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The importance of risk factors in the development of type 2 diabetes

Launch

Welcome to our second course looking at issues in diabetes. This course will cover the importance of risk factors in the development of diabetes and is aimed at both primary and secondary care doctors.

Cost: This course is delivered to you at no charge.

CME credit: This course has been approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 1 category 1 (external) CPD credit.

Learning objectives: This course will cover:

- The long-term impact of risk factors on the development of diabetes
- Lifestyle factors and diabetes control via patient education
- Concordance concerns via patient education
- End-organ damage in diabetes and early detection strategies.

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Continuing professional development for doctors

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This learning module contains the following interactive components

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Taking medical information further

The importance of risk factors in the development of type 2 diabetes

You are currently on section 1 of 4

The long-term impact of risk factors on the development of diabetes Introduction

Learning objectives: This section covers the key risk factors for the development of diabetes including obesity, impaired glucose tolerance, gestational diabetes and the genetics of the disease.

Type 2 diabetes mellitus (T2DM) is characterised by increased peripheral resistance to insulin action, impaired insulin secretion and increased hepatic glucose output. Both genetic and environmental factors contribute to the development of insulin resistance and progressive beta cell dysfunction seen in type 2 diabetes. Obesity is the major risk factor for insulin resistance, although not all obese people have diabetes. This is because insulin resistance can be overcome by healthy beta cells in the pancreas, but when insulin secretion fails, diabetes will ensue.

Figure 1: A photomicrograph of a section through the pancreas of a patient with Type II diabetes, showing amorphous amyloid (pink) replacing more than 80% of islet cells. The remaining beta cells are labelled brown, nuclei blue.

Figure 1: Clinical picture available to OnMedica members only

Read the resource text now which will explore the risk factors for diabetes and their long-term impact then attempt the questions below.

Resource text

Obesity

Obesity causes peripheral resistance to glucose uptake and may also decrease the sensitivity of the β cells to glucose. Central obesity has a much greater association with insulin resistance than more peripheral obesity. The reasons for this are not completely understood. We now know that adipose tissue is an active endocrine organ and certain adipokines are thought to be implicated in the pathogenesis of insulin resistance. For example, leptin deficiency and resistance are associated with obesity and insulin resistance. Adiponectin deficiency and over-production of TNF-α from adipocytes may also play a role in the impairment of insulin action.

In addition, free fatty acid concentrations are higher in obese patients and impair the uptake of glucose in peripheral tissues. An elevation of free fatty acids can also be lipotoxic to the beta cells of the pancreas which can contribute to insulin deficiency seen with diabetes of a longer duration.

The rising prevalence of diabetes worldwide mirrors the rise in obesity and is the predominant risk factor for the development of diabetes. The National Diabetes Audit found that approximately 90% of people with T2DM have a BMI of >25 and an increasing number of people with T1DM are becoming overweight and therefore a rise in insulin resistance has been seen in these patients.

Impaired glucose tolerance/impaired fasting glucose (IFG)

These 'pre-diabetic' states dramatically increase the risk of developing diabetes by as much as eight-fold. The Finnish Diabetes Prevention Study (1) found that the cumulative risk of incidence of T2DM in people with pre-diabetes was 23% at a mean of 4 years follow-up.

The trial randomly assigned 522 middle-aged, overweight subjects with impaired glucose tolerance to either the intervention group or the control group. Each subject in the intervention group received individualized counselling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fibre and physical activity. An oral glucose-tolerance test was performed annually; the diagnosis of diabetes was confirmed by a second test. The mean duration of follow-up was 3.2 years.

Genetics

A genetic influence on the development of T2DM is supported by the fact that monozygotic twins have a 90% concordance rate and 40% of patients with T2 DM have at least one parent with the disease. The lifetime risk for a first-degree relative of a patient with T2DM is 5-10 times higher than for those without a family history of diabetes. Currently genetic testing has no place in the diagnosis or management of patients with typical type 2 diabetes. Monogenic causes of diabetes are rare.

Maturity onset diabetes of the young (MODY) is a rare genetic form of Type 2 diabetes that usually develops in teenagers. It is thought to account for about <1% of all cases of Type 2 diabetes. It is defined by autosomal dominantly inherited, early-onset diabetes and is characterised by beta-cell dysfunction the absence of obesity. The disease results from mutations in transcription factors (types 1, 3, 4, 5 and 6) involved in insulin signalling and the glucokinase gene (type 2).

The principles of treatment differ from Type 2 diabetes as these patients are rarely obese or insulin resistant and respond differently to drugs. Patients with glucokinase mutations usually only need healthy dietary advice throughout their life (although they typically need insulin during pregnancy). In contrast over 60% of patients with the transcription factor mutation will require pharmacological treatment. Some patients may be very well controlled on very small doses of sulphonylureas), but do not respond to metformin or glitazones.

Gestational diabetes mellitus (GDM)

Under normal physiology during pregnancy, maternal insulin resistance rises by week 24. This is an adaptive response to ensure that the foetus receives enough glucose for growth. To counteract this, the pancreas will secrete more insulin to ensure glucose homeostasis. However, in certain predisposed groups e.g. older mothers, those with a family history of GDM, ethnic groups such as Middle Eastern, the change in physiology from week 24 results in disruption of glucose homeostasis, so that insulin resistance prevails. Essentially pregnancy unmasks mothers who are predisposed to IGT and subsequent type 2 diabetes.

This physiology usually reverses straight after birth, but leaves the mother at greater increased risk of developing diabetes. GDM is reported to confer a seven-fold risk for future type 2 diabetes, especially in South Asian women (2), and up to one third of women with type 2 diabetes have been previously diagnosed with GDM (3).

A large prospective cohort found that women exposed to GDM had an increased risk of hypertension in the years after pregnancy even after adjusting for other major risk factors of hypertension. Exposure to GDM appears to increase the subsequent risk of hypertension by 26% (3).

Other risk factors for developing diabetes are:

1. Past medical history of a large baby (>4.5Kg)
2. Past medical history of a stillbirth
3. Polycystic Ovarian Syndrome (PCOS) (through increased insulin resistance)
4. Pancreatic diseases
5. Endocrinopathies e.g. Cushing's disease and acromegaly
6. Drug induced diabetes e.g. thiazides and glucocorticoids
7. Genetic syndromes associated with diabetes e.g. myotonic dystrophy and Down syndrome (although this is often type 1 diabetes).

Related Links

1. Finnish Diabetes Prevention Study. Tuomilehto J et al. N Engl J Med (2001) 344, 1343-50.
2. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Bellamy L,et al. Lancet 2009;373(9677):1773-9.
3. Population health significance of gestational diabetes. Cheung NW, Byth K. Diabetes Care 2003; 26(7): 2005-9.
4. Increased risk of hypertension after gestational diabetes mellitus: findings from a large prospective cohort study. Tobias DK, Hu FB, Forman JP, Chavarro J, Zhang C. Diabetes Care. 2011 Jul; 34(7):1582-4. Epub 2011 May 18.

1. Men are more prone to insulin resistance.

- ○ True
- ○ False

2. 90 % of people with T2DM are overweight in England.

- ○ True
- ○ False

3. Which of the following statements are true regarding The Finnish Diabetes Prevention Study?

- ☐ It was a randomised controlled trial.
- ☐ It looked at lifestyle intervention on the development of T2DM.
- ☐ It only included people with impaired glucose tolerance.
- ☐ It looked at lifestyle intervention and metformin on the development of T2DM.

4. Which of the following statements are true regarding Maturity Onset Diabetes of the Young (MODY)?

- ☐ It is a monogenic cause of diabetes.
- ☐ It is generally autosomal dominant.
- ☐ Patients end up needing to be treated with insulin.
- ☐ It is uncommon.

5. During pregnancy it is normal for insulin resistance to increase in the third trimester.

- ○ True
- ○ False

6. Women with previous gestational diabetes are twice as likely to develop T2DM in the future.

- ○ True
- ○ False

7. Insulin resistance is a feature of Polycystic Ovarian Syndrome.

- True
- False

8. Gestational diabetes does not put the mother at future risk of hypertension.

- True
- False

The importance of risk factors in the development of type 2 diabetes

You are currently on section 2 of 4

Lifestyle factors and diabetes control via patient education
Introduction

Learning objectives: This section covers the importance of lifestyle in diabetes and how best to educate patients on the risks posed by this.
Lifestyle factors such as a healthy diet, weight reduction in overweight people and regular physical activity have been shown to delay and prevent the onset of diabetes and delay the progression of the disease. This is the real challenge in diabetes management and can be difficult to achieve. However with the rising prevalence of diabetes globally, addressing these factors through patient education and support will be crucial to controlling the so-called 'diabetes epidemic'.

Read the resource text now, which looks at key trial evidence and risk factors in diabetes then attempt the questions below.

Resource text

Primary prevention of T2DM

The Finnish Diabetes Prevention Study (DPS) (1) was the landmark randomised controlled trial to demonstrate that type 2 diabetes can be prevented in high-risk patients through lifestyle changes. 522 patients with impaired glucose tolerance and a BMI >25 were enrolled in the study and randomised to a control or intervention group. Individuals in the control group were given oral advice and written information on diet and exercise. Those in the intervention group were given detailed individualised dietary and exercise advice with preset goals and guidance on how these could be achieved.

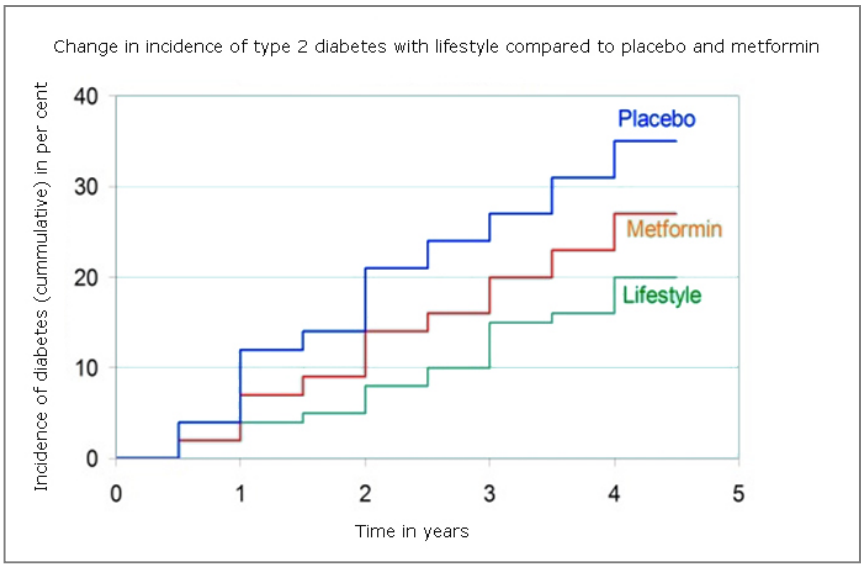
The study was curtailed at two years following the randomisation process (originally planned to run for 6 years) as clear beneficial effects were evident in the intervention group. The cumulative incidence of diabetes in the intervention group was 11% compared to 23% in the control group.

These results have been confirmed on a larger scale by a USA-based RCT, known as the Diabetes Prevention Program (DPP). This RCT randomised 3234 patients who were overweight and had impaired glucose tolerance to the following groups:

1. Metformin 850mg twice daily plus standard lifestyle measures
2. Placebo twice daily plus standard lifestyle measures
3. Individualised intensive programme of lifestyle modification - the target being to lose 7% body weight and to do 150 min of exercise per week.

The results are outlined below in the table below.

Graph 1: Results from the Diabetes Prevention Programme Study. (Adapted from N Engl J Med 2002; 346:393-403)



The key message from this study was that, in patients with IGT, intensive lifestyle modification and to a lesser extent, metformin, significantly reduce the incidence of type 2 diabetes. The benefits of other pharmacological agents in preventing T2DM have been examined in other trials and produced mixed results. However the evidence for lifestyle intervention in reducing the incidence of the disease is consistently striking.

These are the other studies (and drugs):

- STOP-NIDDM: acarbose
- NAVIGATOR: nateglinide and valsartan
- DREAM: rosiglitazone and ramipril
- XENDOS: orlistat
- ORIGIN: glargine insulin
- ACT NOW: pioglitazone

The results from the above trials are reasonably consistent with thiazolinedones, metformin and acarbose reducing progression (whilst Netaglinide was negative). However the evidence for lifestyle intervention in reducing the incidence of the disease is consistently striking.

A recent study (PREPARE) has examined similar high risk individuals and found that those who have a three hour structured education programme focussing on lifestyle improvement with a personalised pedometer showed a significant reduction in the 2-hour glucose value of the OGTT that was sustained at 2 years follow-up2.

Secondary prevention of T2DM

Lifestyle factors such as physical activity and modest weight reduction have been shown to significantly reduce the HbA1c in people with established T2DM.

Physical activity and diet

A systematic review and meta-analysis of 47 RCTs (3) found that structured exercise training that consists of aerobic exercise, resistance training, or both combined was associated with HbA1c reduction in patients with T2DM. Structured exercise training of more than 150 minutes per week is associated with greater HbA1c declines than that of 150 minutes or less per week. Importantly, it found that physical activity advice is associated with lower HbA1c, but only when combined with dietary advice.

Smoking cessation

It is well documented that people with T2DM who smoke have a considerably higher rate of micro-and macrovascular complications than those who do not. Counselling and treatment for smoking cessation has also been shown to be cost-effective at controlling the complications and comorbidities associated with disease. (4).

A systematic review of the literature of the cost-effectiveness of diabetes interventions recommended by the ADA between 1998 and 2008, found that counselling and treatment for smoking cessation was very effective, even more so than the cost-effectiveness of prescribing angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) in preventing end stage renal failure4.

Weight loss

Given that the pathophysiology of insulin resistance is in part due to the level of adiposity and its distribution around the body, it is unsurprising that weight reduction improves insulin sensitivity. However it has been demonstrated that even small weight reductions have significant beneficial effects.

A weight loss of 5-10% of initial body weight lowers the risk for diabetes and cardiovascular disease and results in significant improvements in HbA1c, HDL, TG and blood pressure (5). In a meta-analysis of 9 studies of 162 obese patients with T2DM, a 9.6% reduction in starting body weight over 6 weeks was associated with a decrease in fasting plasma glucose concentration to <50% of initial values (6).

To conclude, lifestyle interventions have been shown to be highly effective at delaying the onset of diabetes and controlling the progressive nature of the disease. It has also been demonstrated that these interventions are cost-effective. Therefore all health care professionals who manage people with diabetes should be offering lifestyle advice and support in following this advice. The National Service Framework for Diabetes (2003) advocates that all people with type 1 and type 2 diabetes should be offered a place on a structured education programme, including those who are newly diagnosed and those who have pre-existing disease.

Video 1: The importance of lifestyle in diabetes.

Related Links

1. Finnish Diabetes Prevention Study. Tuomilehto J et al. N Engl J Med (2001) 344, 1343-50.
2. The Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE) programme study: are improvements in glucose regulation sustained at 2 years? Yates T et al. DiabetMed 2011 Oct 28 (10):1268-71.
3. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. Umpierre D et al. JAMA 2001 May 4:305(17):1790-9.
4. Cost-effectiveness of interventions to prevent and control diabetes mellitus: as systematic review. Li R et al. Diabetes Care. 2010 Aug: 33(8):1872-94.
5. Behavioral aspects of weight loss in type 2 diabetes. Wing RR, Marquez B. Curr Diab Rep. 2008 Apr; 8(2):126-31.
6. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. Anderson JW, Kendall CW, Jenkins DJ. J Am Coll Nutr. 2003 Oct; 22(5):331-9.

1. Intensive lifestyle intervention is more effective than metformin alone at preventing the onset of diabetes.

- True
- False

2. Using a pedometer can delay the onset of diabetes in high-risk individuals.

- True
- False

3. Following the results of a systematic review and meta-analysis of 47 RCTs regarding lifestyle, what is the best advice to give to people with diabetes?

- Do two hours of aerobic exercise a week and aim to lose 20% of weight.
- Do 50 minutes of exercise a week and follow a healthy diet.
- Do two hours of exercise a week and aim to lose 15% of weight.
- Do more than 150 minutes of exercise a week and follow a healthy diet.

4. Which of the following is the most cost-effective intervention in diabetes?

- ACE inhibitors
- Intensive glycaemic control
- Smoking counselling and cessation
- Yearly retinal screening

5. A 9.6% reduction in body weight over 6 weeks is associated with a <50% decrease in fasting blood glucose.

- True
- False

6. A combination of aerobic and resistance training or either alone results in a HbA1c reduction in patients with diabetes.

- True
- False

The importance of risk factors in the development of type 2 diabetes

You are currently on section 3 of 4

Concordance in patients with diabetes
Introduction

Learning objectives: This section covers the definition of concordance in diabetes, the clinical scenarios where this is challenging and the role of specialist psychological support.

Ensuring that the behaviour of the patient mirrors the expectations of the clinician is important in all areas of medicine. If a condition is not well controlled then it may be useful to look in depth at how the patient is managing it on a daily basis. A doctor, who prescribes treatment without exploring barriers to adherence to that treatment, may render the whole consultation process redundant.

Read the resource text which covers concordance in greater detail and looks at diabetes in particular, then attempt the questions below.

Clinical picture available to OnMedica members only

Resource text

Definitions

Compliance is defined as: 'The extent to which the patient's behaviour matches the prescriber's recommendations.' However, its use is declining as it implies lack of patient involvement.

Adherence is defined as: 'The extent to which the patient's behaviour matches agreed recommendations from the prescriber.' It has been adopted by many as an alternative to compliance, in an attempt to emphasise that the patient is free to decide whether to adhere to the doctor's recommendations and that failure to do so should not be a reason to blame the patient. Adherence develops the definition of compliance by emphasising the need for agreement.

Concordance is a relatively recent term, predominantly used in the United Kingdom (UK). Its definition has changed over time from one which focused on the consultation process, in which doctor and patient agree therapeutic decisions that incorporate their respective views, to a wider concept which stretches from prescribing communication to patient support in medicine taking. Concordance is sometimes used, incorrectly, as a synonym for adherence.

Concordance in diabetes

Non-concordance in diabetes care is a considerable problem across the country. A physician, who prescribes treatment without exploring barriers to adherence to that treatment, may easily overlook the man with depression or the woman with an eating disorder who has no intention of taking the prescribed treatment rendering the whole process futile.

The following are a few examples of clinical scenarios where concordance is problematic:

1. Paediatric and adolescent patients.
2. Patients who are fearful of having insulin initiated
3. Insulin treated patients who have a fear of hypoglycaemia
4. Fear of losing driving license, job etc
5. Patients with psychological difficulties such as
   - Eating disorders / fear of weight gain with insulin
   - Depression / anxiety / diabetes 'burn-out'
   - Needle phobia
6. Cultural expectation e.g. participation in religious fasts or reluctance to inject insulin in public
7. Lack of understanding of diabetes and failure to engage regularly with the HCP either due to learning difficulties or mental health problems or in people who cannot face dealing with their condition and therefore avoid almost all reminders of the problem

Initiating insulin

Although crucially important to management of this condition, there has been little formal evaluation of concordance and/or adherence to diabetes treatments. Several studies have explored the barriers to initiating insulin which is a common clinical scenario. The reasons for this range from the perceived pain of injecting, to inconvenience and the commonly held belief that insulin signifies failure on the part of the patient to manage their disease effectively. In clinical practice, these barriers can delay in some optimal disease management for years.

Intensifying insulin treatment

One study has explored participants' experiences of intensifying insulin therapy during the Treating to Target in Type 2 Diabetes trial (4-T). In depth interviews were conducted with 41 trial participants who had their insulin therapy intensified during this trial. The authors found that the vast majority of participants were receptive towards intensifying treatment. However the need to inject insulin whilst in public arose more commonly post intensification and was a consistent source of anxiety. Those who were worried about injecting in public would actively avoid doing so by injecting in toilets or by advancing or delaying the timing of their injections. This is one example of how psychological factors affect health behaviours.

Depression and other psychological problems

Depression is often cited to be as high as 40% in people with diabetes. It is associated with hyperglycaemia, increased rate of complications, increase in cardiovascular disease, lost productivity, increase in economic expenditure and mortality. Other psychological conditions such as eating disorders and needle phobias are associated with poor glycaemic control and raised HbA1c.

National Guidance

The National Institute of Health and Clinical Excellence states that ‘diabetes professionals should ensure they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds, while arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with well-being or diabetes self-management’. This statement suggests a pivotal role for specialist psychological services for people with diabetes.

Despite the known high prevalence of psychological and emotional problems encountered by people with diabetes, and the acknowledged need and demand for support and care with regard to these problems, currently only 31.5% of diabetes services state that they have some form of specialist psychological care and often the availability is a ‘postcode lottery’ (2). Overall, 85% of people with diabetes do not have a defined link to psychological services or at best are offered generic non-specialist services who may not be equipped with the knowledge about their condition. Given that there are 6 national standards relating to this area of diabetes care, these percentages are not encouraging (table 1).

Table 1: The relevant two NSF standards and four NICE guidance recommendations [2].

1. NSF Standard 3: that there should be 'person centred care' which includes counselling and behaviour change support skills.
2. NSF Standard 12: that there should be 'regular surveillance for, and effective management of depression'.
3. NICE: 'Multidisciplinary teams (MDTs) should be alert to the development or presence of clinical or subclinical depression and/or anxiety, especially if there are problems with self-management'.
4. NICE: diabetes professionals should be 'Able to detect and basically manage non-severe psychological disorders in people from different cultural backgrounds'.
5. NICE: diabetes professionals should be 'Familiar with counselling techniques and drug therapy, while arranging prompt referral to specialists, especially if there is significant interference with well-being or diabetes self-management'.
6. NICE: diabetes professionals should be 'Alert to eating disorders and insulin dose manipulation if there is either poor glucose control, low BMI or over concern with body shape and weight. Early, and occasionally urgent, referral to local eating disorders services should be considered'.

A survey carried out by Diabetes UK in 2008 found that only 2.6% of all diabetes centres felt they were providing all these national standards to their patients. One area for definite improvement is ability of diabetes professionals to recognise and have the confidence to treat depression in their patients. In the same survey it was found that the majority of diabetes professionals do not feel adequately trained in this area and therefore the expansion and integration of psychological services and formal training into diabetes services is a key recommendation from Diabetes UK.

Related Links

1. Participants' experiences of intensifying insulin therapy during the Treating to target in Type 2 Diabetes (4-T) trial: qualitative interview study. Jenkins et al. Diabetic Medicine 2011 May;28(5):543-8
2. Minding the gap. The provision of psychological support and care for people with diabetes in the UK. Diabetes UK, 2008

1. Concordance is a consultation process in which both doctor and patient agree on therapeutic decisions.

- True
- False

2. 20 % of people with T2DM are depressed.

- True
- False

3. Most diabetes specialist centres have specialist psychological services that they can refer their patients to.

- True
- False

4. It is the responsibility of the GP should to diagnose and treat depression in all their patients with diabetes.

- True
- False

5. 10% of specialist centres are meeting all 6 national standards relating to psychological care in diabetes.

- True
- False

The importance of risk factors in the development of type 2 diabetes

You are currently on section 4 of 4

End-organ damage in diabetes and early detection strategies
Introduction

Learning objectives: This section covers the pathophysiology and impact of end organ damage in diabetes.

In the previous module, the morbidity, mortality and economic impact of the complications of diabetes was explored. Diabetes remains the most common cause for renal replacement therapy, the most common cause of blindness under the age of 65 and the most common cause of a limb amputation in the UK.

Read the resource text now then attempt the questions below.

Clinical picture available to OnMedica members only

Resource text

Pathophysiology of end-organ damage in diabetes

The pathophysiology of persistent hyperglycaemia causing end-organ microvascular damage is not completely understood. It is thought that intracellular hyperglycaemia activates certain growth factors and signalling molecules that result in microvascular tissue damage. Microvascular complications are strongly associated with cardiovascular disease and in both cases it is thought that an underlying genetic process also contributes to the development of complications. The genetic side of the coin perhaps help explain why some people with diabetes are more prone to certain complications than others irrespective of glycaemic control. For example, genetic predisposition seems to matter more for nephropathy (where <30% of people with T1DM appear to be at risk) versus retinopathy where glycaemic exposure seems to be dominant.

However early-detection strategies and effective treatments for both the micro- and macrovascular complications of diabetes has revolutionised the course of the disease process. This section shall explore those early detection strategies and management of early complications.

Retinopathy

Certain individuals are more at risk of developing retinopathy. Clearly, the longer the duration of diabetes, the higher the risk and poorer glycaemic control as demonstrated in the DCCT Trial (T1DM) and UKPDS trial (T2DM) (See previous module) significantly increases the risk of retinopathy. Diabetes patients who are hypertensive and/or have microalbuminuria are also at higher risk. Poor glycaemic control followed by rapid correction of blood glucose also appears to pre-dispose to retinopathy.

Diabetic retinopathy may worsen during pregnancy. The Diabetes in Early Pregnancy study (1) showed that the risk of progression of retinopathy is related to the severity of retinal involvement before pregnancy and the initial HbA1c levels. Changes in hormones, growth factors, systemic haemodynamics and lower retinal blood flow, may contribute to the exacerbation seen. It may also be due to the rapid improvement in glycaemic control.

As a result pregnant women should be screened more frequently in pregnancy. Ideally they should be screened every trimester of pregnancy. Treatments are the same as for other patients. Laser photocoagulation can be carried out safely and women can be reassured that their long-term risk of retinopathy progression is not increased by pregnancy.

Figure 1: Retinal, fluorescein angiogram showing severe diabetic retinopathy.

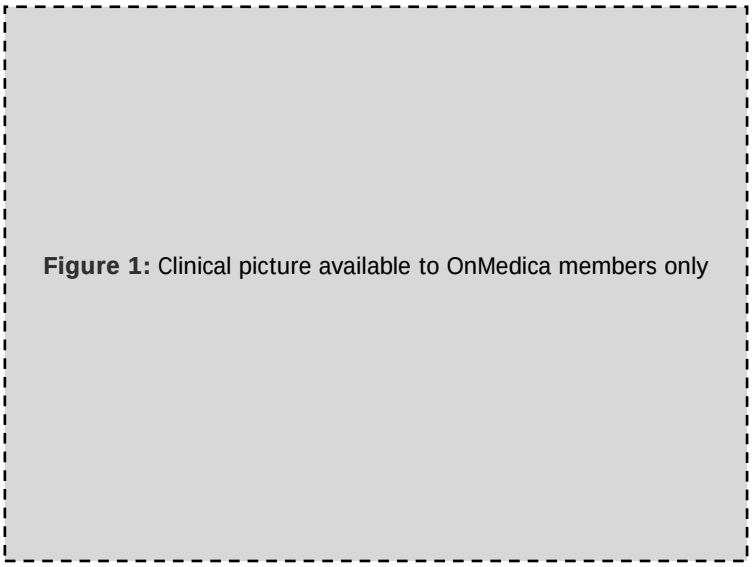
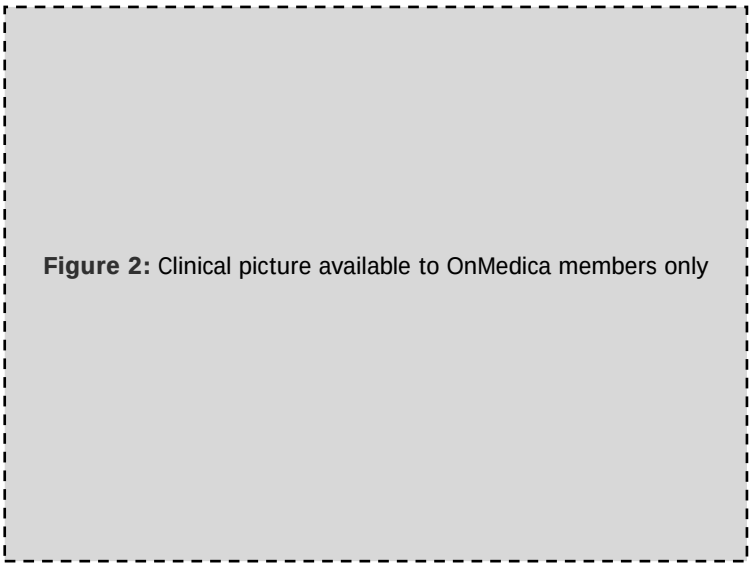


Figure 2: Diabetic retinopathy pre and post treatment.



Treatment for retinopathy

Evidence has shown that early referral and treatment of early retinopathy can prevent blindness in the overwhelming majority of patients who at risk. Although newer agents are being trialled, the mainstay of treatment of very early proliferative retinopathy is laser photocoagulation. This treatment is thought to be beneficial in two ways. Cautery to peripheral retina in proliferative retinopathy is thought to switch off damaging signalling pathways and can therefore preserve vision elsewhere (especially the macula). In pre-proliferative retinopathy, it is also thought to seal off leaking vessels that can cause large haemorrhages and vitreous haemorrhages.

Screening for diabetic retinopathy

In response to the National Service Framework for Diabetes, the Department of Health has rolled out a National Screening Programme over the last 10 years. All people with diabetes in the country over the age of twelve are offered yearly digital retinal photography (usually 2 views to offer increased sensitivity and specificity) in either the community or hospital setting. People with pre-proliferative retinopathy and above, maculopathy, loss of visual acuity (amongst other markers) are referred to an ophthalmologist for consideration of treatment and further reviews usually then take place in the hospital setting.

Nephropathy

Microalbuminuria is the earliest clinical finding in diabetic nephropathy. It is defined as urinary albumin excretion rate of between 30 and 300mg per day. 24 hour urine collections have been superseded by the albumin-to-creatinine-ratio (ACR) which is measured in a first-voided urine sample. Abnormal values are >2.5mg/mmol in men and >3.5mg/mmol in women. If an elevated value is found, it should be repeated at least 2-3 times over the next 3-6 month period to exclude false-positive results (e.g, exercise, fever).

Microalbuminuria is potentially reversible and therefore is an ideal screening tool to detect early kidney damage.

National guidelines advocate a yearly assessment of microalbumin and blood pressure for all people with type 2 diabetes. However, for type 1 diabetes, screening for microalbuminuria can be deferred for 5 years following diagnosis as it is uncommon before this time.

Treatments for early kidney disease

ACE inhibitors have been shown to lower urinary protein excretion and slow the rate of disease progression even in the absence of hypertension. The first RCT to demonstrate this assigned captopril or placebo to normotensive individuals with T1DM (2). The captopril group had a significantly lower mortality rate, progression of renal impairment and dialysis.

There is equally good evidence for use of Angiotensin II receptor antagonists (ARBS) such as losartan in type 2 diabetes (3). Therefore both ACE inhibitors and ARBs have become first line treatment for treatment of microalbuminuria in patients with diabetes who may or may not have hypertension. There is no long term data on the added benefit of using an ACEi inhibitor in combination with an ARB. The ON TARGET trial (4) suggested that patients on the combination did worse than those on a single agent. Therefore there is no current evidence to advocate the use of using both and potential hyperkalaemia is a concern.

Aldosterone antagonists e.g. spironalactone can additionally reduce albumin excretion and blood pressure, although caution needs to be exerted regarding potassium levels which can be a real problem.

Blood pressure

In addition, tight control of blood pressure (if elevated) with conventional agents has also been shown to reduce the progression of nephropathy. The current national guidelines (NICE) for blood pressure targets are as follows.

140/80 mmHg for the majority of people with diabetes 130/80 mmHg for those who are additionally at risk e.g. those with microalbuminuria, GFR <60 ml/min/m2, or who have a previous stroke or TIA.

In addition to microalbuminuria, a yearly measurement of renal function is recommended by NICE. With declining GFR, early rather than late referral to a nephrologist is advocated. The figure below gives a guide as to when to refer to the nephrology department.

Neuropathy

If patients with diabetic neuropathy whose feet have a risk of ulceration are given appropriate education, footwear and foot care, then their amputation rate can be reduced by 30-50%.

There is no one specific test to screen for peripheral neuropathy but rather relies on symptom inquiry and examination. Every year, the healthcare professional should inquire about symptoms e.g. numbness/burning in the feet, ask about previous ulceration and whether there are any current problems with foot care. The feet should then be inspected for any lesion or deformity and a neurological assessment using a 10g monofilament, 128 Hz tuning fork and non-traumatic pin prick should be performed. An assessment of co-existent peripheral vascular disease should also be performed.

Those with peripheral neuropathy at high risk of ulceration should be referred to a local podiatrist and those with foot ulcers ideally should be managed in a diabetes specialist centre with expertise at managing diabetic foot disease. In addition, glycaemic control should be optimised in these patients and for painful neuropathy drug treatment such as duloxetine, gabapentin and amitriptyline may be beneficial at controlling symptoms.

Figure 3: A diabetic neuropathic foot ulcer.

Figure 3: Clinical picture available to OnMedica members only

Macrovascular disease

Screening for macro vascular disease rests on symptoms of angina or claudication and the HCP should have a low threshold for further investigation. A 12 lead resting electrocardiogram has low sensitivity and specificity, although does provide a useful baseline.

Aspirin currently has no role in the primary prevention of cardiovascular disease in diabetes, under the age of 50. Above the age of 50, NICE recommends considering it. However, aspirin of course has a value in secondary prevention.

Dyslipidaemia

Dyslipidaemia in diabetes is (typically low HDL-C and elevated triglycerides) increases the risk of cardiovascular disease in diabetes. The Collaborative Atorvastatin Diabetes Study (5) found that a dose of 10mg of atorvastatin versus placebo, significantly reduced the rates of coronary event, revascularisation and stoke. Statins are therefore advocated as primary prevention in people with T2DM where one additional risk factor for CVD exists, including those with 'normal' cholesterol levels above the age of 40.

The current national targets for total cholesterol is <4 mmol/L and LDL cholesterol <2 mmol/L.

Regarding a raised triglyceride level, modest elevations can be treated with lifestyle advice. There is no evidence for reduction of CVD in diabetes using fibrates. However with levels above 10mmol/L and especially over 20mmol/L the risk of pancreatitis is very high and a fibrate should be added. It is important to note that the combination of statin and a fibrate increases the risk of myositis, particularly in patients with renal impairment.

Figure 4: Atherosclerosis in an arterial vessel.

Figure 4: Clinical picture available to OnMedica members only

Video 1: End organ screening in diabetes

Related Links

1. Metabolic Control and Progression of Retinopathy: The Diabetes in Early Pregnancy Study. Emily Y Chew et al. MD Diabetes Care May 1995 vol. 18 no. 5 631-637.
2. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. Lewis EJ et al. N Engl J Med. 1993 Nov 11;329(20):1456-62.
3. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy RENAAL Study Investigators. N Engl J Med. 2001 Sep 20;345(12):861-9.
4. Telmisartan, ramipril, or both in patients at high risk for vascular events. The ONTARGET Investigators. N Engl J Med 2008; 358:1547-59.
5. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. CARDS investigators. Lancet. 2004 Aug 21-27;364(9435):685-96.

1. Diabetic retinopathy can worsen during pregnancy.

- True
- False

2. Retinal screening in the UK is offered every year to everyone as soon as they are diagnosed with diabetes.

- True
- False

3. Regarding the treatments for microalbuminuria, which statement is correct?

- ACE inhibitors are better than angiotensin II receptor blockers.
- An ACE inhibitor should be started immediately if the UACR is raised.
- There is no evidence that combination treatment of ACE inhibitors and ARBII is preferable.
- Aldosterone antagonists can cause hypokalaemia.

4. What is the current target BP recommended by NICE for people with diabetes and a previous TIA?

- 140/80 mmHg
- 125/75 mmHg
- 130/80 mmHg
- 130/70 mmHg

5. When the GFR falls to 30 or less, the patient should be referred to the nephrology department.

- True
- False

6. Duloxetine is the first line treatment (as recommended by NICE) for the treatment of painful peripheral neuropathy.

- True
- False

7. Aspirin should be given to all people with diabetes for primary prevention.

- True
- False

8. If the total cholesterol value is normal, statins should not be used in people with diabetes.

- True
- False

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