Type 2 Diabetes Mellitus

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Diagnosis and management of type 2 diabetes mellitus

chapter 4

Type 2 diabetes mellitus (T2DM) is hyperglycemia due to insulin resistance and relative insulin deficiency. In contrast to type 1 diabetes mellitus (T1DM), it tends to have an insidious onset and is often diagnosed through screening of people who are at high risk.

The increasing incidence of T2DM worldwide is attributed to rising obesity levels and an ageing population. A healthy diet, exercise and weight loss are the cornerstones of prevention and treatment.

The main clinical aim is to reduce the occurrence and progression of diabetic complications. This chapter focuses on the diagnosis of T2DM and management of the hyperglycemia itself; the complications of the diabetes are discussed in chapters 5–12. Primary prevention of diabetes is discussed in chapter 13.

4.1 Clinical scenarios

Recurrent thrush

Presentation

Donna Robinson, aged 55 years, presents to her GP with white vaginal discharge and severe pruritus of 1 week's duration.

Diagnostic approach

Sexually transmitted diseases should always be considered in cases of vaginal discharge. However, the most common cause in a woman over 50 years old is *Candida albicans* (thrush).

Further history

Donna has had two episodes of thrush in the past 6 months, which she treated with clotrimazole pessaries (vaginal tablets)

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from the pharmacy. Her symptoms improved but then recurred a few weeks later.

Her partner has no symptoms, and she has had no new sexual contacts in the past 30 years. She feels tired most of the time and has gained 10 kg in the past year. Osteoarthritis in her right knee limits her mobility.

Donna takes ramipril for her hypertension, which was diagnosed 3 years ago. She smokes 20 cigarettes a day. Her older sister has recently been diagnosed with T2DM. Her mother had T2DM and died of a stroke at age 64.

Examination

On examination, Donna is obese, with a BMI of 34.2 kg/m^2. She does not have acanthosis nigricans (dark, thickened skin) or abdominal striae. Her blood pressure is 150/92 mmHg.

Her vagina has a thick, white curdy discharge, a sample of which is sent for smear and culture.

Diagnostic approach

Donna is an obese woman of 55 years with recurrent candidiasis and a strong family history of diabetes mellitus. High blood glucose and systemic immunosuppression associated with diabetes allow *Candida* to flourish.

It is likely that obesity is contributing to her osteoarthritis. The tiredness is a consequence of hyperglycemia or other obesity-related complications, such as sleep apnea. T2DM must be suspected.

Investigations

Urinalysis shows glycosuria. A random venous plasma glucose is 216 mg/dL (12 mmol/L). HbA_{1c} is also high, at 8.5% (69 mmol/mol).

Diagnosis

Donna is prescribed clotrimazole pessaries for the candidiasis. A second HbA_{1c} test is arranged 2 weeks after the first and being well over 6.5% (48 mmol/mol) confirms a diagnosis of T2DM (**Table 4.1**). A second random plasma glucose test shows 212 mg/dL (11.8 mmol/L). As well as her diabetes, she has

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Test		Normal	Prediabetes	Diabetes
HbA_{1c}	ADA 2018	<5.6% (≤38 mmol/mol)	5.7–6.4% (39–47 mmol/mol)	≥6.5% (≥48 mmol/mol)
	WHO 2012	6.0% (≤41 mmol/mol)	6.0–6.4% (42–47 mmol/mol)	
FPG	ADA 2018	<100 mg/dL (≤5.5 mmol/L)	100–125 mg/dL (5.6–6.9 mmol/L): impaired fasting glucose	126 mg/dL (≥7.0 mmol/L)
	WHO 2012	<108 mg/dL (≤6.0 mmol/L)	110–125 mg/dL (6.1–6.9 mmol/L)	
RPG		–	–	≥200 mg/dL (≥11.1 mmol/L) – with symptoms of hyperglycemia
2-h glucose in oral glucose tolerance test		≤139 mg/dL (≤7.7 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L): impaired glucose tolerance	≥200 mg/dL (≥11.1 mmol/L)

Table 4.1 Diagnosis of diabetes mellitus according to the American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2018), World Health Organisation (WHO) 2012. The UK National Institute for Health and Care Excellence (NICE) 2015 guidelines follow those of WHO 2012. Repeat testing is required for confirmation unless presentation is unequivocal. FPG, fasting plasma glucose; RPG, random plasma glucose.

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other major risk factors for cardiovascular disease: obesity, smoking, hyperlipidemia, hypertension and a family history of T2DM and vascular disease. The modifiable factors need to be tightly controlled to decrease her risk.

She is given diet and lifestyle advice to treat her diabetes and will be reassessed after 3 months. Her candidiasis will improve as her glucose is controlled.

Clinical insight

Many people fear a diagnosis of diabetes, because they have seen a relative develop complications such as a leg amputation or severe hypoglycemia. Early education usually helps allay the fear and engage patients in the necessity of good control.

A patient with poor motivation

Presentation

The medical center nurse has been trying to contact Tyler Rice, aged 45 years, for a diabetes review. His recent blood tests suggest poor glycemic control. Mr Rice keeps cancelling appointments, rarely answers the phone and has not picked up his prescriptions recently.

Diagnostic approach

There are several reasons why patients do not engage with treatment (**Table 4.2**), including:

- Cost (depending on healthcare system) and loss of income if missing work
- Forgetting to attend appointments, or other life events taking priority
- Difficulty getting to the clinic
- Denial or not wanting to consider certain diagnoses or treatments
- Depression and anxiety
- Not appreciating the necessity of the appointment
- Not wishing to appear a failure if their blood glucose control is poor
- Feeling intimidated by the physician or nurse

Clinical insight

Patients with diabetes have average medical expenditures 2.3 times more than those without diabetes.

Further history

The nurse eventually talks to Tyler over the phone. He has recently lost his job, and has been feeling low in mood. At the last consultation, the GP had discussed stopping smoking, losing weight and suggested starting insulin.

On the telephone, Tyler responds that he feels OK and that he 'doesn't need another lecture'. His wife also has diabetes and has recently had a heart attack. However, he admits he is concerned about his blurry vision.

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Category	Cause	Remedial strategy
Appointments	Difficulty to attend (transport, location, time off work, disability)	Phone and email consultations, home visits, assistance with transport
	Forgot or mistook time	Text, email or telephone reminder
	Patient's denial of problem or not ready to discuss it	Psychological support, change personnel (nurse/doctor)
Lifestyle adjustments (diet exercise, smoking)	Peer pressure	Family education (change as a family)
	Habit/addiction/apathy	Psychological and drug support (e.g. nicotine replacement)
	Not feeling well due to associated symptoms	Improve control/modify treatment
	Cost of healthy living (e.g. healthier food choices)	Government support for low-cost healthy options and education
Drug treatment	Patient does not read information, hear instructions or forgets them due to hearing, vision or memory impairment	Family assistance or help from district nurses. Pill (dosette) boxes and blister packs
	Behavioural factors (e.g. no symptoms, no immediate consequences of nonconcordance, no motivation, low priority, denial of problem)	Education on importance and self-monitoring (e.g. blood pressure) so can see benefit; motivational interviewing; text email or phone reminder
	Treatment factors (e.g. multiple tables a day, size and tolerability, side effects)	Slow-release preparations, alternative preparations or combination tablets
	Relationship to healthcare provider (e.g. motivation and education about efficacy of tablets)	Computer prescription logs that flag noncompliance that allow early intervention, patient-centerd care

Table 4.2 Underlying causes of nonconcordance and strategies to deal with them

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Examination

The records show Tyler is obese, with a body mass index (BMI) of 36 kg/m^2. His last recorded blood pressure was 150/90 mmHg.

Approach to management

Nonconcordance with therapy, obesity, and hypertension are causing Tyler's poorly controlled diabetes. He also has limited understanding of healthy living. By exploring his concern regarding his vision, and explaining the relationship to glycemic control – as well as the risks of more serious complications – his engagement with self-management may be improved.

Allowing Tyler a 'vacation' from blood glucose testing, but agreeing stages of simple targets could help him engage with health professionals and improve his diabetes self-management:

- Attending appointments
- Taking tablets
- Seeing a dietician with his family

New targets can be agreed once these are met, and so on. Too many (unrealistic) goals will discourage most patients. Similarly, trying to scare patients into concordance rarely leads to behavioral change. Allowing patients to set their own agenda is usually more successful.

Guiding principle

Changing behaviors in T2DM prevention and management requires that patients:

- Believe it is possible
- Understand what they need to do
- Find their own motivation
- Are supported socially and medically to make the changes

Long term change is most likely to take place if his entire family can be engaged and motivated to practice self-management, to support Tyler to make healthy behavioral changes (**Figure 4.1**).

Low mood and clinical depression are common in people with diabetes. This must also be assessed and treated, not least to make healthy changes seem possible.

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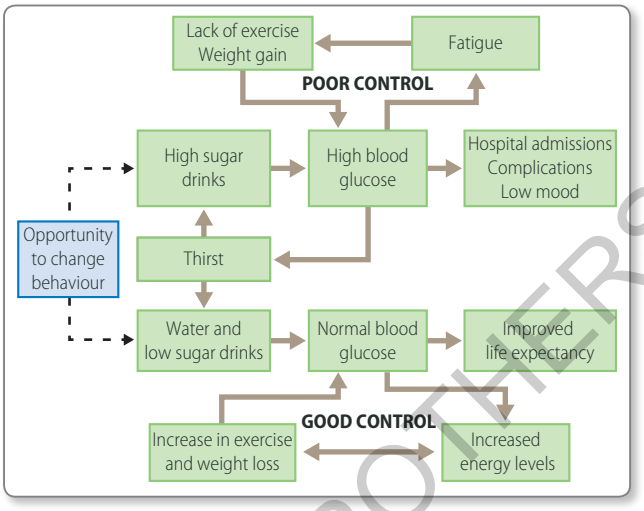

Figure 4.1 Patient control of diabetes management.

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4.2 Introduction to type 2 diabetes mellitus

T2DM is hyperglycemia that is not due to autoimmune or other secondary causes (**Table 4.3**). It is largely the result of metabolic changes secondary to insulin resistance and relative insulin deficiency, and often associated with obesity.

Epidemiology

Globally, T2DM accounts for 85–95% of diabetes mellitus. Its prevalence increases with age. However, earlier onset is being seen in tandem with earlier onset of obesity: incidence in youth has increased significantly in the last 20 years, with 5000 new cases a year in the USA for example. Prevalence in the under 20s is estimated to quadruple in 40 years.

Classification	Cause(s)
Type 1 diabetes mellitus	Autoimmune disease
Type 2 diabetes mellitus	Genetic and environmental causes (mainly obesity)
Monogenic diabetes mellitus	Single gene mutations
Diseases of the pancreas as well as shared genetic factors	Trauma Pancreatitis Pancreatectomy Hemochromatosis Cystic fibrosis
Secondary diabetes mellitus	Endocrine (e.g. Cushing syndrome and acromegaly) Drug-induced (e.g. corticosteroids, nicotinic acid, thiazides, and β-adrenergic agonists)
Diabetes mellitus associated with other genetic syndromes	Down syndrome Klinefelter syndrome Turner syndrome Wolfram syndrome Friedreich ataxia Laurence–Moon syndrome Prader–Willi syndrome
Gestational diabetes mellitus	Genetic predisposition and obesity

Table 4.3 Causes of diabetes mellitus.

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15% of adults in Europe and the USA have some form of impaired glucose regulation (IGR). Most will progress to T2DM if untreated; 5–12% develop it every year.

Compared with Caucasians populations, Asian, Hispanic, and African ethnic groups have a higher risk of T2DM, largely due to higher levels of obesity and physical inactivity. This increased incidence is associated with urbanization, lack of exercise, and easy access to high-calorie foods. South Asian populations have a faster rate of progression to T2DM, at lower BMI.

Etiology

Genetics

T2DM is influenced by multiple genes. The concordance rate of T2DM or IGT in monozygotic twins is nearly 100%, 10% of patients have an affected sibling, and 40% have at least 1 affected parent. Much of this is due to shared environmental factors.

Environmental risk factors

People with obesity (BMI >30 kg/m^2) are at increased risk of T2DM and are usually insulin-resistant. Over 10 years, an obese person is 10 times more likely to develop diabetes.

Foods and beverages that are high in sugar (e.g. soda) and saturated fats are independent risk factors. A daily increase of sugar consumption by 150 kcal is associated with a 1.1% increase in T2DM prevalence.

Age and lack of physical activity are also major risk factors. Recent evidence suggests that low cardiovascular fitness is an important T2DM risk factor independent from obesity.

Many of the anti-psychotic medications used on a long-term basis are associated with a raised incidence of T2DM.

Prevention

Prevention is far preferable to treatment and is discussed in detail in Chapter 13.

Pathogenesis

Insulin resistance increases with adiposity. This requires increased insulin secretion to maintain euglycemia. Pancreatic β-cell function is strained until slow atrophy leads to relative insulin deficiency.

Insulin resistance

As well as storing fatty acids as triglycerides, adipocytes release cytokines (cell-signaling chemicals) called adipokines, such as leptin and adiponectin. Their excessive release causes insulin resistance in skeletal muscle, and therefore hyperglycemia.

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The excess blood glucose is then converted to free fatty acids that increase serum triglyceride concentration.

Pancreatic β-cell failure

Patients also have significantly reduced β-cell function at diagnosis. The toxic effects of free fatty acids and hyperglycemia on β-cells further impair insulin secretion. A progressive loss of β-cell function occurs over time.

Type	Complications
Acute complications (Chapter 5)	Hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state episodes, diabetic amyotrophy
Microvascular complications (Chapter 6)	Retinopathy (Chapter 9), nephropathy (Chapter 11), sensory neuropathy, and autonomic neuropathy, including sexual dysfunction and gastroparesis
Macrovascular complications (Chapter 6)	Coronary heart disease, cerebrovascular disease, and peripheral artery disease
Sexual dysfunction (Chapter 8)	(May result from microvascular neuropathy and vascular disease, but also systemic changes causing low libido)
Diabetic foot disease (Chapter 10)	Ulceration, ischemia, deformity, infection, Charcot arthropathy
Skin lesions (Chapter 2)	Diabetic dermopathy, i.e. shin spots or pretibial pigmented patches (associated with microvascular disease, and thought to be trauma-induced)
Infections	Urinary tract and skin infections, e.g. *Staphylococcus*, erythrasma, candidiasis (rise in risk correlates strongly with mean hyperglycemia)
Psychological (Chapter 2)	Diabetes distress' (when acute); often stages of grief; depression and anxiety in 20–25% (Psychological burden is barriers to good management)
Neuro-degenerative	Dementias in general (risk raised by 73%) Alzheimer disease (risk raised by 56%) Vascular dementia (risk raised by 127%) Parkinson disease risk possibly raised

Table 4.4 Complications of diabetes.

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Complications

Complications of diabetes are listed in **Table 4.4**. They are largely due to vascular disease accelerated by hyperglycemia (see **Figure 6.5**). The main complications are discussed in detail in Chapters 5–12.

Microvascular complications occur first in tissues that are:

- Highly metabolically active
- Capillary-rich
- Sensitive to ischemia
- Lack collateral circulation and lymphatics
- Slow or unable to regenerate
- Lack reserve

4.3 Diagnosis of type 2 diabetes mellitus

Clinical features

There are five typical presentations:

- Incidental diagnosis on blood glucose testing (e.g. when admitted to hospital)
- Case finding when testing patients with other cardiovascular risk factors such as hypertension and hyperlipidemia
- Osmotic symptoms including dry mouth, thirst, and polyuria, usually developing over weeks or months
- Complications of diabetes mellitus, e.g. neuropathic foot ulcer or a macrovascular event such as myocardial infarction
- Acute presentation with a hyperosmolar hyperglycemic state [HHS; blood glucose 600 mg/dL (>33 mmol/L), hypovolemia, and raised serum osmolality (>320 mOsm/kg)]

Most patients have insidious onset, with malaise, thirst, nocturia, and blurred vision over months before presentation. HHS is more common with a precipitant and in the elderly.

All diagnosed individuals should have a thorough review that is repeated at least yearly (see Table 2.6). Signs of complications at presentation reflect late stage disease.

Investigations

Diagnosis is based on confirmed hyperglycemia or raised hemoglobin A_{1c} (HbA_{1c}) (**Table 4.1**). The World Health Organization

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Condition(s)	Details
Rapid onset of diabetes mellitus	Suspected T1DM Use of steroids and antipsychotics After pancreatitis or pancreatic surgery
Pregnancy	Physiological changes due to pregnancy lowering HbA_{1c}
Conditions with reduced red cell survival	Hemoglobinopathy (sickle cell anemia or thalassemia) Renal dialysis for patients on erythropoietin Splenomegaly Hemolytic anemia Severe blood loss or transfusion Use of antiretroviral drugs
Conditions with increased red cell survival	Splenectomy
Iron and vitamin B_{12} deficiency	Decreased erythropoiesis

Table 4.5 When not to use hemoglobin A_{1c} (HbA_{1c}) for diagnosis and monitoring.

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(WHO) advocates diagnosis based on HbA_{1c} measurement; however, HbA_{1c} is unsuitable for diagnosis and monitoring of diabetes in some conditions (**Table 4.5**), and measurements can be affected by age, race or ethnicity.

Guiding principle

Patients with impaired glucose regulation have progressive impairment of β-cell function, which causes progressive hyperglycemia and T2DM.

Diagnostic thresholds are based on large population studies correlating glycemic measurements with the risk of complications and are somewhat arbitrary. Borderline results mandate a repeat of the same test. If the initial test was HbA_{1c}, re-testing should be within 2 weeks; both tests must be ≥6.5% (≥48 mmol/mol) for diagnosis.

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2018) advises testing of any individuals over 45 years of age with a BMI ≥25 kg/m^2 (or ≥23 kg/m^2

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ISBN 978-1-909836-68-6

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