COST-EFFECTIVE MANAGEMENT OF DIABETES MELLITUS

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Diabetes is one of the most common noncommunicable diseases (NCD) globally and a leading cause of death in many countries; the global epidemic of type 2 diabetes will most affect the developing world. The burden of diabetes is related to its chronic complications, both the specific microvascular and the nonspecific macrovascular (atherosclerosis), making diabetes one of the leading causes of death in some countries and an enormous financial burden. The costs of diabetes care, both direct and indirect, are high.

Single and multiple risk-factor intervention studies have provided evidence that targeting hyperglycemia and other nonglycemic risk factors reduces the risk of chronic complications; most national guidelines recommend intensified, multitargeted intervention of known modifiable risk factors.

The aim in management is optimal control, both glycemic and non-glycemic (blood pressure, lipid and weight control). Management strategies for hyperglycemia include standard methods and individualized options. Given the complexities of the therapeutic choices (classes/agents) and regimens and on the basis of proven benefit, long familiarity, known side-effects, and reduced cost of sulfonylureas, biguanides, and insulin, one should start with standard methods. Despite the evidence for benefit of glycemic control, wide therapeutic choices and regimens and clearer targets for control, glycemic control is far from ideal.

The cost-effectiveness of interventions to reduce the burden of diabetes-related complications compares favorably with that of other accepted uses of healthcare resources and provides convincing economic rationale for improving standards of care for patients with type 2 diabetes. (*Ethn Dis*. 2006;16[suppl 2]:S2-79–S2-84)

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INTRODUCTION

Diabetes mellitus has been known since antiquity, it affects millions of people of all social classes and ethnic groups throughout the world, and despite exciting advances in virtually every field of research, it continues to pose a major personal and public health problem.[1–4] It is characterized by chronic hyperglycemia and disordered carbohydrate, protein, and lipid metabolism; the fundamental defect lies in insulin secretion (type 1, type 2) and/or insulin action (type 2).

When compared with the general population, the death rate is increased 4–7 fold in type 1 diabetes and 2–3 fold in type 2 diabetes, as is the morbidity. The medical and socioeconomic burden of diabetes results, in the main, from its associated chronic complications, both the specific microvascular (retinopathy, nephropathy, and neuropathy) as well as the nonspecific macrovascular (atherosclerosis and coronary, cerebral, and peripheral vascular disease) complications, making diabetes one of the leading causes of death in some countries and an enormous financial burden.[1–4]

However, there is now evidence in both type 1 and type 2 diabetes that tight glycemic control will delay the onset and slow the progression of the chronic complications, especially microvascular complications. Consequently, the major goals of current research have focused on prevention and early detection and treatment of the disorder and its complications.[5–13]

Also, over the last decade, the number of classes of antihyperglycemicagents available for treating diabetes has increased; however, the management of type 2 diabetes is far from satisfactory, as judged by common standards of glycemic control.[14]

The aim in management is optimal glycemic control, with the use of one or more of the available therapeutic modalities (lifestyle modification, oral antidiabetic drugs, and insulin). Also, the current targets dictate that although defined by hyperglycemia, type 2 diabetes is a multifaceted disorder that is often accompanied by hypertension, dyslipidemia, and obesity and that these additional atherogenic risk factors need to be addressed and controlled.[1–5]

This review focuses on the cost-effective glycemic management of type 2 diabetes, with a brief overview of the evidence base for the current management approaches. PubMed was searched with the terms ''type 2 diabetes,'' ''epidemiology,'' ''pathogenesis,'' ''management,'' ''cost-effective management,'' ''anti-diabetic drugs,'' ''prevention,'' and combinations of these terms. The known landmark references and most recent references and reviews were selected.

EPIDEMIOLOGY

Classification and Diagnostic Criteria

The American Diabetes Association (ADA) in 1997 and the World Health Organization (WHO) in 1998 issued the current standardized classification

and diagnostic criteria for diabetes mellitus.[1,2]

The classification encompasses three clinical stages and four etiologic types of glycemia; the clinical stages include normal glucose regulation (normoglycaemia), pre-diabetes (impaired glucose regulation: impaired glucose tolerance [IGT], or impaired fasting glucose [IFG]) and diabetes. The etiologic types of diabetes include type 1, type 2, other specific types, and gestational diabetes. Type 2 accounts for most diabetes (>90%) and may be predominantly the insulin-resistant or insulin-secretory defect variety. IGT and IFG are stages that are intermediate between normal glucose regulation and diabetes; IGT is a risk marker for future diabetes and cardiovascular disease (CVD).

Based on 1999 WHO diagnostic criteria[1] using both fasting plasma glucose (FPG) and two-hour (mmol/L) post glucose (75 g) load plasma glucose (LPG) during oral glucose tolerance test (OGTT), diabetes is diagnosed if FPG≥7.0 or LPG is ≥11.1; IFG if FPG ≥ 6.1 and LPG (if measured) <7.8; IGT if LPG is ≥7.8 but ≤11.1 and FPG (if measured) <7.0; and normoglycemia if FPG <6.1 and LPG <7.8.

Prevalence of Diabetes and Its Complications

Diabetes is one of the most common noncommunicable diseases globally and the fourth leading cause of death in developed countries. Diabetes has reached epidemic proportions and currently affects >71 million people worldwide.[3,16] Global estimates for the years 1995–2025 suggest that diabetes prevalence will increase from 4.0% to 5.4%; the numbers of adults with diabetes will increase by 122% (135–300 million) for the world, with the greatest increase (170%) in developing countries (84–227 million).[3,16] From available studies, risk factors for development and prevalence of diabetes include ethnicity and race, urbanization, age, sex, family history, adiposity, physical inactivity, and unhealthy diet.[1–4]

Complications include the increased illness and death associated with the acute and chronic complications of diabetes.[1–5] The prevalence of chronic complications varies: for microvascular complications, prevalance varies from 2%–90% for retinopathy, 3%–35% for nephropathy, and 10%–100% for neuropathy; for macrovascular complications, CVD and strokes are 2–4 times more common in diabetes patients when compared with the nondiabetes population. Major risk factors for development and progression of microvascular complications in addition to hyperglycemia include the impact of blood pressure, lipids, age, sex, genes, and structural and functional abnormalities of the microvasculature.[3,4]

Costs of Diabetes

The costs of diabetes care both direct and indirect are high; for the United States, the total annual cost was estimated at $132 billion in 2002, with direct costs (diabetes care, chronic complications, increased prevalence of general medical conditions) accounting for $92.1 billion.[4] Direct costs have increased since 1997 ($44 billion) and represents 19% of the total personal healthcare expenditure in the United States. However, diagnosed diabetes accounts only for 4.2% of the total US population; the single largest contributor was in-patient hospital care accounting for $40.3 billion (47%); CVD was the most costly complication, accounting for $17.6 billion. Indirect costs, which account for the remainder, include costs related to lost work days, decreased activity days, and permanent disability.

PATHOPHYSIOLOGY OF HYPERGLYCEMIA

Insulin is the key hormone for regulation of blood glucose. Following ingestion of glucose, maintenance of normoglycemia depends on stimulation of pancreatic insulin secretion and insulin-mediated (insulin action) suppression of hepatic glucose output, increased peripheral glucose uptake, and suppression of lipolysis in the adipose tissues (free fatty acids).[15,17]

In type 2 diabetes, overt (fasting) hyperglycemia develops because of four major pathogenic disturbances: a variety of genetic and acquired (especially obesity, physical inactivity) factors affect both insulin secretion leading to beta-cell dysfunction and insulin action leading to insulin resistance: (i) the reduced insulin secretion decreases insulin signaling in its target tissues (liver, muscle, and adipose tissue); insulin resistance pathways affect the action of insulin in each of the major target tissues leading to (ii) increased hepatic glucose output, (iii) decreased peripheral glucose uptake, and (iv) reduced suppression of lipolysis, with resultant hyperglycemia and increased circulating free fatty acids characteristic of type 2 diabetes; these in turn, will feed back to worsen both the insulin secretion and resistance, ie, glucotoxicity and lipotoxicity and the resultant "dysharmonious quartet" involved in the pathogenesis.[15,17]

SIGNIFICANCE OF GLYCEMIC CONTROL IN TYPE 2 DIABETES

Several studies have examined the impact of glycemic control on the development and progression of micro- and macrovascular complications of diabetes; these drive the current targets in management.[5–9]

For type 2 diabetes, the 33rd United Kingdom Prospective Diabetes Study (UKPDS 33)[6] conclusively showed that in newly-diagnosed subjects, when compared with conventional treatment with diet, intensive blood glucose control (FPG <6 mmol/L) with sulfonylurea or insulin reduced the risk of microvascu-

lar complications but not macrovascular complications. In UKPDS 34,[7] in overweight patients, intensive glycemic therapy with metformin was associated with a reduced risk for both micro- and macrovascular complications. An epidemiologic analysis of UKPDS data showed that for every 1% reduction in hemoglobin A1C, there was a lower risk of diabetes-related deaths and micro- and macrovascular complications.[14]

In the Kumamoto study, intensive insulin therapy for type 2 diabetes lowered the risk of microvascular complications; the main thresholds included hemoglobin A1C <6.5%, FPG <6.1 mmol/L and OGTT <9.98 mmol/L.[11]

Such studies were single risk factor intervention studies, targeting hyperglycemia. Other such studies included for microvascular complications, targeting blood pressure (UKPDS 38) and for cardiovascular disease, blood pressure (UKPDS 38) and the use of aspirin, statins and angiotensin-converting enzyme inhibitors.[13] Multi-factorial intervention studies include the Steno-2 study,[9] which showed that targeted, intensified, and multifactorial (glucose, blood pressure, lipids, microalbuminuria, CVD) intervention in a high-risk group of type 2 diabetes subjects (diabetes plus microalbuminuria) (target hemoglobin A1C <6.5%) was associated with a 50% lower risk of developing micro- and macrovascular complications.

The outcome of these studies has changed the management of type 2 diabetes over the last 10 years, and most national guidelines recommended intensified multitargeted intervention of known modifiable risk factors for complications of diabetes.

GOALS OF THERAPY

Based on the available evidence, the current aim in management is optimal control, ie, euglycemia without any hypoglycemic episodes and the control of other (nonglycemic) modifiable risk factors for diabetes and its complications. Table 1 shows some of the current recommended goals for nonpregnant adults; these dictate good glycemic, blood pressure, lipid, and weight control.[3,5,14]

Table 1. Glycemic and nonglycemic targets for control in type 2 diabetes mellitus*

Glycemic targets	
Glycated haemoglobin (%)	<7.0
Preprandial plasma glucose (mmol/L)†	5.2–7.2
Postprandial plasma glucose (mmol/L)	<10.0
Nonglycemic targets	
Blood pressure (mm Hg)	<130/80
Body mass index (kg/m^2)	<25
Waist circumference (cm)(M:F)	<94:82
Physical activity ‡(min/day)	≥30
(per week)	≥3
Serum lipids (mmol/L)	
Total cholesterol	<3.99
Total triglycerides	<1.7
LDL-cholesterol	<2.6
HDL-cholesterol	>1.1

* Adapted from references 3,4,5.
† Capillary (finger-prick) plasma glucose.
‡ Moderate physical activity, eg, brisk walking.

PHARMACOLOGIC MANAGEMENT OF HYPERGLYCEMIA

The recommended initial therapy and the cornerstone in management of type 2 diabetes is lifestyle modification (diet and exercise), isocaloric diet if normal weight and weight reducing if overweight. The significance of lifestyle modification cannot be overemphasized; it is associated with reduction in weight, blood glucose and lipids, blood pressure, and other cardiovascular risk factors and decreases the cost and side effects associated with drugs; it is also superior to drugs for the prevention of diabetes.[5,10,11] If lifestyle modification fails to achieve control, antihyperglycemic agents (oral antidiabetes drugs or insulin) are added.[3–9,13–15,18]

Antihyperglycemic Agents

Table 2 summarizes some properties of each class of antihyperglycemic agents with respect to mechanism of action, effect on hemoglobin A1C, side effects, contraindications, nonglycemic effects, evidence for benefit, and cost.[14,15,18] Currently, a large number of therapeutic choices (AHG classes, agents) and regimens are available, and within each, the individual choices have multiplied, and these pose a challenge for the busy clinician.[14,15,18] Until the 1990s, only three classes of antihyperglycemic drugs were available: secretagogs (sulfonylureas), insulin potentiators (biguanides), and insulin (semisynthetic human). Over the last decade, an additional three classes of oral agents (α-glucosidase inhibitors, thiazolidinediones [TZD], and meglitinides [non-SU secretagogs]) and monomeric insulin analogs have become available, with a few more in the pipeline. Treatment regimens include oral (monotherapy, combination oral, oral plus insulin) and insulin (combination regimens.[14,18]

Management Strategies

Management strategies for type 2 diabetes are shown in Figure 1. Given

Table 2. Some properties of available antihyperglycemic classes

	Secretagog					
	Sulfonylurea	**Meglitinide**	**Biguanide**	**Thiazolidinedione**	**α-glucosidase inhibitor**	**Insulin**
Mode of action	↑ pancreatic insulin secretion		↓ HGP	↑ insulin sensitivity (liver, muscle, fat)	↓ GIT absorption of carbohydrate	↓ HGP; ↓ lipolysis; ↑ PGU
Hemoglobin A1C reduction (%)	1.5–2.0	0.5–1.0	1.5–2.0	0.75–2.0	0.5–1.0	unlimited
Contraindications	GFR <30mL/min†	• active liver disease‡ • pregnancy • breast feeding	• conditions predisposing to lactic acidosis • renal impairment§	• active liver disease‡ • edema • cardiac failure • anemia • pregnancy • breast feeding	• chronic GIT disease	nil
Side effects	• hypoglycemia • weight gain		• GIT (nausea; diarrhea) • lactic acidosis	• weight gain • edema • cardiac failure • anemia	• flatulence • diarrhea	• hypoglycemia • weight gain • transient edema
Non-glycemic effects		none	• ↓ cardiovascular risk markers • limits weight gain	• ↓ cardiovascular risk markers	• ↓ cardiovascular risk markers	• ↓ cardiovascular risk markers
Evidence for benefit for complications¶						
microvascular	++	−	++	−	−	++
macrovascular	0	−	+	+/−	+/−	+ (strongest)
Cost	low	high	low	high	high	± high

* ↑ : stimulates; ↓ : suppresses; HGP: hepatic glucose production; GIT: gastrointestinal; PGU: peripheral glucose uptake ; GFR: glomerular filtration rate.
† Should be used with caution if GFR <70 mL/min.
‡ Alanine transaminase (ALT) >2.5 × upper limit of normal.
§ GFR <70mL/min; persistent proteinuria; elevated serum creatinine.
¶ ++: strong; +: moderate; +/−: weak; 0: none; −: not tested.

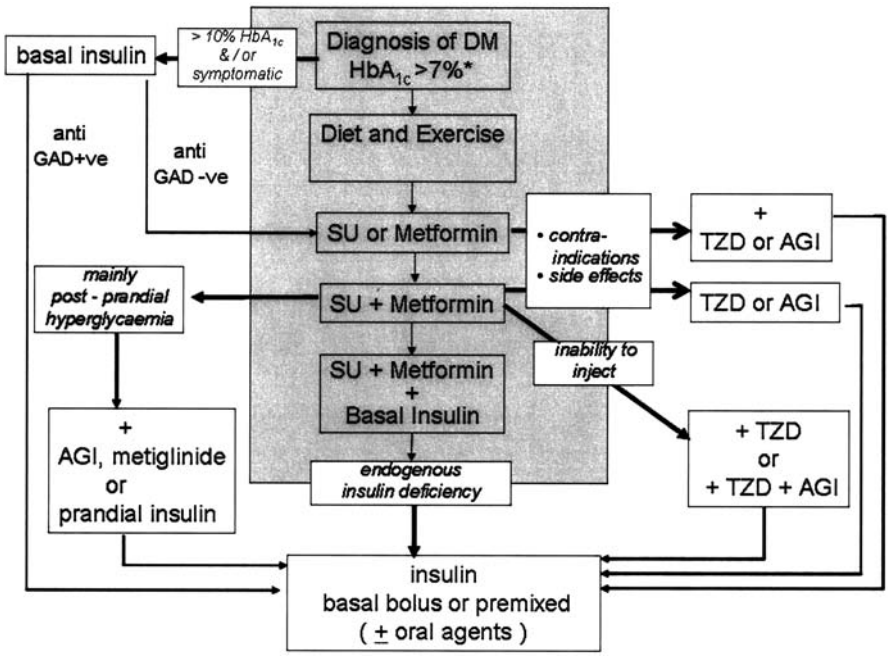

Fig 1. Management strategies for type 2 diabetes. (Adapted from Reference 14). The shaded portion reflects the standard methods. Boxes with italic text represent the indications for the individualized options, which are shown outside the shaded area. *: or if asymptomatic with fasting plasma glucose 6–15 mmol/L. GAD: glutamic acid decarboxylase; SU: sulfonylurea; TZD: thiazolidinedione; AGI: α-glucosidase inhibitor

the complexities of the large numbers of therapeutic choices and regimens and on the basis of proven benefit, long familiarity, known side effects, and decreased cost of sulfonylureas, biguanides (metformin), and insulin, one should start with standard methods (oral antidiabetes drug monotherapy, combinations, or two oral drugs plus basal insulin). New management strategies include fixed-dose oral agent combinations, three oral agents, biphasic insulin three times daily, and forced rapid titration.[14,15,18]

Standard Methods

At diagnosis, if hemoglobin A1C is >7% but <8% or if disease is asymptomatic with FPG 6–15 mmol/L, the initial therapy is lifestyle modification alone. If no control is achieved, then oral agents are added, as monotherapy (sulfonylurea or biguanide) then combination (sulfonylurea plus biguanide). Failure to achieve control with combination oral drugs necessitates the initiation of insulin either as an addition (combination therapy) or substitution (monotherapy). For combination therapy, the preferred method is the addition of basal (bedtime) insulin to the combined oral regimen. Substitution (monotherapy) therapy implies discontinuing oral agents and initiating at least two insulin injections per day. The standard approach is suitable for most patients with type 2 diabetes and in most instances should maintain control for up to 10 years after diagnosis.

Individualized Options

At least 5 indications exist for individualized options. Symptomatic hyperglycemia or other acute illness: if at diagnosis hemoglobin A1C is >10% in the symptomatic patient or patient with other acute illness, insulin therapy is indicated. Following control, the therapy can be switched to standard methods, provided the patient does not have late-onset type 1 diabetes, latent autoimmune diabetes of adults in which the blood will be positive for serum glutamic acid decarboxylase antibodies. Contraindications to or side effects from sulfonylureas or metformin necessitates the use of a third oral agent: TZD or α-glucosidase inhibitor may be used as oral monotherapy or as combination therapy (TZD + α-glucosidase inhibitor + sulfonylurea or biguanide) if one or both of the agents in the standard therapy are contraindicated. If initiating insulin therapy is difficult, a third oral agent may be added, ie, TZD or α-glucosidase inhibitor. If the problem is mainly one of post-prandial hyperglycemia, one can add mealtime insulin, α-glucosidase inhibitor, or non-sulfonylurea secretagogs. Failure to achieve control with standard methods may be an indication of endogenous insulin deficiency and the need for multiple injections of insulin, ie, intensive insulin therapy, either basal-bolus (four injections) or at least two injections of premixed insulin per day plus oral therapy.

Is Control Achieved with Conventional Therapy?

Despite the evidence for benefit of glycemic control, wide therapeutic choices/regimens, and clearer targets for control, glycemic control is far from ideal; treatment failures are encountered as frequently in academic clinics as in primary health care facilities.[14] In the recent analysis of the National Health and Nutrition Examination Survey III, when compared with the period 1988–1994, for the period 1998–2000, hemoglobin A1C worsened (7.8% vs. 7.6%), fewer patients achieved hemoglobin A1C <7% (35.8% vs. 44.5%), the proportion on insulin or diet alone decreased, while the proportion of those on oral therapy alone or on combination oral therapy increased. Multiple factors underlie this failure of treatment, including starting treatment too late and not titrating aggressively, financial con-

straints, patients' reluctance to use some of the therapies (especially insulin) and the lack of conviction by medical providers that treating diabetes is effective and worthwhile.[14]

PREVENTING DIABETES

The goal of ultimately reducing the population burden of diabetes by prevention and early treatment is of prime importance. Several studies have shown that in individuals at increased risk (IGT or gestational diabetes), diabetes can be prevented or delayed by intervention with lifestyle modification (DaQing, Diabetes Prevention Study) and drugs (Diabetes Prevention Program [lifestyle modification, metformin, troglitazone] and STOP-NIDDM [acarbose]).[5,10–12,15,19]

COST-UTILITY OF TREATMENT

The recently published UKPDS 72[20] was a cost-utility analysis of three different interventions in the UKPDS: intensive blood glucose control with sulfonylurea/insulin, metformin for overweight patients, and tight blood pressure control in type 2 diabetes with hypertension, using the UKPDS outcomes model. The analysis showed an incremental cost per quality of life-years (QALYs) gained for intensive blood glucose control (sulfonylurea/insulin) (£6028) and for tight blood pressure control (£369); metformin treatment was cost-saving and increased life expectancy.

The conclusion was that each of three intervention policies to reduce the burden of diabetes complications has a lower cost/QALYs gained than many other accepted uses of healthcare resources and that the results provide an economic rationale for improving standards of care with type 2 diabetes, ie, care should be at least to the level of these interventions.

CONCLUSIONS

Diabetes is one of the most common and expensive noncommunicable diseases; it is a leading cause of death and illness from its associated complications. However, evidence shows and that the disorder can be prevented and that early detection and a multifactorial, targeted approach to management will delay the onset and slow the progression of the disease and its complications and that such measures are cost-effective.

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