas or glinides are usually the first choice. Any combination is possible; and the choice depends upon the presumed dominant defect in particular patient (i.e. insulin resistance or insulin secretion failure) (Figure 2).

Insulin is necessary in type 2 patients for correction of acute metabolic disturbance or when it is no longer possible to maintain good control by basic principles and oral treatment.

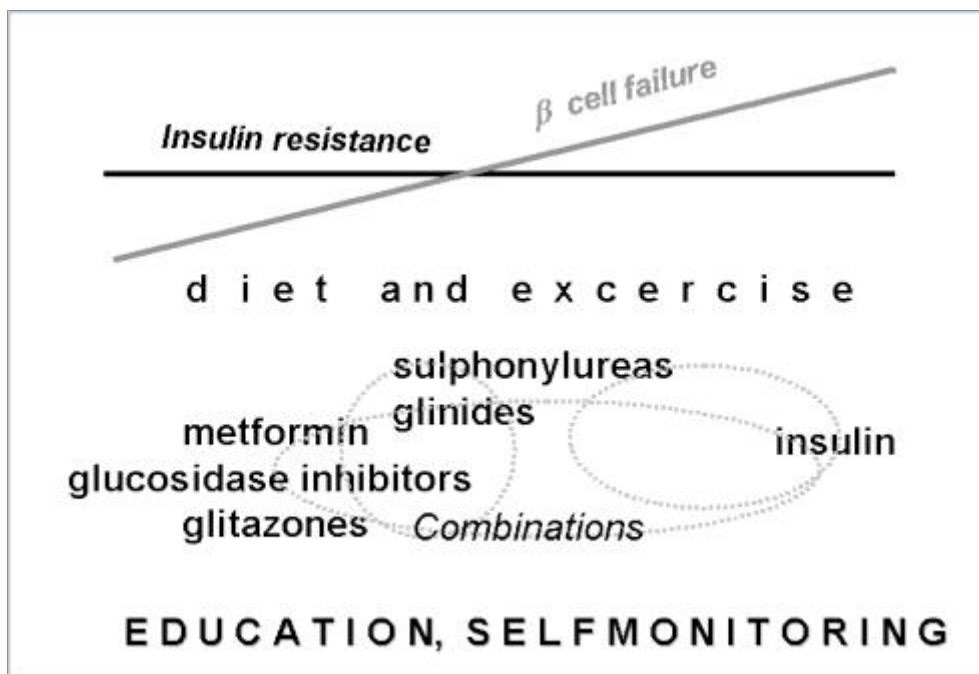


Figure 2. Type 2 diabetes - staged treatment

Finally, it should be stressed that for achievement of treatment goals in diabetic patients as a group, a comprehensive programme of follow up and continuous education should be developed (17).

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