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TYPE 2 DIABETES MELLITUS: DIAGNOSIS, ASSESSMENT AND MANAGEMENT

- **The prevalence of type 2 diabetes mellitus (T2DM), which is a major cause of morbidity and mortality, is increasing**
- **The management of T2DM should be patient-centred and include multifactorial behavioural and pharmacological therapies to prevent or delay the onset of cardiovascular disease (CVD) and other complications**
- **Glycaemic targets should be individualised to the patient and include consideration of age, risk of complications, frailty and comorbid conditions**
- **The management of hypertension, dyslipidaemia, and other cardiovascular risk factors should be optimised in patients with T2DM to reduce the risk of CVD**

INTRODUCTION

Diabetes mellitus (DM) is a major public health issue;[1] approximately 6.7 million adults worldwide (1.1 million in Europe) were estimated to have died due to DM in 2021.[2] The prevalence of DM is increasing worldwide; there were 529 million people living with DM in 2021, and this figure is expected to increase to 1.31 billion by 2050, primarily driven by type 2 diabetes mellitus (T2DM).[1] **There were 1 in 11 adults living with DM in Europe in 2021, of which one third were undiagnosed.[2]** In Ireland, there were >300,000 people with DM in 2022.[3]

Patients with DM are at increased risk of developing atherosclerotic cardiovascular disease (ASCVD).[4,5] **DM is a major cause of blindness, renal failure, myocardial infarction, stroke and lower limb amputation.[6,7]** T2DM is the most common cause of DM, representing 90% of the diabetes population.[4] The Irish Longitudinal Study on Ageing (TILDA) (2015) reported that 10% of adults aged ≥50 years had T2DM, which increased to 16% in those aged ≥80 years, and that one in ten people with DM in the older population were undiagnosed.[8]

This, the first of two bulletins on the management of T2DM, reviews the diagnosis and assessment of patients with T2DM. The second bulletin will review the non-insulin glucose-lowering therapies used for T2DM.

PATHOPHYSIOLOGY

T2DM is characterised by insulin resistance and loss of insulin-producing capacity in the pancreas. Insulin resistance is the initial state, which results in increased production of insulin from the beta cells in the pancreas.[9] Over time, pancreatic insulin production falls, due to progressive beta cell dysfunction. It is considered that **by the time T2DM is diagnosed, the pancreas has lost half of its insulin-producing capacity.[9]** Persistent hyperglycaemia is associated with metabolic changes which results in damage to both small (microvascular) and large (macrovascular) blood vessels.[9]

Genetic and acquired/environmental factors play an important role in the development of T2DM.[9] There is a strong hereditary component to the disease; T2DM is more common in certain ethnic groups (e.g. people of African, African-Caribbean and South Asian family origin).[9] **Acquired/environmental risk factors include obesity, physical inactivity, dyslipidaemia, existing CVD, or long-term corticosteroid use;[1,9]** it is considered that these risk factors unmask the effects of genetic susceptibility which results in the development of T2DM.[9]

Pre-diabetes is an intermediate stage of glucose dysregulation that may precede T2DM; in 2021 it affected approximately 720 million people globally, which is expected to increase to 1 billion in 2045.[10] Prediabetes is associated with an increased risk of CV events and mortality.[10] A Danish population-based study estimated that within 5 years, one in five with prediabetes progress to T2DM and one in six dies.[11] **A healthy diet, regular physical activity, maintaining a normal body weight, weight loss and avoiding tobacco use are ways to prevent or delay the onset of T2DM.[7]**

COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

T2DM is a heterogenous disease with variable age at onset, related degree of obesity, insulin resistance and tendency to develop complications.[12] The risk of complications associated with T2DM increases with younger age at diagnosis and higher glucose levels.[13-15]

Macrovascular complications of T2DM include CVD, cerebrovascular disease and peripheral arterial disease (PAD);[13,16] CVD is the primary cause of death in patients with T2DM.[16] Individuals with T2DM are at a two to four-fold higher risk of developing CVD during their lifetime;[13] CVD affects approximately 30% of all people with T2DM,[13] of whom many are undiagnosed.[4] The increased risk for CVD in T2DM occurs especially in those who develop T2DM at a younger age; evidence suggests that the risks are higher in women with T2DM compared to men.[4,12,17-19]

Microvascular complications: DM is a leading cause of chronic kidney disease (CKD); 25% to 40% of people with T2DM have CKD.[13] Other microvascular complications include diabetic retinopathy which affects approximately 25% of patients, and diabetic neuropathy which affects almost 50%.[20] The duration of T2DM in addition to poor glycaemic, blood pressure and lipid control are common risk factors for the development of these complications.[9,20] Early detection of and intervention for microvascular complications is associated with better outcomes.[20]

DIAGNOSIS OF DIABETES

The symptoms of T2DM (e.g. polydipsia, polyuria, fatigue, weight loss and recurrent infections) are less marked than those experienced by people with T1DM.[4,7] In addition, **T2DM may be asymptomatic because it progresses slowly in the early stages (including in those presenting with CVD) and is undiagnosed in over 40% of adults,[4]** therefore, individuals with risk factors for DM should be regularly screened, especially those aged >45 years.[4] The Irish College of General Practitioners (2019) recommends screening for DM in a number of groups (see figure 1).[21] **The 2023 European Society of Cardiology (ESC) guidelines on DM recommend that it is mandatory to screen all patients with CVD for DM.[4]**

Figure 1: Screening for diabetes mellitus[21]

- **Test for DM* all asymptomatic adults from age 40 to 45 years (if normal, retest every 3 years or more frequently depending on initial results and risk status)**
- **Patients with prediabetes (HbA1c 42 to 47 mmol/mol) should have annual diabetes tests**
- **Women with gestational DM should have lifelong testing every 3 years**
- **Consider testing for DM* in adults who are overweight (BMI ≥25) or obese (BMI ≥30) with ≥1 risk factor such as:**
  - **First degree relative with DM**
  - **High-risk race/ethnicity (e.g. traveller community, African American, Arab, Asian)**
  - **History of cardiovascular disease**
  - **Hypertension (BP ≥140/90 mm/Hg) or on antihypertensives**
  - **HDL cholesterol <0.90 mmol/L and/or triglycerides >2.8 mmol/L**
  - **Consider screening in people in lower socio-economic groups**
  - **Consider screening people with polycystic ovary syndrome, gout, psychotic illness/on antipsychotic medication or obstructive sleep apnoea**
  - **Physical inactivity**

**see table 1; BMI-body mass index; BP-blood pressure; DM-diabetes mellitus; HbA1c-glycated haemoglobin A1c; HDL-high-density lipoprotein*

When screening for DM in individuals, it is recommended to do a glycated haemoglobin (HbA1c) (which can be done non-fasting) and/or fasting blood glucose, or a 2-hour oral glucose tolerance test (OGTT) if there is doubt about the diagnosis (see table 1).[4,22] Certain conditions (e.g. haemoglobin variants, sickle cell disease, anaemia, pregnancy, haemodialysis and treatment with medicines such as protease inhibitors) may interfere with HbA1c measurements, therefore blood glucose criteria should be used to diagnose diabetes in these circumstances.[23,24]

Table 1: Diagnosis of diabetes and pre-diabetes[4,21,25]

Diagnosis of diabetes mellitus	**Fasting plasma glucose ≥7 mmol/L, and/or HbA1c ≥48 mmol/mol (≥6.5%) Repeat testing is advised to confirm the diagnosis if the patient is asymptomatic OGTT 2-hour plasma glucose ≥11.1 mmol/L (if doubt about the diagnosis)**
Diagnosis of pre-diabetes*	**Fasting glucose 6.1 to 6.9 mmol/L, and/or HbA1c 42 to 47 mmol/mol (6.0 to 6.4%) OGTT 2-hour glucose 7.8 to 11.0 mmol/L**

*HbA1c-glycated haemoglobin A1c; OGTT-oral glucose tolerance test; *the American Diabetes Association defines pre-diabetes as fasting glucose levels 5.6 to 6.9 mmol/L and HbA1c 5.7 to 6.4% (39 to 47 mmol/mol)*

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

The management of T2DM includes multifactorial behavioural and pharmacological therapies to prevent or delay CVD complications and to maintain quality of life for the individual patient.[12,13] **Patient-centred care can significantly improve outcomes for people with T2DM,[13]** and the management approach should involve the patient in the decision making to determine the best treatment course for that individual.[12,13] The HSE National Clinical Programme for Diabetes recommends integrated care for T2DM, whereby healthcare professionals (HCPs) work together in primary and secondary care to take joint responsibility for patients with T2DM on a proactive basis. The majority of routine T2DM management occurs in primary care, which focuses on an integrated multidisciplinary team approach involving GPs, specialists, dietitians, nurses, pharmacists, physiotherapists and other health and social care professionals.[13,21] T2DM is included in the HSE Chronic Disease Management Programme, which was launched in 2019.[26] The HSE Enhanced Community Care scheme includes T2DM which has consultant-led community specialist teams that GPs can refer into.[27]

T2DM management includes assessment of the patient's co-morbidities, CV risk factors and CV complications, in addition to glycaemic control;[12] interventions include self-management education, lifestyle modification, nutrition advice, appropriate weight loss, physical exercise and pharmacotherapy.[12,13,21] The prevention of CVD is an essential aspect in the management of a patient with T2DM.[22] Patient self-management, education and support is a key intervention, which is as important in the management of T2DM as is the selection of pharmacotherapy,[12,28] and should be considered at diagnosis, annually and once complications are encountered.[12] Structured educational support programmes significantly improve knowledge and glycaemic levels, reduce hospital admissions and all-cause mortality, and are cost effective.[12] The focus of educational support for patients includes lifestyle behaviours (healthy eating, physical activity and weight management), medication taking behaviour (with a particular focus on adherence), self-monitoring when needed and problem solving.[12] The HSE organises a DISCOVER (Diabetes Insights and Self Care Options via Education and Reflection) course that is freely available for people with T2DM.

CARDIOVASCULAR RISK ASSESSMENT

It is important to assess the CV risk in individuals with DM and evaluate them for CVD and CKD, and to screen all patients with CVD for DM.[4] The assessment of CV risk should consider medical and family history, symptoms, findings from examination, laboratory and other diagnostic test results, and the presence of ASCVD or severe target organ damage (TOD) (e.g. nephropathy, neuropathy, retinopathy).[4] The 2023 ESC guidelines on DM recommend that individuals with T2DM should be categorised into CV risk groups, based on a number of criteria, which can be used to inform treatment decisions (see table 2).

A variety of risk scores can be used to estimate CVD risk in patients with DM.[4,13,29] SCORE2-Diabetes algorithm is a new validated algorithm that was developed by extending SCORE2, which is calibrated to estimate the 10-year risk of CVD events in individuals aged >40 years with T2DM without previous CVD, in 4 regions in Europe;[30] it is available on the ESC CVD Risk Calculation App. The CVD risk calculator QRISK®3-2018 available at QRISK3 that is also used in Ireland, estimates the CVD risk of patients with T2DM.[31]

Table 2: Cardiovascular risk categories in patients with type 2 diabetes mellitus[4]

Patients with type 2 diabetes	Category
Patients with T2DM and: • Clinically established ASCVD or • Severe TOD (defined as): ○ eGFR <45 mL/min/1.73m^2 irrespective of albuminuria or ○ eGFR 45-59 mL/min/1.73m^2 and microalbuminuria (UACR 30-300 mg/g; stage A2) or ○ Proteinuria (UACR >300 mg/g; stage A3) or ○ Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria [stage A2] plus retinopathy plus neuropathy) or • 10-year CVD risk ≥20% using SCORE2-Diabetes	Very high CVD risk
• Patients with DM not fulfilling the very high-risk criteria and a: ○ 10-year CVD risk 10 to <20% using SCORE2-Diabetes	High CVD risk
• Patients with DM not fulfilling the very high-risk criteria and a: ○ 10-year CVD risk 5 to <10% using SCORE2-Diabetes	Moderate CVD risk
• Patients with DM not fulfilling the very high-risk criteria and a: ○ 10-year CVD risk <5% using SCORE2-Diabetes	Low CV risk

ASCVD-atherosclerotic cardiovascular disease; CVD-cardiovascular disease; DM-diabetes mellitus; eGFR-estimated glomerular filtration rate; T2DM-type 2 diabetes mellitus; TOD-target organ damage; UACR-urinary albumin-to-creatinine ratio

GLYCAEMIC TARGETS

Glycaemic treatment targets should be individualised to the patient and include consideration of the patient's age, risk of CV complications, frailty and comorbid conditions (including CVD), and their risk of adverse effects from specific pharmacotherapies (e.g. hypoglycaemia and weight gain).[12,22]

Intensive glucose-lowering in patients with T2DM reduces the risk of complications, in particular microvascular disease,[32-35] however the effects on macrovascular disease are more complex.[32-38] Some studies report that lower glucose levels (e.g. HbA1c <6%) in certain patients (those with pre-existing CVD) may be associated with increased mortality,[34,39] however intensive glucose-lowering may be associated with reduced CV events (e.g. myocardial infarction) in patients without CVD.[36,37] The greatest absolute risk reduction of glucose-lowering therapy comes from improving very elevated blood glucose levels, while more modest reduction results from near normalisation of plasma glucose levels.[12] Target HbA1c levels in patients with CVD should ideally be achieved by using glucose-lowering medications with proven CV benefit (e.g. sodium-glucose cotransporter-2 inhibitors [SGLT2i] and glucagon-like peptide-1 receptor agonists [GLP-1RA]) – see next bulletin.

Many guidelines recommend a HbA1c target of ≤53 mmol/mol (≤7%) for most non-pregnant adults;[4,22,40] this is considered to be an appropriate target for individuals with sufficient life expectancy to see microvascular benefits (generally approx. 10 years).[12] A lower HbA1c level (e.g. ≤48 mmol/mol [6.5%]) may be beneficial in younger patients with a short duration of T2DM, no evidence of CVD and those using pharmacological agents not associated with hypoglycaemia.[12,22,23,40] A higher HbA1c level may be appropriate for elderly patients with longstanding DM, limited life expectancy and frailty with multiple co-morbidities including hypoglycaemic episodes.[12,23] Therefore, the glycaemic target needs to be individualised to the patient (see figure 2).

Glycaemic management is primarily assessed by HbA1c measurements.[12] In general, for most people with T2DM routine blood glucose monitoring (BGM) is of limited additional clinical benefit (while adding burden and cost).[12,41-46] However BGM is recommended in circumstances such as in patients on insulin, those with a history of hypoglycaemic episodes, those on medicines associated with hypoglycaemia (e.g. sulfonylureas) and those planning a pregnancy or pregnant, and may be considered in those with acute illness and those commencing steroids.[40,46,47] Continuous glucose monitoring is currently reimbursed for patients on insulin with T1DM only (https://www.hse.ie/eng/about/who/cspd/medicines-management/glucose-monitoring/continuous-glucose-monitoring/).

Figure 2: Glycaemic targets for patients with T2DM (ESC 2023)[4]

- It is recommended to aim for HbA1c ≤53 mmol/mol (≤7%) to reduce microvascular complications
- It is recommended to avoid hypoglycaemia particularly in patients with CVD
- It is recommended to individualise HbA1c targets according to comorbidities, diabetes duration and life expectancy

CVD-cardiovascular disease; DM-diabetes mellitus

In addition to achieving HbA1c targets, the management of hypertension, dyslipidaemia, and other CV risk factors also need to be optimised to reduce the risk of CVD and mortality.[4,22]

OTHER CARDIOVASCULAR RISK CONSIDERATIONS

Management of hypertension: Up to 87% of women and 80% of men with T2DM have hypertension.[49] Patients with T2DM require regular blood pressure (BP) measurements (at every routine clinical visit).[4] The 2023 ESC guideline on DM recommends BP treatment targets for individuals with T2DM (see figure 3).[4] Lifestyle changes are recommended for all patients with hypertension and T2DM. Pharmacological therapy for hypertension in patients with T2DM includes the use of a renin-angiotensin system inhibitor where possible;[4] further detail on the management of hypertension is available in the ESC guidelines of CVD prevention (2021).

Figure 3: Blood pressure targets for patients with T2DM[4]

- Antihypertensive drug treatment is recommended for people with T2DM when office BP is ≥140/90 mmHg
- It is recommended to treat hypertension in patients with diabetes in an individualised manner
  - The BP goal is to target SBP to 130mmHg and <130 mmHg if tolerated, but not <120 mmHg
  - In older people (age >65 years), it is recommended to target SBP to 130 to 139 mmHg
- An on-treatment SBP target of <130 mmHg may be considered in patients with diabetes at particularly high risk of a cerebrovascular event to further reduce their risk of stroke

BP-blood pressure; SBP-systolic blood pressure; T2DM-type 2 diabetes mellitus

Management of lipids: T2DM is associated with the development of atherogenic diabetic dyslipidaemia secondary to insulin resistance. This is characterised by increases in non high-density lipoprotein cholesterol (non-HDL-C) (includes triglyceride rich very low density lipoprotein [VLDL] and cholesterol rich low-density lipoprotein cholesterol [LDL-C]), associated with reduced levels of the protective HDL-C particles.[50] Atherogenic diabetic dyslipidaemia is associated with an increased risk of CVD events and mortality.[4,22] The development or progression of CVD can be mitigated by lowering non-HDL-C levels.[4,22] ESC guidelines on DM recommend LDL-C and non-HDL-C targets for patients with T2DM (see figure 4).[4,22,51] Lifestyle changes are recommended in all patients with dyslipidaemia and T2DM.[4,22,51] Statins

are recommended as first-choice lipid lowering therapy in patients with T2DM; combination lipid lowering therapy with ezetimibe may be required in those not reaching their LDL-C targets.[4,22,51] Further information on lipid lowering therapy is available in the NMIC bulletins (NMIC 2023;Vol. 29, No. 3 and 4).

Figure 4: Low-density lipoprotein cholesterol targets for patients with T2DM[4,22,51]

- **In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L**
- **In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L and LDL-C reduction of at least 50%**
- **In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L and LDL-C reduction of at least 50%**
- **In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L in very high CV risk patients and <2.6 mmol/L in high CV risk patients**

CV-cardiovascular; LDL-C-low-density lipoprotein cholesterol; non-HDL-C- non high-density lipoprotein cholesterol; T2DM-type 2 diabetes mellitus

Antiplatelet therapy: The use of antiplatelet agents such as low-dose aspirin to reduce CV morbidity and mortality as secondary prevention is recommended in patients with T2DM who have established CVD;[4,40] clopidogrel is recommended as an alternative in those with aspirin intolerance.[4] There is less of a consensus on the use of aspirin for primary prevention in patients with T2DM; aspirin use should be considered on an individual basis depending on CV risk.[4]

Smoking cessation is an important lifestyle intervention that has been shown to be associated with reduced CVD and mortality in patients with T2DM.[52,53] Individuals with T2DM should be encouraged to stop smoking and offered cessation support.[4,22] If advice, encouragement and motivation are not adequate, pharmacotherapy such as nicotine replacement therapy, bupropion or varenicline may be considered.[4] A consensus regarding the efficacy and safety of using electronic cigarettes has yet to be reached.[54,55]

PREVENTION/DIAGNOSIS OF MICROVASCULAR COMPLICATIONS

Nephropathy: CKD which is often underdiagnosed, is associated with a high risk of major and preventable adverse CV events.[21] Early CKD is usually asymptomatic, therefore screening (testing both estimated glomerular filtration rate [eGFR] and urinary albumin creatinine ratio [ACR]) for CKD should be performed at diagnosis and annually.[21] Albuminuria is an early marker of nephropathy and predicts both the risk of kidney failure and CVD independently of eGFR.[4] A diagnosis of CKD is made if the patient has persisting eGFR <60 mL/min/1.73m^2, and/or ACR ≥2 mg/mmol, in at least 2 of 3 samples over 3 months.[21] Patients with CKD require optimisation of their BP, HbA1c, lipids and vaccines, monitoring of their renal function and referral to a nephrologist.[21] The use of statins, angiotensin converting enzyme inhibitor or angiotensin receptor blocker and a SGLT2i (with proven renal benefits) is recommended in patients with T2DM and CKD to reduce the risk of CVD and kidney failure.[4]

Retinopathy: HbA1c and BP at target delays the onset and progression of diabetic retinopathy.[21] All patients should have a retinal screening examination performed at diagnosis and regularly thereafter; specialist referral is needed for new vessel formation or macular disease.[9] The HSE Diabetic RetinaScreen programme is freely available for people with DM; patients need to register online.

Neuropathy: All patients should be examined for evidence of diabetic peripheral neuropathy and PAD at diagnosis, and have a formal footcare assessment at least annually thereafter.[21] The HSE has a Diabetic Foot Model of Care (2021) on their website. Potential non-diabetic causes of neuropathy (e.g. vitamin B12 deficiency, excessive alcohol intake, hypothyroidism, renal disease) should be excluded and/or managed if present.[9,21]

Autonomic neuropathy: erectile dysfunction (ED) may affect up to 50% of males with T2DM.[9,21] Male patients should be asked about ED at diagnosis and annually thereafter; other causes/contributory factors should be considered (e.g. excess alcohol, beta blockers, verapamil, selective serotonin reuptake inhibitors).[9,21] Phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) may be considered if lifestyle interventions (e.g. exercise and weight loss) are not effective or if ED is associated with severe stress.[9,21]

LIFESTYLE INTERVENTIONS

Lifestyle changes are recommended as a priority in the management of T2DM and prevention of CVD.[4,22,23,29,40] Lifestyle interventions delay the onset of T2DM and reduce the incidence of macrovascular and microvascular complications, and increase life expectancy.[56]

Weight reduction delays the progression of patients with prediabetes to T2DM,[57,58] and reduces the risk of CVD in patients with T2DM who have a BMI ≥25.[12,22,58] Recent guidelines recommend at least 5% reduction in weight via energy restricted diet and increased physical activity in those who are overweight/obese to prevent T2DM; a reduced calorie diet programme delivered by HCPs should be considered in those with T2DM who are overweight/obese.[59] A UK randomised controlled trial (2018) conducted in primary care reported that an intensive weight management programme (which included a low calorie diet) resulted in mean weight losses of 10kg and remission of DM in 36% of patients at 2 years in the intervention arm.[60] The use of glucose-lowering agents such as GLP-1RA should be considered in patients with T2DM who are overweight/obese (see next bulletin).[12] Metabolic surgery (which is associated with remission in certain people with T2DM) may be considered as a treatment option in appropriate adults.[12]

Nutrition: A range of foods and dietary patterns are suitable for diabetes management.[59] A Mediterranean diet supplemented with small amounts of olive oil and/or nuts reduces the incidence of major CV events.[12,23] Greater glycaemic benefits are seen with the Mediterranean and low carbohydrate diets,[12] and a Mediterranean diet is associated with greater reductions in body weight and HbA1c levels compared to a low-fat diet.[12]

Physical activity and exercise: Physical activity delays the conversion of patients with pre-diabetes to T2DM, and improves glycaemia and CVD complications in those with T2DM;[12,23,53] moderate to vigorous physical activity of ≥150 min/week is recommended for the prevention and control of DM.[12,23] Even small regular changes can make a difference to long-term health,[61] with an increase of only 500 steps/day associated with a 2 to 9% decreased risk of CV morbidity and all-cause mortality.[12] In addition, adults with T2DM should be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks.[12]

List of references available on ePublication on www.nmic.ie.
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