Non-insulin-dependent (type II) diabetes mellitus

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Non-insulin-dependent (type II) diabetes mellitus is an inherited metabolic disorder characterized by hyperglycemia with resistance to ketosis. The onset is usually after age 40 years. Patients are variably symptomatic and frequently obese, hyperlipidemic and hypertensive. Clinical, pathological and biochemical evidence suggests that the disease is caused by a combined defect of insulin secretion and insulin resistance. Goals in the treatment of hyperglycemia, dyslipidemia and hypertension should be appropriate to the patient's age, the status of diabetic complications and the safety of the regimen. Nonpharmacologic management includes meal planning to achieve a suitable weight, such that carbohydrates supply 50% to 60% of the daily energy intake, with limitation of saturated fats, cholesterol and salt when indicated, and physical activity appropriate to the patient's age and cardiovascular status. Follow-up should include regular visits with the physician, access to diabetes education, self-monitoring of the blood or urine glucose level and laboratory-based measurement of the plasma levels of glucose and glycated hemoglobin. If unacceptably high plasma glucose levels (e.g., 8 mmol/L or more before meals) persist the use of orally given hypoglycemic agents (a sulfonylurea agent or metformin or both) is indicated. Temporary insulin therapy may be needed during intercurrent illness, surgery or pregnancy. Long-term insulin therapy is recommended in patients with continuing symptoms or hyperglycemia despite treatment with diet modification and orally given hypoglycemic agents. The risk of pancreatitis may be reduced by treating severe hypertriglyceridemia (fasting serum level greater than 10 mmol/L) and atherosclerotic disease through dietary and, if necessary, pharmacologic management of dyslipidemia. Antihypertensive agents are available that have fewer adverse metabolic effects than thiazides and β-adrenergic receptor blockers. New drugs are being developed that will enhance effective insulin secretion and action and inhibit the progress of complications.

Le diabète sucré non insulinodépendant (de type II) est un trouble métabolique héréditaire caractérisé par l'hyperglycémie avec résistance à la cétose. La maladie se révèle habituellement après l'âge de 40 ans. Les malades présentent des symptômes variables, et ils sont fréquemment obèses, hyperlipidémiques et hypertendus. Des données cliniques, pathologiques et biochimiques suggèrent que la maladie est causée par une anomalie combinée de la sécrétion d'insuline et de l'insulinorésistance. Les objectifs du traitement de l'hyperglycémie, de la dyslipidémie et de l'hypertension devraient tenir compte de l'âge du malade, de la gravité des complications diabétiques et de la sécurité du régime. Le traitement non pharmacologique fait appel à la planification des repas pour atteindre un poids indiqué de manière à ce que les glucides fournissent entre 50 % et 60 % de l'apport quotidien en énergie, la réduction de l'apport en graisses saturées, en cholestérol et en sel s'il y a lieu et l'activité physique selon l'âge et l'état cardio-vasculaire du malade. Le suivi devrait comporter des visites régulières

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chez le médecin, l'accès à l'information sur le diabète, l'autosurveillance de la glycémie ou de la glycosurie et la mesure en laboratoire des taux plasmatiques de glucose et d'hémoglobine glycosylée. Si des taux de glucose plasmatique trop élevés (p. ex., 8 mmol/L ou plus avant les repas) persistent, l'utilisation d'hypoglycémiants (un sulfamide hypoglycémiant ou de la metformine ou les deux) est indiquée. L'insulinothérapie temporaire peut s'avérer nécessaire pendant une maladie intercurrente, la chirurgie ou la grossesse. L'insulinothérapie prolongée est recommandée chez les malades dont les symptômes ou l'hyperglycémie sont persistants malgré un traitement accompagné d'une modification de l'alimentation et des hypoglycémiants administrés par voie orale. Le risque de pancréatite peut être réduit en traitant l'hypertriglycéridémie grave (taux sérique à jeun supérieur à 10 mmol/L) et l'athérosclérose par un traitement alimentaire et, au besoin, pharmacologique de la dyslipidémie. Certains antihypertenseurs provoquent moins d'effets métaboliques défavorables que les thiazidiques et les bloqueurs des récepteurs β-adrénergiques. De nouveaux médicaments sont en cours d'élaboration pour améliorer l'efficacité de la sécrétion et de l'action de l'insuline et inhiber l'aggravation des complications.

Diabetes mellitus is a disease of excess glucose in the plasma, qualitative and quantitative abnormalities of carbohydrate and lipid metabolism, characteristic pathological changes in nerves and small blood vessels, and intensification of atherosclerosis.[1] Repeated fasting plasma glucose levels of 7.8 mmol/L or more (or 11.1 mmol/L or more at any time) establish the diagnosis.[2] Of the 3% to 4% of the general population known to be affected 90% have non-insulin-dependent (type II) diabetes (formerly known as maturity-onset diabetes), of whom 60% to 90% are obese (over 20% above the desirable body weight).[1-3]

In this paper I review the use of orally administered hypoglycemic agents and insulin in the context of currently accepted goals of management of type II diabetes, recent review articles and position papers on hypertension, lipoprotein risk factors and dietary therapy.[4-12]

Development of type II diabetes

Type II diabetes is genetically based.[13] The hyperglycemia is attributable to disordered insulin secretion and decreased insulin effects. The primary defect is not known and may differ among patients.[14] Obesity, a common precursor of type II diabetes, is associated with insulin resistance (decreased binding of insulin to cell membranes accompanied by decreased numbers of receptors, the highly specific sites of insulin–cell interaction responsible for activating transmembrane glucose transport and use).[15] Alternatively, there may be dysfunction of the intracytoplasmic effectors of the insulin-receptor message (e.g., the activation of glucose transporters).[15]

Current evidence suggests that the earliest abnormality in populations that go on to manifest type II diabetes (e.g., first-degree relatives) is insulin resistance, but with sufficient hyperinsulinemia to prevent elevation of the plasma glucose level.[16] Superimposition of a defect in insulin secretion is necessary for type II diabetes to evolve.[14] Defective transport of glucose into pancreatic β cells is one possible mechanism.[17] Thus, the high serum insulin levels typically found in people with early type II diabetes are always lower than those in nondiabetic subjects at comparable serum glucose levels.[18] Further secretory failure leads to hypoinsulinemia. Increased hepatic gluconeogenesis and glucose output result in fasting hyperglycemia.[14] These hepatic effects are in part attributed to hyperglucagonemia resulting from failure of the normal paracrine effect of insulin to suppress α cell function.[19] In addition, recent evidence suggests that hyperglycemia perpetuates the insulin secretion defect and the state of insulin resistance.[20]

Rationale and goals of therapy

Goals of therapy in type II diabetes include relieving the symptoms of hyperglycemia and hypoglycemia, attaining optimal body composition, and identifying and managing long-term diabetic complications and their consequences. Target glucose levels[2,7] (Table 1) should be adjusted to suit individual needs.[6-8,21] For example, in patients for whom hypoglycemia may have serious consequences (e.g., patients with stroke or seizure disorders or elderly patients) a premeal plasma glucose level of 10 mmol/L would be acceptable.[20,21]

The importance of tight control (i.e., maintaining the blood glucose level as close to normal as possible to prevent or delay vascular and neurologic complications) is supported by evidence from animal studies[7] and from natural history, cross-sectional and epidemiologic studies.[22-24] In addition, renal transplantation as well as up to 2 years of continuous subcutaneous insulin infusion in patients with type I diabetes were shown to benefit glomerular structure and function; symptomatic improvement in nerve function and lessening of neuropathic pain were also observed.[25] However, randomized controlled trials of

the effect of treatment on the progress of established microvascular and macrovascular complications in type II diabetes[26,27] and of retinopathy in type I diabetes[25,28] have given negative or inconclusive results. The risks and benefits of sustained near-normoglycemia in type I diabetes are being examined in the Diabetes Control and Complications Trial, a prospective 10-year program sponsored by the US National Institutes of Health.[29] Until the results are available it is sensible to assume that the onset or progress of microvascular complications may be delayed or reduced by glycemic control.[30]

Epidemiologic evidence suggests that dyslipidemia is an important contributing factor in atherosclerotic disease in type II diabetes.[31] Although there have been no clinical trials to test the effect of therapy, it is reasonable to apply management strategies and therapeutic goals known to reduce the effect of macrovascular disease on the health of nondiabetic patients.[31,32] The Canadian Consensus Conference on Cholesterol has recommended that in patients with hypercholesterolemia who are 30 years of age or more the target serum cholesterol level should be 5.2 mmol/L or less, with a triglyceride level of 2.3 mmol/L or less and a high-density lipoprotein (HDL) cholesterol level of 0.9 mmol/L or more.[10]

Hypertension is a risk factor for diabetic angiopathy and is prevalent in type II diabetes at approximately twice the rate in nondiabetic subjects.[33,34] The Canadian Hypertension Society Consensus Conference on Hypertension and Diabetes has advised that the target systolic and diastolic blood pressures during treatment should be below 160 and 90 mm Hg respectively; in patients over 65 years a systolic pressure below 180 mm Hg is acceptable.[9,35] In the presence of early diabetic nephropathy (as evidenced by increased urinary excretion of albumin) target values of less than 140/90 mm Hg have been recommended.[36]

Approach to management

Type II diabetes may be diagnosed incidentally or in association with an acute illness. In any case the contribution of medications known to promote hyperglycemia should be reviewed. Epinephrine, glucocorticoids, thiazide diuretics, salbutamol, phenytoin, niacin and syrup additives are known to raise the blood glucose level, whereas β blockers, salicylates, ethyl alcohol and phenylbutazone are known to lower it.[37] Thus, a thiazide diuretic might be replaced by an angiotensin-converting-enzyme (ACE) inhibitor.[9,33] Immediate intervention with insulin may be indicated in cases of hyperglycemia during pregnancy, acute illness, hyperosmolar coma or surgery.[21]

The patient or the family must receive instruction in the elements of diet and diabetes monitoring, preferably in a diabetes education centre. Adherence to the treatment program may be improved through a judicious mixture of didactic teaching and reinforcement by the physician and nurse-educators.[38] Instructions should be clear, particularly with respect to insulin dosage.[39]

Nonpharmacologic approach

Meal planning should be based on a diet provided by a qualified dietitian according to recommendations published by the Canadian Diabetes Association: the daily energy intake should be 80 to 150 kJ/kg of desirable body weight, the daily protein intake 0.8 g/kg of desirable body weight, the fat intake 30% or less of the energy intake (with saturated fatty acids not exceeding 10% of the energy intake) and the carbohydrate intake 55% to 60% of the energy intake (the fibre intake should be 6 g/1000 kJ).[10-12] Ideally, carbohydrates should be from foods known to reduce the rate and magnitude of glucose absorption, such as oats, beans and lentils (which contain soluble fibre) and pasta and barley (which contain starch).[11] Energy and protein demands are increased during growth, pregnancy, lactation and physical training. Energy demands are decreased with obesity and inactivity and in elderly people; protein demands are decreased in renal failure.

In obese patients diet therapy may increase insulin sensitivity and lower the glucose level before substantial weight loss occurs, but considerable

Table 1: Recommended target levels of plasma glucose and glycated hemoglobin in non-insulin-dependent (type II) diabetes mellitus[2,7]

Level	Normal*	Acceptable	Poor
Plasma glucose, mmol/L			
Before meals	4–6	< 8	> 11
2 h after meals	< 8	< 11	> 13
Hemoglobin A_{1c}†	0.04–0.06	< 0.085	> 0.10

*Only normal levels are acceptable in pregnancy.
†For the total glycated hemoglobin level multiply by 1.2.

weight (typically 20 kg) must be lost before insulin secretion is enhanced to the extent that fasting plasma glucose levels are normalized.[40,41] The sugar content of medications may be substantial.[42] Small amounts of artificial sweeteners (e.g., aspartame, saccharin and cyclamate) or nutritive sweeteners (e.g., sucrose, fructose or sorbitol) may improve compliance.[11] In cases of persistent hypercholesterolemia it may be necessary to restrict the cholesterol intake to 300 mg/d or less.[32] Alcohol, which contributes to obesity (energy value 29 kJ/g), hypertension and hypertriglyceridemia and predisposes to adverse effects of hypoglycemic medications, should be excluded if possible.[12,32,43,44] In newly diagnosed or poorly controlled cases with long-standing glucosuria osmotic diuresis may lead to vitamin or mineral depletion; in such cases supplementation, particularly with potassium (e.g., potassium chloride, 20 to 40 mmol/d), may be needed for a few weeks.[45] Some authorities have recommended limiting the salt intake to 3 g/d in patients with hypertension.[43]

Physical training enhances sensitivity to insulin, glucose uptake and glycogen deposition in muscle.[46] Long-term glycemic control may be unaffected or improved by physical training; dyslipidemia is favourably affected.[47] In one study walking 14.5 km per week was found to enhance weight loss in patients on controlled energy diets and to decrease hypoglycemic medication requirements.[48] Physical activity should be appropriate to the cardiovascular status of the patient. To ensure the safety of certain exercise regimens stress testing may be needed to rule out significant coronary artery disease.

Pharmacologic approach

Largely because compliance with therapeutic diets is poor,[49] the rate of success in achieving target glucose levels varies from 10% to 50%, inversely reflecting the degree of hyperglycemia at the time of diagnosis.[40] If acceptable glucose levels or progress toward them is not achieved within a reasonable length of time (e.g., 3 to 6 months), pharmacotherapy in association with continued dietary efforts is indicated.[7,21]

Sulfonylurea therapy: Orally given hypoglycemic agents derived from the sulfonamide group of drugs bind to specific receptors on the β-cell membrane, which depolarizes, permitting entry of calcium ions through voltage-dependent channels. This increases insulin secretion at any given glucose level,[7] resulting in decreased hepatic glucose production and decreased plasma glucose levels.[7,50] The short-term effect of sulfonylureas is thus to increase insulin secretion, with consequent hypoglycemia. In contrast, during long-term sulfonylurea therapy decreased plasma glucose concentrations are observed despite unchanged serum insulin levels.[7] This enhancement of the efficiency of endogenous insulin reflects continuing β-cell stimulation as well as increased insulin sensitivity in the liver and skeletal muscle.[7,50,51] Enhanced insulin sensitivity is attributed to a decrease in the toxic effect of glucose,[20] although there is evidence of an extrapancreatic effect of sulfonylureas that promotes glucose uptake.[7,50,51]

Factors favouring the success of oral hypoglycemic therapy include increased age, diabetes of short duration, obesity and moderate hyperglycemia (Table 2).[7] Contraindications include pregnancy, surgery and allergy to sulfonamide-type drugs.[7] Sulfonylureas were recently reported to be in use in 35% of patients with type II diabetes in the United States.[52] The agents currently available in Canada are characterized according to duration of action in Table 3. In appropriately selected patients sulfonylureas are as potent as insulin and may reduce glucose levels by 20% to 40%.[7,54] About 15% of patients fail to respond, in some cases probably owing to noncompliance with the diet.[7] Rates of secondary failure (to be differentiated from loss of control due to noncompliance or intercurrent illness) are 5% to 10% per year, evidently often due to β-cell secretory failure.[55] Although not proven in controlled trials,[4] substituting a "second-generation" sulfonylurea agent (e.g., glyburide) for tolbutamide or chlorpropamide may lead to recovery of glycemic

Table 2: Patient characteristics favouring either oral hypoglycemic or insulin therapy[7]

Characteristic	Oral hypoglycemic therapy	Insulin therapy
Age, yr	> 40	≤ 40
Duration of disease, yr	< 5	≥ 5
Weight	Obese	Not obese
Prebreakfast plasma glucose level, mmol/L	< 10	≥ 10
Other	Visual or manual disability	Organ failure (e.g., renal, hepatic, cardiac)

control.[7] The net benefit of adding sulfonylureas to insulin therapy to improve control has not been established.[7]

In one study episodes of self-treated hypoglycemia during sulfonylurea therapy were observed in 20% of 203 patients over 6 months.[56] Neuroglycopenia with coma or confusion necessitating assistance occurs at the rate of one event per 5000 patient-years, the death rate being 10%.[57] Chlorpropamide, the most frequently used sulfonylurea agent,[52] has been incriminated most often,[58] although in one recent study the prevalence rate of hypoglycemia during glyburide therapy (31%) exceeded that during therapy with chlorpropamide or gliclazide (14%).[56] Risk factors for severe hypoglycemia include poor food intake, advanced age and combination with another agent (e.g., insulin) or a potentiating drug (e.g., alcohol, salicylate, phenylbutazone or an antibacterial sulfonamide).[7,54,58] Hepatic failure may impair the metabolism of sulfonylureas; only tolbutamide is relatively safe in renal failure (Table 3).[53] Ionic binding of certain sulfonylureas to serum albumin (Table 3) may lead to adverse potentiation of effect by such drugs as fibrate hypolipidemic agents and salicylate. Urinary excretion may be limited by the effects of allopurinol or probenecid.[7,44]

Gastrointestinal side effects (e.g., vomiting, cholestasis and abnormal liver function) occur in up to 3% of cases; dermatologic (e.g., pruritus and erythema nodosum) and hematologic (e.g., hemolysis and aplastic anemia) complications are rare.[4,7] Chlorpropamide is occasionally associated with hyponatremia due to an antidiuretic-hormone-like effect or with severe flushing during alcohol ingestion.[7]

An important conclusion of the University Group Diabetes Program (UGDP), a randomized, placebo-controlled prospective trial of the long-term effects of hypoglycemic agents (mainly insulin and tolbutamide) in type II diabetes, was that tolbutamide therapy was associated with excessive rates of sudden death and fatal myocardial infarction.[59] This conclusion prompted debate on the hazards of oral hypoglycemic therapy that persisted through the 1970s. Proponents of sulfonylurea therapy pointed to the unexpectedly low death rates in the placebo-treated group and to the safety of tolbutamide in other trials.[7,60] In the UGDP the well-recognized problem of secondary failure during sulfonylurea therapy was not dealt with as is now recommended (i.e., with a revised drug dosage or regimen[8]). As a result, among the patients who died from cardiovascular causes during tolbutamide therapy there was a disproportionate number with antecedent fasting blood glucose levels greater than 11.0 mmol/L. This suggests that in the absence of an adequate hypoglycemic response continuing exposure to tolbutamide or, by inference, to other sulfonylureas is unwise.[60] Thus, the fact that the UGDP's conclusion about the safety of tolbutamide has not been substantiated may be due in part to the application today of more stringent glycemic goals during oral hypoglycemic treatment, an approach engendered by the UGDP itself.

Metformin therapy: Metformin is an orally administered hypoglycemic agent belonging to the biguanide class of drugs. Its mechanism of action has not been definitely established. There is evidence that metformin acts on hepatocytes to decrease

Table 3: Characteristics of currently available sulfonylurea hypoglycemic agents[53]

Duration of action; drug	Daily dosage	% of active metabolites cleared by kidney	Problems
Short-acting (6–10 h)			
Tolbutamide	0.5–3.0 g in two or three doses	0	Displaced from albumin, frequent doses needed, hyponatremia (unusual)
Intermediate-acting (12–24 h)			
Acetohexamide	0.25–1.5 g in one or two doses	60	Displaced from albumin, retained in renal failure
Gliclazide	80–320 mg in one or two doses	< 20	Retained in renal failure
Glyburide	2.5–20 mg in one or two doses	40	Retained in renal failure, hypoglycemia
Long-acting (24–72 h)			
Chlorpropamide	100–500 mg in one dose	20	Displaced from albumin, retained in renal failure, hypoglycemia, hyponatremia, flushing with alcohol ingestion

glucose production.[61] Although evidence of increased insulin binding to tissues has not been consistent, it appears that the drug also intensifies insulin's action on muscle, promoting glucose uptake.[62] Metformin is not dependent on endogenous insulin secretion for its effects.[63] Absorption is almost complete, and the half-life is 2 to 4 hours.[7] The drug is not protein bound and is excreted virtually unchanged by the kidneys.[7]

Metformin therapy may be considered in both nonobese and obese patients in whom treatment with diet and exercise has failed. The hypoglycemic potency of the drug is somewhat less than that of the sulfonylureas, but 75% to 85% of patients may be expected to respond.[7,61,63,64] Metformin alone may be most useful in mildly hyperglycemic patients, or it may be combined with a sulfonylurea agent to effectively regain control.[65,66] Groop and associates[67] reported that in 24 cases of failed glyburide therapy the addition of metformin resulted in a decrease of 30% in glucose levels, equivalent to that obtained with twice-daily insulin mixtures. Inconsistent improvements in serum lipid levels have been reported.[68] Metformin may be used in conjunction with insulin therapy, but its long-term benefits in maintaining glycemic control have not been assessed.[63] In most studies a decrease in body weight has been observed, but of concern is the recent report that lean body mass is replaced by adipose tissue, with little net change in weight noted during 6 months of treatment with metformin–glyburide.[67]

Although the recommended dosage of metformin is 0.5 to 1.0 g two or three times per day before meals, with a maximum of 2.5 g/d, use is limited by dosage-related gastrointestinal symptoms, particularly diarrhea, in up to 20% of patients.[7] Thus, management strategies include starting treatment at a low dosage, or temporarily stopping treatment and then gradually reintroducing the drug. Because the use of metformin in renal failure (in which toxic levels occur), alcoholism, hepatic failure and ischemic disease may cause lactic acidosis, these conditions are absolute contraindications. However, lactic acidosis appears to be rare, being reported at a rate of less than one case per 10 000 patient-years of treatment; the death rate is 30% to 50%.[57,69]

Insulin therapy: Overall, perhaps 30% of patients with type II diabetes are insulin receiving.[1] Insulin may be used as the initial hypoglycemic agent in patients who are relatively young (40 years or less) and lean (within 120% of the desirable weight) (Table 2). It should be used without delay, regardless of age, in patients whose condition is clearly catabolic or ketotic.[4,20] In cases of failure of diet therapy insulin may be given to patients who are considered good candidates for treatment with orally given agents or who have had adverse effects with such agents. The chances of success (i.e., a median decrease in the fasting plasma glucose level of about 2.0 mmol/L) are similar with insulin and with orally administered agents.[64] In a 9-month randomized controlled trial a single daily dose of an intermediate-acting insulin preparation and a single daily dose of glyburide were found to be equally effective.[70] Insulin therapy is indicated when poor control persists with diet therapy and treatment with orally given hypoglycemic agents at maximum dosage.[21,65] However, following failed therapy with orally given agents, insulin therapy may be no more successful, possibly owing to noncompliance.[65] In such cases reversion to an orally administered agent is not contraindicated.[71]

Impairment of vision or of manual dexterity does not necessarily preclude the use of insulin, since helpful strategies are available: magnifiers that can be attached to the barrel of the syringe, the use of prefilled syringes by a visiting nurse or relative and pen-like injection devices that permit immediate, accurate injection without the need to fill a syringe (e.g., Novolin-Pen II [Connaught Novo Ltd., Willowdale, Ont.] and Insuject X [Nordisk Gentofte Canada Inc., Mississauga, Ont.]).[72]

Insulin preparations are classified as short acting (maximum duration of action 4 to 8 hours), intermediate acting (14 to 24 hours) and long acting (20 to 36 hours). Short-acting insulin preparations include regular and semilente (duration of action up to 16 hours), intermediate-acting preparations include isophane (NPH [neutral protamine Hagedorn]) and lente, and long-acting preparations include ultralente and protamine zinc.

Treatment with a single prebreakfast injection of an intermediate-acting insulin preparation may be effective and may be started in outpatients under the daily supervision of a nurse or physician.[73] Human insulin and animal insulin are of equal efficacy.[74,75] The starting dosage should be in the range of 0.3 to 0.5 U/kg per day to avoid hypoglycemia, particularly in an outpatient setting. The glycemic response may be assessed through the blood or, initially at least (the imprecision of the method being kept in mind), the urine glucose levels before the main meals. Dosage increases of 2 to 5 U/d should be made at intervals of at least 3 days. If the afternoon blood glucose value is satisfactory but early-morning hyperglycemia persists a second injection may be added such that 50% to 70% of the daily dose is given before breakfast and 30% to 50% at supper. If prelunch or bedtime hyperglycemia persists small amounts (e.g., 4 to 10 U) of regular insulin may be added before breakfast or supper and the dosage adjusted according to the subsequent prelunch or bedtime blood glucose values. In such "split-mixed" regimens, which in practice are necessary in most

cases, control is often achieved with a ratio of regular to intermediate-acting insulin of 1:1 or 1:2.[73] The eventual dosage requirement may approach or surpass 1 U/kg per day, presumably owing to the inherent insulin resistance of type II diabetes.[14] For convenience and to reduce the frequency of dosing errors regular and NPH preparations may be obtained premixed in ratios selected by the manufacturer (i.e., 15:85, 30:70 and 50:50). These preparations as well as regular and NPH preparations alone are available in ampoules for insertion into insulin "pens."

In cases of persistent early-morning hyperglycemia a less preferable alternative to splitting the dose of intermediate-acting insulin is injection before breakfast of a long-acting preparation as the sole agent, particularly if the prebreakfast plasma glucose level was greater than 10 mmol/L before insulin therapy was started.[64] Alternatively, the concept of administering intermediate-acting or long-acting insulin at bedtime is attractive, but the criteria for selecting patients and appropriate dosage have not been determined.[76] To avoid overnight hypoglycemia with such regimens consumption of a bedtime snack containing carbohydrate should be considered.

Because of resistance to insulin[14] and the relatively intact hormonal responses (primarily of pancreatic glucagon and epinephrine) to hypoglycemia in type II diabetes, insulin reactions are less frequent and less severe than in type I diabetes.[77] Nevertheless, to prevent hypoglycemia with an unusual amount of exercise a decrease in the preceding insulin dosage or intake of extra carbohydrate may be necessary.[73] Decreases in the dosage may be necessary in the first few weeks of treatment, since sensitivity to insulin improves with control of hyperglycemia and, over the long term, with decreased adiposity or renal failure.[40,73,78] Increased body fat, commonly attributed to the storage of energy formerly lost as glucosuria, is a frequent complication.[64,70,79] However, in such cases one should assess the adverse effects of poor compliance with diet.

Antibody-mediated problems (e.g., local or generalized allergy and lipoatrophy at the injection site) occur less frequently with human insulin than with animal insulin, whose amino acid composition differs slightly.[74] In cases in which animal insulin is being used treatment with similar formulations of human insulin is indicated.[74,75,80] Insulin insensitivity is most commonly due to reduced binding of insulin to receptors or to impaired receptor function. The requirement of more than 200 U/d for more than 2 days in the absence of acute illness suggests antibody-mediated insulin resistance, which is increasingly rare.[15,81] In such cases if substitution of human for animal insulin is proposed a substantially decreased dosage should be used to avoid hypoglycemia. Because in many cases insulin resistance appears to represent an anamnestic response to a previous course of insulin therapy, human insulin preparations should be used in patients requiring short-term insulin administration (e.g., those with gestational diabetes or acute illness and those undergoing surgery).[80] Unusually large insulin requirements may also be found during a concurrent severe illness (e.g., shock or neoplasia).[82,83]

Hyperinsulinemia consequent to the insulin dosage necessary to achieve reasonable glycemic control[84] has been incriminated in the development of both hypertension and atherosclerosis.[85] Therefore, therapy with agents not associated with elevated insulin levels (e.g., metformin) may be advantageous provided that adequate glycemic control is achieved.[7,62]

Monitoring

The monitoring program should be practical yet as sophisticated as is necessary to help safely achieve glycemic control. Patients treated with diet modification alone and certain patients treated with orally given hypoglycemic agents may do well testing the urine daily for glucose (Diastix [Miles Canada Inc., Etobicoke, Ont.] or Chemstrip uG 5000 [Boehringer Mannheim (Canada) Ltd., Dorval, Que.]) in association with regular assessment of the plasma glucose concentration.[38,65] Although self-monitoring of the blood glucose level was not found to improve control in patients with type II diabetes in a clinical trial,[86] some patients may prefer or need (owing to a high renal threshold for glucose excretion) a visually based or meter-based monitoring system. The immediate feedback may improve patient satisfaction and may increase the rate of detection of asymptomatic hypoglycemia during oral hypoglycemic therapy.[87] The glycated hemoglobin level should be measured at least twice a year, four times a year if possible in patients receiving insulin.[38]

Management of dyslipidemia

The management of dyslipidemia in type II diabetes, including strategies for dietary intervention, has recently been reviewed.[32,88] Abnormalities of serum lipid levels may resolve with weight loss and glycemic control. Persistent moderate elevation of the fasting serum triglyceride level (3.0 to 8.0 mmol/L) due to elevated levels of very-low-density lipoprotein (VLDL) cholesterol with or without decreased HDL-cholesterol levels (less than 0.9 mmol/L) may respond to treatment with a fibric acid derivative, such as gemfibrozil (600 to 1200 mg/d) or fenofibrate (300 mg/d); adverse effects include predisposition to gallstone formation, myopathy (partic-

ularly with renal failure) and abnormal liver enzyme levels. Therapy with niacin, 1.5 to 6 g/d, may be effective and is highly recommended in the general population;[32] however, niacin is poorly tolerated in diabetic patients, contributing to hyperglycemia and hyperuricemia.[89] Severe hypertriglyceridemia (fasting serum level greater than 10 mmol/L), which usually reflects decreased clearance of chylomicrons through lipolysis, predisposes to acute pancreatitis.[90] The patient should receive prompt, aggressive treatment with a low-fat diet, a fibrate and acceptable glycemic control. Hypercholesterolemia may reflect elevated serum levels of VLDL-cholesterol or low-density lipoprotein (LDL) cholesterol. Hypercholesterolemia due to persistently elevated LDL-cholesterol levels despite restriction of dietary fat and cholesterol responds well to treatment with the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor lovastatin, 20 to 80 mg/d.[32,88] There has been less clinical experience with the related agents simvastatin (10 to 40 mg/d) and pravastatin sodium (10 to 40 mg/d). The bile acid sequestrants cholestyramine resin (12 to 24 g/d) and colestipol hydrochloride resin (15 to 30 g/d) may be effective but may further elevate serum triglyceride levels or decrease absorption of other orally administered medication (e.g., digoxin and levothyroxine sodium). If necessary, gemfibrozil may be combined with a bile acid sequestrant, but combination with lovastatin is relatively contraindicated since there is a danger of severe myopathy.[32,88] Although therapy with probucol, 1 g/d, reduces LDL-cholesterol levels and has a potentially beneficial antioxidant effect, an undesirable decrease in HDL-cholesterol levels also occurs.[88] Despite their hypolipidemic and antithrombotic effects, the highly polyunsaturated (omega-3) fatty acids derived from fish oil are not recommended in non-insulin-receiving patients since these compounds have been reported to inhibit insulin secretion.[91]

The xanthine derivative pentoxifylline (800 mg/d) decreases blood viscosity and may be effective in the symptomatic treatment of intermittent claudication.[92] The finding of an improved prognosis after stroke in patients treated with acetylsalicylic acid (ASA) or dipyridamole[93] suggests that therapy with a platelet-aggregation inhibitor, such as ASA (325 to 750 mg/d) or dipyridamole (150 to 300 mg/d) or both, should be considered in the absence of contraindications (e.g., predisposition to retinal hemorrhage).

Management of hypertension

After mild to moderate hypertension is diagnosed a 6-month period of nonpharmacologic treatment with weight control, exercise, and restriction of salt intake, alcohol intake and cigarette smoking is recommended.[43] Agents chosen to treat hypertension should not disrupt glycemic control or contribute to existing complications. Adverse effects on the adrenergic response to hypoglycemia may be reduced if β blockers are cardioselective (e.g., metoprolol, 100 to 400 mg/d), although cardioselectivity is lost at higher dosages (about 200 mg/d with metoprolol).[47] However, hypertriglyceridemia, impotence and peripheral arterial insufficiency may be worsened.[33,94,95] Treatment with an ACE inhibitor, such as captopril (25 to 150 mg/d) or enalapril maleate (2.5 to 40 mg/d), decreases intraglomerular pressure and thus may be advantageous in cases complicated by diabetic nephropathy.[96] However, in patients with renal insufficiency hyperkalemia may be a problem.[96] Evidence for a hypoglycemic effect is conflicting.[96] Therapy with a calcium-channel blocker, such as nifedipine (20 to 80 mg/d) or diltiazem hydrochloride (120 to 360 mg/d), may slightly elevate the plasma glucose level; vasodilatation may be useful in cases of coronary artery disease but disadvantageous in those of postural hypotension (i.e., with autonomic neuropathy).[94,95] The latter characteristics are shared by α_1-adrenergic receptor blockers, such as prazosin hydrochloride and terazosin hydrochloride (1 to 20 mg/d). The centrally acting agents methyldopa (0.5 to 2 g/d) and clonidine (0.1 to 0.6 mg/d) may be useful in systolic hypertension, although impotence and postural hypotension may be worsened.[95] These agents may be combined with the vasodilator hydralazine hydrochloride (40 to 300 mg/d) without undue effect on blood glucose levels.

Although thiazide diuretics have long been an important component of antihypertensive regimens, particularly in elderly patients, recently there has been concern about the worsening of hyperlipidemia and recognition of the association of the hypokalemic and hyperglycemic effects.[9,94,95] Initial monotherapy with one of the newer agents (ACE inhibitors or calcium-channel blockers) is preferable. If a thiazide is to be used the dosage should be low (e.g., hydrochlorothiazide, 12.5 to 25 mg/d).[9] With hypokalemia a potassium supplement (25 to 50 mmol/d) or a potassium-sparing diuretic (e.g., amiloride hydrochloride, 5 to 10 mg/d, or spironolactone, 50 to 100 mg/d) should be added, with continued monitoring to maintain normokalemia. In cases of chronic renal failure (serum creatinine level greater than 200 μmol/L) a loop diuretic such as furosemide (40 to 80 mg/d) should be used.[9]

Management of neuropathic complications

Neuropathy affects an estimated 50% of patients with long-standing diabetes.[97] Pain and deformity in

the extremities with susceptibility to ulcers on the soles of the feet are the main clinical manifestations of distal symmetric sensorimotor polyneuropathy.[97] In the management of pain, which is typically nocturnal, the contributions of ischemia, alcohol or neurotoxic medication (e.g., hydralazine) should be identified. Symptoms should initially be managed with mild analgesics and hypnotics. If the symptoms are not controlled tricyclic antidepressants (e.g., amitriptyline hydrochloride, 10 to 150 mg/d) are useful but may induce orthostatic hypotension. Alternatively, carbamazepine (100 to 600 mg/d) is also effective under controlled conditions but has numerous toxic effects.[97]

In the management of autonomic neuropathy the aim is to improve the function of the affected organs. Orthostatic hypotension may respond to salt supplementation or to therapy with fludrocortisone acetate (0.05 to 0.2 mg/d). The delayed gastric emptying secondary to gastropathy may respond to treatment with metoclopramide hydrochloride (15 to 80 mg/d) or domperidone (30 to 80 mg/d) given before meals.[97] Extrapyramidal manifestations and tachyphylaxis, which are associated with these medications, are not found with cisapride monohydrate (15 to 40 mg/d given before meals), a new prokinetic agent that is effective under controlled conditions.[98] Diabetic diarrhea may respond to treatment with a mild opiate receptor agonist (e.g., loperamide hydrochloride, 4 to 16 mg/d) and diabetic cystopathy to therapy with a parasympathomimetic agent (e.g., bethanechol chloride, 20 to 200 mg/d).[97,99]

Future directions

New orally given hypoglycemic agents capable of enhancing insulin secretion or tissue sensitivity are being studied.[7] The antihyperglycemic effect of acarbose, a competitive inhibitor of the enzymatic hydrolysis of dietary starch and sucrose, is being assessed.[100] Alternative routes (e.g., nasal) of administration of insulin are being explored.[101] Attempts to mitigate pharmacologically the pathological effects of hyperglycemia include the use of the experimental aldose reductase inhibitors, which limit the intracellular accumulation of the sugar alcohol sorbitol, with potential benefit to function of nerve, retina and renal glomerulus;[102] lessening of painful neuropathy was found after 1 year of treatment with one such agent, tolrestat.[103] An effect of ACE inhibitors independent of their antihypertensive effects, the potential to reverse incipient nephropathy, is being examined.[104] In the future the management of type II diabetes should be increasingly effective.

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