Diabetes mellitus
an update for healthcare professionals

British Medical Association
Board of Science and Education

www.bma.org.uk
Diabetes mellitus
an update for healthcare professionals

February 2004
Editorial Board

A publication from the BMA science and education department and the Board of Science and Education

Chairman, Board of Science and Education  Professor Sir David Carter
Director of professional activities  Dr Vivienne Nathanson
Head of science and education  Dr Caroline Seddon
Project manager  Nicky Jayesinghe
Editor  Angela Sharpe
Contributing authors  Dr John Casey
                           Dr Fiona Green
Editorial secretariat  Dalia Ben-Galim
                               Fleur Conn
                               Hilary Forrester
                               Louise Lakey
                               Elaine Martyn

British Library Cataloguing-in-Publication Data.
A catalogue record for this book is available from the British Library.

ISBN: 0 7279 1856 7
Cover photograph: Getty Images Creative
Printed by the BMA publications unit

Figure 12: ©International Islet Transplant Registry

© British Medical Association 2004 – all rights reserved. No part of this publication may be reproduced, stored in a retrievable system or transmitted in any form or by any other means that be electrical, mechanical, photocopying, recording or otherwise, without the prior permission in writing of the British medical Association.
Board of Science and Education

This report was prepared under the auspices of the Board of Science and Education of the British Medical Association, whose membership for 2003/2004 was as follows:

Professor Sir Brian Jarman
Dr George Rae
Mr James Johnson
Dr David Pickersgill
Professor Sir David Carter
Dr P Maguire
Dr P H Dangerfield
Dr G D Lewis
Professor S Lingam
Dr J Long
Dr S Minkoff
Dr S J Nelson
Dr S J Richards
Dr G Smith
Dr S J L Smith
Dr D M B Ward
Dr G Buckley
Professor B R Hopkinson
Dr N D L Olsen

President, BMA
Chairman, BMA representative body
Chairman, BMA council
Treasurer, BMA
Chairman, Board of Science and Education
Deputy chairman, Board of Science and Education
Co-optee
Co-optee
Deputy member

Approval for publication as a BMA policy report was recommended by BMA Board of Professional Activities on 19 November 2003.

Acknowledgements

The Association is very grateful for the help provided by the BMA committees and many outside experts and organisations. We would particularly like to thank Professor John Tooke (Consultant Diabetologist, Peninsula Medical School, Plymouth), Professor Andrew Morris and Professor Ray Newton (Consultant Diabetologists, Ninewells Hospital and Medical School, Dundee).
Foreword

The Board of Science and Education, a standing committee of the British Medical Association (BMA), provides an interface between the medical profession, the government and the public. One major aim of the board is to contribute to the improvement of public health, and it has developed a wide range of policies on the health of specific groups such as children, the elderly, and asylum seekers. Furthermore, the board’s work on diseases has resulted in a number of publications including the *BMA guide to rabies* (1995), *Bloodborne viruses and infection control: a guide for healthcare professionals* (1998), *Sexually transmitted infections* (2002) and *Childhood immunisation: a guide for healthcare professionals* (2003).

Diabetes mellitus is a serious complex chronic condition that is a major source of ill health. It predisposes to the development of potentially life-threatening conditions. Current estimates are that diabetes affects 1.3 million of the UK population, is a major component of the work of general practitioners and consumes approximately 10 per cent of hospital resources. Meticulous management of diabetes can reduce the risk and rapidity of development of a range of serious long-term complications, notably heart disease, stroke, blindness, renal failure and peripheral vascular disease.

This report focuses on recent changes in our understanding of the epidemiology, aetiology and clinical management of diabetes, placing emphasis on controversial issues and recent advances.

Professor Sir David Carter  
Chairman, Board of Science and Education  
February 2004

Please note that this report is primarily a guide for healthcare professionals on some of the recent advances in the clinical management of diabetes – it is not intended to be a comprehensive text on the disease.
Contents

Introduction .................................................................................. 1

Classification of diabetes and disorders of glucose homeostasis ......................................................... 2
  i) Type 1 diabetes ....................................................................... 2
  ii) Type 2 diabetes .................................................................... 2
      Type 2 diabetes in childhood .................................................. 2
  iii) Impaired glucose regulation .................................................. 3
      Impaired glucose tolerance ................................................... 3
      Impaired fasting glucose ...................................................... 3
  iv) Gestational diabetes .............................................................. 3
  v) Other specific forms of diabetes ............................................. 3

Diagnostic criteria ....................................................................... 4

Aetiology ...................................................................................... 4
  Type 1 diabetes ......................................................................... 4
  Type 2 diabetes ......................................................................... 5

Epidemiology ............................................................................... 6
  Type 1 diabetes ......................................................................... 6
  Type 2 diabetes ......................................................................... 6

Morbidity and mortality associated with diabetes .................................................................................... 7
  Atherosclerotic disease ............................................................. 7
  Atherosclerotic disease and dysglycaemia ................................. 8
  Microvascular disease .............................................................. 9
  Diabetic eye disease ................................................................. 9
  Diabetic nephropathy ............................................................... 11
  Diabetic neuropathy .................................................................. 12
  Erectile dysfunction ................................................................... 13
  The diabetic foot ........................................................................ 13
    Charcot’s foot ......................................................................... 14
    Hypoglycaemia ...................................................................... 14

Management of diabetes .............................................................. 15
  The Diabetes Control and Complications Trial (DCCT) ........... 15
  The United Kingdom Prospective Diabetes Study (UKPDS) .... 15
  Clinical guidelines ..................................................................... 16
  Hyperglycaemia ....................................................................... 16
    Assessing glycaemic control (HbA1c measurements) ............ 16
    Treatment regimes for individuals with type 1 diabetes ...... 17
    Treatment regimes for individuals with type 2 diabetes ...... 17
  Hypertension ........................................................................... 18
  Dyslipidaemia .......................................................................... 18
  Lifestyle .................................................................................... 19
  Additional treatments ............................................................... 19
    Antiplatelet therapy: aspirin and clopidogrel ....................... 19
    ACE inhibitors and angiotensin II receptor blockers ............ 19
  Management of diabetes in the young ................................. 20
Diabetes in pregnancy 21
Pregestational diabetes 21
Gestational diabetes 21

Services 23
The Scottish experience 24
Implications for patient care 26

Diabetes and the workplace 27

Recent advances in the management of diabetes 28
Human insulin 28
Human analogue insulins 28
Short-acting analogues: Lispro and Aspart 28
Long-acting analogues: Glargine 28

Solid pancreas transplantation 28
Patient selection 29
The donor 30
Surgical techniques 30
Immunosuppression 30

Islet transplantation 30
Stem cells and islet transplantation 32
The future of pancreas transplantation 32

Conclusion 33

Websites providing further information on diabetes 34

Appendix I: St Vincent Declaration 36
Appendix II: Clinical guidelines 37

References 38
Introduction

Diabetes mellitus is one of the most common chronic diseases in both western and developing countries. It has a prevalence of approximately eight per cent in much of Europe and the USA and exacts a high cost in terms of morbidity and mortality. This metabolic disorder is characterised by hyperglycaemia and disturbances of carbohydrate, protein and fat metabolism, secondary to an absolute or relative lack of the hormone insulin. The incidence of diabetes continues to rise throughout the world. Indeed, by 2010 it has been estimated that the diabetic population will increase to 221 million (three million in the UK) from 110 million in 1994. The majority of the new cases will be those with type 2 diabetes and most of these will be in China, the Indian subcontinent and Africa. It is estimated that from 65 million cases of type 2 diabetes in Asia and Oceania in 1995, the number will double to 135 million by 2010.

Type 2 diabetes has a significant sub-clinical phase that may last several years, and it is estimated that there are approximately one million people in the UK currently undiagnosed with the disease. Healthcare professionals working in primary care are excellently placed to help identify the missing million and give them appropriate treatment that can minimise and prevent disabling and costly complications. Currently, however, widespread screening for type 2 diabetes has not been advocated by the National Screening Committee, but research is ongoing as to whether screening high risk groups (for example, the obese, those with a family history of diabetes and particular ethnic groups) may be warranted.

* Hereafter shortened to diabetes.
Classification of diabetes and disorders of glucose homeostasis

The classification and diagnostic criteria used for the diagnosis of diabetes and disorders of glucose homeostasis has been the subject of much debate. Currently, there are five major clinical categories of disordered glucose homeostasis (figure 1).

Figure 1: Categories of disordered glucose homeostasis

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Impaired glucose tolerance/impaired fasting glucose</td>
</tr>
<tr>
<td>Gestational diabetes</td>
</tr>
<tr>
<td>Other rare forms include maturity-onset diabetes of the young (MODY), pancreatic diseases</td>
</tr>
</tbody>
</table>

i) Type 1 diabetes

Type 1 diabetes is characterised by beta cell destruction, thereby resulting in an absolute deficiency of insulin. It has an autoimmune basis, and islet cell antibodies and glutamic acid decarboxylase antibodies are present in up to 80 per cent of patients. Research suggests that in genetically susceptible individuals, unknown environmental agents such as viruses may initiate the process, which is possibly mediated via cytokines. Type 1 diabetes is classically a disease of the young and is generally of rapid onset, but it can occur at any age. Diabetes should therefore be suspected in a patient of any age who presents with sudden weight loss and raised blood glucose. The presence of ketonuria in the absence of fasting in this context may aid in the differentiation between type 1 and type 2 diabetes.

ii) Type 2 diabetes

By contrast, type 2 diabetes is characteristically a disease of the middle aged or elderly and usually begins insidiously. Insulin resistance and a family history are the hallmarks. More than 90 per cent of all identified cases of diabetes are classified as type 2. Type 2 diabetes is frequently undiagnosed with perhaps as many as half the individuals who have this type of diabetes being unaware of their condition. Most type 2 diabetes is preceded by an asymptomatic period of impaired glucose tolerance, which is characterised by a response to an oral glucose challenge that is not normal, but is not diagnostic of diabetes. The distinction between type 1 and type 2 diabetes is often blurred. Up to 10 to 15 per cent of phenotypic type 2 diabetic patients have autoantibodies to glutamic acid decarboxylase and hence they may have an incomplete form of type 1 disease.

Type 2 diabetes in childhood

Recently, it has been recognised that type 2 diabetes can develop in early adulthood and even in childhood. It was first described in children in 1979. An increasing prevalence is now being recognised in association with obesity, particularly in certain ethnic groups (such as American Hispanics and indigenous American Indians) and in individuals with a family history of type 2 diabetes. It is distinct
from maturity-onset diabetes of the young (MODY) which is a rare form of diabetes associated with genetic defects. Significant numbers of children with type 2 diabetes also have other features of the metabolic syndrome such as increased central obesity (ie obesity more marked in the trunk than the limbs), dyslipidaemia and higher blood pressure than their peers, all of which are features that may worsen over time.

iii) Impaired glucose regulation

Impaired glucose tolerance and impaired fasting glucose refer to a metabolic state between normal glucose homeostasis and diabetes. It has been suggested that these disorders should be considered as a stage in the natural history of disordered carbohydrate metabolism, indicating risk of future diabetes and/or cardiovascular risk, rather than discrete clinical entities.

Impaired glucose tolerance

Impaired glucose tolerance is a common problem affecting approximately 17 per cent of the UK population aged 40 to 65 years. The importance of this condition is debatable. Controversy has arisen partly because of the high variability in the response to the oral glucose tolerance test. Up to 50 per cent of persons initially classified as having impaired glucose tolerance are reclassified on repeat testing as having normal glucose tolerance. Nonetheless, impaired glucose tolerance is a strong risk factor for the development of type 2 diabetes. It also identifies a group of individuals at higher risk of developing coronary heart disease (CHD).

Impaired fasting glucose

More recently, impaired fasting glucose (fasting plasma glucose 6.1 to 6.9 mmol/l) has been introduced as a new category of impaired glucose regulation. The exact significance of impaired fasting glucose is yet to be determined, but it would appear to be a stronger predictor of the risk of progression to diabetes than impaired glucose tolerance. The importance of impaired fasting glucose as a risk factor for cardiovascular disease is, however, less clear.

iv) Gestational diabetes

Gestational diabetes is a form of carbohydrate intolerance which is first identified during pregnancy. Therefore, this definition may also include glucose intolerance which was present prior to pregnancy but unrecognised. It is generally agreed that gestational diabetes is a prediabetic state and associated with an increased cardiovascular risk.

v) Other specific forms of diabetes

Diabetes can result from a number of rare genetic, endocrine and infectious processes that affect the exocrine pancreas. MODY is associated with abnormal beta cell function, inherited in an autosomal dominant fashion. It is genetically and clinically heterogeneous. Unlike type 2 diabetes, the underlying defects do not produce insulin resistance and individuals with MODY are seldom obese.
Diagnostic criteria

Diabetes is classically associated with symptoms of thirst and polyuria, and if the disease is severe enough, weight loss. At present, the diagnosis of diabetes and impaired glucose homeostasis in the UK relies on the measurement of blood glucose either in the fasting state or following a standard glucose challenge, as in the oral glucose tolerance test. In symptomatic individuals only one confirmatory blood test is required to diagnose diabetes, whereas two tests are needed in asymptomatic patients.

The American Diabetes Association (ADA) published its new criteria for the diagnosis of diabetes in 1997. These revised criteria aim to encourage the use of fasting glucose alone as a simpler and more accurate means of diagnosing diabetes. The ADA wishes to discontinue use of the difference between fasting and two hour glucose values that was previously seen as important in the diagnosis of diabetes. The World Health Organisation (WHO) continues to advocate the use of the glucose tolerance test, but its recommendations are otherwise similar to the ADA guidelines. The main change is a lowering of the fasting plasma glucose from 7.8mmol/l to 7.0mmol/l. In addition, both groups have introduced a new category of impaired fasting glucose (figure 2). The WHO criteria are the most widely endorsed for use in the United Kingdom.

Figure 2: Comparison of diagnostic criteria for the diagnosis of diabetes, impaired glucose tolerance and impaired fasting glucose

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Impaired glucose tolerance</th>
<th>Impaired fasting glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current ADA criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fasting blood glucose (mmol/l)</td>
<td>≥7.0</td>
<td>–</td>
<td>≥6.1 but &lt;7.0</td>
</tr>
<tr>
<td>two hour blood glucose (mmol/l)</td>
<td>≥11.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Current WHO criteria</strong></td>
<td></td>
<td>&lt;7.0</td>
<td>≥6.1 but &lt;7.0</td>
</tr>
<tr>
<td>fasting blood glucose (mmol/l)</td>
<td>≥7.0</td>
<td>≥7.8 but &lt;11.1</td>
<td>&lt;7.8 (if measured)</td>
</tr>
<tr>
<td>two hour blood glucose (mmol/l)</td>
<td>≥11.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aetiology

Type 1 diabetes

Type 1 diabetes is considered to be an autoimmune process in which T lymphocytes infiltrate the islets of the pancreas and destroy the insulin-producing beta cell population. Glutamic acid decarboxylase is a strong candidate autoantigen in triggering beta cell specific autoimmunity. The majority of patients with type 1 diabetes have anti-glutamic acid decarboxylase antibodies in their sera at diagnosis. However, both genetic and environmental factors have also been implicated as important factors in the initiation of the autoimmune process (figure 3).

Up to 20 chromosomal regions have been linked with the development of type 1 diabetes. The most important gene loci in defining the risk of type 1 diabetes are located within the human leucocyte antigen (HLA) gene region. HLA-DQ molecules are of primary importance, but HLA-DR may modify the risk conferred by HLA-DQ. The largest contribution from a single locus comes from several genes located in
the major histocompatibility complex (MHC) on chromosome 6p21.3 (IDDM 1 Locus). This aggregation accounts for 40 per cent of the familial aggregation of type 1 diabetes. A second locus (IDDM 2) on chromosome 11p15.5 has been confirmed using case control and family based studies. Confirmation of other potential gene loci for type 1 diabetes has been difficult as the results can be variable and difficult to replicate partly due to differences in genetic susceptibility within different ethnic groups.

Environmental agents, which interact with genetic factors, have also been implicated in the aetiology of type 1 diabetes. Enteroviruses have been suggested as having the potential to trigger beta cell damage in a significant proportion of patients. Dietary factors such as vitamin D deficiency and early exposure to cow’s milk have also been explored as potential triggers of the immune process underlying type 1 diabetes.

Two large multicentre trials are currently ongoing in the USA and Europe to assess whether early insulin treatment (Diabetes Prevention Trial – 1 (DPT)) or nicotinamide treatment (European Nicotinamide Diabetes Intervention Trial (ENDIT)) can reduce the rate of developing type 1 diabetes in high risk individuals. These studies are due to report by 2005.

**Type 2 diabetes**

Insulin resistance is coupled with beta cell dysfunction in type 2 diabetes but debate remains as to which is the primary defect. The roles of hyperinsulinaemia and insulin resistance in the pathogenesis of type 2 diabetes are now well recognised. A combination of genetic and environmental factors influence the progression of insulin resistance to diabetes. The finding that non-diabetic relatives of individuals with type 2 diabetes are insulin resistant suggests a strong genetic component, but as yet, the search for the candidate gene(s) has been unrewarded. Several epidemiological studies have indicated that a sedentary lifestyle promotes the development of insulin resistance and it is well established that physical exercise can improve glucose tolerance and insulin sensitivity (figure 3). The change in insulin sensitivity is independent of obesity and can occur in the absence of any weight loss. As physical fitness improves there is a reduction in hyperinsulinaemia, with serum lipid profile and other metabolic parameters showing some improvement. In prospective studies improved physical fitness has been shown to reduce cardiovascular disease and total mortality by up to 44 per cent. Excessive food intake is also detrimental to insulin sensitivity and its effects are to some extent independent of fat accumulation.

Intrauterine factors may also be important in that type 2 diabetes is significantly more prevalent in adults who had low birth weight for gestational age. This relationship is independent of adult body weight and social class. The effects of impaired foetal growth may be modified by subsequent growth and the risks of developing type 2 diabetes is highest in those who are small at birth and become overweight. Undernutrition in foetal life may result in permanent physiological changes that would be beneficial if nutrition remained scarce after birth. But, if nutrition becomes plentiful these changes predispose to obesity and impaired glucose tolerance. This has been described as the thrifty phenotype hypothesis.
Figure 3: Potential mechanisms implicated in the pathogenesis of type 1 and type 2 diabetes

| Type 1 diabetes | Genetic factors: | HLA-DQ molecules  
|                |                | IDDM 1 Locus (chromosome 6p21.3)  
|                |                | IDDM 2 Locus (chromosome 11p15.5)  
| Autoimmunity:  | antibodies to glutamic acid decarboxylase  
| Environmental: | for example, early exposure to cows milk  
|                | enteroviruses  
|                | vitamin D deficiency  

| Type 2 diabetes | Lifestyle: | sedentary lifestyle  
|                | excessive food intake  
| Intrauterine:  | decreased birth weight  
|                | thrifty phenotype  
| Genetic:       | strong familial tendency  
|                | no candidate genes identified as yet  

Epidemiology

Type 1 diabetes

A large variation exists in worldwide incidence rates of type 1 diabetes. This disease is most common in Finland (45 per 100,000 under the age of 15 years) and least common in China, Japan and parts of South America. The causes of these variations remain unknown, but they are thought to be largely environmental. In many parts of the world the incidence of childhood diabetes is rising by two to five per cent each year. This translates into a rise of about 50 per cent over the last 10 years. Estimates of prevalence in the UK suggest that 0.3 per cent of the population have type 1 diabetes.

Type 2 diabetes

Type 2 diabetes is the most common type of diabetes globally accounting for approximately 90 per cent of all cases of diabetes. Social and behavioural changes are regarded as key factors in the recent global explosion of type 2 diabetes. Obesity is increasingly recognised as one of the major public health problems of our time, and central obesity in particular, is a key factor in determining the rising incidence of diabetes.
The prevalence of type 2 diabetes increases with age and the increased longevity of many societies has undoubtedly contributed to the rise in the overall prevalence of type 2 diabetes. One in 20 people over 65 years of age has diabetes rising to one in five people of more than 85 years of age. Ethnicity also plays an important role in determining the prevalence of type 2 diabetes with a more than 10-fold difference in prevalence between high and low risk populations. Populations such as North American Indians and Aborigines who have experienced a radical change from a traditional to a more ‘westernised’ lifestyle, show particularly high prevalence rates of around 30 to 50 per cent of adults.

Morbidity and mortality associated with diabetes

Diabetes is a progressive and life-threatening condition with potentially devastating consequences for health. It has been estimated to account for at least five per cent of NHS costs, and up to 10 per cent of hospital inpatient resources, although this figure does not take into account the indirect costs of diabetes nor the effect on the quality of life for those with the condition.

Diabetes increases the risk of atherosclerotic cardiovascular diseases such as CHD, stroke and peripheral vascular disease (macrovascular disease). It is second only to smoking as the major aetiological factor in atherosclerotic vascular disease which can lead to myocardial infarction, stroke and lower limb amputation.

Diabetes also causes harm throughout the body by damaging small blood vessels. Initially, these changes to the microcirculation are reversible. In the long term, however, poorly controlled diabetes can lead to a range of serious complications, which include diabetic retinopathy (p9), diabetic nephropathy (p11), and diabetic neuropathy (p12). Diabetes is also a leading cause of blindness, renal failure and neuropathy in the UK.

Atherosclerotic disease

Cardiovascular disease accounts for up to 60 per cent of all deaths from diabetes and is the most common complication in Europeans with type 2 diabetes. Longitudinal studies have shown that the risk of cardiovascular disease is two to four times higher in patients with type 2 diabetes than in non-diabetics. The prevalence rates of cardiovascular disease in the diabetic population show some variation between populations, but in general, the prevalence of diabetes increases the underlying cardiovascular disease in all populations. Even in countries such as Japan, with a low incidence of CHD in the diabetic population, the risk of developing CHD is significantly higher than in the background population. Pima Indians have the highest reported prevalence of type 2 diabetes worldwide, but a relatively low frequency of CHD. This suggests that cultural, ethnic and genetic factors are important in determining the risk of CHD developing in individuals with type 2 diabetes.

The key features of cardiovascular disease in individuals with diabetes can be summarised as follows:

- increased risk of cardiovascular disease
- loss of the protective cardiovascular effects normally conferred on premenopausal females
- a younger age of onset of cardiovascular disease
- worsened prognosis in terms of mortality from cardiovascular disease.

The National Health and Nutrition Examination Survey demonstrated that the prevalence of diabetes increases with age and hence it can be extrapolated that an ageing population will increase the absolute prevalence.
The excess mortality from cardiovascular disease in general is evident in all age groups of diabetics, but is most pronounced in those who develop type 1 diabetes when young. It is further exacerbated by socio-economic deprivation. The efficacy of revascularisation procedures, such as angioplasty, stenting and coronary artery bypass grafting is reduced in patients with diabetes. The fall in the rate of death due to CHD seen in the general population in the last 35 years has not been seen in the diabetic population.

The pattern of cardiovascular disease appears to be similar in both type 1 and type 2 diabetes, although there are less epidemiological data available for type 1 diabetes. In individuals with type 1 diabetes, cardiovascular disease is relatively rare in the first 30 years following diagnosis. However, for individuals who have had type 1 diabetes for more than 40 years, cardiovascular disease accounts for more than 30 per cent of all deaths. In patients with type 2 diabetes, CHD is the major cause of morbidity and mortality accounting for up to two-thirds of all deaths.

The risk factors for cardiovascular disease in the diabetic population are similar to those in the non-diabetic population, but:

- smoking tends to be more prevalent in patients with diabetes and the excess risk is multiplicative
- dyslipidaemia tends to be more prevalent
- hypertension is more prevalent
- microalbuminuria (a feature of diabetic nephropathy) is an independent risk factor associated with a doubling in cardiovascular risk.

Although less well documented, peripheral vascular disease and cerebrovascular disease prevalence rates are probably increased by about two to five times in the diabetic population. Cerebrovascular disease may account for a further 15 per cent of all deaths in patients with diabetes.

**Atherosclerotic disease and dysglycaemia**

More recently, there has been increasing interest in the influence of levels of blood glucose not diagnostic of diabetes on cardiovascular risk. A number of researchers have suggested that there is a continuous relationship between blood glucose and cardiovascular disease. This view has been challenged in that some suggest that the excess CHD mortality only becomes apparent at the upper end of the distribution of glucose intolerance; a threshold effect rather than a continuous relationship. Impaired glucose tolerance and other metabolic disturbances may be present for many years before diabetes becomes evident and it has been suggested that this ‘pre-diabetic’ state may have an important role in determining the risk. The increased cardiovascular risk seen in individuals with impaired glucose tolerance may be partly attributable to the increased prevalence of other cardiovascular disease risk factors. Population directed interventions, which shift the distribution of glucose values downwards, may be effective in reducing the burden of cardiovascular disease in high risk populations.
**Microvascular disease**

The former diagnostic criteria of diabetes was based upon the threshold value of fasting glucose above which microvascular complications may occur (7.8mmol/l fasting; 11.1mmol/l two hours after a 75 gрамme oral glucose tolerance test). The endothelia of the retina, kidney and peripheral nervous system allow glucose entry even in the absence of insulin. As such, they are particularly susceptible to damage induced by hyperglycaemia associated with diabetes. Several potential mechanisms have been suggested as the link between hyperglycaemia and the development of microvascular damage. Currently, the three main mechanisms thought to be involved are:

- increased activity of the polyol pathway
- activation of protein kinase C
- non-enzymatic glycation of proteins (figure 4).

All three mechanisms may enhance oxidative stress and thereby reduce the bioavailability of nitric oxide.

**Figure 4: Potential mechanisms involved in the pathogenesis of microvascular complications**

<table>
<thead>
<tr>
<th>Biochemical mechanism involved in the development of microvascular disease</th>
<th>Potential effects of mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased activity of the polyol pathway</td>
<td>Results in increased levels of osmotically active sorbitol and fructose through the action of aldose reductase enzyme</td>
</tr>
<tr>
<td>Increased protein kinase C activity</td>
<td>Hyperglycaemia results in accumulation of diacylglycerol which results in activation of protein kinase C-β in endothelial cells. This alters vascular permeability and increases basement membrane synthesis.</td>
</tr>
<tr>
<td>Non-enzymatic glycation</td>
<td>Glucose can attach to the amino groups of proteins at a rate proportional to the mean glucose concentration. This can lead to cross-linking and modification of the function of proteins.</td>
</tr>
</tbody>
</table>

**Diabetic eye disease**

Diabetes is the principal cause of partial sight and blindness in middle-aged adults in the western world. Blindness is one of the most feared complications of diabetes with an incidence of 50 to 65 per 100,000 diabetic population per year in Europe. It is more prevalent in type 1 than type 2 diabetes. Within 20 years of diagnosis nearly all patients with type 1 diabetes have a degree of retinopathy as opposed to approximately 60 per cent of individuals with type 2 diabetes. However, severe retinopathy can develop in both types of diabetes.

Diabetic retinopathy can be successfully treated if picked up early. Currently, there is inconsistency in service provision for diabetic retinopathy screening in the UK. There are examples of good practice on the Diabetes UK website that help inform healthcare professionals of innovative practice in retinal screening.

Diabetic retinopathy can be staged according to severity into four main types – these being background retinopathy, preproliferative retinopathy, proliferative diabetic retinopathy, and maculopathy (figure 5).
Hyperglycaemia is a critical factor in the aetiology of diabetic retinopathy and probably initiates basement membrane thickening and retinal capillary non-perfusion. Growth factors such as vascular endothelial growth factor, placental growth factor, and pigment epithelium-derived factor may be important in mediating the response to glucose. Factors other than hyperglycaemia have an important influence on the development of diabetic retinopathy. These include:

- hypertension
- duration of diabetes (but up to 39 per cent of patients with type 2 diabetes have retinopathy at presentation)
- coexisting diabetic nephropathy
- hypertriglyceridaemia
- pregnancy
- smoking (possibly)
- rapid improvement in glycaemic control.

The evidence for modification of these additional risk factors is still, in the most part, lacking. It is certain, however, that control of blood pressure may reduce the risk of eye disease significantly.

In individuals with sight-threatening retinal disease it is recommended that retinal disease is stabilised prior to achieving improvements in glycaemic control.

Diabetic eye disease may have a long asymptomatic phase. Therefore, regular retinal screening must be undertaken by all patients with diabetes to allow early identification and treatment of retinopathy (figure 6). Screening should include visual acuity measurement and visualisation of the fundus. However, there is controversy as to the best method of retinal screening. Retinal photography and slit lamp indirect ophthalmoscopy, in the hands of properly trained operators, are more sensitive screening tools for detecting retinopathy than dilated direct ophthalmoscopy. In general, retinal photography is a more practical means of screening for retinopathy than slit lamp ophthalmoscopy.
Board for Scotland define digital retinal photography as the modality of choice for diabetic eye screening in the UK. The availability of mobile screening units allows eye screening to be provided at sites that are more convenient for the patient. Unfortunately, up to 14 per cent of retinal photographs are ungradeable and these individuals must undergo an alternative form of retinal visualisation. Direct ophthalmoscopy remains a useful opportunistic screening tool.

**Figure 6: Diabetic screening services recommendations for implementation (Scotland)**

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 (mild)</td>
<td>Re-screen 12 months</td>
</tr>
<tr>
<td>R1 (moderate)</td>
<td>Re-screen 12 months</td>
</tr>
<tr>
<td>R2 (severe)</td>
<td>Re-screen 6 months (or refer to ophthalmology if this is not feasible)</td>
</tr>
<tr>
<td>R3 (proliferative)</td>
<td>Refer ophthalmology</td>
</tr>
<tr>
<td>R4 (enucleated)</td>
<td>Refer ophthalmology</td>
</tr>
<tr>
<td>R5 (inadequate)</td>
<td>Re-screen 12 months (other eye)</td>
</tr>
<tr>
<td>R6 (inadequate)</td>
<td>Technical failure: arrange alternative screening examination</td>
</tr>
</tbody>
</table>

Digital retinal photographic screening for all diabetics is being introduced as part of the National Service Framework (NSF) for diabetes. All patients above 12 years of age should be screened at diagnosis and annually thereafter. More frequent examinations may be necessary in high-risk individuals such as those with pre-existing retinopathy, pregnant women and individuals who have undergone a rapid improvement in diabetic control. In addition, cataract formation is more common and progresses more rapidly in patients with diabetes.

Referral to an ophthalmologist is currently recommended for those individuals who have been noted to have:
- sudden loss of vision
- evidence of retinal detachment
- preproliferative or proliferative changes
- vitreous haemorrhage
- rubeosis iridis
- an unexplained drop in visual acuity
- macular oedema
- changes within one disc diameter of the macula.

**Diabetic nephropathy**

Diabetic nephropathy is a leading cause of end-stage renal failure in the western world and is responsible for more than one third of all patients starting renal replacement therapy. Diabetic nephropathy is also a strong predictor of the risk of developing atherosclerotic disease which is the most common cause of death in this group.

Arbitrary but distinct phases exist in the development of diabetic nephropathy:
- *microalbuminuria* is the earliest clinical sign of diabetic nephropathy. It is asymptomatic and is defined as urinary albumin loss of between 30 and 300mg/day. The urinary albumin to creatinine ratio in the first voided sample of the morning is often measured in order to avoid having to acquire overnight timed samples. Values of greater than 2.5mg/mmol in adult men and 3.5mg/mmol in adult females are taken as indicative, which can be confirmed by two or more timed overnight values in the diagnostic range. Alternatively, a urinary albumin concentration of more than 20mg/l may also be used as a diagnostic criterion.
• **diabetic nephropathy** is defined as a urinary albumin excretion of more than 300mg/day. At this stage the albustix test becomes positive. An albumin to creatinine ratio of more than 30mg/mmol is also indicative of diabetic nephropathy. It should be noted that proteinuria may be the result of an alternative renal pathology or related to intercurrent illness, posture or exercise. Alternative causes should be considered and the findings should be confirmed on a second occasion.

Diabetic nephropathy is not only predictive of the development of progressive renal failure it is also an independent risk factor for cardiovascular disease. By the time dialysis is required most patients will have extensive co-morbidities such as retinopathy, neuropathy and autonomic dysfunction.

The prevalence of diabetic nephropathy and its rate of progression vary between type 1 and type 2 diabetes. Approximately 40 per cent of patients who have had type 1 diabetes for more than 30 years develop microalbuminuria. Twenty per cent of type 1 patients will develop proteinuria after a disease duration of 25 years. If proteinuria and hypertension are present, then the standardised mortality ratio is increased 11-fold in men and 18-fold in women. Microalbuminuria has been considered the first step toward proteinuria and renal failure. Yet, the results of a recent study indicate that microalbuminuria is more likely to subside to normal levels than to progress to overt proteinuria. Approximately, 25 to 30 per cent of individuals with type 2 diabetes develop some degree of nephropathy. Twenty per cent of microalbuminuric type 2 patients who survive for 10 years develop proteinuria. If proteinuria and hypertension are present then the standardised mortality ratio is increased five-fold in men and eight-fold in women.

**Diabetic neuropathy**

Diabetic neuropathy is a significant cause of morbidity. Its management remains challenging. A number of clinical syndromes are recognised:

- **symmetrical distal polyneuropathy** may be asymptomatic or present with pain, paraesthesia, numbness, alldynia or impaired position sense leading to an unsteady gait
- **focal neuropathy**, particularly of cranial nerves
- **motor neuropathy**, including diabetic amyotrophy (pain, weakness and wasting of quadriceps) and occasional upper limb girdle and/or truncal muscles
- **autonomic neuropathy** resulting in erectile dysfunction in men, orthostatic hypotension, gastroparesis and diabetic diarrhoea. Cardiovascular autonomic neuropathy increases perioperative risk.

Diabetic neuropathy is associated with other risk factors for macrovascular disease such as poor metabolic control, dyslipidaemia, smoking and high body mass index, and also with other microvascular complications such as retinopathy and microalbuminuria.

A variety of mechanisms have been suggested as important in the development of diabetic neuropathy:

- increased shift through polyol pathway resulting in increased sorbitol levels
- ischaemia secondary to the production of advanced glycation products
- decreased levels of nerve growth factor and laminin β 2 gene expression.

---

7 Allodynia means ‘other pain’. It refers to pain from stimuli which are not normally painful and pain which occurs other than in the area stimulated. It is not synonymous with referred pain (www.painonline.org/allo.htm – accessed September 2003).
Despite a better understanding of the pathogenesis of diabetic neuropathy treatment, options are limited to optimising glycaemic control and symptomatic control with pain-modifying agents such as tricyclic antidepressants, or anticonvulsants such as carbamazepine. If these are not tolerated then simple analgesics or gabapentin (neurontin) may have fewer side effects.

**Erectile dysfunction**

This is the most common manifestation of autonomic dysfunction in men with diabetes. Its prevalence is probably increased by a greater incidence of vascular disease in this group and by the use of drugs such as antihypertensive agents. Diabetic men have a more than three-fold increased prevalence of erectile dysfunction compared with non-diabetic men. This leads to a significant reduction in quality of life. The management of erectile dysfunction in the diabetic population is similar to that in the non-diabetic population. A physical examination should look for features such as Peyronies disease and phimosis, both of which may be more common in the diabetic population. Measurement of prolactin, testosterone and gonadotrophins should be considered if there are features to suggest hypogonadism, or loss of libido. Therapeutic options include the oral phosphodiesterase type 5 inhibitors Sildenafil (viagra®) and the recently introduced Tadalafil (cialis®), intracavernosal injections (caverject® and viridal duo®) or urethral application (muse®) of alprostadil (prostaglandin E1). Sublingual apomorphine (uprima®) has also been introduced for the treatment of erectile dysfunction. Drug treatment for erectile dysfunction may only be prescribed on the NHS under certain circumstances. However, men with diabetes are eligible to receive drug treatment on the NHS. Counselling and mechanical devices may also be useful in this group.

Diabetes UK produces a helpful leaflet, Impotence and diabetes.

**The diabetic foot**

Diabetic foot problems are common. Diabetic foot ulcers have a significant impact on quality of life, as well as contributing to disability and premature mortality. Between 40 to 60 per cent of all amputations are performed in patients with diabetes. A foot ulcer resulting in deep ulceration, uncontrollable infection or gangrene precipitates most amputations. Several studies have shown that a multidisciplinary approach with systematic foot examination, protective footwear, self-care education and risk stratification is effective in the prevention of foot ulceration, but these studies tend to be small with short follow up. Nevertheless, the multidisciplinary approach may reduce limb amputation by up to 50 per cent.

Diabetic foot ulceration is principally associated with peripheral vascular disease and peripheral neuropathy. Previous foot ulceration, amputation, presence of callus, joint deformity, and visual impairment have a cumulative effect on the risk of ulceration.

Lower limb ischaemia is one of the major determinants of the development of diabetic foot ulcers and the most important factor preventing healing. It is therefore essential that vascular surgeons are closely involved in the management and assessment of non-healing foot ulcers. This is due to the possible requirement of revascularisation techniques to promote healing and reduce the need for amputation. New options such as the use of recombinant platelet-derived growth factor in conjunction with good ulcer care have been shown to improve healing outcomes. In addition, subcutaneous granulocyte-colony stimulating factor has been shown to be effective in treating diabetic foot infections. Clinical experience has also shown that application of maggots is an alternative method of debridement.
Charcot’s foot
Charcot’s foot is a complication of diabetes that almost always occurs in those with underlying neuropathy. Although it is rare, it is an important and potentially devastating disorder.® Charcot’s arthropathy is a chronic, progressive degenerative disorder affecting one or more peripheral or vertebral articulations, which develops as the result of a disturbance in the normal sensory innervations of joints. It results in massive osseous destruction and malposition of the articular constituents.® As the patient notices little pain (a result of the neuropathy), they continue to walk. This can lead to severe deformities of the foot, intractable ulceration, culminating in the need for amputation. It is therefore most important to diagnose this condition early because appropriate treatment at this stage can minimise deformities and reduce associated morbidity.® A careful examination of the foot for injuries, neuropathy and early deformity along with timely intervention can reduce the need for amputation.®

Early signs of Charcot’s foot include the foot, or affected part of the foot being warmer than the other. There will be some swelling and redness; this is often all that is initially present and can come on quite suddenly.® Typically, the patient can recall no history of trauma or only a very minor incident, for example, twisting their ankle a few weeks ago. The first clue to the diagnosis is the disproportionate lack of pain. The second clue is the slowness of recovery. X-ray at this stage may be normal or show a minor fracture, but may already show quite gross bone destruction.

The prevention of further joint destruction and foot deformity is the primary initial aim in treatment of Charcot’s foot. Therefore, rest and stabilisation of the area are key. Most cases should be put in a plaster to relieve pressure and to prevent further deformity. These need to be replaced periodically until there is no temperature difference between the two feet. This can take up to six to nine months. Furthermore, care needs to be taken of the other foot to prevent problems developing. Bisphosphonates have been shown to be useful as an adjunct in the management of Charcot’s foot. After the Charcot foot has healed, orthotic advice is critical as specialised footwear and foot orthoses may be needed to prevent reoccurrence, depending on the extent of deformity. If treatment was not started early enough and/or the foot is deformed, the possibility of an ulcer developing is high. Prevention with footwear and foot orthoses is then very important. If the deformity is severe or ulcer recurrence is a problem, surgery can be used to reshape the deformity.®

Hypoglycaemia
Hypoglycaemia has a significant impact on the quality of life of patients treated with both insulin and sulphonylureas. Fear of hypoglycaemia is often a significant barrier to achieving optimal control, particularly in those who have suffered a severe event. Care should therefore be taken to avoid hypoglycaemia, particularly in the newly diagnosed insulin treated patient.® (For further information on driving with diabetes please refer to the Diabetes UK factsheet.)
Management of diabetes

There is robust evidence that good diabetes care (for example, good control of blood pressure, glycaemic control, lipid lowering and lifestyle management) reduces the risk of complications and delays the rate of progression of complications. Two major trials have contributed significantly to our understanding of the importance of optimising control in the diabetic population and these are discussed below.

The Diabetes Control and Complications Trial (DCCT)

This study examined the influence of intensive insulin therapy on the development and progression of long term complications in individuals with type 1 diabetes. It randomly assigned 1,441 patients to conventional diabetes management or to intensive therapy administered either via an insulin pump or multiple daily injections. The intensively managed group received additional education and extensive back up support to help them achieve optimal glycaemic control. The groups were followed for an average 6.5 years. The results showed that intensive therapy improved glycaemic control (median average HbA1c 9.1 per cent in conventional group versus 7.2 per cent in the intensive group) and slowed the onset and the progression of diabetic retinopathy, nephropathy and neuropathy in patients with type 1 diabetes. This benefit persisted for at least four years beyond the conclusion of the DCCT, despite the near convergence of haemoglobin A1c levels (HbA1c 8.2 per cent conventional group versus 7.9 per cent in the intensive group). Unfortunately, the study design was such that it was not possible to separate the effects of intensive insulin therapy from intensive support. While the risk of long-term complications was significantly reduced, this was at the expense of a two to three-fold increase in severe hypoglycaemia.

The United Kingdom Prospective Diabetes Study (UKPDS)

This study concentrated on the role of glycaemic control in individuals with type 2 diabetes. The hypertension in diabetes study was embedded within the UKPDS at a later stage. Five thousand one hundred and two newly diagnosed patients (median age 54 years) with type 2 diabetes were randomly assigned to conventional therapy or intensive therapy and followed for a mean of 10 years. The UKPDS illustrated several key points about type 2 diabetes:

- it is a progressive disease. Even with initial intensive treatment with insulin or a sulphonylurea most patients require a combination of oral antidiabetic agents and/or insulin to optimise glycaemic control
- improved glycaemic control (HbA1c 7.0 per cent in the intensive group versus 7.9 per cent in the conventional group) was associated with a lower rate of appearance and progression of microvascular complications
- intensive treatment with sulphonylureas or insulin carries a risk of hypoglycaemia and weight gain (mean 2.9 kg)
- the first line use of metformin treatment in overweight patients reduced diabetes related end points and death without causing significant weight gain. Furthermore, there was a significant reduction in cardiovascular events. However, this effect was not seen when metformin was added to maximal dose sulphonylurea.
The hypertension in diabetes trial randomised a subgroup of patients to tight blood pressure control or conventional blood pressure control. This study showed the importance of managing hypertension in patients with type 2 diabetes, but also illustrated the difficulties of doing so. It demonstrated that:

- tight blood pressure control (target value of 144/82mmHg) reduced diabetes related end points and deaths, stroke, microvascular disease and combined macrovascular disease end points (myocardial infarction, stroke, peripheral vascular disease, sudden death) compared with less tight control (target value of 154/87mmHg)
- in order to optimise blood pressure control multiple drugs were required. Three or more drugs were needed by 29 per cent of the tightly controlled group. Despite this, only 56 per cent of patients in the tightly controlled group attained the target blood pressure
- the study did not have sufficient power to identify differences between different classes of antihypertensives, but overall it appeared that the blood pressure level attained appeared to be more important than the type of drug used.

Patients are individuals and the evidence from such studies should be interpreted with this in mind. It may not be practical or safe to achieve tight glycaemic control in all groups of patients. For example, in frail elderly patients the benefits of tight glycaemic control in reducing the risk of complications may be far outweighed by the significant risks associated with hypoglycaemia and polypharmacy.

**Clinical guidelines**

The following guidelines for the management of diabetes have been largely adapted from the Scottish Intercollegiate Guideline Network (SIGN), *The management of diabetes*, (SIGN 55, 2001) and NICE guidelines E, F, G and H (2002). NICE guidelines currently deal with the management of retinopathy, renal disease, blood glucose, lipids and blood pressure in patients with type 2 diabetes only (see appendix II for more details).

Diabetes UK produces guidelines, care recommendations and reports. Their document, Recommendations for the management of diabetes in primary care, provides guidance for:

- primary healthcare teams in the organisation and delivery of services for people with diabetes
- those responsible for planning and commissioning diabetes services.

A PDF of this report can be downloaded from the Diabetes UK website: www.diabetes.org.uk.

The Diabetes UK website also has extensive information intended for public consumption, including what diabetes is and how to manage it.

**Hyperglycaemia**

**Assessing glycaemic control (HbA1c measurements)**

HbA1c is a measure of the non-enzymatic attachment of glucose to the β chain of haemoglobin and is expressed as the percentage of haemoglobin that is glycated. In the non-diabetic population this is approximately four to six per cent. Since the life-span of a red blood cell is approximately 120 days, HbA1c gives an indication of average glycaemia over a 60 day period. The relationship between HbA1c and plasma glucose is complex but, by using the extensive data collected from the DCCT a relationship between HbA1c and plasma glucose has been defined (figure 7).
As discussed earlier, both the UKPDS and the DCCT have highlighted the importance of optimising glycaemic control in patients with type 1 and type 2 diabetes. From these studies it would seem that:

- good glycaemic control as defined by an HbA1c of around seven per cent is associated with a significantly reduced risk of developing microvascular complications
- reducing the HbA1c below seven per cent may reduce the risk of diabetic eye disease further
  In those with established retinopathy the maintenance of good glycaemic control is essential to delay progression of the disease
- in the primary prevention of cardiovascular disease there appears to be no level of glycaemic control which confers a reduction in risk
- the evidence for good glycaemic control in those with established diabetic nephropathy (as judged by the presence of microalbuminuria) is less convincing. In type 1 diabetes there appears to be no clear benefit.

A small study of 52 type 2 patients showed stabilisation of urinary albumin excretion, but despite this, creatinine clearance rates fell in both groups.

**Treatment regimes for individuals with type 1 diabetes**

Insulin regimes should be tailored to each patient with type 1 diabetes. There are a variety of different regimes and methods of delivering insulin; some offer increased flexibility offset against a greater need for monitoring, more frequent injections and a greater risk of hypoglycaemia. Advances in insulin pump technology and development of new forms of modified human (analogue) insulins (p28) may improve the future management of type 1 diabetes.

Diabetes UK provides impartial information on the products available to those with diabetes, including why and when to use them. www.diabetes.org.uk

**Treatment regimes for individuals with type 2 diabetes**

If dietary and lifestyle changes are unsuccessful in optimising glycaemia in patients with type 2 diabetes, metformin is now the drug of choice in overweight patients. Once the dose of metformin is maximised, sulphonylureas or thiazolidinediones may be added to optimise control. If metformin is contraindicated or not tolerated then sulphonylureas, thiazolidinediones or a combination can be considered. Although, currently in the UK, thiazolidinediones have no licence for use as a monotherapy. Insulin treatment should be considered for patients with type 2 diabetes in whom glycaemic control has remained poor, despite lifestyle measures and a combination of oral agents.
Hypertension

Hypertension is associated with an increased risk of cardiovascular disease, retinopathy and nephropathy in patients with diabetes. Lowering blood pressure has been shown to reduce the risk of microvascular and macrovascular disease, but not mortality rate.  

- The target blood pressure for patients with uncomplicated diabetes is 140/80 mmHg.
- In patients without established complications, beta blockers, thiazide diuretics, calcium channel blockers and ACE inhibitors have all been shown to be effective in reducing blood pressure and thus reducing the risk of complications.
- In patients with type 1 diabetes and microalbuminuria, a lower blood pressure of 120/70 mmHg may be optimal in reducing the progression of diabetic nephropathy.
- If type 1 patients already have established microalbuminuria or proteinuria, then ACE inhibitors are the drug of choice for managing hypertension as these drugs may offer additional benefit independent of their effect on blood pressure. In patients with type 2 diabetes and microalbuminuria, angiotensin II antagonists have been shown to be effective in reducing the rate of progression of diabetic nephropathy. Again, this effect is independent of blood pressure reduction.

Dyslipidaemia

Patients with type 2 diabetes often have an adverse lipid profile. Elevated total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides are independent risk factors for the development of cardiovascular disease. Decisions on whether to treat dyslipidaemia should take into account the number and extent of concomitant risk factors:

- in the primary prevention of CHD in patients with uncomplicated type 2 diabetes, treatment is usually advocated when the 10 year risk of coronary event is more than 30 per cent using the Joint British Chart. Whether a lower risk threshold, 15 per cent for example, should justify treatment is under discussion and the revised Joint British Guidelines will clarify this.
- in patients with type 1 diabetes and established nephropathy, current risk tables significantly underestimate cardiovascular disease. In these individuals there should be a lower threshold for initiating therapy.
- a small number of patients with established CHD and type 2 diabetes were included in the landmark Scandinavian Simvastatin study (4S) and the Cholesterol and Recurrent Events study (CARE). The limited evidence available suggests that in patients with a cholesterol of more than 5 mmol/l the addition of statin therapy (hydroxymethyl glutaryl coenzyme A (HMG Co-A) reductase inhibitors) may result in a significant reduction in the risk of cardiovascular events.
- in patients not receiving statin therapy and who have a cholesterol level of more than 5 mmol/l, but a low high density lipoprotein (HDL) of more than 1 mmol/l, there may be a role for treatment with fibrates in the secondary prevention of coronary events.

Furthermore, experts would now advocate statins for all diabetic patients with other evidence of cardiovascular risk.
Lifestyle

Lifestyle interventions are important in managing diabetes. Both microvascular and cardiovascular complications are influenced by factors such as smoking. Optimal glycaemic control requires healthy eating and sensible levels of physical activity. It is important that those involved in delivering lifestyle advice are given appropriate training in the delivery of this advice. For lifestyle interventions to be effective, patients may require more frequent contact and additional support. Smoking cessation is essential in diabetics and may be aided by nicotine replacement or bupropion therapy.

Dietary recommendations are set out in the Diabetes UK leaflet entitled Eating well with diabetes. Diabetes UK recommends that all newly diagnosed patients should be assessed by a state registered dietician who will then agree specific dietary targets with the patient.

Additional treatments

Antiplatelet therapy: aspirin and clopidogrel

The role of aspirin therapy (75mg/day) in the secondary prevention of ischaemic heart disease is well established. Subgroup analysis of a large randomised controlled trial had shown that addition of clopidogrel to aspirin therapy in non-ST elevation coronary syndromes may reduce the risk of further vascular events.

The use of aspirin in the primary prevention of cardiovascular disease remains controversial. There is some evidence from the hypertension optimal treatment (HOT) study to support the use of aspirin to reduce cardiovascular risk in patients with well controlled hypertension and diabetes.

ACE inhibitors and angiotensin II receptor blockers

ACE inhibitors and angiotensin II receptor blockers may have additional benefits which are independent of their effects on blood pressure. These drugs can, therefore, be recommended in certain circumstances in normotensive individuals:

- individuals with impaired left ventricular function treated with ACE inhibitors have a significant reduction in mortality
- following myocardial infarction with or without impaired left ventricular function, ACE inhibitors improve mortality (to achieve most protection they should be commenced within 48 hours of the event)
- the Heart Outcomes Prevention Evaluation (HOPE) study has shown that in high risk patients with a combination of risk factors (age more than 55 years, smokers, microalbuminuria and dyslipidaemia), treatment with ramipril may lead to fewer strokes, fewer myocardial infarctions and a reduced mortality
- in patients with established microalbuminuria or proteinuria, ACE inhibitors have been shown to reduce the risk of progression of nephropathy as well as reducing mortality
- angiotensin II antagonists have been shown to delay the progression of renal disease in patients with type 2 diabetes and microalbuminuria or established diabetic nephropathy (although this had no effect on overall mortality).
Management of diabetes in the young

Type 1 diabetes accounts for 90 per cent of diabetes in patients under the age of 25 years. However, over recent years there has been an increase in the frequency of type 2 diabetes in the young along with increasing recognition and awareness of genetic forms of diabetes (for example MODY). Between 12 and 15 per cent of young people with type 1 diabetes have a family history of the disease. The risk of developing diabetes is much higher if the father, rather than the mother, has diabetes. Currently, screening for type 1 diabetes is not recommended, as there are no known preventative strategies. However, the results of ENDIT and DPT are expected in 2005 (see page 5).

The diagnosis of diabetes in childhood can be stressful for both the child and his or her family. Many families go through a process analogous to grieving following diagnosis and an empathic and supporting approach to management is essential. Specific psychological problems such as eating disorders are more common in adolescents with diabetes and it is essential that appropriate psychological interventions are available to help young people develop coping strategies.

Following diagnosis, home-based education packages involving the whole family are thought to be at least as effective as inpatient instruction. The treatment of type 1 diabetes involves initiation of insulin, dietary changes and general diabetes education. The hormonal changes of puberty and the typical pattern of teenage rebellion make the attainment of optimal glycaemic control in this group challenging.

The Scottish Study Group for the Care of Diabetes in the Young has demonstrated that the average glycaemic control in young people with diabetes across Scotland is poor (HbA1c 9.1 per cent). Evidence regarding the optimum treatment regime for individuals with type 1 diabetes is limited. There is some evidence to suggest that intensive insulin therapy either with multiple daily injections or pumps may improve glycaemic control and reduce complications, but it is difficult to differentiate the effects of intensive insulin therapy from intensive support. Analogue insulins have been shown to reduce the risk of hypoglycaemia associated with intensive regimes.

Early signs of microvascular disease are seen in children with type 1 diabetes. Puberty may further accelerate these changes. Current clinical guidelines suggest that young people from the age of 12 years should undergo annual retinal screening, microalbuminuria estimation, and blood pressure measurement.

The Diabetes UK website has sections aimed at teenagers with diabetes and parents of young children with diabetes. The organisation also produces publications for purchase on the same topics. www.diabetes.org.uk
Diabetes in pregnancy

Only 10 per cent of diabetes in pregnancy is pregestational; 90 per cent is gestational diabetes (for a summary of managing diabetes in pregnancy see figure 8, p23).

Pregestational diabetes

Type 1 diabetes is more common than type 2 during the reproductive years. Pregnancy in women with established diabetes is associated with a risk to both the mother and the foetus. Spontaneous abortion, preterm labour, congenital malformations, pre-eclampsia, large-for-dates-babies, birth injury and caesarean section are all more common in pregnant women with diabetes. Furthermore, established end-organ disease such as retinopathy and nephropathy may deteriorate during pregnancy; this may be further worsened by hypertension. Dedicated pre-pregnancy care from a multidisciplinary team may be a means of reducing complications in pregnancy.

There is strong evidence that the avoidance of hyperglycaemia is essential in optimising pregnancy outcomes in type 1 diabetes. Recent evidence suggests that each complication has a different glucose threshold. Therefore, although it is not always possible to achieve optimal glycaemic control (blood glucose levels of between 4 and 6mmol/l) in all patients, any improvement may be beneficial in reducing complications for a given threshold. Hypoglycaemia should also be avoided as this can have both short and long-term consequences for the foetus and the mother. In the short term, hypoglycaemia may result in interuterine growth restriction which is associated with higher rates of age-specific neonatal mortality and long-term cognitive deficits. Furthermore, epidemiological studies suggest that diabetes, CHD and hypertension may be more common in adults who were small for gestational age at birth. Recurrent hypoglycaemia may result in impairment of glucose counter-regulatory responses in the mother and loss of hypoglycaemia awareness.

The risk of neural tube defects is increased in diabetic pregnancies and for this reason all women with diabetes who are planning a pregnancy or who become pregnant should receive 5mg folic acid daily up to 12 weeks gestation.

Labour and delivery should always occur in a maternity unit supported by a neonatal intensive care unit. Following delivery the baby is at risk of hypoglycaemia. Early feeding may help to reduce this risk. Breast feeding should be recommended as it has clear benefits for the baby and is associated with better control of the mother’s diabetes.

Gestational diabetes

Gestational diabetes is defined as carbohydrate intolerance that results in hyperglycaemia which is first recognised in pregnancy. This definition, therefore, includes a diverse group of women with abnormal glucose handling that may revert to normal after delivery, those with previously undiagnosed type 1 and type 2 diabetes, and more rarely women with MODY.

Gestational diabetes develops in two to five per cent of all pregnancies, but usually disappears when a pregnancy is over. Gestational diabetes is more common in certain ethnic groups, such as African Americans, Hispanic/Latino Americans and American Indians. It is also more common in people with a family history of diabetes and in obese individuals. Women who have gestational diabetes are at increased risk for developing diabetes later in life. Indeed, some studies have shown that nearly 40 per cent of women who have gestational diabetes develop diabetes in the future. Thus, gestational diabetes may be
considered as a pre-diabetic state\textsuperscript{134} with an association of increased cardiovascular risk.\textsuperscript{135} There is some evidence to suggest that these individuals can reduce their risk of progression to diabetes with various lifestyle interventions, such as weight loss and exercise programmes.

Impaired glucose metabolism during pregnancy is associated with large-for-dates-babies. Furthermore, several studies have suggested that gestational hyperglycaemia is associated with adverse foetal and maternal outcomes.\textsuperscript{136} Unfortunately, there is a lack of definitive data on the glycaemic threshold for these adverse outcomes. The diagnostic label of gestational diabetes may itself be associated with an increased likelihood of the induction of labour, instrumental delivery and caesarean section.

Currently, there is controversy as to who should be screened for gestational diabetes. The criteria used for diagnosis differ between WHO recommendations and those used in the USA. At present, WHO recommends the use of a 75g oral glucose tolerance test, although it is recognised that reproducibility of this test is poorer during pregnancy.\textsuperscript{137} There are some preliminary studies that suggest fasting glucose may be as sensitive and predictive of morbidity as glucose tolerance testing, but further work is required to confirm this finding.\textsuperscript{138} Unfortunately, at the current time there is no consensus on the definition of gestational diabetes.\textsuperscript{22} The WHO definition of gestational diabetes is a fasting venous plasma glucose of greater than 5mmol/l or more than 9mmol/l two hours after the oral glucose tolerance test.

There is limited evidence to support the use of dietary alterations to reduce accelerated foetal growth.\textsuperscript{140} Intensive management with diet, blood glucose monitoring and insulin should be initiated if, after a trial of dietary intervention, fasting blood glucose levels remain above 6mmol/l or two hours postprandial levels exceed 7mmol/l with evidence of a large foetus on ultrasound (more than 95th centile).\textsuperscript{141} There is, however, some evidence to suggest that intensive treatment with diet or insulin may be detrimental for babies who are not large-for-dates.\textsuperscript{142}

Following delivery of the baby, insulin can be stopped immediately (unless there is suspicion that the individual has developed coincidental type 1 diabetes, i.e. glucose intolerance which was present prior to pregnancy but previously unrecognised). Lifestyle advice should be given, and an oral glucose tolerance test should be carried out six weeks after delivery.
**Figure 8: Summary of diabetes management in pregnancy**

<table>
<thead>
<tr>
<th>Pregestational diabetes</th>
<th>Gestational diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception planning</td>
<td>Initially, lifestyle and dietary measures</td>
</tr>
<tr>
<td>Multidisciplinary team approach</td>
<td>Insulin treatment is indicated if large foetus and fasting glucose &gt;6mmol/l or postprandial glucose &gt;7mmol/l</td>
</tr>
<tr>
<td>Maintenance of blood glucose recordings between 4 and 7mmol/l</td>
<td>Repeat glucose tolerance testing 6 weeks post partum</td>
</tr>
<tr>
<td>Avoidance of hypoglycaemia</td>
<td>Opportunity to give affected individuals advice about reducing risk of future diabetes</td>
</tr>
<tr>
<td>5mg folic acid daily until 12 weeks gestation</td>
<td></td>
</tr>
<tr>
<td>Increased frequency of screening for retinopathy</td>
<td></td>
</tr>
<tr>
<td>Breast feeding recommended</td>
<td></td>
</tr>
</tbody>
</table>

Further information on pregnancy and diabetes can be found on the Diabetes UK website. The organisation also produces a magazine for purchase, this comprehensive guide includes tips on topics such as exercise, diet and maintaining a healthy pregnancy. [www.diabetes.org.uk](http://www.diabetes.org.uk)

**Services**

The care of people with diabetes occurs in a wide variety of settings, including hospital outpatient departments, hospital wards, general practice settings and the patient’s own home. Therefore, a multidisciplinary team of healthcare professionals (including, for example, podiatrists, specialist nurses and physiotherapists as well as doctors) is needed to provide care. Although, diabetes services are generally led by a number of key figures including clinicians, managers, and commissioners, a large part of the burden of diabetes management falls on the patient and their family.

The complexity of diabetes means that its effective management requires collaboration and communication between clinical staff in a range of organisations. They must work with patients and their families to provide integrated and individualised care. In order to establish such a service there must be clear objectives, effective leadership, and an enthusiastic workforce committed to teamwork. The service should be underpinned by effective information technology.
Recent healthcare policy\textsuperscript{143,144} has promoted the creation of high quality services within the NHS that are coordinated, comprehensive and seamless. From this has emerged the concept of a Clinical Network, whereby disease-specific healthcare is integrated across the interface between primary and secondary care within a defined geographical area. The ultimate aim of a clinical network is to improve patient care in terms of quality, appropriateness and access. To achieve this there must be a clear line of responsibility and structure. This has led to the concept of Managed Clinical Networks.

<table>
<thead>
<tr>
<th>Essential features of a managed clinical network:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- promote the delivery of seamless, high quality care across the interface of primary and secondary care</td>
</tr>
<tr>
<td>- multidisciplinary involvement</td>
</tr>
<tr>
<td>- underpinned by the development of evidence-based protocols (eg SIGN guidelines)</td>
</tr>
<tr>
<td>- patient representation and involvement is mandatory</td>
</tr>
<tr>
<td>- clear line of responsibility</td>
</tr>
<tr>
<td>- effective information technology</td>
</tr>
<tr>
<td>- regular audit and feedback</td>
</tr>
<tr>
<td>- production of an annual report accessible by the public.</td>
</tr>
</tbody>
</table>

Managed clinical networks offer opportunities for flexibly planning and delivering services which cut across traditional professional and organisational boundaries to focus on meeting patients’ needs. The success of this model of service development and delivery is critically dependent upon active management and integrated clinical leadership to support collaborative, multidisciplinary teamwork and education. Networks are further strengthened by ongoing, rigorous evaluation underpinned by effective clinical information and management systems. Development of a successful network requires cooperation between multidisciplinary professional groups and the breaking down of organisational barriers. The provision of quality evidence-based care within networks can be aided by the development and application of well-defined clinical protocols derived from a documented evidence base such as SIGN guidelines or the National Service Framework (appendix II).\textsuperscript{145} These protocols should be extended to involve nurses and allied professionals, in accordance with the current philosophy of NHS modernisation. Patient representation is an essential part of any network, and each network should have a clear statement of the specific clinical and service improvements which patients should expect as a result of the establishment of a network.

In order to deliver truly integrated care, clinical information needs to be easily shared, without compromising confidentiality, as patients move between the various professionals within a network. Thus a clinical network must be underpinned by robust information technology systems to facilitate secure transfer of data within and between primary and secondary care sites. Unique patient identifying codes, such as NHS numbers, are essential to allow the correct information about individual patients to be readily available, thus avoiding expensive duplication of investigations and potential delays in treatment. Networks also require disease-specific information systems, based upon nationally-defined datasets, to facilitate the monitoring of both short and long-term outcomes of a particular disease and its management. This will also allow each network to produce a written annual report that is available to the public. This information is essential for the future strategic planning of services and for clinical audit and research.

The Scottish experience

In Scotland, the concept of managed clinical networks has existed since the publication of the Acute Services Review in 1998.\textsuperscript{146} The Tayside region of Scotland (population 391,000) has pioneered the development of a diabetes managed clinical network that is committed to improving diabetes care. This regional diabetes network was developed against the background of a well-established system for diabetes
shared care which had existed within the region for many years. This network has provided a model for the development of managed clinical networks throughout the UK. It has clearly defined aims:

- sustained improvement in health experience and a life-span approaching normal expectation in quality and quantity for all individuals with diabetes
- prevention and cure of diabetes and its complications by intensifying research effort.

The diabetes clinical network is also committed to WHO principles of:

- **equity** by ensuring that the appropriate care is delivered to patients with local accessibility
- **empowerment** by enabling a clinically-led and developed service which is sensitive to patients’ needs
- **cooperation** by delivering a seamless service delivered by primary and secondary care
- **participation** by including in the development patient representation and all disciplines that are currently involved in the delivery of care
- **primary healthcare** by enabling a shift in the point of delivery of care from secondary to primary care where appropriate.

A single health board and two NHS trusts – Tayside Primary Care Trust and Tayside University Hospitals Trust, administer healthcare in Tayside. Services are provided by 75 general practices, two district general hospitals and a major teaching hospital. Four local healthcare cooperatives (LHCCs) operate within the primary care sector, in a similar manner to the primary care trusts (PCTs) that exist in England and Wales.

The development of this network has been made possible due to the existence of a unique 10-digit identifying number. This is known as the Community Health Number (CHNo), with the first six digits corresponding to the individual’s date of birth. Every patient who is registered with a general practitioner in Tayside is allocated this unique identifier. This system has been used for all healthcare activity in the region since the 1970s, regardless of whether contact occurs in primary or secondary care, to allow effective patient tracking throughout the region. This network has a clearly defined organisational structure (figure 9).

The Tayside diabetes managed clinical network has an innovative approach to the use of information technology. By using state of the art information technology to electronically link multiple independent data sources it has been possible to create a validated, comprehensive register of all patients with diabetes in the region. This register conforms to a nationally defined minimum diabetes dataset for determining the clinical outcomes of diabetes and its management. The register and information technology systems form the key part of the clinical network. Up-to-date practice-specific feedback is provided to primary care clinicians in several forms and for numerous process variables such as reversible risk factors and disease outcomes. For example, feedback may consider macrovascular and microvascular end points in which the overall practice data are compared against the regional averages. Individual patient outcomes are also defined. This comprehensive audit and support system provides primary and secondary care clinicians with the information necessary to deliver quality care to the diabetic population throughout the region. The system acts as a prompt to highlight patients who display parameters outside agreed targets and those who have not undergone monitoring and screening for complications within an agreed time-scale. Clinicians have thus been able to direct their efforts towards those patients who may be at highest risk of developing diabetes-related complications.

---

8 See www.diabetes-healthnet.ac.uk
Implications for patient care

In 1989, WHO and the International Diabetes Federation formulated a strategy which aimed to improve the identification, prevention and treatment of diabetes and its various complications. This became known as the St Vincent Declaration \(^{149}\) (appendix I). Effective networks are essential to allow for implementation of the terms of the St Vincent Declaration. The development of the Tayside diabetes managed clinical network has allowed the incidence and prevalence of diabetes in Tayside to be determined with greater precision. \(^{147}\) Detailed information on diabetes-related end points within the region has also been collected, including the burden of macrovascular and microvascular diseases by using the database. Analysis of anonymised prescribing data has yielded insights into patient behaviour, in particular, adherence to diabetes treatment regimens. \(^{150}\) This has had a major influence on local treatment policies. Clearly the regional approach to diabetes care in Tayside is cohesive and inclusive. The principal reason for this has been the enthusiastic support and participation of all general...
practitioners in the region. Ongoing evaluation will determine whether these developments will translate into improved patient outcomes.

**Diabetes and the workplace**

Unfortunately, discrimination against people with diabetes is an all too common occurrence. The 1995 Disability Discrimination Act (DDA) introduced new laws aimed at ending the discrimination that many people with disabilities face, especially in the area of employment. The DDA does not specify which conditions are covered but the conditions must have a 'substantial and long term effect on a person’s ability to carry out normal day to day activities.' Although most people with diabetes do not generally consider themselves to be disabled, the Act therefore probably covers type 1 diabetes in that if insulin were not taken the disease would most likely be very disabling. Type 2 diabetes may also be covered but there have been no law cases to date, so each case would need to be reviewed on its own merits.

Although the DDA is quite far reaching it does not cover all areas of employment or discrimination. Certain occupations are exempt from the DDA and can thus refuse to employ someone with a disability. These include:

- prison service
- armed forces
- fire service
- police force
- work on board a ship, hovercraft or aircraft
- work wholly or largely outside the UK
- businesses employing fewer than 15 people.

As a result of these exclusions from the DDA, certain jobs are not open to people with diabetes, especially if they are treated with insulin. Individuals with tablet-treated diabetes may continue to be employed in many of these 'banned' professions, but if they require to transfer to insulin therapy this may affect their employment. The government may consider extending the DDA in the near future and thus some of the current blanket bans may be overturned.

Jobs with a blanket ban on employment for those on insulin are:

- airline pilot
- jobs requiring a large goods vehicle or passenger carrying vehicle licence
- working off-shore regardless of the type of job
- train driver.

Some jobs have a blanket ban on recruiting individuals with insulin-treated diabetes but will allow individuals to continue working if they are diagnosed in post as long as certain medical standards are met. These include:

- armed forces
- police and fire services
- some airline crew (generally short haul flights only).
Recent advances in the management of diabetes

Human insulin

Human insulin was first introduced for clinical use in the early 1980s. Before this, animal insulins, such as porcine or bovine insulin, were used in the management of diabetes. Unfortunately, before the introduction of human insulin there were few adequate clinical studies to allow comparison of efficacy with animal insulin. Furthermore, there were concerns that many patients were switched to human insulin as a result of promotional pressure rather than because of evidence of clinical superiority. Following its introduction, there was a suggestion that use of human insulin was associated with reduced awareness of hypoglycaemia. Since that time, a number of randomised controlled trials have shown no difference between the adverse reaction profile of human insulin and animal insulin. However, these studies also failed to demonstrate any significant improvement in glycaemic control with human insulin. Currently, a small but significant number of patients, who are convinced that the conversion from porcine to human insulin resulted in a loss of hypoglycaemia awareness, choose to remain on animal insulin. Optimal metabolic control can be achieved with either animal insulin or human insulin provided appropriate regimes are instituted and support offered.

Human analogue insulins

Since 1996, ‘analogue’ insulins have been introduced in which there is a slight change in the positioning in the amino acid sequence of the human insulin molecule. These alterations confer slight changes in the action of the insulin (see below) and thus make it more convenient to use. There are three analogue insulins available in the UK, these are Lispro (Humalog), Aspart (Novorapid) and Glargine (Lantus).

Short-acting analogues: Lispro and Aspart

The alteration in the structures of Lispro and Aspart means that they are absorbed more quickly and thus act more quickly than traditional animal insulins. This means that they can be given just before eating or even just after eating. This is more convenient for some people and there is a perceived improvement in quality of life. There is also some evidence to suggest that individuals treated with short-acting insulin may experience fewer hypoglycaemic events than those treated with traditional insulin, but there appears to be no improvement in overall control.

Long-acting analogue: Glargine

The alteration in the structure of Glargine has resulted in a much slower absorption rate than other insulins. Therefore, the effects last longer (around 24 hours) than traditional long-acting insulins. Again, there is evidence to suggest that this insulin may reduce the risk of hypoglycaemia but no improvement in overall control has been demonstrated.

Solid pancreas transplantation

The last decade has seen the emergence of pancreas transplantation as an established treatment option for a select group of type 1 diabetic patients. Several transplant units throughout the UK now routinely offer pancreas transplantation and, as such, activity is increasing year on year (figure 10). Morbidity as a result of the surgical procedure has now been reduced to less than 20 per cent. One year graft survival as defined by insulin independence exceeded 80 per cent.

Three groups of diabetic patients are currently considered for pancreas transplantation. The majority are patients with end stage diabetic nephropathy who require simultaneous pancreas and kidney transplantation (SPK). Pancreas transplantation is sometimes performed after kidney transplantation.
(PAK), particularly in patients who have previously received a kidney from a live donor. Pancreas transplantation alone (PTA) is less commonly performed in the UK. PTA can be considered in patients with severe hypoglycaemic unawareness and/or rapidly progressive secondary complications. Insulin independence and euglycaemia are usually established within 24 hours of solid pancreas transplantation with hypoglycaemic counter-regulation restored and maintained.

Graft survival for primary transplants at one year following cadaveric pancreas transplants in the USA in the period 1997 to 2001 (n=4805) was 83 per cent for SPK, 79 per cent for PAK and 78 per cent for PTA. Overall outcomes for SPK, PAK and PTA have improved significantly from previous eras. Primary cadaveric pancreas transplants performed outside the USA between 1997 and 2001 (n=1,726) have statistically similar outcomes, apart from PTA where graft survival rate is significantly lower. SPK pancreas graft survival at one year was 82 per cent, PAK 64 per cent and PTA 54 per cent.

**Figure 10: Kidney/pancreas transplants and active waiting list at year end 1992-2001**

Addenbrookes NHS Trust website has frequently asked questions about combined kidney and pancreas transplantation which is ideal to print out for patients. Furthermore, the trust also has a patient information booklet, *Kidney handbook – international transplant nurses society* (2002), which contains a section with similar information for patients. www.cambridge-transplant.org.uk.

**Patient selection**

Selection of the most appropriate recipients for pancreas transplantation has resulted in reduced morbidity and mortality. Patients with cerebrovascular and ischaemic heart disease are not suitable for transplantation (due to the risk of post-operative myocardial infarction and stroke) although peripheral vascular disease is only a relative contraindication.
The donor

Donor age has been identified as the single most important selection criterion for the cadaveric heart beating pancreas donor, and patients aged between eight and 50 years are normally considered. Mild hyperglycaemia is common in heart beating organ donors and is not a contraindication to pancreas donation. The pancreas retrieval procedure is technically demanding. The pancreas can be removed en bloc with the liver and then separated from it. The shortage of cadaveric donor organs has encouraged a few units (notably the University of Minnesota) to attempt segmental live donor pancreas transplants. Although equivalent graft survival rates have been reported, live donor pancreas transplantation only accounts for around one per cent of pancreas transplants worldwide, almost certainly reflecting the obvious risks to the donor.

Surgical techniques

Preparation of the pancreas is technically difficult and takes around two to three hours. In essence, the splenic and superior mesenteric arteries are joined and anastomosed to the recipient iliac artery, and the portal vein is anastomosed to the inferior vena cava, iliac vein or portal vein. The duodenal segment of the transplant is anastomosed to the jejunum to drain pancreatic exocrine secretions. Bladder drainage was initially preferred (since urinary amylase could be used to indicate acute rejection) but was associated with severe chemical cystitis, balanitis, bicarbonate loss and dehydration.

Immunosuppression

The pancreas graft appears to be more immunogenic than a kidney and a more aggressive immunosuppression regimen is required. Triple therapy consisting of tacrolimus, mycophenolate mofetil and prednisolone is the regimen used in some units. However, induction with monoclonal antibodies (daclizumab or basiliximab) or antilymphocyte globulin is commonly used in North America. Improved pancreas graft survival over the last 20 years is almost certainly due to such regimens and may be further improved with newer immunosuppressants such as rapamycin (Sirolimus®). These newer immunosuppressants may also allow more rapid tapering and even the eventual elimination of steroids usage.

Islet transplantation

The pancreatic islets only account for around one per cent of the volume of the pancreas and transplantation of exocrine pancreatic tissue is unnecessary to treat diabetes. Transplantation of islets alone offers the potential for a lower incidence of serious complications and wider applicability. However, low yields of islets and difficulties of purification remain as obstacles.

The Diabetes UK website contains information about islet transplantation and patient selection criteria. Diabetes UK formed the Diabetes UK Islet Transplantation Consortium (Diabetes UKITC) which brings together medical researchers interested and/or involved in islet cell research in the UK. The consortium has been looking at ways to take islet cell transplantation forward in the UK (www.isletservice.org).

Over the last 15 to 20 years, many units throughout the world have attempted islet transplantation for type 1 diabetes, but with poor long-term success. Of over 400 islet transplants reported to the International Islet Transplant Registry between 1990 and 2000, less than 15 per cent resulted in long-term insulin independence (figure 12). These transplants were carried out on a heterogeneous group of diabetic patients and in most cases, glucocorticoids were included in the immunosuppression protocol.
A recent report by the Edmonton group involving seven consecutive type 1 diabetic patients who attained long-term (median 11 months) insulin independence after islet transplantation has renewed interest in this option. The patients were managed by glucocorticoid-free immunosuppression. The islets were infused into the portal vein after percutaneous cannulation under fluoroscopic control. Patients were normally discharged home within 24 hours. Despite complete correction of severe hypoglycaemia, metabolic testing indicates that islet graft recipients have only one-fifth of the insulin reserve of normal subjects and that less than 50 per cent of the transplanted islet mass survives.

The decision to offer islet transplantation remains difficult. Potential benefits include elimination of hypoglycaemic unawareness and need for insulin injections and should outweigh the potential hazards of the infusion procedure and the side effects of immunosuppression. Segmental portal vein thrombosis has been detected in two Edmonton patients and transient elevation of liver function tests was seen in three, but to date there have been no serious complications of immunosuppression. Long-term complications such as post transplant lymphoproliferative disease may yet occur.

Although, several islet transplant units in North America and Europe are now producing comparable results to Edmonton, islet transplantation remains an option only for a small group of patients. Less toxic immunosuppression and induced immunological tolerance, may in future widen its applicability.

Up-to-date information about progress in the UK can be obtained from Diabetes UK. The Juvenile Diabetes Research Foundation website (www.jdrf.org) has information about worldwide progress. If GPs require local information they should contact their local centre in the UK consortium (www.isletservice.org).
Stem cells and islet transplantation

The main limiting factor in islet transplantation, as in all aspects of clinical transplantation, is the limited supply of islets from cadaveric donors. The recent success of clinical islet transplantation has stimulated research into alternative and/or renewable sources of insulin producing cells. The high levels of immunosuppression required and the risk of transmission of porcine viral infections means that xenotransplantation is still a distant prospect. Stem cells are clonogenic cells capable of self-renewal that offer an alternative prospect. They have the potential to proliferate and differentiate into any type of cell and can be genetically modified in vitro, thus providing a renewable source of cells for transplantation.

Pancreatic islets have been produced in animal models by in vitro manipulation of both embryonic stem cells and adult pancreatic ductal stem cells. These islets can produce endocrine hormones and islet differentiation markers, and release insulin in response to glucose stimulation in vitro. In vivo, they can reverse experimentally induced diabetes in mice and maintain vascularised islet-like clusters. Production of functional beta cells for transplantation is the goal of many research laboratories, but clinical application remains uncertain.

The future of pancreas transplantation

Less toxic and more potent immunosuppression is likely to improve the survival of solid pancreas organ grafts and increase the potential recipient population who will benefit from PTA. Improved isolation of human islets, along with better immunosuppression and/or the development of immunological tolerance, could allow more diabetic patients to benefit from islet transplantation. The development of islets from stem cells could provide a future alternative for islet transplantation.
Conclusion

The number of people in the world with diabetes has increased dramatically over recent years, and is set to continue rising unless interventions are made. Healthcare professionals have a role to play in prevention (reducing risk) and early detection of diabetes. In order to keep those with diabetes well and healthy, good and regular healthcare is needed. The control of diabetes and the early detection and treatment of any possible problems is essential. Education of diabetic patients should be a planned lifelong process, starting from the point of diagnosis and remaining as an essential component of diabetes care. In turn, the expert patient has a lot to offer.

The provision of diabetes services is necessarily complex. Care is provided by a team of healthcare professionals, including GPs and their staff, community healthcare staff and specialist diabetes teams, as well as the patients themselves and their carers. The achievement of good outcomes for people with diabetes is dependent on the provision of well organised and integrated diabetes care.

GPs retain a pivotal role in ensuring that people with diabetes receive effective diabetes care. They have overall responsibility for ensuring that all patients with diabetes registered on their lists receive planned care. It is usually the GP who makes the initial diagnosis of diabetes and it is the GP who, in consultation with other members of the specialist diabetes team, is responsible for agreeing with patients where they receive each element of care. Increasingly, the routine follow up of patients with diabetes is undertaken within primary care.

This report provides an update for healthcare professionals on some of the issues involved in clinical management of diabetes and also signposts sources of further information that may be useful to them and their patients. It is hoped that by improving the management of diabetes, the large number of people with this condition will be allowed to live as full and active lives as possible.
Websites providing further information on diabetes

These websites are suggested for further information only and this does not suggest an endorsement of their content in any way by the BMA. Furthermore, the BMA can make no warranty, expressed or implied, as to the accuracy of any information or advice provided by external sources for which links are provided here. The views of other organisations do not necessarily reflect those of the BMA.

Websites for the public

- **Diabetes UK**: is the leading charity working for people with diabetes in the UK. The organisation funds research, campaigns and helps people to live with the condition. www.diabetes.org.uk
- **Diabetes insight**: provides information to the public on living with diabetes and has a comprehensive list of diabetes related websites. www.diabetes-insight.info
- **diabetes.co.uk**: aims to provide information, services, products and resources for those with diabetes and those caring for diabetics. www.diabetes.co.uk
- **Diabetes portal**: this website (i) provides information about advanced treatments for insulin-dependent diabetes; (ii) provides up-to-date and comprehensive information about cure-oriented diabetes research activities; (iii) creates an online diabetes community for the exchange of information, support and awareness; and (iv) supports the medical community in their efforts to cure diabetes. www.diabetesportal.com
- **BBCi Health – Diabetes Guide**: this guide explains what diabetes actually is, its main causes and symptoms, together with the treatments currently available. The guide also gives advice on how to prevent diabetes, as well as offering a comprehensive list of organisations and associations that can offer further information and help. www.bbc.co.uk/health/diabetes
- **Juvenile Diabetes Research Foundation (JDRF)**: their mission is to find a cure for diabetes and its complications through the support of research. www.jdrf.org
- **British Nutrition Foundation**: promotes the nutritional wellbeing of society through the impartial interpretation and effective dissemination of scientifically based nutritional knowledge and advice. www.nutrition.org.uk
- **Diabetes in Scotland**: NHS Scotland. www.diabetesinscotland.org
- **Insulin Pumpers UK (International Charity)**: formed in September 1997 by Michael Robinton as a voluntary organisation providing a support forum on the internet for pump users. www.insulin-pumpers.org.uk
- **International Diabetes Federation**: is the only global advocate for people with diabetes and their healthcare providers. It is a non-governmental organisation in official relations with WHO and the Pan American Health Organisation. Their mission is to work with their member associations to enhance the lives of people with diabetes. www.idf.org/home
- **NHS Direct Online – Diabetes**: the NHS Direct health encyclopaedia provides information on illnesses, conditions, tests and treatments. It is intended to complement the NHS Direct self help guide which focuses on common family symptoms. www.nhsdirect.nhs.uk/nhsdoheso/display.asp?sSection=Complications&sTopic=Diabetes
- **Disability Rights Commission (DRC)**: has been set up to help people with disabilities under the DDA. They can provide information, advice and assistance. The Disability Rights Commission Helpline can be contacted at: telephone 08457 778 878, textphone 08457 622 644. www.drc-gb.org
- **The American Diabetes Association**: the USA’s leading non-profit health organisation providing diabetes research, information and advocacy. www.diabetes.org
Websites for a professional audience

- **Association of British Clinical Diabetologists**: the national organisation of consultant physicians in Britain who specialise in diabetes mellitus. Most are also acute general physicians, and many are specialists in endocrinology and lipid metabolism. www.diabetologists-abcd.org.uk
- **Audit Commission – Commissioning Diabetes Services**: this site contains audit data and examples of innovative practice. www.diabetes.audit-commission.gov.uk.
- **Diabetes UK**: is the leading charity working for people with diabetes in the UK. The organisation funds research, campaigns and helps people to live with the condition. www.diabetes.org.uk
- **National Service Framework (NSF) for Diabetes**: NSF sets national standards and define service models for a defined service or care group; put in place strategies to support implementation; establish performance milestones against which progress within an agreed time-scale will be measured; form one of a range of measures to raise quality and decrease variations in service, introduced in The New NHS and A First Class Service. The NHS Plan re-emphasised the role of NSF as drivers in delivering the Modernisation Agenda. www.doh.gov.uk/nsf/diabetes
- **National Service Framework for Diabetes – Wales**: The Diabetes NSF standards were published in England in December 2001 and have been adapted for use in Wales. The Diabetes NSF Standards (Wales) was published on 29 April 2002. www.wales.nhs.uk/sites/page.cfm?orgid=334&pid=931
- **WHO – Diabetes Programme of the Division of Noncommunicable Diseases and Mental Health (NMH/DIA)**: the Diabetes Programme of the NMH/DIA, is responsible for providing advice to WHO’s 190 member states, on appropriate policies and strategies for monitoring, prevention and control of diabetes. www.who.int/ncd/dia/
- **Worldwide Initiative for Diabetes Education**: provides support by an unrestricted educational grant from Aventis Pharma and Pfizer Inc. www.worldwidediabetes.com/system/html_site/index.htm
- **Juvenile Diabetes Research Foundation International (JDRF)**: the world's leading non-profit, non-governmental funder of diabetes research with 120 chapters, branches and affiliates worldwide, which have helped to raise more than $600 million for diabetes research. www.jdrf.org

Online journals and search facilities

- **NHS National electronic Library for Health – Diabetes website**: This website has been designed to answer all of the frequently asked questions that are asked by UK healthcare professionals relating to diabetes – using current synthesised research evidence. cebmh.warne.ox.ac.uk/diabetes/professional/
- **National Electronic Library for Health (NeLH)**: the role of the NeLH is to provide healthcare professionals and the public (through NHS Direct Online and the New Library Network) with knowledge and know-how to support healthcare-related decisions. www.nelh.nhs.uk
- **Sciencenet**: this contains information on science on the internet. www.sciencenet.org.uk

Surveillance data

- **WHO – Diabetes prevalence estimates**: diabetes prevalence estimates produced by WHO. www.who.int/ncd/dia/databases.htm
Appendix I: St Vincent Declaration

In October 1989, representatives of government health departments and patients’ organisations from all European countries met with diabetes experts under the aegis of WHO and the International Diabetes Federation (IDF) in St Vincent, Italy. The following recommendations were unanimously agreed:

**General goals for people with diabetes**

- Sustained improvement in health experience and a life approaching normal expectations in quality and quantity.
- Prevention and cure of diabetes and of its complications by intensifying research effort.

**Five year targets**

- Elaborate, initiate and evaluate comprehensive programmes for detection and control of diabetes and of its complications with self-care and community support as major components.
- Raise awareness in the population and among healthcare professionals of the present opportunities and the future needs for prevention of diabetes and its complications.
- Organise training and teaching in diabetes management and care for people of all ages with diabetes, for their families, friends and working associates and for the healthcare team.
- Ensure that care for children with diabetes is provided by individuals and teams specialised both in the management of diabetes and of children, and that families with a diabetic child get the necessary social, economic and emotional support.
- Reinforce existing centres of excellence in diabetes care, education and research. Create new centres where the need and potential exist.
- Promote independence, equity and self-sufficiency for all people with diabetes; children, adolescents, those in the working years of life and the elderly.
- Remove hindrances to the fullest possible integration of the diabetic citizen into society.
- Implement effective measures for the prevention of costly complications:
  - reduce cases of new blindness due to diabetes by one third or more
  - reduce numbers of people entering endstage diabetic renal failure by at least one third
  - reduce by one half the rate of limb amputations for diabetic gangrene
  - cut morbidity and mortality from coronary heart disease in the diabetic by vigorous programmes of risk factor reduction
  - achieve pregnancy outcome in the diabetic women that approximates that of non-diabetic women.
  - establish monitoring and control systems using state of the art information technology for quality assurance of diabetes healthcare provision and for laboratory and technical procedures in diabetes diagnosis, treatment and self-management
  - promote European and international collaboration in programmes of diabetes research and development through national, regional and WHO agencies and in active partnership with diabetes patients’ organisations
  - take urgent action in the spirit of the WHO programme Health for all to establish joint machinery between WHO European Region and IDF to initiate, accelerate and facilitate the implementation of these recommendations.
Appendix II: Clinical guidelines

The Scottish Intercollegiate Network (SIGN)
SIGN came into existence in 1995 with the aim of improving the quality of healthcare for patients by developing and disseminating national clinical guidelines. A multidisciplinary working group develops the guidelines with representation drawn from across Scotland. Each guideline is developed using well-described methodology to review the current literature systematically and critically and grade the level of supporting evidence.

The National Institute for Clinical Excellence (NICE)
NICE works in England and Wales to produce guidance on the management of specific conditions and on the use of new and existing health technologies. NICE was launched in 1999 and to date has produced nine clinical guidelines, four of which deal with aspects of the management of type 2 diabetes. Its clinical guidelines are also developed using recognised methodology to grade the level of evidence. NICE also has guidance on the use of patient-education models for diabetes. New guidelines on diabetes type 1 and diabetes type 2 footcare are expected during 2004, and on obesity in 2006.

National Executive
The National Executive is currently in the process of deciding who will develop guidance for the NHS in Northern Ireland.
References


Apelqvist J & Larsson J (2000) What is the most cost effective way to reduce the incidence of amputation in the diabetic foot? Diabetes Metabolism and Research Reviews 16: 575-83.


113 Personal communication: Professor John Tooke, Consultant diabetologist, October 2003.


Department of science and education publications

- Adolescent health
- Appraisal: a guide for medical practitioners
- Sign-posting medical careers for doctors
- Childhood immunisation: a guide for healthcare professionals
- Health & ageing: an internet resource
- Housing and health: building for the future
- Sunbeds: an internet resource
- Communication skills education for doctors: a discussion paper
- Towards smoke-free public places
- Asylum seekers: meeting their healthcare needs
- Drugs in sport, the pressure to perform
- Driving under the influence of drugs: an internet resource
- Sexually transmitted infections
Diabetes mellitus
an update for healthcare professionals

Diabetes mellitus is a serious complex chronic condition that is a major source of ill health. It predisposes to the development of potentially life-threatening conditions. Current estimates are that diabetes affects 1.3 million of the UK population, is a major component of the work of general practitioners and consumes approximately 10 per cent of hospital resources. Meticulous management of diabetes can reduce the risk and rapidity of development of a range of serious long-term complications, notably heart disease, stroke, blindness, renal failure and peripheral vascular disease.

This report focuses on recent changes in our understanding of the epidemiology, aetiology and clinical management of diabetes, placing emphasis on controversial issues and recent advances.