Management of type 2 diabetes mellitus for general practitioners

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Case scenario

A 55-year-old Asian man presents with a history of intense thirst, polyuria, blurring of vision and weight loss over a period of several weeks. He is obese with a waist circumference of 110 cm and a body mass index (BMI) of 32 kg/m^2. His blood pressure is 170/110 mmHg. Laboratory investigations indicate the following: random blood glucose 13.6 mmol/l, haemoglobin A1c (HbA1c) 9.5%, total serum cholesterol 6.8 mmol/l, low-density lipoprotein (LDL) cholesterol 3.5 mmol/l, high-density lipoprotein (HDL) cholesterol 0.7 mmol/l, triglycerides 3.2 mmol/l, and serum creatinine normal. His urine shows glycosuria and microalbuminuria.

What would be your approach to this patient's management?

Introduction

In 1985 there were approximately 30 million people with diabetes worldwide. This figure had risen to 285 million by 2010, and is projected to rise to 438 million by 2030. This exponential increase is associated to a large extent with a growing obesity epidemic. Type 2 diabetes mellitus is associated with an approximately twofold increased mortality, largely due to macrovascular diseases such as coronary artery disease and stroke. Patients with type 2 diabetes mellitus are also prone to microvascular complications such as retinopathy, which is the main cause of blindness in the developed world, and neuropathy, which is also responsible for much suffering and disability. Macrovascular disease and neuropathy are important factors causing lower extremity amputations. It is estimated that the cost of diabetes complications accounts for five to 10% of the total healthcare spending in the world.[1]

Principles of management in non-pregnant adults

Diabetes is a chronic illness which requires not only continuing medical care, but also continuing patient self-management, education and support.[2] Diabetes management extends beyond glycaemic control: the Steno-2 study showed that intensive multifactorial intervention, which included strict attention to the management of cardiovascular risk factors, was more cost-effective than conventional treatment.[3] An organised multidisciplinary team is essential for the implementation of comprehensive care for type 2 diabetes mellitus.

Initial evaluation of a patient with type 2 diabetes mellitus should include a comprehensive clinical assessment. Medical history should include age and initial presentation, eating patterns, physical activity, and associated conditions and therapies. Physical examination should include height, weight, body mass index (BMI), waist circumference and blood pressure (BP) measurement, and fundoscopic examination, skin and comprehensive foot examination.[2]

According to the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), laboratory examination should include HbA1c, a lipid profile, urine for microalbumin and serum creatinine at the initial consultation.[4]

Lifestyle interventions

Medical nutritional therapy should be individualised and should be provided by a registered dietitian. Weight loss by reduction in total calorie intake is recommended for all overweight patients; even a modest reduction of 5% of body weight has been associated with significant health benefits. Eliminating simple sugars and reducing the amount of rapidly absorbed carbohydrates with substitution of more slowly assimilated fibre-rich starches is strongly advised. A reduction in saturated fat intake, with substitution of polyunsaturated with monounsaturated fats, is recommended. Regular physical activity, both aerobic

and strength training, should be part of comprehensive care. Current recommendations are at least 150 minutes per week of moderate-intensity exercise.[5] Patients must be evaluated, not only for contraindications and limitations to physical activity, but also for weight loss targets. Exercise prescription should be developed to improve functional capacity, to decrease risk of falls and fractures, and to effect weight loss. Regular exercise helps to maintain weight loss, and improves insulin sensitivity, the lipid profile, and glycaemic and BP control. Caution should be exercised in those with coronary artery disease. Smoking should be prohibited in all patients.

Glycaemic control

There is incontrovertible evidence that good glycaemic control is of benefit, especially with respect to prevention or reduction of microvascular complications.[6] The aim of glycaemic treatment is to achieve the recommended targets with as few adverse events as possible. Monitoring of glucose may be achieved by self-monitoring by the patient or long-term monitoring of glycated haemoglobin by the healthcare provider. HbA1c is formed by non-enzymatic attachment of glucose to the N-terminal valine of the β chain of haemoglobin. It represents glycaemic control over the preceding eight to 12 weeks, as the life span of the erythrocyte is approximately 120 days.[7] It has many advantages but it is important to be aware of some of the pitfalls with this measurement, such as conditions that may alter the erythrocyte lifespan or interfere with measurement such as haemoglobinopathies, as well as cost and lack of routine availability and standardisation.

Self-monitoring of blood glucose (SMBG) should be carried out three or more times daily by patients using multiple insulin injections. For patients on less frequent injections SMBG should still be encouraged, and for patients on non-insulin therapies, SMBG is not essential but may be a useful guide to success of therapy.[2]

The HbA1c target has been a subject of much controversy lately. SEMDSA recommends HbA1c of less than 7%, but emphasises that goals should be individualised based on duration of diabetes, co-morbid conditions, pregnancy status, hypoglycaemia unawareness, age and individual patient considerations.[4] The American Diabetes Association (ADA) is in agreement with SEMDSA, also recommending an HbA1c target of less than 7%.[2] HbA1c should be measured twice yearly in those patients who are meeting their goals, and quarterly in those whose therapy has changed or who are not meeting their glycaemic goals. The major benefit of the HbA1c measurement is the strong predictive value for microvascular complications.[8] The benefits of intensive glycaemic control on microvascular and neuropathic complications are well established and should not prompt

clinicians to abandon the target of an HbA1c under 7%.[9,10] However, less stringent goals may be appropriate for some selected patients, as "one size does not fit all." A recent study has prompted a reconsideration of the target HbA1c level in patients with type 2 diabetes mellitus: it showed a general U-shaped association between the HbA1c and outcome, with the lowest hazard ratio at an HbA1c of about 7.5%.[11]

Pharmacological treatment of diabetes mellitus should complement lifestyle modification. It is important to emphasise to the patient that the natural history of diabetes will invariably lead to escalation of the initial therapy with time and that insulin therapy is almost invariably required, despite the fact that there are significant barriers to starting insulin therapy.[12]

Pharmacotherapy

Metformin

Metformin is the initial therapy of choice and should be commenced at the time of diagnosis in all patients, unless contraindicated. Metformin is a biguanide and its mode of action includes reduction of hepatic insulin resistance, gluconeogenesis and glucose release. The expected decrease in HbA1c is about 1 to 2%. It is recommended that metformin be continued when other therapies (including insulin) are added.[13] The major adverse effects are gastrointestinal in nature and, rarely, include lactic acidosis (in patients with impaired renal, hepatic and cardiac dysfunction, as well as alcohol abuse).

Recently, a number of publications have attested to the fact that metformin is associated with lower cancer risk in patients with type 2 diabetes mellitus.[14-17] New extended-release tablets should be considered when gastrointestinal side-effects pose a problem and prevent continuation of metformin. It is worth noting that metformin use may be associated with vitamin B_{12} deficiency over time.[5]

Sulphonylureas

Sulphonylureas may be used as first-line therapy when HbA1c is above target and the patient is of normal weight or is intolerant to metformin. They can also be added as second-line agents to metformin.[4] Sulphonylureas belong to a group of drugs known as insulin secretagogues, and lower glycaemia by enhancing insulin secretion. They lower HbA1c by approximately 1.5% and cause weight gain of around 2 kg.[18] The other common adverse effect is hypoglycaemia.

Thiazolidinediones

Thiazolidinediones (e.g. pioglitazone) are peroxisome pro-liferator-activated receptor γ modulators, and thus increase

the sensitivity of muscle, fat and liver to endogenous insulin ("insulin sensitisers"). Caution should be advised when initiating this group of drugs, as they carry an increased risk of fluid retention, congestive heart failure and fractures in women.[18,19] SEMDSA recommends the use of thiazolidinediones in a selected group of patients, such as obese individuals who cannot tolerate metformin. They reduce HbA1c by 0.5 to 1.4%. There are no long-term outcome studies on these agents as yet.

Incretin-based therapies

These are newer therapies available in South Africa. The two most recently approved classes of therapeutic agents for the treatment of type 2 diabetes mellitus are glucagon-like peptide-1(GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP4) inhibitors. They exert their action through potentiation of incretin receptor signalling. Incretin hormones are released from the small intestine at mealtimes and increase glucose-dependent insulin secretion from the pancreas. GLP-1 also suppresses glucagon production and works on the brain, promoting a feeling of satiety as well as regulating gastric emptying.

This group of drugs provides a new option for the treatment of type 2 diabetes mellitus and enables intensification of therapy whilst controlling body weight and lowering the risk of hypoglycaemia.[20] The most common adverse effect is nausea, which wanes over time. In addition, association with pancreatitis has been suggested but remains contentious. A major benefit of GLP-1 analogues is weight loss. The incretin-based therapies are less well-validated therapies and there are no long-term outcome studies as yet.

Insulin

Insulin may be considered a first-line therapy or second- or third-line therapy as add-on to oral agents. SEMDSA recommends insulin as first-line therapy in the case of severely uncontrolled diabetes with catabolism. This includes patients with fasting plasma glucose of greater than 14 mmol/l, random glucose levels consistently in excess of 16.7 mmol/l, HbA1c over 10%, or the presence of ketonuria, or in a patient who is symptomatic with polyuria, polydipsia, and significant weight loss.

Once-daily basal insulin may be an appropriate transition. Analogue basal insulin may be considered in patients with hypoglycaemia. Because of their pharmacokinetic profile, analogues have the advantage of lessening the risk of hypoglycaemia and thus allowing patients to achieve their glycaemic targets at lower risk of developing hypoglycaemia. Biphasic insulin would be the next appropriate step, during which time metformin should be continued. Multiple daily injections should be considered if the above does not result in glycaemic targets being met; however, it is important to

realise that this regimen may be the method of choice at the outset in selected patients.

SEMDSA recommends the following insulin implementation: Basal insulin should be started with 10 units of intermediate-acting (NPH) or long-acting insulin at bed time. This should be increased by two units every three to seven days until the fasting glucose target is met. SEMDSA recommends a preprandial target of 4-7 mmol/l. One should continue with metformin and possibly sulphonylurea when adding basal insulin. Biphasic insulin should be started with a total dose of 0.4 U/kg, with two-thirds initially administered before breakfast and one-third before supper. The morning dose is titrated according to pre-supper readings and the evening dose according to pre-breakfast readings. If the glycaemic targets are not met, intensive insulin therapy with multiple daily injections should be considered. Specialist referral should be considered at any stage, especially if glycaemic targets are not met, as the above guidelines may have to be individualised to ensure safe insulin implementation. The role of a diabetes educator as well as a registered dietitian cannot be emphasised enough, especially once the patient is on insulin therapy. Injection technique, safe handling of medical waste and in-depth knowledge of the insulin regimen, as well as insulin type and mode of action, are crucial to safe and effective implementation.

Cardiovascular risk management

The Steno-2 study emphasises the importance of intensified multifactorial intervention.[21]

Blood pressure control

Diagnosis of hypertension is made if the BP is found to be ≥ 130 mmHg systolic and ≥ 80 mmHg diastolic on two separate days.[2,4] A goal of systolic BP < 130 mmHg and diastolic BP < 80 mmHg is appropriate for most patients. A recently published article suggests that reducing systolic BP to < 130 mmHg among patients with diabetes and coronary artery disease (CAD) is not associated with further reduction in morbidity beyond that associated with systolic BP < 140 mmHg. The findings of this study indeed suggest that such lowering of systolic BP is in fact associated with an increase in risk of all-cause mortality.[22] The ADA suggests that, pending further analyses and results, previously suggested targets are appropriate.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) should be considered as first-line therapies, while monitoring of serum potassium and creatinine is recommended. SEMDSA recommends that low-dose thiazide or loop diuretics (if the estimated glomerular filtration rate is ≤ 50 ml/minute) should be added if BP target is not achieved. SEMDSA also recommends that a combination of an ACE inhibitor and ARB should be

avoided, as well as the combination of either of the two with spironolactone, as potassium may rise to dangerous levels. If BP is refractory to optimal doses of at least three antihypertensive agents of different classes, the clinician should consider evaluation for a secondary causes of hypertension.

Dyslipidaemia management

A fasting lipid profile should be obtained at least annually. SEMDSA recommends statin therapy as the first-line agent for lowering low-density lipoprotein (LDL) cholesterol in diabetic patients. Statin therapy should be added to lifestyle interventions, irrespective of baseline lipid profile, for all patients with existing CAD and those older than 40 years of age who have one or more additional cardiovascular risk factors. For patients at lower risk, statin therapy should be considered if the LDL cholesterol remains above 2.5 mmol/l, despite adequate lifestyle modification and glycaemic control.

SEMDSA recommends the following targets: LDL cholesterol < 2.5 mmol/l, HDL cholesterol > 1.0 mmol/l in men and > 1.2 mmol/l in women, and triglycerides < 1.7 mmol/l.[4] The ADA recommends the following targets: LDL cholesterol < 2.6 mmol/L in those without overt cardiovascular disease (CVD), < 1.8 mmol/l in those with CVD, HDL cholesterol of > than 1.0 mmol/l in men and > 1.3 mmol/l in women, and triglycerides < 1.7 mmol/l.[2] The primary objective with the majority of the patients with diabetes is to lower the LDL cholesterol, an exception being patients presenting with severe hypertriglyceridaemia.[23]

Lifestyle intervention, including nutritional intervention, weight loss, increased physical activity and smoking cessation, should also be emphasised. Two trials were specifically designed to investigate lipid management in patients with diabetes. In the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), the primary end-point did not reach statistical significance but the point estimate for CVD benefit observed in the secondary prevention cohort for fatal and nonfatal myocardial infarction supported the rationale for statin therapy in patients with diabetes.[24] Primary prevention of CVD with atorvastatin in type 2 diabetes mellitus in the Collaborative Atorvastatin Diabetes Study (CARDS) posed the interesting question of whether any patient with type 2 diabetes mellitus is at sufficiently low risk for statin therapy to be withheld.[25]

Antiplatelet agents

In January 2011, the ADA issued recommendations regarding antiplatelet therapy in patients with type 2 diabetes mellitus. One should consider aspirin therapy as a primary prevention strategy in those with type 2 diabetes mellitus at increased

cardiovascular risk (10-year risk > 10%). This includes most men over 50 years of age or women over 60 years of age who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidaemia or albuminuria). Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year risk < 5%, such as in men under 50 years of age and women under 60 years of age with no major additional CVD risk factors), since the potential adverse effects from bleeding probably offset the potential benefits. In patients in these age groups with multiple other risk factors, clinical judgement is required.

Aspirin therapy should be used for secondary prevention in those with diabetes and history of CVD. The use of aspirin as primary prevention in patients with diabetes at increased CV risk, including those over 40 years or those with additional risk factors, was previously recommended by the ADA and the American Heart Association (AHA). However, the net benefit of aspirin in primary prevention is controversial and, based on more recent evidence in 2010, a position statement has been issued by the ADA, AHA, and the American College of Cardiology Foundation, updating the prior recommendations for primary prevention.[26]

Smoking cessation

It is recommended to advise all patients not to smoke.

Treatment goals

The treatment goals recommended by SEMDSA for patients with type 2 diabetes mellitus are summarised in Table I, and those recommended by the ADA in Table II.

Table I: The proposed targets of SEMDSA for most adults with type 2 diabetes mellitus (2009)

Glycated haemoglobin	HbA1c (%)	< 7
Body mass index	BMI (kg/m^2)	< 25
Blood pressure	Systolic mmHg	< 130
	Diastolic mmHg	< 80
Total cholesterol	mmol/l	< 4.5
[a]LDL cholesterol	mmol/l	< 2.5
[b]HDL cholesterol	mmol/l	> 1.0 (men), > 1.2 (women)
Triglycerides	mmol/l	< 1.7

Table II: The proposed targets of the ADA for most adults with type 2 diabetes mellitus (2011)

Glycated haemoglobin	HbA1c (%)	< 7
Blood pressure	mmHg	< 130/80
[a]LDL cholesterol	mmol/l	< 2.6

a = low-density lipoprotein

Screening for complications

Cardiovascular disease

In asymptomatic patients, routine screening for CAD is not recommended. All CVD risk factors should be treated and assessed at least annually. A full discussion of the screening for CVD is beyond the scope of this review and was updated in a recent consensus statement.[27]

Nephropathy

Annual tests to assess urine albumin excretion are recommended. Serum creatinine should be measured at least annually and should be used to calculate the glomerular filtration rate (GFR) and stage the level of chronic kidney disease. The rationale for this stems from the well-documented observation that GFR may decline in a patient with type 2 diabetes mellitus without a concurrent increase in albumin excretion. Microalbuminuria is defined as excretion of 30 to 299 mg of albumin per day in a random urine specimen. This progresses to macroalbuminuria, defined as excretion of 300 mg or more per day of albumin or an albumin:creatinine ratio over the above-mentioned limits, or higher in a random urine specimen. In patients with type 2 diabetes mellitus, hypertension and microalbuminuria, ACE inhibitors and ARBs have been shown to delay progression to macroalbuminuria.[28] In patients with type 2 diabetes mellitus, hypertension, macroalbuminuria and renal insufficiency, ARBs have been shown to delay progression to nephropathy.[29] It is important to also emphasise the importance of monitoring serum potassium when using ACE inhibitors or ARBs.

Retinopathy

All patients with type 2 diabetes mellitus should have an initial dilated and comprehensive eye examination by an ophthalmologist shortly after the diagnosis of diabetes, as eye complications may be evident at diagnosis. This is because type 2 diabetes mellitus often has a long asymptomatic phase and there may be a gap of many years between onset and diagnosis. Cataracts also need to be identified and managed accordingly. Subsequent examination should be performed annually or more frequently if retinopathy is progressing.

Neuropathy

Similarly, all patients with type 2 diabetes mellitus should be screened for distal symmetric polyneuropathy at diagnosis and at least annually, using simple diagnostic tests such as pin-prick sensation, vibration perception using a 128 Hz tuning fork and 10 g monofilament, and ankle reflexes.

Similarly, screening for signs and symptoms of autonomic neuropathy should be instituted at diagnosis. Pointers include resting tachycardia, exercise intolerance, ortho-static hypotension, constipation, gastroparesis, erectile dys-function, sudomotor dysfunction and autonomic failure in response to hypoglycaemia.

Foot care

Annual comprehensive foot examination is recommended for all patients with type 2 diabetes mellitus. The foot examination should include inspection for any abnormalities, assessment of foot pulses, 10 g monofilament testing, vibration perception, pinprick sensation and ankle reflexes. It is important to provide education in foot self-care. A comprehensive foot examination and risk assessment report was published in 2008.[30]

Education and team approach

It is widely accepted that successful care of a patient with type 2 diabetes mellitus relies on a team approach. Type 2 diabetes mellitus is a chronic disease and lifetime support by a multidisciplinary team, as well as education in self-care, is vital. The team should consist of a certified diabetes educator, a registered dietitian, a registered nurse and a primary care physician with specialist support. Other team members, such as cardiologists, nephrologists, ophthalmologists, psychologists and podiatrists, may be warranted.[5] Patient education is a cornerstone of effective diabetes care, as emphasised by SEMDSA.

Patient self-management is the key to success and education should be provided by appropriately trained educators and registered dietitians. Small-group education is an option if this is acceptable to the patient (remember confidentiality). Basic knowledge of diabetes, importance of good and comprehensive control, lifestyle interventions, use of medications, recognition and management of acute and chronic complications, foot care, pregnancy, smoking and alcohol, and psychosocial issues, should all be covered during the education.

Summary and conclusion

Diabetes causes approximately 5% of deaths globally each year. Eighty per cent of patients with diabetes live in low-income and middle-income countries. What is most disturbing is the World Health Organization (WHO) prediction that without urgent action, diabetes deaths will increase by more than 50% in the next 10 years.[31] World Diabetes Day raises the global awareness of diabetes, thus providing an additional opportunity to educate patients, healthcare professionals, carers, spouses and family, as well as the public in general. This day, initiated by the International Diabetes Federation and the WHO, and celebrated on 14 November, marks the birthday of Frederick Banting, who, together with Charles Best, played a crucial role in discovery of insulin in 1922.[32]

Returning to the case scenario, this patient clearly has type 2 diabetes mellitus with major risk factors for CVD. Therapy should be initiated with lifestyle interventions, including a weight-reducing diabetic diet and a graduated exercise programme. Metformin should be first-line therapy. If glycaemic targets are not met, a sulphonylurea-type drug should be added. Basal insulin therapy is indicated if this combination of oral hypoglycaemic agents fails to achieve glycaemic targets. The patient should be made aware of new therapies such as incretins, which are now available. The patient's cardiovascular risk factors need to be addressed. His BP must be reduced to target, starting with an ACE inhibitor (or ARB if intolerant). Most often multiple drug therapy is required to reduce the BP to target. The dyslipidaemia needs to be addressed with lifestyle interventions and statin therapy. He meets the criteria for low-dose aspirin therapy. Screening for complications should be implemented at diagnosis, especially as this patient presented with visual symptoms and microalbuminuria. Comprehensive diabetes education is crucial to ensure successful management of this patient.

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