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TREATMENT OF TYPE 2 DIABETES

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Summary

Type 2 diabetes is an heterogeneous disease resulting from a dynamic interaction between defects in insulin secretion and insulin action. As most subjects are overweight or obese, the initial treatment is optimization of the meal plan and enhancement of physical activity in order to obtain sustained weight reduction. In case of failure of life-style changes, various oral antihyperglycaemic agents may be used. Some are targeting defective insulin secretion (sulphonylureas, glinides) while others are targeting insulin resistance (metformin, thiazolidinediones). Criteria of drug selection should

include both patient's characteristics (body weight, age, degree of hyperglycaemia, age, comorbidities) and pharmacological properties of the compound (mode of action, safety profile, cost). Monotherapy is usually recommended first, but combined therapy using drugs with additive or synergistic effects may be required to obtain appropriate blood glucose control. As the natural history of the disease is characterized by a progressive exhaustion of beta-cells, exogenous insulin may be required in the long term, usually in combination with oral agents. Finally, as patients with type 2 diabetes are insulin-resistant and often have a metabolic syndrome, a multifactorial intervention including aggressive treatment of arterial hypertension and dyslipidaemia is recommended in order to reduce the incidence of cardiovascular complications.

Key-words : Cardiovascular risk - Combined therapy - Insulin - Oral antidiabetic agents - Type 2 diabetes

1) Introduction

Type 2 diabetes mellitus is one of the leading cause of death by disease in the western world and also contributes to higher rates of severe morbidity as people with diabetes are at higher risk for heart disease, blindness, kidney failure, extremity amputations, and other chronic conditions. Eliminating or reducing the health problems caused by diabetes through factors such as better access to preventive care, more widespread diagnosis and more intensive disease management could significantly improve the quality of life for diabetic individuals and their families while at the same time potentially reducing the enormous cost burden to society (1).

Type 2 diabetes is an heterogeneous condition caused by both genetic and environmental factors. Hyperglycaemia results from a dynamic interaction between defects in insulin secretion and insulin action (2). It is characterized by a progressive deterioration of the metabolic status over years that essentially results from a progressive decline of insulin secretion by pancreatic islet beta-cells. Therefore, the management of the disease usually requires a stepwise adjustment of pharmacological therapies in combination with life-style modifications, which ultimately may lead to insulin requirement (3). Such a strategy includes a progressive increase in the daily dosages of each molecule used and/or appropriate combinations of various glucose-lowering agents with complementary and, ideally, synergistic modes of action (4,5).

Most patients with type 2 diabetes are obese or have an increased percentage of body fat distributed predominantly in the intra-abdominal (peri-visceral) region (6). Besides hyperglycaemia, other abnormalities are frequently present and most probably related to visceral adiposity : dyslipidaemias (hypertriglyceridaemia, low HDL cholesterol, increased small dense LDL particles, postprandial hyperlipaemia, ...), arterial hypertension (in about half of overweight patients with type 2 diabetes), fibrinolytic disturbances (increased plasminogen-activator inhibitor-1 or PAI-1 levels) and increased inflammation markers (C-reactive protein, fibrinogen). All these abnormalities are well-documented cardiovascular risk factors. They are related to insulin resistance (syndrome X or metabolic syndrome) and may be present even in absence of severe hyperglycaemia (7). Consequently, therapeutic guidelines of type 2 diabetes should not focus only on the correction of hyperglycaemia, but should encourage to consider the patient globally and to treat all risk factors present in each individual, more particularly weight excess, arterial hypertension and dyslipidaemias (8).

Type 2 diabetes is a common disease whose prevalence markedly increases with age (> 10 % above 65 years) (9). The objectives of therapy should be clearly defined in each patient in order to adapt both treatments and glycaemic targets individually (10). The key recommendation is based on the

premise that the benefits of treatment outweigh the risks. As an example, treating a modest hyperglycaemia with sulphonylureas or insulin may expose the older patient to severe hypoglycaemia that could be more harmful than the initial metabolic disturbance. However, even if *primum non nocere* should be the rule, the antihyperglycaemic treatment of patients with type 2 diabetes should not be neglected, especially in younger individuals (40-60 years). Indeed, chronic hyperglycaemia is clearly responsible for microangiopathy (retinopathy, nephropathy) and may also favour the development of macroangiopathy (coronary heart disease, cerebrovascular diseases, peripheral arteriopathy), in combination with other risk factors (7,8). The positive effects of improved glycaemic control on the incidence and severity of such complications have been emphasized in the landmark United Kingdom Prospective Diabetes Study (UKPDS) in newly diagnosed type 2 diabetic patients followed up to 15 years (11,12).

2) Aims of treatment and basic principles

The goals of treating a patient with type 2 diabetes are twice : first, in the short term, to improve the quality of life (less fatigue, reduced polyruria, no urogenital infections) and to avoid acute metabolic complications (severe hyperglycaemia leading to hyperosmolar coma or severe iatrogenic hypoglycaemic episodes); and second, in the long term, to preserve the patient from both micro- and macro-angiopathy complications. Most of the burden of type 2 diabetes results from these long-term complications (1). To reach these goals the physician may use non-drug and drug therapies (13,14).

The initial treatment of choice in patients with type 2 diabetes is optimization of the meal plan and enhancement of physical activity (14). Reduction of excessive body weight should be a main target in most patients (6). Unfortunately, traditional dietary strategies, and even very-low-calorie diets, have usually not been effective in achieving long-term weight loss. Therefore, several additional strategies can be implemented to favour and/or maintain weight loss, such as anti-obesity drugs (orlistat, sibutramine) and even, in well-selected extreme cases, bariatric surgery (gastroplasty or gastric bypass) (6). The emphasis for medical nutrition therapy in type 2 diabetes should also be placed on achieving glucose (50-55% of energy intake as carbohydrates, with limitation of sucrose and advices of consuming fibres), lipid (reduction in saturated fat and cholesterol consumption), and blood pressure (no more than 3,000 mg/day of sodium) goals (14). An appropriate exercise programme should be an adjunct to diet and/or drug therapy to improve glycaemic control, reduce certain cardiovascular risk factors, and increase psychological well-being in individuals with type 2 diabetes mellitus (14).

However, attention must be paid to minimizing potential exercise complications and a careful pre-exercise evaluation should be recommended in all individuals with type 2 diabetes.

If progress toward glycaemic goals is not apparent within a 3-month period after initiation of diet and exercise therapy, then the use of a pharmacological agent is appropriate (15). Various oral antihyperglycaemic agents have been developed during the last 40 years (Table 1) (16,17). Mechanisms of action aim at targeting defective insulin secretion (sulphonylureas and more recently meglitinide analogues) or defective insulin action (metformin and more recently thiazolidinediones) (Figure 1). Alternatively, α-glucosidase inhibitors (acarbose) acts at the intestinal level by slowing the absorption of carbohydrates. Insulin can also be used in type 2 diabetes, as initial therapy or most often after secondary failure to oral drug treatment. Criteria of drug selection in daily practice should include not only patient's clinical characteristics (body weight, degree of hyperglycaemia, age, renal function, ...), but also the pharmacological properties of the various compounds available (mode of action, side-effects, safety profile, and cost) (see below) (5). Updated recommendations for the management of type 2 diabetes have been published by the European NIDDM Policy Group (18).

3) Stepwise pharmacological strategy

Clinical management of type 2 diabetes mellitus currently employs a stepwise approach, in which failure to maintain glycaemic control prompts the introduction of progressively more intensive treatment strategies (Figure 2). However, this represents an inherently reactive strategy, with treatment decisions following the consequences (i.e. hyperglycaemia) rather than addressing the underlying pathology. This approach may explain why treatment of type 2 diabetes is a failure in most cases. Even if good glycaemic control remains a key element in the clinical management of type 2 diabetes, treatment guidelines will need to be reassessed with the aim of achieving good glycaemic control through measures that address the underlying pathogenic mechanisms responsible for type 2 diabetes.

a) First step : oral monotherapy

After diet failure, patients with type 2 diabetes can be treated with one of the various available oral antidiabetic drugs before considering the use of combined therapy or even insulin (Figure 2). It is classically recognized that metformin should be preferred in insulin-resistant, hyperinsulinaemic, obese patients while sulphonylureas should be prescribed first in non-obese or only modestly overweight, insulin-deficient patients (5). However, recent studies have suggested that metformin may be as

effective in non-obese as in obese diabetic subjects. Acarbose appears to be preferable as monotherapy in diabetic patients with only modest fasting hyperglycaemia but rather high postprandial glucose excursions. In such patients, acarbose can improve glycaemic control without inducing hypoglycaemia. The place of the recently developed compounds of the thiazolidinedione family in the general treatment strategy of type 2 diabetes still remains to be more precisely specified. Owing to their mode of action, pioglitazone and rosiglitazone may be preferred as initial pharmacological therapy after diet failure in insulin-resistant patients, as an alternative to metformin, an indication accepted in the United States. However, the European Agency for the Evaluation of Medicinal Products (EMEA) has postpone such an indication in Europe to reserve the used of these new (more expensive) agents in second line (see below).

The UKPDS (11,12) showed that sulphonylureas (either chlorpropamide or glibenclamide) and metformin initial monotherapy are as effective as insulin in controlling fasting plasma glucose concentrations and HbA_{1c} levels during the first ten years after diagnosis and significantly superior to diet therapy alone. One advantage of metformin in the obese group with type 2 diabetes was the absence of weight gain which contrasted with a significant weight increase in the group treated by sulphonylureas or insulin. However, none of these pharmacological approaches was able to avoid a progressive deterioration of the metabolic control (assessed by a progressive increase in HbA_{1c} levels) that was attributed to an exhaustion of beta cell. A better protection of the beta cell is expected from the administration of glitazones although it is not yet proven that such therapy is able to provide a longer stabilization of the disease.

b) Second step : combined oral therapy

As the four classes of antidiabetic drugs currently available (sulphonylureas or glinides, biguanides, α-glucosidase inhibitors and thiazolidinediones) have different modes and sites of action (Figure 1), they may be combined in a stepwise fashion to further improve glycaemic control for most patients (Figure 2) (5,15,18).

The most common combined therapy associates a sulphonylurea compound that stimulates insulin secretion and metformin that facilitates insulin action. Numerous studies have demonstrated that both compounds have an at least additive antihyperglycaemic effect, without increasing the side-effects of either pharmacological class. Other combinations of oral drugs may also be used. For instance, pioglitazone or rosiglitazone may be added after failure of metformin (in obese patients) or sulphonyurea (in non obese patients who can not be treated with metformin because of contra-

indications or side-effects) monotherapy. While there is a rationale for a triple therapy (sulphonylurea to increase insulin secretion, metformin to reduce hepatic glucose output and glitazone to enhance muscular glucose utilisation), no extensive study has yet proven the efficacy and safety of such strategy yet.

c) Third step : insulin therapy

Seventy-five years after the discovery of insulin, insulin therapy is still controversial in the management of patients with type 2 diabetes so that the questions why, when and how to prescribe insulin in those individuals remain without definite answers. The minimum goal of insulin therapy is to suppress clinical symptoms of diabetes and the ultimate goal is to prevent long-term complications. Insulin therapy may be used as an alternative to oral drugs after diet failure, following secondary failure of maximal oral treatment, or when oral agents are contraindicated or become temporarily ineffective. While insulin is used rather early in the natural history of the disease in United Kingdom or Scandinavian countries, it is used at a much later stage in the south part of Europe, generally after secondary failure to oral antidiabetic therapy. Insulin can be administered once daily (long-acting insulin, preferably the new insulin glargine), twice daily (a mixture of short- and intermediate acting – NPH - insulins before breakfast and dinner) or sometimes using a basal–bolus scheme (regular insulin or fast-acting insulin analogue before each meal and long-acting insulin at bedtime) (19). Besides the risk of hypoglycaemia (however much lower than in patients with type 1 diabetes), insulin may trigger weight gain in patients wit type 2 diabetes and insulin therapy should always be accompanied by diet counseling.

In contrast to the use of insulin as only treatment in type 1 diabetes, a disease characterized by a pure beta-cell defect, insulin may be combined with various oral antidiabetic drugs in type 2 diabetes, a more complex disease combining partially defective insulin secretion and action (Figure 2) (20,21). Insulin-sulphonylurea is the combination which has been the most extensively studied. Intermediate insulin at bedtime combined with pre-meal sulphonylurea has been shown to be effective in most studies, but requires the persistence of significant residual endogenous insulin secretion. Metformin may be used in combination with insulin to reduce insulin requirements in obese patients, to improve glycaemic control and/or to correct associated metabolic abnormalities. Similar effects of sparing insulin dosage and improving metabolic disturbances are expected from the association of insulin sensitizers such as glitazones to insulin therapy but some concern has been raised about this combination that might be associated with a higher risk of fluid retention and, in rare cases, of

congestive heart failure (such an indication is not admitted by the EMEA, in contrast to the US Food and Drug Administration or FDA). Finally, acarbose may be added to insulin to reduce blood glucose variations, especially postprandial early hyperglycaemia and late hypoglycaemia.

4. Therapy risk and benefits

As the prevalence of type 2 diabetes and the risk of severe side-effects of oral antidiabetic agents are markedly increased with aging, special focus should be put on the specific group of elderly diabetic patients (9). In general, the same measures of management are appropriate in the older as in the younger patient with diabetes, but may need to be modified in the presence of comorbidities, polymedication or social isolation. In particular the risk of severe sulphonylurea-induced hypoglycaemia or biguanide-associated lactic acidosis is higher in the elderly, so that those drugs must be prescribed with caution in the older population. Meglitinide analogues (repaglinide and nateglinide) are more rapidly absorbed and have a shorter half-life than sulphonylureas (16,17). Therefore, they may exert a better control of postprandial hyperglycaemia and reduce the risk of hypoglycaemia at distance of the last meal. In addition, they are not excreted by the liver and may be safely used even in case of renal insufficiency. Recently launched glitazones (pioglitzone, rosiglitazone) appear to have a good safety profile as they do not share the liver toxicity described with troglitazone; however, glitazones, which may promote fluid retention, are contra-indicated in patients with congestive heart failure, a condition that is more frequently observed in the elderly population. Finally, acarbose can be safely used in elderly diabetic patients although it may induce intestinal side-effects.

As for the management of arterial hypertension, the increase of different available drugs will probably favour the use of combined therapy, although it remains to be established which combination will provide the best results in a given patient with type 2 diabetes (5). In addition, the cost/benefit ratio of combined therapy remains to be assessed in large randomised trials, as well as remains to be answered the question of whether better metabolic control may be maintained in the long-term with a combined therapy as compared with monotherapy. Finally, it is noteworthy that, until now, no long-term studies in type 2 diabetic patients have shown the superiority of any kind of antihyperglycaemic oral agents for postponing or preventing micro-angiopathic complications (11). The UKPDS showed a greater reduction in macrovascular complications in the group of overweight diabetic patients treated with metformin as compared to the groups treated with diet alone or with intensive therapy including sulphonylureas or long-acting insulin (12). Large ongoing studies with pioglitazone or rosiglitazone have been designed to demonstrate that these new insulin sensitizers, not only may offer a better beta-

cell protection and more sustained metabolic control, but also may exert a specific cardiovascular protection due to pleiotropic effects resulting from improvement of insulin sensitivity (22).

Aggressive treatment of other risk factors has been shown to significantly reduce the incidence of cardiovascular complications in patients with type 2 diabetes. Treating arterial hypertension with either a beta-blocker (atenolol) or an angiotensin-converting enzyme inhibitor (captopril) significantly and remarkably reduced the incidence of diabetic complications in the UKPDS (23). Adequate treatment of hypertension has acquired a major importance in the overall management of individuals with type 2 diabetes (24). Similarly, aggressive treatment of even modest lipid disturbances should not be neglected in diabetic patients. In the subgroup of diabetic patients of the Heart Protection Study (25), the subjects who received simvastatin exhibited a significant reduction of cardiovascular morbidity and mortality as compared to patients on placebo, even in absence of severe hypercholesterolaemia. Therefore, statin administration is now recommended in the management of any patient with type 2 diabetes at high risk of cardiovascular diseases. Consequently, a maximum benefit would be expected from a multifactorial therapy (optimal control of blood glucose, adequate treatment of arterial hypertension and dyslipidaemia, prevention of thrombotic state using aspirin). Such a multifactorial intervention has been recently shown to reduce by half the incidence of cardiovascular complications in patients with type 2 diabetes (8).

5. Conclusions

Type 2 diabetes mellitus is a complex disease whose treatment remains a real challenge. Indeed, long-term compliance to life-style modifications is difficult to obtain in diabetic patients and no current pharmacological treatment is able to avoid the progression of the disease and the metabolic deterioration over years. The possibility that earlier aggressive intervention, potentially involving polypharmacy, directed against the pathogenic mechanisms underlying type 2 diabetes, and not just the resulting hyperglycaemia, may improve the clinical management of diabetes requires consideration. There is at least a strong rationale for intervention that counter both beta-cell dysfunction and insulin resistance. In addition, a multifactorial intervention should be recommended to reduce other cardiovascular risk factors such as arterial hypertension and lipid disturbances in order to improve cardiovascular prognosis. As the cost of type 2 diabetes appears enormous, essentially due to vascular complications, and the treatment has proven numerous limitations yet, prevention of type 2 diabetes should be considered as a major public health objective.

References

1. Massi-Benedetti M (Ed). The cost of diabetes type II in Europe. The CODE-2 study. *Diabetologia* 2002; 45 (Suppl 1): S1-S28.
2. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003; 46: 3-19.
3. Turner RC, Cull CA, Frighi V, Holman RR. Glycaemic control with diet, sulfonylurea, metformin or insulin in patients with type 2 diabetes mellitus : progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999; 281: 2005-12.
4. Scheen AJ, Lefèbvre PJ. Le diabète non insulinodépendant : de la physiopathologie au traitement. *Bull Mem Acad Roy Med Belg* 1996; 151: 395-405.
5. Scheen AJ, Lefèbvre PJ. Oral antidiabetic agents : a guide to selection. *Drugs* 1998; 55: 225-36.
6. Scheen AJ. Current management of coexisting obesity and type 2 diabetes. *Drugs* 2003; 63: 1165-84.
7. Scheen AJ. Insulin resistance syndrome and atherosclerotic cardiovascular disease. *Acta Clin. Belg* 1996 ; 51 : 65-9.
8. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383-93.
9. Scheen AJ. Non-insulin-dependent diabetes mellitus in the elderly. *Baillière's Clin Endocrinol Metab* 1997; 11: 388-406.
10. Winocour PH. Effective diabetes care : a need for realistic targets. *BMJ* 2002; 324: 1577-80.
11. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-53.
12. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854-65.
13. Scheen AJ, Lefèbvre PJ. Treatment of diabetes mellitus. In : *Clinical Pharmacology*, (Ed : C. Sirtori), Mc Graw Hill, London, 2000, 685-98.
14. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2003; 26 (Suppl 1): S33-S50.
15. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131: 281-303.

16. Scheen AJ. Drug treatment of non-insulin-dependent diabetes mellitus in the 1990s : achievements and future developments. *Drugs* 1997; 54: 355-68.

17. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes : scientific review. *JAMA* 2002; 287: 360-72.

18. European Diabetes Policy Group. A desktop guide to Type 2 diabetes mellitus. *Diabet Med* 1999; 16: 716-30.

19. Edelman SV, Henry RR. Insulin therapy for normalizing glycosylated hemoglobin in Type II diabetes. *Diabetes Rev* 1995; 3: 308-34.

20. Scheen AJ, Castillo MJ, Lefèbvre PJ. Combination of oral antidiabetic drugs and insulin in the treatment of non-insulin-dependent diabetes. *Acta Clin Belg* 1993; 48: 259-68.

21. Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. *Diabetes Care* 2001; 24: 758-67.

22. Campbell IA. Antidiabetic drugs present and future : will improving insulin resistance benefit cardiovascular risk in type 2 diabetes mellitus ? *Drugs* 2000; 60: 1017-28.

23. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 1998; 317: 703-13.

24. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes mellitus. *Diabetes Care* 2002; 25: 134-47.

25. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes : a randomised placebo-controlled trial. *Lancet* 2003; 361: 2005-16.

Legends to the Figures

Figure 1 : Current status of drug treatment of type 2 diabetes : sites of action of sulphonylureas (or glinides), metformin, acarbose, thiazolidinediones (glitazones) and exogenous insulin (adapted from reference 16).

Figure 2 : Stepwise treatment of type 2 diabetes : a guide to selection of oral antidiabetic agents from monotherapy to combined therapy, including insulin (adapted from reference 5).

Table 1 : Pharmacotherapy for the management of patient with type 2 diabetes and other comorbidities

1) Glucose-lowering agents
    Sulphonylureas
        carbutamide, tolazamide, tolbutamide, chlorpropamide
        glibenclamide, glipizide, gliclazide, gliquidone, glimepiride
    Biguanides
        metformin
    Thiazolidionediones
        pioglitazone, rosiglitazone
    α-glucosidase inhibitors
        acarbose
2) Antihypertensive agents
    Angiotensin converting enzyme inhibitors or angiotensin AT1 receptor blockers
    Beta-blockers
    Diuretics
    Calcium channel antagonists
3) Lipid-lowering agents
    Statins
    Fibrates

4) Others

Aspirin