Diabetes and Kidney Disease: Time to Act

The mission of the IDF is to work with our member associations to enhance the lives of people with diabetes.

International Diabetes Federation

The International Society of Nephrology's goal is worldwide advancement of education, science and patient care in nephrology.

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Time to Act

Time to Act

The world is facing a huge epidemic. Diabetes and its complications is now a major killer, not only in the developed world but in developing countries as well. A person with diabetes requires a huge amount of medical resources, incurring four times the medical attention and costs as someone without diabetes. The cost of treatment of diabetes has doubled over the past decade as the number of people with diabetes continues to climb.

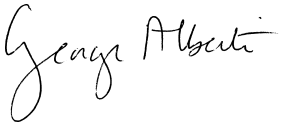
One of the main complications of diabetes is kidney disease. This occurs in about one third of people with either type 1 or type 2 diabetes and adds enormously to the morbidity, mortality and cost of treatment. It is extremely important to draw attention to the consequences of diabetes and kidney disease, encourage early detection and evaluation, and try to prevent what is essentially a preventable disease.

It is therefore time to act. It is time for people to understand and make dietary and life-style changes to prevent the ravages of diabetes; time for healthcare workers to diagnose and manage people with diabetes and its complications, and time for health providers to recognize the problem and tackle what is potentially the world's greatest epidemic.

To highlight the extent of the problem, diabetes and kidney disease has been chosen as the theme of this year's World Diabetes Day. Therefore, the International Diabetes Federation and the International Society of Nephrology have joined forces to draw attention to an issue of such profound medical and financial implications that affects every country in every corner of the world.

There is an urgent need to galvanize action for the benefit of people with diabetes and for those who may develop it in the future. We encourage everyone to participate and at every level.

Professor Robert C Atkins
President
International Society of Nephrology (ISN)



Professor Sir George Alberti
President
International Diabetes Federation (IDF)

Introduction

Introduction

Diabetes and Kidney Disease: Time to Act is an up-to-date report on one of the most prevalent and costly long-term complications of diabetes, diabetic nephropathy (diabetic kidney disease). The objectives of this publication are to raise awareness of diabetic nephropathy and to recommend courses of action to prevent or delay this complication of diabetes.

Who is it for?

This publication seeks to inform healthcare decision makers of the huge public health burden posed by diabetic nephropathy and to point to possibilities of and urgent need for prevention. IDF's member associations are encouraged to make use of this book to lobby their governments for investment in preventive and delaying strategies.

Diabetes and Kidney Disease: Time to Act can also be used as a tool for sensitizing healthcare professionals to the need for aggressive management of all risk factors for diabetic nephropathy, active screening to identify early disease and appropriate management to delay progression of early disease to end-stage disease requiring dialysis or transplantation.

This publication is also a source of background information for member associations' public awareness campaigns (the theme of World Diabetes Day 2003 being Diabetes and the Kidney).

Finally, anyone interested in learning more about the effects of diabetes on the kidney can consult this publication.

Summary of chapters

Chapter 1 sets the scene by giving some background information on diabetes, its classification, risk factors and prevalence around the world.

Chapter 2 defines diabetic nephropathy and discusses how it develops over many years. The effects of end-stage kidney failure are described, as are the close links of diabetic nephropathy to cardiovascular disease and the other long-term complications of diabetes.

Chapter 3 outlines how diabetic nephropathy is diagnosed. A scheme for screening everyone with diabetes for the early signs of kidney disease is outlined and more detailed investigations for people with early changes are given.

Chapter 4 examines the risk factors of diabetic nephropathy.

Chapter 5 describes how risk factors for diabetic nephropathy can be managed, to prevent kidney disease developing or to slow its progression to end-stage disease.

Chapter 6 reviews treatment possibilities for end-stage diabetic nephropathy.

Glossary Readers who are unfamiliar with the medical terminology can make use of the glossary. Terms included in the glossary are printed in bold when first used in the text.

Annex The studies of diabetic nephropathy which are referred to in the text are explained in more depth.

Bibliography The research on which *Diabetes and Kidney Disease: Time to Act* is based is documented in the bibliography.

CHAPTER 1

Diabetes

Diabetes mellitus is a chronic condition that arises when the **pancreas** does not produce enough **insulin**, or when the body cannot effectively use the insulin produced. Failure of insulin secretion, insulin action or both leads to raised **glucose** levels in the blood and other metabolic changes which, if not controlled, can cause serious complications. The most important of these complications are **nephropathy** (affecting the kidneys), **retinopathy** (affecting the eyes), **neuropathy** (affecting the nerves) and **cardiovascular disease** (affecting the **circulatory system**).

Classification

One problem over the years has been the classification of diabetes into different categories. Most recently, a World Health Organization (WHO) Consultation and the American Diabetes Association (ADA) Expert Committee have divided diabetes in to 4 main types.

What was previously called insulin-dependent diabetes mellitus (IDDM) is now known as **type 1 diabetes** under this new classification, and non-insulin dependent diabetes mellitus (NIDDM) is now known as **type 2 diabetes**.

Lesser degrees of abnormal glucose levels are also recognized. These include **impaired glucose tolerance (IGT)** and **impaired fasting glycaemia (IFG).** IGT describes blood glucose levels higher than normal but below the level of someone with diabetes. IFG describes raised fasting levels of glucose. IGT is now considered a risk category rather than a type of diabetes, and IFG represents a risk of 25% to 50% of developing diabetes in the next 10 years. However, these are both particularly amenable to lifestyle interventions.

Table 1-1
The four main types of diabetes

1	**type 1 diabetes**
	Insulin required for survival due to a lack of insulin produced by the body as a result of beta cell destruction
2	**type 2 diabetes**
	Characterized by disorders of both insulin action or secretion, either of which may predominate, both of which are usually present. Usually controlled by diet, exercise and **oral hypoglycaemic agents**. Insulin may be required for metabolic control
3	**Other specific types of diabetes**
	Other types of diabetes where the cause is known (eg genetic defects in beta cell function or insulin action, diseases of the pancreas, certain other hormonal disorders or drug induced disorders)
4	**Gestational diabetes**
	Diabetes appearing for the first time in pregnancy

The other major result of the new classification is metabolic syndrome. This reflects the clustering of type 2 diabetes or IGT with several other major disease risk factors such as **obesity**, abnormal levels of lipids (**dyslipidaemia**), high blood pressure (**hypertension**), insulin resistance and a slightly increased excretion of protein in the urine (**microalbuminuria**).

Risk Factors

No clear-cut risk factors have been identified for type 1 diabetes. However, the risk factors for type 2 diabetes have been recognized.

Risk Factors for type 2 diabetes
• Age
• Ethnicity
• Family History
• Obesity
• Physical inactivity
• Westernized diet

The Extent of the Problem

Diabetes is fast becoming a world epidemic.

There are currently more than 177 million people with diabetes worldwide. WHO figures estimate that this will rise to 300 million by 2025. Diabetes is the fourth main cause of death in most developed countries. Both type 1 and type 2 diabetes are spreading rapidly across the world. Type 1 diabetes accounts for less than 10% of the total and is a particular problem in young Northern Europeans. It should be stressed that type 1 diabetes can occur at any age, and that there are as many people in the world with type 1 diabetes over the age of 20 years as there are under the age of 20. Type 2 diabetes, which accounts for about 90% of all cases of diabetes, is recording the most growth, particularly in rapidly developing countries.

Fact

There are currently more than 177 million people with diabetes worldwide. WHO figures estimate that this will rise to 300 million by 2025.

Fact

Diabetes is the fourth main cause of death in most developed countries.

No part of the world is spared from diabetes. Table 1-2 shows a selection of countries around the world and their diabetes **prevalence** now and in 2025.

Table 1-2
Diabetes prevalence now and estimated for 2025

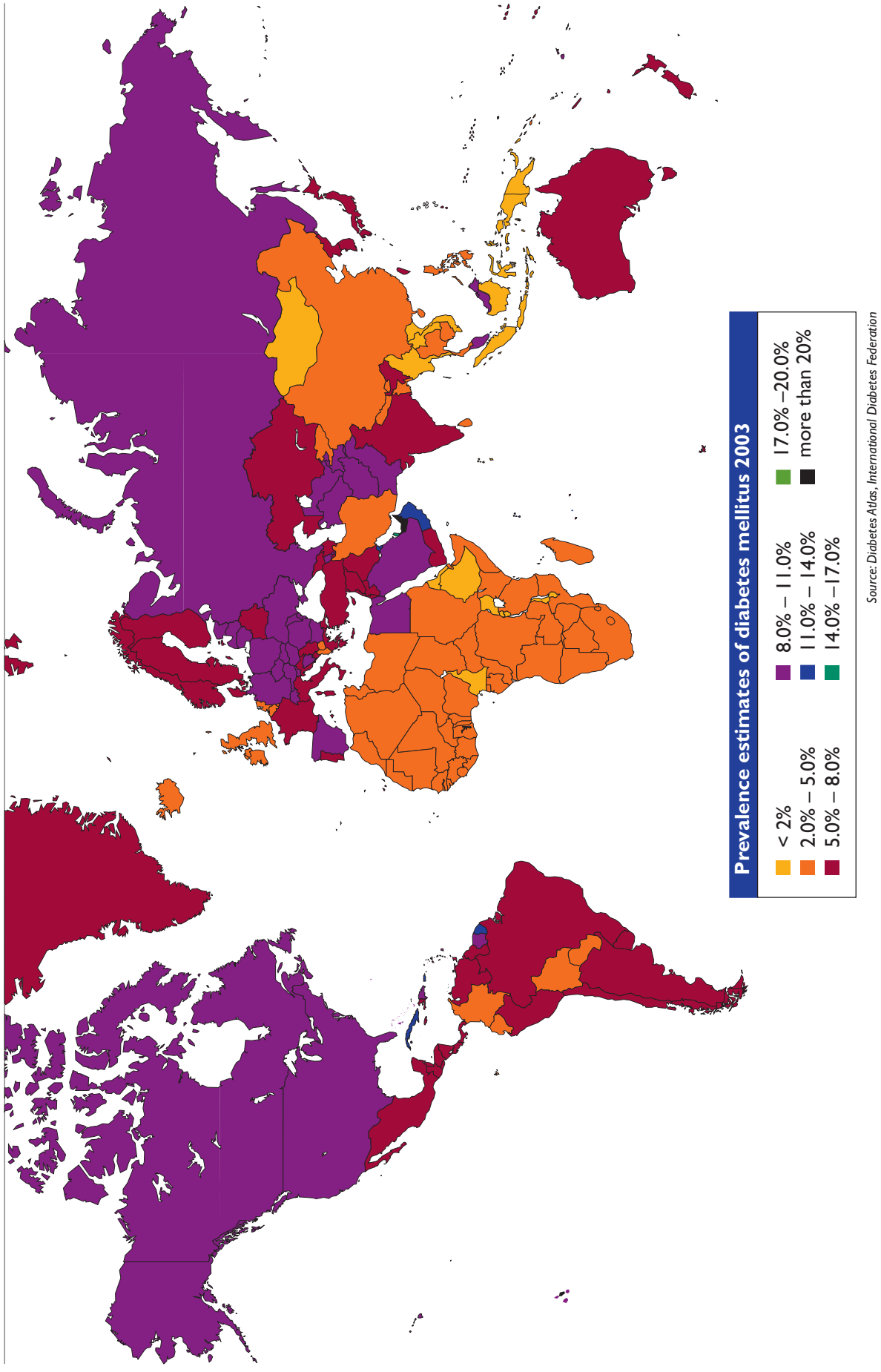
Estimated Diabetes Prevalence (%)		
	2003	2025
United Arab Emirates	20.1	24.5
Cuba	13.2	17.3
China, Macau	8.2	12.9
China, Hong Kong	8.8	12.8
Germany	10.2	11.9
Czech Republic	9.5	11.7
Belarus, Republic of	6.9	10.7
USA	8.0	9.3
New Zealand	7.6	9.0
Denmark	6.9	8.3
Japan	6.9	7.9
France	6.2	7.3
Algeria	4.1	5.5
Cameroon	0.8	1.2

Source: Diabetes Atlas, Second edition, International Diabetes Federation 2003

In addition to these alarming absolute rises in numbers, there is also a worsening trend for the disease affecting younger age groups. In developed countries, the sharpest increase affect people over 65 years of age, whereas in the developing countries most new cases are occurring in those aged between 44 and 65 years. In all parts of the world type 2 diabetes is also now emerging in children and adolescents at an alarming rate, thereby raising the threat of the onset of complications at an earlier age.

Future Outlook

Although there is no evidence that type 1 diabetes is preventable, it is clear that there are ways to help prevent type 2 diabetes. If action is not taken now to stem the tide of type 2 diabetes, the outlook for the health of the world is very bleak. The devastating complications of diabetes such as retinopathy, nephropathy and cardiovascular disease are



Source: Diabetes Atlas, International Diabetes Federation

imposing a huge burden on national healthcare services. It is estimated that diabetes accounts for between 5-10% of a nation's health budget.

Fact

If action is not taken now to stem the tide of type 2 diabetes, the outlook for the health of the world is very bleak.

Studies in China, Tanzania, Finland and Sweden have proven that lifestyle changes can slow the development of diabetes in high-risk groups. Losing weight, eating healthily, and doing regular exercise have all shown to help prevent type 2 diabetes. The epidemic of type 2 diabetes CAN be prevented but needs a high degree of dedication and commitment on a global scale. Investing in prevention, particularly early detection, in order to avoid the onset of diabetic complications, can significantly reduce the human and economic costs of diabetes.

Fact

It is estimated that diabetes accounts for between 5-10% of a nation's health budget.

The message needs to be made loud and clear that type 2 diabetes is a rapidly increasing disease but that lifestyle change can help prevent it. Put simply: 'Eat Less, Walk More'.

CHAPTER 2

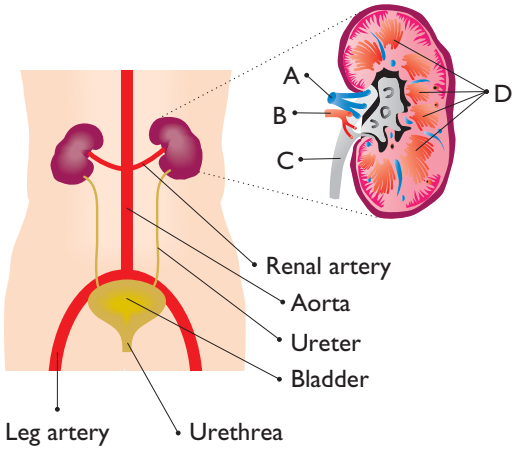
The Kidney

The two kidneys are located at the back of the body, with their upper portions behind the lower ribs. Each kidney is about the size of a fist and weighs about 150g. The word "renal" is often used interchangeably with "kidney".

The kidneys are important internal organs of the body. Their primary function is to remove waste products from the body. Each kidney consists of millions of tiny filtering units called **glomeruli**. When blood passes through the kidney, the glomeruli filter it and remove nutrients from digested food and drink which cannot be used in the body. They expel this waste as urine. A tube called the ureter allows urine to flow down from each kidney into the bladder. Urine passes from the bladder out of the body through another tube called the urethra.

Figure 2-1
The kidneys in the body

A. *Vein: clean blood goes out of kidney*
B. *Artery: blood and waste come into kidney*
C. *Ureter: waste and fluids go out in urine*
D. *Glomeruli: tiny filters throughout kidney*



Adapted from: Australian Kidney Foundation

The kidneys also make and regulate important hormones, or chemical messengers:

- **Erythropoietin**, which stimulates the bone marrow to make red blood cells
- **Renin**, which is involved with the control of blood pressure
- **Vitamin D**, which controls calcium absorption from the bowel and helps keep bones strong

When the kidneys become damaged, they cannot clean the blood properly, and waste and fluids build up. This can lead to kidney failure, resulting most commonly in **anaemia**, high **blood pressure** and weak bones.

What is Diabetic Nephropathy?

Diabetic nephropathy (a term often used interchangeably with 'diabetic kidney disease') is a chronic, progressive kidney disease that develops in about one third of all people with diabetes.

Table 2-1
What is Diabetic Nephropathy?

The signs of diabetic nephropathy are:
• Rising urine albumin and protein excretion • Rising blood pressure • Declining kidney function
This is associated with:
• A greatly increased risk of cardiovascular disease • An increased risk of diabetic eye disease (retinopathy) • An increased risk of diabetic nerve damage (neuropathy)

Diabetic nephropathy is characterized by increasing amounts of the protein albumin in the urine, rising blood pressure and failing kidney function. It evolves over many years of the person being diagnosed with diabetes, with kidney failure occurring after 20-30 years of diabetes. People with diabetic nephropathy are also at much higher risk of cardiovascular disease and of the other complications of diabetes. The development of end-stage kidney disease has a major impact on the individual, with the need for a kidney **transplant** or **dialysis** treatment and associated other medical problems. The cost to society is huge, both transplantation and dialysis being extremely expensive. Approximately 25% of people with type 1 diabetes develop kidney failure. In people of Caucasian origin with type 2 diabetes, 5-10% reach end-stage kidney disease, whilst in non-Caucasian populations the proportion is higher.

Signs of Diabetic Nephropathy

Rising Urine Albumin and Protein Excretion

People with diabetes who develop nephropathy have no symptoms until the disease is very advanced. The earliest sign of nephropathy is the excretion of slightly increased amounts of the protein albumin in the urine (micro-albuminuria).

Fact

People with diabetes who develop nephropathy have no symptoms until the disease is very advanced.

Microalbuminuria can only be detected by tests specific for albumin. At this stage in the disease, 20-200 mg/l albumin are excreted each day. Without specific treatment, the amount of albumin in the urine gradually increases until quite large amounts are present. At this point, other proteins in addition to albumin leak into the urine and can be measured by conventional urine tests, either urine "dip-stick" testing or in the laboratory. When the excretion of proteins in the urine becomes large (greater than 200 mg/l of albumin and of all proteins >500 mg/l) this is called **proteinuria**. Over time, the level of protein in the urine increases even further, sometimes to massive amounts, over 2.5 g/day. If very large amounts of protein are lost in the urine, the level of protein in the blood may fall below normal and people may develop ankle swelling (peripheral oedema) and other problems with fluid balance. The level of albumin and other proteins in the urine is very variable from day to day and may increase temporarily if another serious illness is present, or if blood glucose control deteriorates acutely. It is in those people where the urine albumin level rises continuously that **end-stage kidney disease** is eventually reached.

Rising Blood Pressure

The slow increase in the amount of albumin in the urine is accompanied by a gradual rise in blood pressure. In general, people with high blood pressure are more likely to develop kidney disease than people with normal blood pressure. However, in type 1 diabetes, blood pressure is probably normal at diagnosis, whereas high blood pressure is common at diagnosis of type 2 diabetes. In those people who develop nephropathy, studies have suggested that there is a rise in blood pressure either at the same time as microalbuminuria first appears or shortly thereafter. The increase in blood pressure is initially very small and may only be detected by measuring blood pressure continuously throughout the 24-hour period. In healthy individuals, blood pressure usually falls at night. In the very early stages of diabetic nephropathy, the first sign of rising blood pressure may be a failure of the blood pressure to dip at night. [See figure 3-3 on page 26]

Fact

People with high blood pressure are more likely to develop kidney disease than people with normal blood pressure.

Blood pressure slowly rises as the level of microalbuminuria increases, so that without treatment almost all individuals will have high blood pressure by the time they have

proteinuria. Even the initial small increases in blood pressure are very important, as there is very strong evidence that any increase in blood pressure makes a person more likely to develop kidney disease and drives the disease process faster.

Declining Kidney Function

The filtration function of the kidney does not usually begin to fall until the amount of albumin in the urine is quite high, either towards the top end of the microalbuminuric range or proteinuria. Indeed, in the initial microalbuminuric phase, kidney function may be normal. Once the filtration function begins to fail, it falls at a steady rate in any one individual, although the rate varies from person to person. Eventually, the excretion of waste products and toxins is so poor that symptoms of kidney failure develop. These may include general malaise, weakness, ankle swelling, shortness of breath, loss of appetite (anorexia), weight loss, nausea, and vomiting. Treatment in the form of renal replacement therapy (dialysis or transplantation) is required. As the kidney filtration function fails, the kidneys are also unable to make other chemicals necessary for good health, such as vitamin D and erythropoetin. In the absence of sufficient vitamin D, a specific bone disease associated with kidney failure (renal osteodystrophy) develops and requires specific treatment. Erythopoetin is a chemical made in the kidney that stimulates bone marrow to make blood cells. As the kidney fails, the levels of erythropoetin also fall, the bone marrow does not work properly and anaemia may develop. The anaemia may lead to **heart failure**. The situation can be corrected by treatment with injections of erythropoetin.

The Stages of Diabetic Nephropathy

The development of diabetic nephropathy can be considered in stages.
In the initial years after diagnosis of diabetes, urine albumin excretion, blood pressure and kidney function are normal. The majority of people will remain in this stage. In early kidney disease, urine albumin excretion is increased into the microalbuminuric range and blood pressure is slightly increased. Kidney filtration function is normal. In the proteinuric stage, urine albumin and protein excretion are high, blood pressure is high in most people and the kidney filtration function begins to fail. In advanced or end-stage disease, urine protein excretion can be extremely high, blood pressure can be very elevated and kidney filtration can fail.

Table 2-2
Stages in the development of diabetic nephropathy

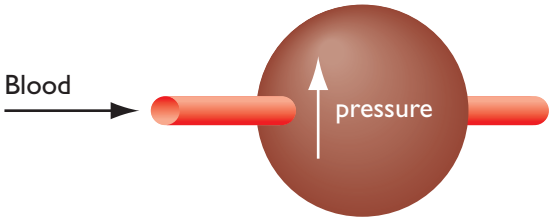
Stage	Time after diagnosis of diabetes	Function
Normal	0-15 years	• Normal urine protein excretion • Normal blood pressure • Normal or high kidney function
Early kidney disease	5-15 years	• Microalbuminuria • Slight increase in blood pressure • Normal kidney function
Proteinuria	10-20 years	• High levels of urine protein • High blood pressure • Failing kidney function
End-stage disease	15-30 years	• Very high urine protein • Very high blood pressure • Kidneys fail

What is Happening Within the Kidney?

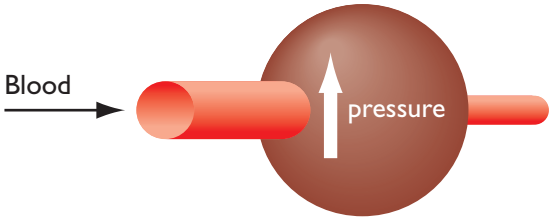
Several changes occur inside the kidney which underlie the development of diabetic nephropathy. The pressure inside the glomerulus (the filtering unit of the kidney) is increased (glomerular hypertension) because of alterations to size of the blood vessels into and out of the glomerulus. This leads to damage to the very small glomerular capillaries and to leakage of albumin and other proteins across the filter into the urine.

Figure 2-2
Changes to the pressure inside the filter of the kidney (glomerulus) in diabetic nephropathy. In diabetes, the artery to the filter is dilated and thus exposes the filter to increased blood pressure, causing kidney damage.

Normal glomerulus



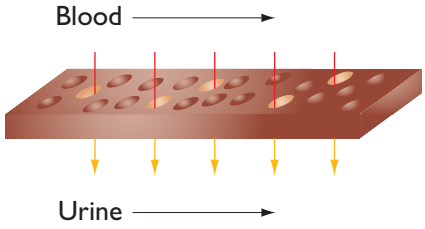
Glomerulus in diabetic nephropathy



The structure that forms the filter is called the basement membrane. The filter thickens and its chemical composition and structure change. Chemicals with high negative charge (glycosaminoglycans) are lost from the filter, making the passage of negatively charged albumin across the filter into the urine easier. Normally, there are pores or channels of a specific size across the filter, which control the

Figure 2-3
The upper diagram depicts the normal kidney filter (the basement membrane). The solid circles are the negatively charged chemicals and open circles are the pores or channels through which proteins pass from the blood into the urine. The lower diagram shows the kidney filter in diabetic nephropathy. The membrane is much thicker than normal, the channels are much bigger and there is less negative charge. Thus more proteins pass across the membrane from the blood into the urine.

Kidney filter in health



Kidney filter in diabetic nephropathy

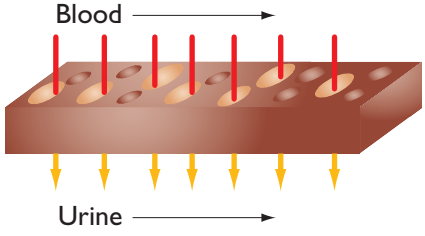
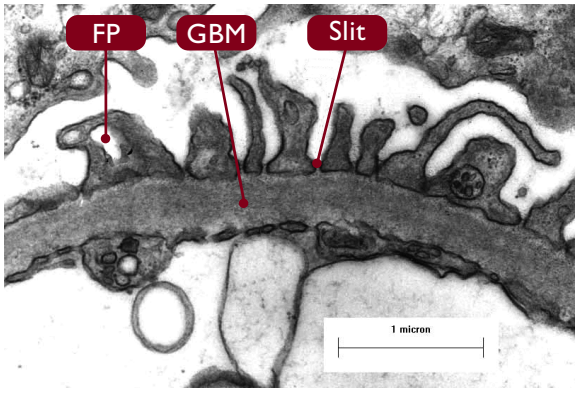


Figure 2-4
This is a high-powered electron micrograph showing the kidney filter (basement membrane; GBM), with attached foot processes (FP) which are part of the podocyte cells. Protein is filtered from the blood across the basement membrane via the slits between the foot processes, and into the urine.



Photograph supplied by Dr KE White and Professor RW Bilous, University of Newcastle upon Tyne

passage of small quantities of some proteins into the urine.
In diabetes, the size of these channels increases, so that more proteins of larger size can cross into the urine and be excreted.

Cells that cover the outside of the filter (podocytes) are lost, allowing more protein to pass across into the urine.

The presence of increased amounts of protein in the urine leads to further damage to other parts of the kidney, including the interstitium, (the tissue lying between the glomeruli) and the renal tubules, the small channels down which urine flows to eventually leave the kidney and reach the bladder. The presence of increased quantities of protein stimulates inflammation in the interstitium and tubules, leading to progressive scarring that further reduces kidney function.

In areas of the glomerulus between the very small glomerular capillaries, the material that forms the filter (mesangial matrix) accumulates. This eventually blocks off the filter and glomerular capillaries. When the kidneys fail, the glomerulus is filled with scar tissue and cannot function as a filter. These changes can be seen on **renal biopsy**, when a small piece of the kidney is removed and examined under a high-powered microscope.

The changes seen in the kidney are essentially identical in type 1 and type 2 diabetes, although in type 2 diabetes, changes associated with poor blood supply to the kidney (ischaemia) or with damage from high blood pressure are more common.

Figure 2-5a
This shows a high power electron microphotograph of a normal glomerulus. There are many open small capillary blood vessels (C) surrounded by thin basement membrane. The amount of material which forms the kidney filter (mesangium) (M) is quite sparse.

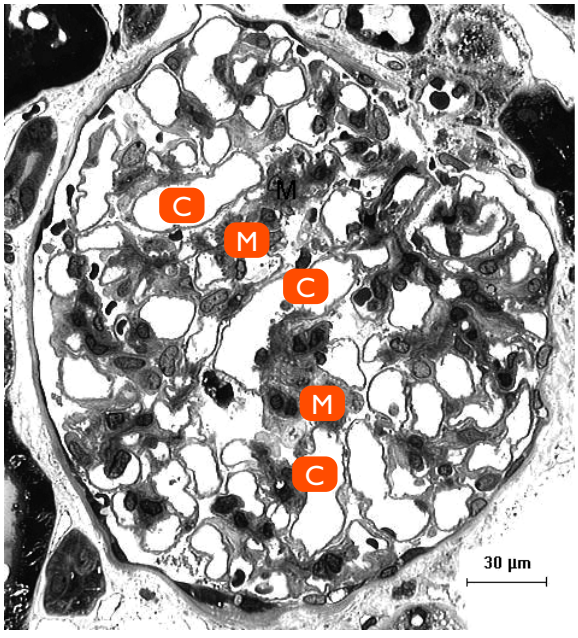
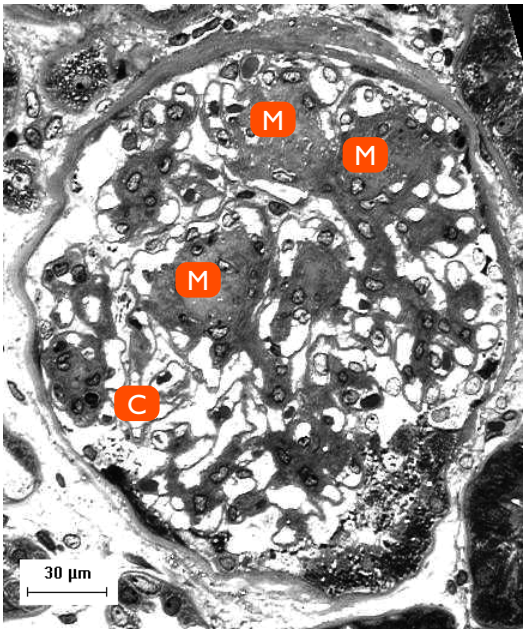


Figure 2-5b
This shows a high power electron microphotograph of a glomerulus from someone with advanced diabetic nephropathy. There are a few open capillary blood vessels (C) surrounded by much thicker basement membranes than in a normal glomerulus. There is also a greater amount of mesangium (M) than in the normal glomerulus, which is blocking capillary loops.

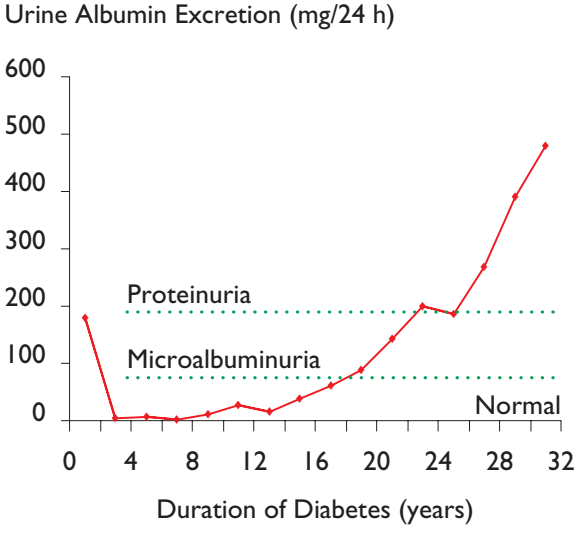


Photographs supplied by Dr KE White and Professor RW Bilous, University of Newcastle upon Tyne

Time Course of the Development of Diabetic Nephropathy

In type 1 diabetes, microalbuminuria may be present within the first 5 years of diabetes, but usually appears within 5-10 years. In type 2 diabetes, microalbuminuria may be found at any time, including at diagnosis, as some people may have had diabetes for a number of years before the diagnosis is made. Without specific treatment, levels of microalbuminuria will slowly rise, reaching proteinuria within a further 10-15 years and then end-stage kidney disease by a further 10 years.

Figure 2-6
Graph demonstrates the increase in urine albumin excretion over the duration of diabetes in years.



Association of Diabetic Nephropathy and Cardiovascular Disease

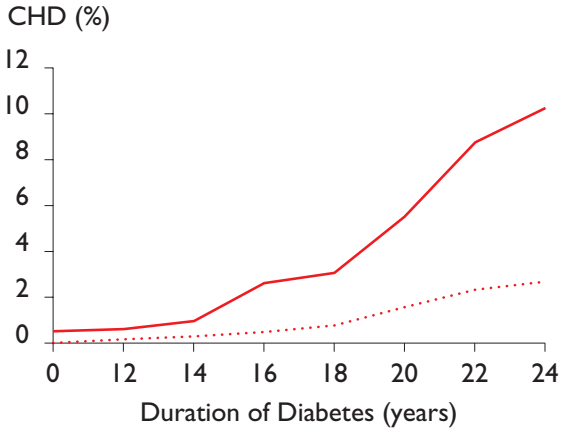
Everyone with diabetes is at increased risk of premature morbidity and mortality from cardiovascular disease. However, people with microalbuminuria and proteinuria are at greater risk than those with normal albumin excretion, the risk increasing as the amount of protein in the urine increases. Many studies have shown that in type 2 diabetes the risk of developing cardiovascular disease is 2-3 times higher in someone with microalbuminuria compared to a person with normal albumin excretion, whilst in people with proteinuria, the risk is increased at least 10 fold. Once the kidneys have failed, the risk is enormous, and the average life expectancy of someone with type 2 diabetes beginning renal dialysis is 2 years, most dying of cardiovascular disease. In type 1 diabetes, the risk of cardiovascular disease is 10-fold higher in people with proteinuria compared to those without.

Fact

In type 2 diabetes the risk of developing cardiovascular disease is 2-3 times higher in someone with microalbuminuria compared to a person with normal albumin excretion

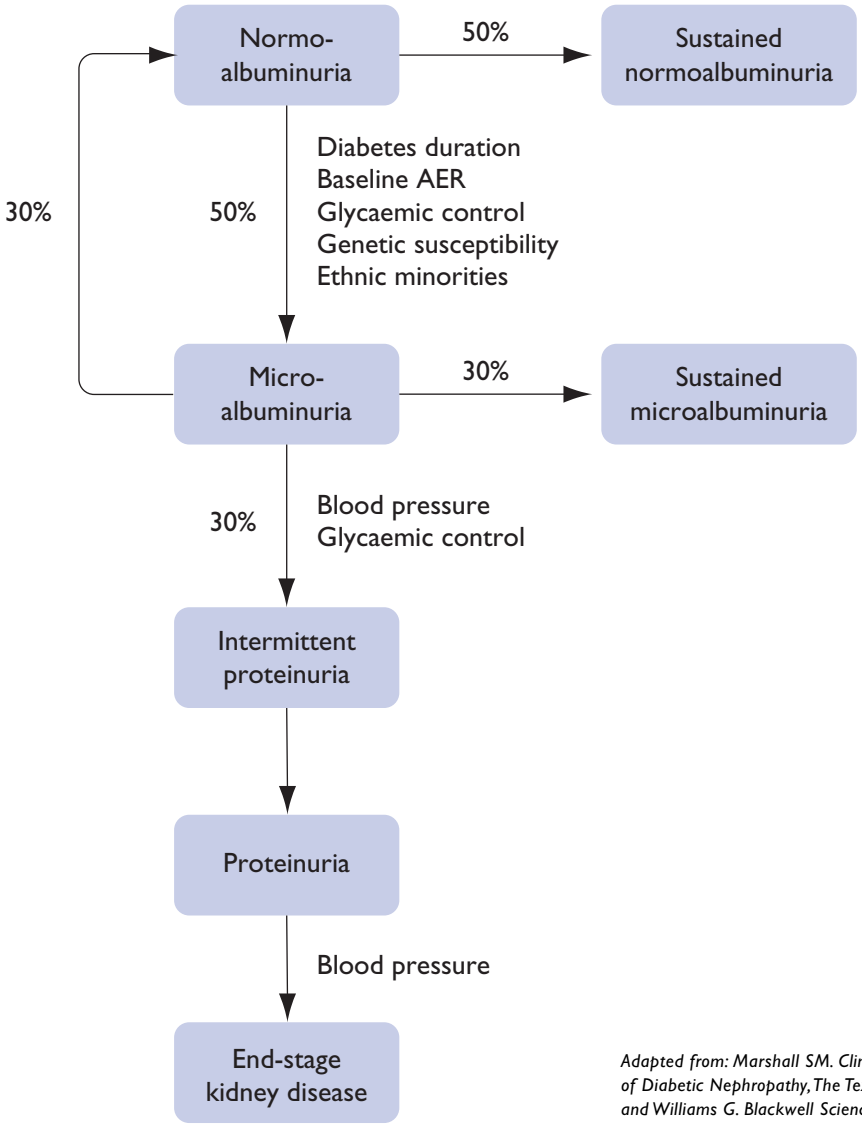
Many people, particularly those with type 2 diabetes, will not survive long enough to develop end-stage kidney disease, but instead will die whilst still in the microalbuminuric or proteinuric stage from cardiovascular disease. The reasons for this close link between nephropathy and cardiovascular disease are

Figure 2-7
Culmulative incidence of coronary heart disease (CHD) in people with type 1 diabetes with (solid line) proteinuria and without (dashed line) proteinuria.



Source: Tuomilehto J et al, The incidence of Cardiovascular disease in type 1 diabetic subjects with and without diabetic nephropathy in Finland, Diabetologia 1998;41:784-790

Figure 2-8
The stages and determinants of diabetic nephropathy.



Adapted from: Marshall SM. Clinical Features and Management of Diabetic Nephropathy, The Textbook of Diabetes 3rd ed. ED Pickup JC and Williams G. Blackwell Science Publishers, Oxford.

unclear, but suggest a common underlying mechanism that may be inherited.

How Common is Diabetic Nephropathy?

The early stages of diabetic nephropathy are common. Over a lifetime of diabetes, about 50% of people with type 1 diabetes develop microalbuminuria, the others having normal albumin excretion throughout. In perhaps one third of those with microalbuminuria, the level of albumin in the urine gradually increases until proteinuria is present. In another third, the albumin level remains in the microalbuminuric range for many years, and in the remainder, the level returns to normal and remains normal thereafter. In those people who reach the proteinuric stage, almost all progress further to end-stage kidney disease.

Fact

Over a lifetime of diabetes, about 50% of people with type 1 diabetes develop microalbuminuria

Approximately 20% of people with type 1 diabetes develop proteinuria and reach end-stage kidney disease. This proportion appears to have declined over the last 20 years. In people diagnosed in the 1933's and 1940's, approximately 40% developed proteinuria.

Fact

In the Pima Indians of North America, where type 2 diabetes develops at an early age and is extremely common, more than 50% develop proteinuria within 20 years.

Recent studies of people diagnosed in the 1970's and 1980's have shown that the proportion has fallen to 20-25%. This change is probably due to general improvements in diabetes care, particularly in blood glucose and blood pressure control.

In people with type 2 diabetes of Caucasian origin, the course of nephropathy is very similar to that in type 1 diabetes, although many more people succumb to cardiovascular disease before reaching end-stage kidney disease. Approximately one third of people with type 2 diabetes and microalbuminuria develop proteinuria within 5 years. After 20 years duration of diabetes, the cumulative incidence of proteinuria is 27%. In people of non-Caucasian origin, microalbuminuria is more common, being present in more than 50% of people. In the Pima Indians of North America, where type 2 diabetes develops at an early age and is extremely common, more than 50% develop proteinuria within 20 years.

Fact

Microalbuminuria and proteinuria are more common in people with type 2 diabetes of Asian and of Afro-Caribbean origins.

Fact

Diabetic nephropathy is the single most common cause of entry to renal replacement programmes (dialysis or transplantation) in most countries in the world.

Microalbuminuria and proteinuria are also more common in people with type 2 diabetes of Asian and of Afro-Caribbean origins. Some studies suggest that nephropathy progresses faster in people of non-Caucasion origin. In contrast to the fall in the numbers of people with type 1 diabetes developing proteinuria in recent years, the numbers of people with type 2 diabetes developing proteinuria has increased. This may reflect improved survival from cardiovascular disease or an environmental factor.

Fact

In the USA and Germany, over 40% of people with end stage kidney disease have diabetes.

Diabetic nephropathy is the single most common cause of entry to renal replacement programmes (dialysis or transplantation) in most countries in the world. In the USA and Germany, over 40% of people with end stage kidney disease have diabetes. The numbers of people requiring replacement therapy continues to increase

Table 2-3
Increase in the incidence of people with diabetes with end stage kidney failure over a decade

	1984	1994
Australia	4.0	14.0
Austria	7.3	18.0
Catalonia (Spain)	8.0	26.6
Denmark	6.5	16.9
Iceland	0.0	10.0
Japan	23.4	66.0
Lombardy (Italy)	6.5	13.0
New Zealand	6.0	28.0
Norway	6.5	15.4
Sweden	15.3	23.4
Taiwan	-	59.0
The Netherlands	4.2	10.4
United States	29.0	107.0

(Note: Data expressed as people per million population per year)

rapidly, although wide variation in the absolute rates remains between countries.

The highest annual **incidence** is in the USA (107 people with diabetes per million population in 1995), with Japan and Taiwan reporting rates of approximately half this. In the European Union, the annual incidence in 1995 was 11.5 people with diabetes per million of the population. This increase is almost entirely due to the rise in number of people with type 2 diabetes. In Germany, approximately 90% of people with diabetes beginning dialysis have type 2 diabetes.

Fact

In Germany, approximately 90% of people with diabetes beginning dialysis have type 2 diabetes.

Reasons for this include the increasing incidence of type 2 diabetes, progressively declining premature mortality from cardiovascular disease, and greater willingness to treat frail, elderly people. However, there does also appear to be a real increase in the numbers reaching end-stage kidney disease in non-Caucasian people.

CHAPTER 3

Assessing Kidney Function in a Person with Diabetes

As described in the preceding chapter, diabetic nephropathy (diabetic kidney disease) develops slowly over many years and is characterized by gradual increases in urine protein (albumin) and other protein excretion, rising blood pressure and eventually a decrease in kidney filtration function.

In assessing kidney function in a person with diabetes, it is important to measure:

- The amount of albumin or protein in the urine
- Kidney filtration function
- Blood pressure

There are two aspects to monitoring diabetic nephropathy. The first involves regular, systematic screening of everyone with diabetes for signs of diabetic nephropathy. This data allows assessment of the effectiveness of **primary prevention** strategies and also identifies individuals with early signs of the disease. The second part involves more detailed assessment of people with diabetes who are found at screening to have abnormalities in kidney function.

Annual Screening for Diabetic Nephropathy

Authorities now recommend screening all young people and adults with diabetes for signs of kidney disease on an annual basis. Screening relies on the measurement of urine albumin excretion, as this is the first clinically identifiable sign of diabetic kidney disease. Although the best estimate of urine albumin excretion is made on a timed urine collection, (either over 24 hours or overnight) this is often inconvenient for the people involved and the laboratory, so that it is now generally agreed that screening should be based on an untimed urine sample. Since the effects of standing and exercise on albumin excretion are exaggerated in diabetes, an early morning urine sample should be used if possible.

Fact

Authorities now recommend screening all young people and adults with diabetes for signs of kidney disease on an annual basis.

Table 3-1
Annual screening for diabetic nephropathy in type 1 and type 2 diabetes.

List of conditions to be satisfied before screening:
• Post puberty
• In stable glucose control
• Free of another acute illness
• Free of urinary tract infection

The method of assessment used should be specific for albumin; most are immunologically based. If possible, a laboratory based test should be used, measuring both urine albumin and **creatinine**, and the albumin:creatinine ratio calculated. This adjusts for the effects of different urine flow rates. The dip-stick tests specific for albumin are at best semi-quantitative and give only a urine albumin concentration. Definitions for normal and abnormal values are given in Table 3.2. Lower values for albumin:creatinine ratio are used in

Table 3-2
Definitions of microalbuminuria and proteinuria in diabetic nephropathy

	Normal	Microalbuminuria	Proteinuria
Albumin Concentration (mg/l)	< 20	20-200	> 200
Albumin: Creatinine ratio (mg/mmol)	< 2.5 (men) < 3.5 (women)	2.5-30 3.5-30	> 30 > 30
Overnight Urine albumin (µg/min)	< 20	20-200	> 200
24 h Urine albumin (mg/24 h)	< 30	30-300	> 300
24 h Total protein (mg/24 h)	-	-	> 500

men because of their higher muscle mass and therefore higher urine creatinine excretion.

Blood pressure and serum creatinine, a simple blood test which gives an approximate indication of kidney filtration function, should also be measured. If all these tests are normal, they should simply be repeated in one year. If urine albumin excretion and/or serum creatinine are abnormal, more detailed assessment of kidney function is required. A flow chart describing a plan for screening everyone with diabetes for kidney disease is given in Figure 3-1.

More Detailed Kidney Function Assessment

Urine Albumin and Protein Excretion

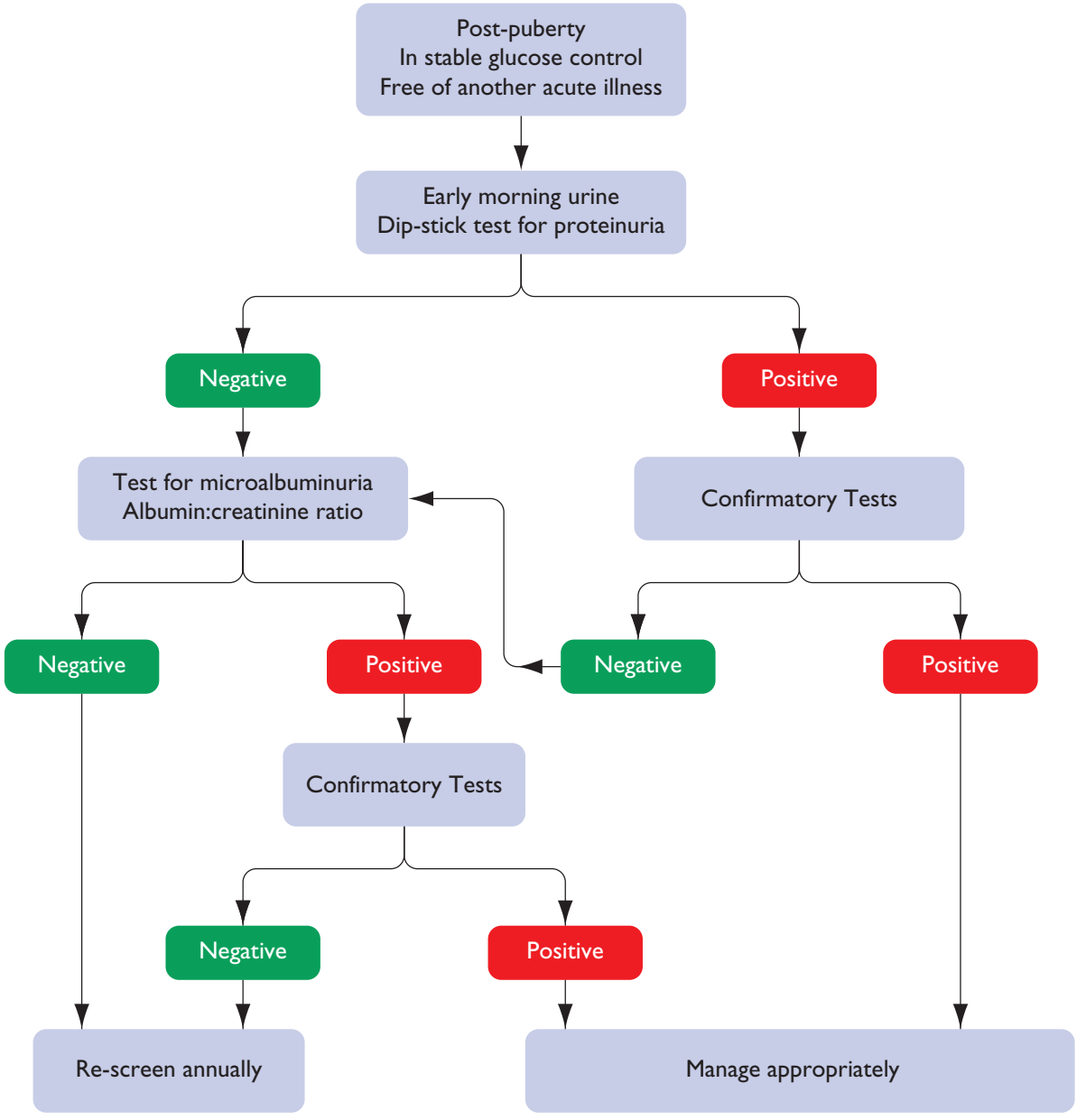
If the screening test for urine albumin:creatinine ratio described previously is elevated, then the test should be repeated two or three times. There is a large day-to-day variation in **urine albumin excretion**, so at least 2 out of 3 tests should be positive before a diagnosis of microalbuminuria or proteinuria is made. Urine albumin is stable at room temperature for at least one week, so people may collect several early morning urine samples in the few days prior to their clinic visit, and bring them all to clinic at the same time. If the person does have microalbuminuria or proteinuria, this should be measured at each clinic visit.

Once the urine albumin level is very high (albumin:creatinine ratio >30 mg/mmol), the urine excretion of many other proteins is generally also increased, so that the total protein level may be quite high. At this stage, it may be helpful to accurately quantify urine protein loss in 24-hour urine samples.

Measuring Kidney Filtration Function

Measurement of serum creatinine in a simple blood test gives an indirect indication of kidney function. This is sufficient in individuals with normal urine albumin excretion. However, serum creatinine remains normal until approximately 50% of kidney function has been lost. It is also a poor reflection of kidney function in individuals with low muscle mass because they produce a low amount of creatinine. Thus in people with high urine albumin excretion, it may be useful to perform a more accurate assessment of kidney filtration function. This can be done using equations

Figure 3-1
A plan for screening for diabetic nephropathy in people with type 1 and type 2 diabetes



based on the serum creatinine measurement but which take into account an individual's muscle mass. The most widely used is the Cockroft and Gault equation, given in table 3-3.

Other ways of measuring kidney function more accurately are time consuming and laborious. They require the injection of a tracer substance into the blood and then further blood samples being taken over 4-6 hours to estimate how quickly the tracer substance is cleared from the blood by the kidneys.

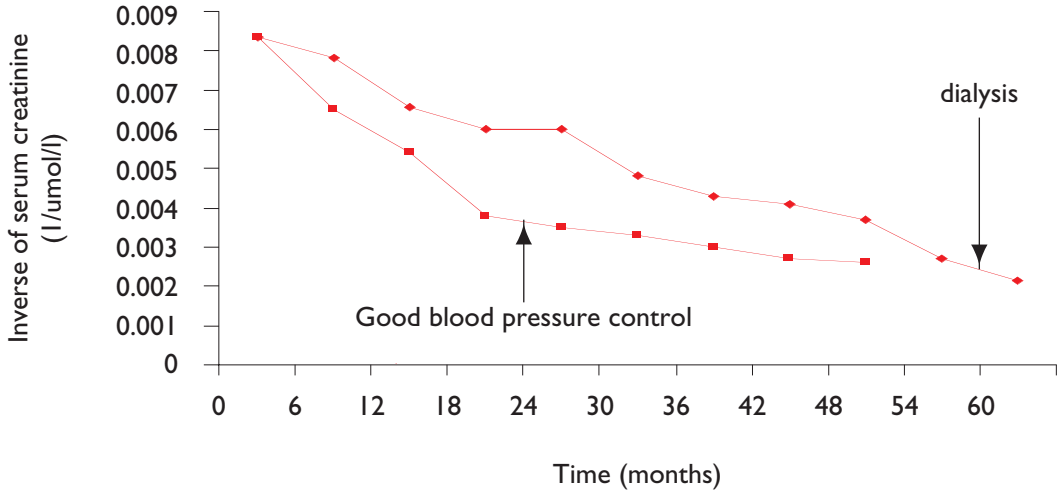
Table 3-3
The Cockroft-Gault formula for estimating kidney filtration (creatinine clearance)

$$C_{cr}\ (\text{ml/min}) = \frac{(140\text{-age}) \times \text{weight} \times 0.85 \text{ if female}}{72 \times \text{serum creatinine}}$$

Figure 3-2

Graph showing the usefulness of plotting the inverse of serum creatinine with time in monitoring the decline in kidney function.

This gives a good indication of the rate of fall of kidney function and to the response to treatment such as blood pressure control. In the lower line, good blood pressure control was achieved after 18 months, which meant the rate of decline of kidney function was slowed. In the top line, good blood pressure control was not achieved, so the decline of kidney function continued and the person required dialysis after 60 months.



The tracers used can be radioactive or chemical (iohexol or cystatin C). These tests are generally not done regularly. Once the serum creatinine begins to rise out of the normal reference range, a simple and useful indication of the rate of fall of kidney function can be obtained by plotting the inverse of the serum creatinine against time. This allows an estimate of the effect of interventions and of the time when dialysis may be required.

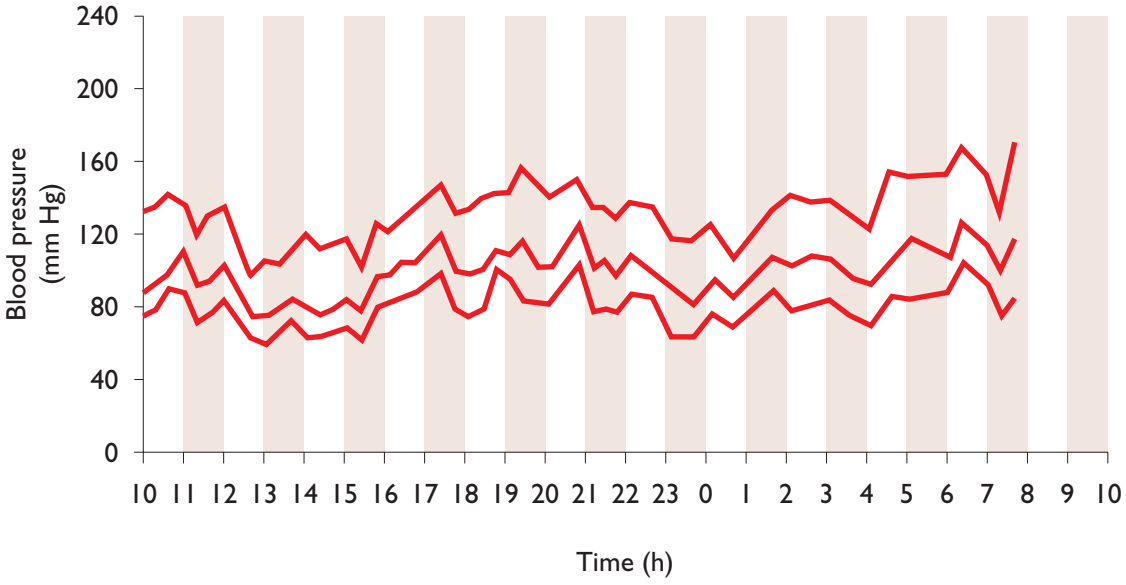
Table 3-4

Recommendations for correct blood pressure measurement

- Allow the person to sit for several minutes in a quiet room before beginning blood pressure measurement
- Use a standard cuff (12-13 by 35 cm), with a large cuff for large arms and a smaller cuff for children
- Use the disappearance of sound (phase V Korotkoff) to indicate the lower (diastolic) blood pressure
- Measure blood pressure in both arms at the first visit
- Measure the blood pressure in the standing position in elderly people, people with diabetes and in other conditions in which low blood pressure on standing is common
- Place the blood pressure cuff at heart level, whatever the position of the person

(After the 1999 World Health Organisation / International Society of Hypertension Guidelines for the Management of Hypertension)

Figure 3-3
24-hour blood pressure monitoring in a person with diabetic nephropathy.



Note that the blood pressure does not fall during the night-time. (22.00-06.00 hrs)

Blood Pressure

As already discussed earlier, blood pressure rises in parallel with urine albumin excretion. Blood pressure should therefore be assessed at every visit in people with diabetic nephropathy. The WHO recommendations should be followed. [See table 3-4]

Early in nephropathy, the rise in blood pressure may be minimal and not easily detected in routine clinic blood pressure measurement. Use of 24 hour continuous blood pressure monitoring may be helpful, particularly in detecting a failure for blood pressure to fall as normal overnight, which may be the first abnormality in diabetic nephropathy.

In people with diabetes and advanced kidney disease complicated by autonomic nerve damage, or those who are on several different agents to control blood pressure, the blood pressure may fall on standing (orthostatic hypotension). This may give rise to symptoms such as dizziness or feeling faint. It may be detected by measuring the blood pressure on standing or more reliably by 24-hour blood pressure monitoring.

Table 3-5
Potential indications for renal biopsy in people with diabetes

Biopsy *not* considered when:
• Course of the kidney disease is typical of diabetes • Significant diabetic eye disease (retinopathy) is present
Biopsy should be considered if:
• Kidney abnormalities present at shorter duration of diabetes than would be expected (<10 years) • Abnormal red blood cells or casts in the urine • Rapid deterioration of kidney function • Elevated serum creatinine without high urine albumin or protein levels

Further Investigations

If there is doubt on the cause of abnormalities in kidney function, then it is sometimes necessary to perform further investigations. Generally, if the clinical presentation fits with the pattern expected in type 1 diabetes, the chances that further investigation will yield information that alters therapy are very low. In type 2 diabetes, the issue is more complex, as the duration of diabetes is not reliably known. Ultrasound examination of the kidneys and **renal tract** may be helpful. Occasionally a renal biopsy may be necessary. Done under ultrasound control and using biopsy guns of predetermine depth, the risks of renal biopsy are low.

CHAPTER 4

Risk Factors for Diabetic Nephropathy

Risk Factors

What is a Risk Factor?

Why do some people with diabetes develop kidney disease while others do not? What are the conditions that predispose someone to the development of this complication? In other words, what are the risk factors for diabetic nephropathy?

A risk factor is defined as a condition that increases a person's chances of developing a health-related problem. The link between a supposed risk factor and a disease is established by repeated observations that exclude chance. However, the presence of a risk factor does not necessarily imply that the disease will develop.

Fact

A risk factor is defined as a condition that increases a person's chances of developing a health-related problem.

A risk factor may be genetic or may be acquired during life. It may be an altered blood test such as high **cholesterol**, a lifestyle factor such as smoking, drinking alcohol etc, or another medical condition such as high blood pressure.

Fact

The identification of risk factors is important because, through specific intervention or by modification of lifestyle, a disease can be prevented or limited.

The identification of risk factors is important because, through specific intervention or by modification of lifestyle, a disease can be prevented or limited. Other risk factors, such as a familial predisposition to a disease are not easily modified. Nevertheless, it is important to identify such risk factors, as they may be used to identify high-risk populations who require closer observation and follow-up.

This chapter will examine the role of several risk factors in both the development of kidney damage and in the progressive loss of kidney function when nephropathy is established.

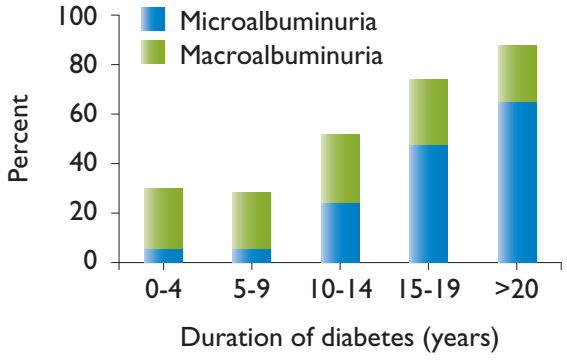
Table 4-1
Risk factors for diabetic nephropathy (diabetic kidney disease) in type 1 and type 2 diabetes.

Risk factors for diabetic nephropathy
• Duration of diabetes
• Familial and genetic factors
• Hyperglycaemia
• High blood pressure
• Dyslipidaemia
• Proteinuria
• Smoking

Duration of Diabetes

Diabetic nephropathy develops 10-15 years after the onset of the disease in both type 1 and type 2 diabetes. Some studies show that the incidence of albuminuria in people with diabetes is less than 10% during the first 10 years of disease, and then rises to between 20 and 30% over the following 10 years. Duration of diabetes is therefore a risk factor for diabetic nephropathy. Sometimes, albuminuria is already present in people with type 2 diabetes at the time of diagnosis. This occurs because diabetes has been present for several years before the diagnosis is made.

Figure 4-1
The figure reports the prevalence of albuminuria by duration of diabetes in Pima Indians with type 2 diabetes.



Adapted from: Nelson et al. Diabetologia 32:870;1989

Familial and Genetic Factors

Some studies suggest that a predisposition to develop diabetic nephropathy may be inherited. A study in Pima Indians showed that the chance of developing diabetic nephropathy was more than double in people whose parents were both affected by diabetic nephropathy as compared to people whose parents did not have nephropathy. Those people with only one parent with diabetic nephropathy were somewhere in between. Other studies have shown that there is a greater risk of diabetic nephropathy in particular families. In addition, a family history of **hypertension** has been associated with an increased risk of diabetic nephropathy.

At the present time, the gene or genes responsible for determining diabetic nephropathy have not been identified, although several candidate genes have been proposed. In particular, attention has been focused on the **renin-angiotensin system**. When specific markers of risk are found, high-risk individuals should be identified early in the course of diabetes and closely monitored for the development of albuminuria.

Fact

At the present time, the gene or genes responsible for determining diabetic nephropathy have not been identified.

Hyperglycaemia

There are several studies that link **hyperglycaemia** with the risk of nephropathy. Originally suggested by Nyberg, the association between high levels of glycated **haemoglobin** (HbA_{1c}) and diabetic nephropathy was demonstrated in a group of 18 people with type 1 diabetes in Wisconsin, USA. They were all taking insulin, younger than 30 years when diabetes was diagnosed, and had had diabetes for more than 4 years. The level of HbA_{1c} correlated directly with the incidence of albuminuria: the higher the HbA_{1c} level, the higher the incidence of albuminuria in these people. [See figure 4.2]

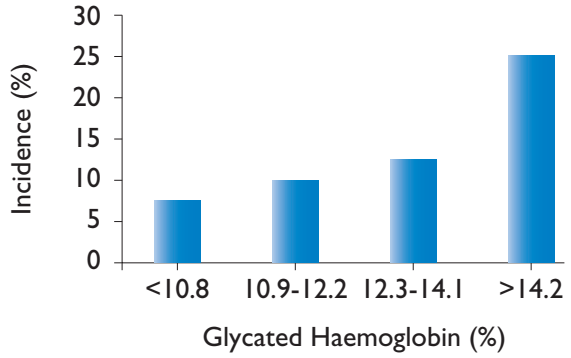
Table 4-2
The renal status of siblings of people with type 1 diabetes, with or without diabetic nephropathy (DN) was assessed in 31 people. Siblings of people with DN had a higher prevalence of kidney disease than those of people without DN. ESRD=End-Stage Renal Disease.

Familial and genetic factors in diabetic nephropathy

	The person has diabetic nephropathy?	
The sibling has:	**Yes**	**No**
ESRD	41%	0%
Albuminuria	41%	17%
No Nephropathy	17%	83%

Adapted from: Seaquist et al. N Eng J Med 320:1161;1989.

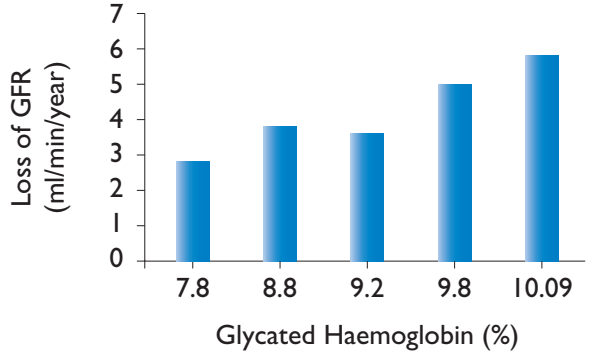
Figure 4-2
The figure shows the incidence of albuminuria in a population of people with type 1 diabetes according to their value of glycated haemoglobin at the beginning of the study.



Adapted from: Klein et al. Arch Intern Med 151:1344;1991.

Hyperglycaemia is also a risk factor for developing albuminuria in type 2 diabetes. A number of population-based studies conducted in several countries have shown that hyperglycaemia is a strong risk factor for developing nephropathy. The evidence linking hyperglycaemia with the progression of diabetic nephropathy towards end-stage kidney disease is not as strong.

Figure 4–3
This figure shows that in people with type 1 diabetes, the loss of renal function as defined by the loss of glomerular filtration rate (GFR) is correlated with the level of HbA_{1c}, a marker of glycaemic control.



Adapted from: Hovind et al. Kidney Int 59:702;2001.

A Korean study showed that **glycaemia** is an important factor for the development of albuminuria, but that progression to clinical nephropathy was more closely related to high blood pressure. Hyperglycaemia may be more important for initiating nephropathy, while other factors may be responsible for its progression.

Hyperglycaemia is associated with damage to the small blood vessels of the kidney, particularly to the glomerular capillaries. Initially, there is an increase in how well the kidneys are filtering blood (the glomerular filtration rate), a phenomenon defined as hyperfiltration or filtration greater than normal. In the long term, the consequences of hyperfiltration are increased permeability of the capillaries and passage of albumin into the urine.

High Blood Pressure

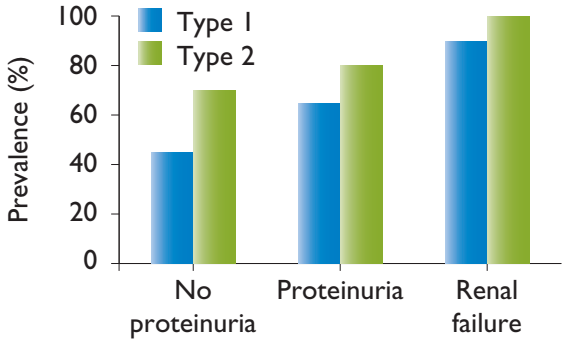
High blood pressure (hypertension) is closely related to kidney damage in diabetes. While people with type 1 diabetes develop hypertension later in the course of diabetes, a very large proportion of people with type 2 diabetes (up to 50%) have high blood pressure even before they develop diabetes. Hypertension may be present for years before the time of diagnosis and precedes the development of diabetic nephropathy. In a study performed in Germany, blood pressure was measured in 92 people with newly diagnosed diabetes using continuous 24 hour blood pressure monitoring. 57% of them had high blood pressure (according to the WHO definition), while only 23% had normal blood pressure. [See figure 4-4]

High blood pressure significantly increases the risk of subsequent albuminuria. In a retrospective analysis, it was found that people with diabetes who subsequently

Fact
Once kidney damage is established, high blood pressure is a strong risk factor for the deterioration of kidney function over time.

developed albuminuria had high blood pressure (which was more severe in the pre-albuminuric period) more often than people who did not develop albuminuria. Once kidney damage is established, high blood pressure is a strong risk factor for the deterioration of kidney function over time.

Figure 4–4
Prevalence of high blood pressure (by WHO criteria) in people with type 1 and type 2 diabetes according to their renal status.



Adapted from: Ritz et al. in Laragh and Brenner eds. Hypertension–Pathophysiology, Diagnosis and Management, vol 2. New York, Raven 1990. p.1705.

A close correlation between hypertension and the rate of loss of kidney function has been documented in both type 1 and type 2 diabetes. People with diabetes who have high blood pressure experience a more rapid loss of glomerular filtration rate than people with diabetes with normal blood pressure.

A recent study at the Steno Diabetes Center in Denmark monitored 301 people with type 1 diabetes for 7 years. Every year their kidney function was measured. The study showed that the loss of kidney function was directly associated with hypertension. Those with higher blood pressure also had a faster decline of kidney function.

Dyslipidaemia

An abnormal level of lipids (fats) in the blood is called dyslipidaemia. This is often present in people with kidney disease and is usually regarded as a consequence of kidney dysfunction. However, this abnormality can also play a role in causing and aggravating the glomerular damage. Several studies in type 1 and type 2 diabetes have found a correlation between high cholesterol and the progression of diabetic nephropathy. Research has shown that people with cholesterol higher than 7 mmol/l had a faster decline of glomerular filtration rate than people with cholesterol below that threshold (the two groups of people had similar blood pressure, albuminuria, and HbA_{1c}).

Fact

Several studies in type 1 and type 2 diabetes have found a correlation between high cholesterol and the progression of diabetic nephropathy.

However, statistical analysis did not demonstrate that cholesterol is an independent risk factor for diabetic nephropathy. The Steno Diabetes Center's study previously mentioned showed that elevated cholesterol acts as an independent progression promoter in diabetic nephropathy. It should also be remembered that dyslipidaemia remains a strong risk factor for cardiovascular complications of diabetes.

Proteinuria

The excretion of proteins in the urine is called proteinuria. It is a hallmark of kidney damage. Diseased glomerular capillaries let protein pass through their walls and spill into the urine. Recent animal and human studies have suggested that excessive urinary protein excretion is not only a marker of damage, but is also a risk factor that

Fact

Excessive urinary protein excretion is not only a marker of damage, but is also a risk factor that accelerates the rate of loss of kidney function.

Table 4-3

Prevalence of proteinuria in people with type 1 diabetes according to their smoking status.

Smoking and proteinuria in diabetes

	No. of people	Age (years)	Hypertension (%)	Proteinuria (%)
Smokers	192	32	13	19.3
Non smokers	192	32	12	8.3

Adapted from: Mühlhauser et al. Diabetologia 29:500;1986.

accelerates the rate of loss of kidney function. Increased leakage of proteins through the kidney filter results in the accumulation of proteins in other parts of the kidney, such as in the proximal tubular cells, the cells that line the tubes taking urine from the filter out of the kidney. The presence of these proteins may trigger the activation of substances which cause blood vessels to dilate or constrict (vasoactive substances) and also of chemicals which cause inflammation (inflammatory substances). This contributes to the formation of scar tissue and inflammation, ultimately leading to complete shut-down of the filter (sclerosis of the glomerulus).

Indeed, people with severe proteinuria have a faster rate of loss of kidney function than people with less proteinuria. The worst prognosis is for people who have type 1 diabetes and nephropathy and **nephrotic syndrome** (a condition characterized by urinary excretion of proteins in excess of 3 g/24 hours). A Japanese study showed that people with proteinuria greater than 2.5 g/24 hours at the beginning of follow up were 3.8 times more likely to progress to end-stage kidney disease than people with proteinuria less than 2.5 g/24 hours. Proteinuria is also a powerful predictor of cardiovascular mortality in diabetes.

Smoking

Smoking is a strong predictor of kidney risk in type 1 diabetes. Smoking also increases the risk of developing type 2 diabetes by a factor of 1.9 in heavy smokers. In people with diabetes who smoke more than 25 cigarettes a day, the risk of developing proteinuria is two times greater than in non-smokers.

Some studies have also suggested that heavy

Fact

In people with diabetes who smoke more than 25 cigarettes a day, the risk of developing proteinuria is two times greater than in non-smokers.

Table 4-4

Relationship between diabetic nephropathy and some of the major microvascular and macrovascular complications of diabetes

Macrovascular and microvascular complications

In presence of diabetic nephropathy these conditions are:		
	More frequent	**More severe**
• Retinopathy	+	++
• Neuropathy	+	++
• Coronary heart disease	+	+++
• Cerebrovascular disease	+	++
• Peripheral vascular disease	+	+++

Adapted from: Raz et al. in Ritz, Rychlik eds. Nephropathy in type 2 diabetes. Oxford, Oxford University Press 1999 p.159.

Fact

Some studies have suggested that heavy smoking can accelerate the progression of diabetic nephropathy to end-stage kidney disease.

smoking can accelerate the progression of diabetic nephropathy to end-stage kidney disease. While the mechanisms are not well understood, some studies have shown that smoking acutely increases blood pressure. This rise in blood pressure may be responsible for damage to glomerular capillaries.

Nephropathy and other Complications

The presence of diabetic nephropathy is a bad sign for people with type 1 and for people with type 2 diabetes, not only because they are at risk of end-stage kidney failure and may end up on dialysis, but also because the other complications of diabetes are exacerbated by the presence of kidney involvement.

Diabetic complications are often described as **microvascular** and **macrovascular** complications, since they are caused by alterations of small, medium or large arterial vessels of vital organs. The relationship between diabetic nephropathy and other complications has been the subject of intense scrutiny. The grim conclusion is that diabetic nephropathy makes all those complications worse.

Cardiovascular Disease

Cardiovascular complications are the most significant cause of death in people with diabetes. The risk of cardiovascular complications is much higher in people with diabetes than in people without diabetes, and is even greater in the presence of diabetic nephropathy.

Fact

Cardiovascular complications are the most significant cause of death in people with diabetes.

In people with type 1 diabetes and nephropathy, it has been estimated that the risk of **mortality** for cardiovascular disease is 40 times greater than in people without diabetes. Even in the early phase of diabetic nephropathy, when microalbuminuria is present, people with type 2 diabetes are already at greater risk of cardiovascular complications. In fact, microalbuminuria is one of the best predictors of cardiovascular **morbidity** and mortality. It is an even more potent predictor than

Table 4-5

Mortality (expressed as rate per 1000 person-years) and relative risk for coronary heart disease (CHD) and stroke according to renal status in people with type 2 diabetes.*
Relative risk is the relation between the risk of a given event for a group of people and the risk for the same event in a reference population, whose relative risk is 1. In the below table, the relative risk for fatal CHD is more than 2 times in people with microalbuminuria than in normoalbuminuric.

Cardiovascular and cerebrovascular deaths in diabetic nephropathy

	Albuminuria		
	Normo	**Micro**	**Proteinuria**
Number of people	460	208	172
Deaths from CHD*	23.3	58.3	85.5
Relative risk	1	2.39	3.85
Deaths from stroke*	8.9	22.7	23.4
Relative risk	1	2.45	3.05

Adapted from: Valmarid et al. Arch Intern Med 160:1093;2000.

smoking, high blood pressure and elevated cholesterol.

As far as specific cardiovascular disease is concerned, one study showed coronary artery disease was present in 46% of people with diabetes with **macroalbuminuria**, 26% with microalbuminuria and 22% with **normoalbuminuria**. People with **coronary artery disease** and diabetes have higher levels of albuminuria than people without diabetes.

High blood pressure is an important risk factor for **stroke** and **myocardial infarction** in the general population and even more relevant in people with diabetes. Mortality is increased by a factor of 4 to 7 in people with diabetes with high blood pressure in comparison to people without diabetes.

People with diabetes have an abnormal lipid profile. **Low-density lipoprotein (LDL)** and **tryglycerides** are increased, while **high-density lipoprotein (HDL)** is reduced. This lipid pattern is associated with increased cardiovascular morbidity and mortality. The presence of early diabetic nephropathy worsens the abnormal lipid profile, thereby increasing the risk of cardiovascular complications. As diabetic nephropathy progresses to proteinuria and kidney insufficiency, the lipid profile is even worse.

Retinopathy

Retinopathy is a debilitating complication of diabetes that can cause visual impairment or blindness. The incidence of blindness is 25 times higher in people with diabetes than in the general population. Furthermore, diabetic retinopathy is the most common cause of blindness in middle-aged people (12% of all new cases in the United States each year). The prevalence of retinopathy is increased in people with diabetic nephropathy and is worsened by poor glycaemic control, hypertension and dyslipidaemia. The association of retinopathy with nephropathy is particularly strong in type 1 diabetes, but is not well documented in type 2 diabetes. Some ethnic groups are at greater risk than others.

Fact

The incidence of blindness is 25 times higher in people with diabetes than in the general population.

Retinopathy develops through stages from an early phase (non-proliferative) to a later phase (proliferative). Both types of retinal damage are characterized by abnormalities of the small blood vessels in the retina. The resemblance of the retinal capillary arteries to the glomerular vessels, together with the close link between retinopathy and nephropathy, suggest that a common mechanism is responsible for both conditions.

Neuropathy

People with diabetes may suffer from **neuropathy**, damage to the nerve fibres caused by diabetes. **Peripheral neuropathy** leads to numbness and sometimes pain and weakness in the limbs. **Autonomic neuropathy** causes problems in every organ, including the digestive tract, heart and sexual organs. There is a close relation between the duration of diabetes and nerve problems.

Fact

There is a close relation between the duration of diabetes and nerve problems.

However, the relation between neuropathy and diabetic nephropathy is less clear. One study has suggested that neuropathy may play a role in damaging the kidney. In type 1 diabetes, continuous monitoring of blood pressure for 24 hours showed that night-time blood pressure in people with diabetic nephropathy remained higher than in people without diabetes. This loss of blood pressure regulation may be due to autonomic neuropathy and may contribute to the development of diabetic nephropathy. [See Figure 3-3].

CHAPTER 5

Prevention and Treatment of Diabetic Nephropathy

Recent clinical studies have indicated that it is possible to reduce the incidence and the rate of progression of diabetic nephropathy. This chapter will summarize the available evidence and provide a concise set of recommendations for the prevention and management of diabetic nephropathy.

Glycaemic Control

Several studies have shown that control of blood glucose slows down the development of diabetic nephropathy. These studies are described below.

The Diabetes Control and Complication Trial (DCCT) studied 1441 people with type 1 diabetes over a ten-year period. One group of people received intensive treatment over this period. This included in-depth education, frequent contact with healthcare professionals, self-monitoring of blood glucose levels and multiple injections of insulin. Blood glucose was kept around 8.3 mmol/l (150 mg/dl) on average, with an HbA_{1c} of 7.0%. The other group followed what was then conventional therapy, with some education, less frequent contact with healthcare professionals, infrequent blood glucose monitoring and one or two injections of insulin daily. The mean HbA_{1c} in this group was around 9.0%. After ten years, the kidney function in people whose albumin excretion was normal at the beginning of the study was assessed. In the intensive treatment group, 50% fewer people developed diabetic nephropathy as compared to those in the conventional treatment group. However, in

Fact

Control of blood glucose slows down the development of diabetic nephropathy.

Table 5-1
Management of renal risk factors in people with diabetes

Risk factor	Treatment	Result of treatment
Hyperglycaemia	Tight glycaemic control with insulin, oral hypoglycaemic agents, lifestyle modification	Prevent appearance of albuminuria, may delay progression of nephropathy
High blood pressure	Drugs: ACE inhibitors, angiotensin receptor antagonists, diuretics, non-dyhydropiridinic calcium blockers, beta blockers Lifestyle modification: salt restriction, exercise, loss of excess weight	Prevent diabetic nephropathy, delay progression
Dyslipidaemia	Lifestyle modification Drugs: statins, fibrates (caution if renal failure)	May delay progression of nephropathy
Smoking	Stop smoking	May prevent nephropathy May delay progression

those who already had albuminuria at the beginning of the study, there was no advantage from intensive glycaemic control.

The United Kingdom Prospective Diabetes Study (UKPDS) studied people with type 2 diabetes. The findings showed that intensive control of blood glucose with oral hypoglycaemic agents or insulin reduced the risk of diabetic nephropathy and other microvascular complications of diabetes, but not macrovascular complications. For participants in the UKPDS who were overweight (defined as >120% of ideal body weight), the effect of the oral hypoglycaemic agent **metformin** in reducing the risk of kidney failure was similar to that of other hypoglycaemic agents, but metformin resulted in a significantly lower risk of heart attack (myocardial infarction).

In another study conducted in people with type 2 diabetes in Japan, those receiving intensive glucose control with three or more insulin injections per day had a lower rate of new or progressive nephropathy over a period of six years than people taking conventional therapy (7.7% vs. 28%).

These studies have not demonstrated a threshold for glycaemic control. Nevertheless, it has been shown that the lower the HbA_{1c}, the lower the risk of nephropathy. However, this must be balanced against the risk of **hypoglycaemia** (low blood glucose levels). Thus, the current practice guidelines suggest that target levels for HbA_{1c} level should be less than 7.0% provided there is no hypoglycaemia.

Fact

In people with type 2 diabetes, high blood pressure (hypertension) increases the risk of the person developing diabetic nephropathy.

Blood Pressure Control

In people with type 2 diabetes who have initially normal albumin levels, high blood pressure (hypertension) increases the risk of the person developing diabetic nephropathy. In people with diabetes (type 1 and type 2) who have nephropathy, high blood pressure accelerates the loss of kidney function. Both effects are prevented or limited by drugs that lower blood pressure (antihypertensive drugs).

Choice of Drug

Research has shown the positive effects of antihypertensive therapy on diabetic nephropathy. At the end of the 1980's, studies described the beneficial effects of a new class of antihypertensive drugs, the **Angiotensin Converting Enzyme (ACE) inhibitors**. In 1993, a clinical study demonstrated that the ACE inhibitor captopril significantly reduced the risk of the progression of nephropathy in people with type 1 diabetes. These results have been confirmed by subsequent studies.

Fact

Research has shown the positive effects of antihypertensive therapy on diabetic nephropathy.

In the **Heart Outcomes Prevention Evaluation (HOPE) study**, it was found that when people with diabetes and similarly high blood pressures were treated with an ACE inhibitor or placebo, there was a 24% greater decrease in the rate of progression to nephropathy compared to people not taking the ACE inhibitor.

In the **Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study**, treatment with irbesartan (an **angiotensin receptor antagonist**) at a dose of 300 mg per day decreased the level of urinary albumin excretion by 38% and reduced the risk of progression to proteinuria by 70% as compared with **placebo**.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study showed that, as compared with conventional treatment alone, losartan combined with conventional treatment decreased the level of urinary protein

excretion by 35% and reduced the risk of end-stage kidney disease by 28%.

In the **Irbesartan Diabetic Nephropathy Trial (IDNT)**, the risk of significant decline in kidney function, the onset of end-stage kidney disease, or death from any cause was 20% lower in people treated with irbesartan than in those treated with conventional therapy, and 23% lower than in those treated with amlodipine.

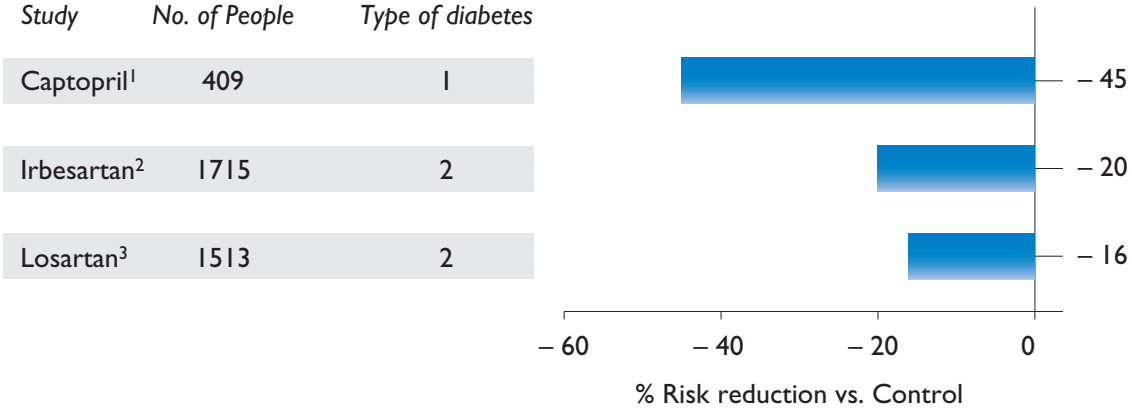
A high blood potassium level (hyperkalemia), which can cause heart rhythm problems, is a recognized risk of treatment with the ACE inihibitors and angiotensin receptor antagonists used in the above studies. However, data from numerous clinical trials suggest that the risk is low. Only 1.5% of people treated with ACE inhibitors or angiotensin II receptor antagonists were withdrawn from trials because of hyperkalemia, and no deaths were reported in association with hyperkalemia in any treatment group.

Other types of drugs for lowering blood pressure have been used in diabetic nephropathy. **Dihydropyridine calcium-channel blockers** (eg nifedipine and amlodipine) may worsen proteinuria and accelerate the progression of diabetic nephropathy. These findings are at variance with the effects of the **nondihydropyridine calcium-channel blockers**, (eg diltiazem and verapamil) which may reduce proteinuria and reduce the passage of large proteins through the kidney filter in people with nephropathy due to type 2 diabetes.

At any level of blood-pressure control, people with diabetes who were treated with dihydropyridine calcium-channel blockers had more severe proteinuria and a faster decline in the glomerular filtration rate than those treated with other antihypertensive agents. However, in the RENAAL study, the effect of losartan in reducing the risk of kidney events was not diminished by simultaneous use of dihydropyridine calcium-channel blockers.

Beta-blockers may also be beneficial in the treatment of diabetic nephropathy. In the UKPDS, beta-blockers and ACE inhibitors were equally effective in lowering the incidence of

Figure 5-1
The effect of ACE inhibitors or Angiotensin II receptor blockers on end-stage kidney disease in diabetic nephropathy.



The results of three large clinical studies demonstrate an additional kidney protective benefit by these agents above that attained by the control of blood pressure alone.

Adapted from: Lewis et al, N Engl J Med *329:1456;1993 • Lewis et al,* N Engl J Med *345:851;2001 • Brenner et al,* N Engl J Med *345:861;2001*

microalbuminuria and proteinuria in people with type 2 diabetes. A study involving people with **overt** nephropathy also found that beta-blockers and ACE inhibitors had similar protective effects on kidney function. The question of whether beta-blockers offer as much kidney protection as angiotensin II receptor antagonists needs to be answered by a direct comparison of the two classes of drugs. No large studies have compared the effects of **diuretics**, beta-blockers, or calcium-channel blockers with the effects of ACE inhibitors or angiotensin receptor antagonists in people with diabetes who have proteinuria.

Combination of Antihypertensive Drugs

Usually more than one drug is required to obtain ideal blood pressure control in people with diabetes. This is confirmed by the IDNT and RENAAL studies. Therefore the question is raised over which is the best combination of drugs. The favourable effects of ACE inhibitors and angiotensin II receptor antagonists on proteinuria are increased by dietary salt (sodium) restriction and by simultaneous administration of diuretics or nondihydropyridine calcium-channel blockers. In people with type 2 diabetes who have microalbuminuria, the combined treatment with lisinopril and candesartan was more effective in reducing blood pressure and albuminuria than either drug alone in a short-term study.

Fact

All the studies in type 1 and type 2 diabetes suggest that the lower the blood pressure, the lower the risk of developing nephropathy, and the slower it will progress.

Blood-Pressure Goals

All the studies in type 1 and type 2 diabetes suggest that the lower the blood pressure, the lower the risk of

Table 5-2
Summary of results from selected trials

Diabetes type	Study	Treatment	Results
PRIMARY PREVENTION			
Type 1	DCCT	Glycaemic control	Intensive treatment delays onset of microalbuminuria
Type 2	UKPDS-35	Glycaemic control	Reduction of HbA_{1c} associated with reduced incidence of nephropathy
	UKPDS-39	Blood pressure control	Both ACE inhibitors and atenolol delay onset of microalbuminuria and progression
	ABCD		ACE inhibitors reduce cardiac events
SECONDARY PREVENTION			
Type 1	Captopril Study	Blood pressure control	ACE inhibitors slow progression to macroalbuminuria and to end-stage kidney failure
Type 2	IRMA IDTN RENAAL	Blood pressure control	Angiotensin II receptor blockers slow progression of kidney disease
	UKPDS 33	Glycaemic control	Intensive treatment slows down progression of microvascular damage

developing nephropathy, and the slower it will progress.

However, the optimal range of blood pressure in people with type 2 diabetes is unclear. In recent trials involving people with type 2 diabetes, there were no more cardiovascular events when diastolic blood pressure was 70 to 84 mm Hg than when it was 85 mm Hg or higher. However, if blood pressure was less than 70 mm Hg, the rates of cardiovascular events increased by 11% for each additional reduction of 5 mm Hg, with an increase in mortality. Thus it may be unwise to reduce diastolic blood pressure less than 70 mm Hg.

Treatment of Dyslipidaemia

Dyslipidaemia is common in people with diabetes, especially in those with proteinuria. An analysis of 13 controlled trials (involving a total of 362 people, 253 of whom had diabetes) showed that the cholesterol lowering agents (statins) decreased proteinuria and preserved the glomerular filtration rate in people with chronic kidney disease; effects that are not entirely explained by a reduction in blood cholesterol.

Dietary Protein Restriction

It has been suggested from experimental studies that reduced dietary protein intake may protect the kidney against loss of function. Indeed, a study involving people with type 1 diabetes and nephropathy showed that, as compared with a high intake of protein and phosphorus, the restriction of protein and phosphorus (0.6 g of protein per kilogram of body weight per day and 500 to 1000 mg of phosphorus per day) reduced the rate of fall of the glomerular filtration rate, lowered blood pressure, and stabilized kidney function in some people.

Fact

Reducing dietary protein intake may protect the kidney against loss of function.

Restriction of protein intake to 0.8 g per kilogram of body weight per day, corresponding to about 10% of total daily calorific intake (which is consistent with the recommended daily allowance) also reduces the rate of progression to end-stage kidney disease in people with type 1 diabetes. This has been rigorously studied only in people with type 1 diabetes. There have been no large randomized trials of protein restriction in people with type 2 diabetes, but it may also be beneficial to those with type 2 diabetes.

Smoking Cessation

Smoking, besides increasing the risk of cardiovascular events, is an independent risk factor for the

Fact

Smoking cessation alone may reduce the risk of disease progression by 30%, which means that smoking cessation may be more effective measure than any pharmacological intervention.

Table 5-3

Current practice guidelines for the management of diabetic nephropathy

Variable	Target
Blood glucose	HbA_{1c} < 7 %
Systolic blood pressure	<125 mm Hg
Diastolic blood pressure	< 75 mm Hg
LDL Cholesterol	< 3.0 mmol/l (115 mg/dL)
Dietary protein	< 0.8 g per kg body weight per day
Other measures	stop smoking, weight loss, physical exercise, moderate alcohol intake

Adapted from: Remuzzi et al. N Engl J Med 346:1145; 2002.

development of nephropathy in people with type 2 diabetes and is associated with accelerated loss of kidney function. Smoking cessation alone may reduce the risk of disease progression by 30%, which means that smoking cessation may be a more effective measure than any pharmacological intervention.

Recommendations

In conclusion, clinical studies have provided a great deal of information which allows for the development of a set of recommendations aimed at preventing the development of diabetic nephropathy, reducing the risk of disease progression and preventing cardiovascular complications.

Ways to prevent diabetic nephropathy should include:

- **smoking cessation**
- **lifestyle modifications such as weight loss, exercise, and reduction in alcohol intake**
- **control of high blood pressure**
- **tight glucose control**
- **treatment of dyslipidaemia**
- **moderate restriction of dietary protein intake**

The first choice for blood pressure treatment should be an ACE inhibitor or angiotensin II receptor antagonist because they decrease both blood pressure and albuminuria. A low dose should be used initially. The dose should be adjusted upward, as high as tolerated, to achieve a **systolic pressure** below 125 mm Hg and a **diastolic pressure** below 75 mm Hg. Serum potassium and creatinine should be checked in all people seven days after the initiation of treatment with these drugs and after any increase in dosage.

If ACE inhibitors or angiotensin II receptor antagonists are insufficient to achieve the target blood pressure, then other drugs should be added. A beta-blocker or diuretic are the next anti-hypertensive drug to add, with a nondihydropyridine calcium-channel blocker next to add to the others if the blood pressure is still not controlled. Dihydropyridine calcium-channel blockers or **alpha-blockers** should only be considered when the target for blood pressure is not met with the use of these other agents.

The same approaches are advisable in people with high blood pressure and normoalbuminuria in order to delay or prevent nephropathy. If tolerated, drugs that inhibit the rennin-angiotensin system are also recommended for **normotensive** people with microalbuminuria or macroalbuminuria; reduction of the albumin level is the main goal in such people.

Although studies of statins have not been designed specifically to examine their use in people with kidney disease, available data suggests that these medications may not only reduce the risk of cardiovascular disease but also slow the loss of kidney function.

CHAPTER 6

Treatment of End-Stage Kidney Disease in People with Diabetes

Treatment

People with diabetes and advanced kidney (renal) disease usually have many more complications than people with diabetes who do not have kidney disease. Complications of diabetes such as diabetic eye disease (retinopathy), damage to the nerves (neuropathy) and cardiovascular disease are all much more common in people with diabetes when they have diabetic nephropathy. Thus, in addition to specific measures directed at managing kidney failure, intensive effort must be directed at identification and management of these other problems. Regular examination of eyes and feet and assessment of **vascular disease** is vital. Other common problems, specific to end-stage kidney disease, are listed in table 6-1 and are discussed below.

Fact

Complications of diabetes such as diabetic eye disease (retinopathy), damage to the nerves (neuropathy) and cardiovascular disease are all much more common in people with diabetes when they have diabetic nephropathy.

Particular Problems in Managing End-Stage Kidney Disease in Diabetes

Blood Pressure

At any given level of kidney filtration, blood pressure tends to be higher in people with

Table 6-1
Major microvascular and macrovascular complications in people with diabetic nephropathy

Microvascular Complications

- Diabetic eye disease (retinopathy)
- Nerve damage to nerves to feet (peripheral neuropathy) and to the internal organs (autonomic neuropathy), resulting in:
  - Delayed emptying of stomach, with nausea and vomiting
  - Poor movement of large bowel, with diarrhoea and constipation
  - Difficulty in emptying bladder (detrusor instability)
  - Angina, but without pain
  - Impotence
  - High blood pressure when lying but low pressure when standing

Macrovascular Complications

- Coronary heart disease, enlargement of heart (left ventricular hypertrophy), heart failure
- Stroke (cerebrovascular disease)
- Poor circulation to the legs and feet (peripheral vascular disease)

Mixed Micro- and Macrovascular Complications

- Foot ulceration, infection, poor blood supply, all leading to amputation

diabetes compared to people without diabetes. The main causes are salt (sodium) retention and inappropriate activity of the renin-angiotensin hormone system which affect blood pressure. This influences the choice of medication used to control blood pressure. Dietary salt restriction, use of water tablets (diuretics) which aid sodium excretion, angiotensin converting enzyme inhibitors and **angiotensin receptor blockers**, which inhibit the renin-angiotensin system, are all used first. Other drugs are added as needed. Generally, at least three or four different types of tablets are needed to obtain adequate control of blood pressure in end-stage kidney disease.

Blood Glucose Control

Blood glucose control may be difficult. The kidney disease itself causes the body tissues to become less responsive to circulating insulin, so that the blood glucose may rise. However, as the kidneys fail, less and less of the insulin or tablets used to lower blood glucose are excreted in the urine. They may thus accumulate in the blood stream and lower the blood glucose too much, causing hypoglycaemia. Loss of appetite in end-stage disease, with significant weight loss, may also contribute to low blood glucose levels. Metformin, one type of tablet used to lower blood glucose, should be stopped when serum creatinine is >150 µmol/l, because of the risk of a build up of **lactic acid** in the blood. Doses of other types of tablets and insulin may need to be reduced. Insulin, usually in low doses, is being used more and more to achieve satisfactory blood glucose control.

Nutrition

Malnutrition is another potentially serious problem, particularly during periods of acute illness and fasting. Whilst reducing dietary protein intake to a moderate level (around 1g per kg body weight per day) is important to help slow the loss of kidney function, severe dietary protein restriction must be avoided. Many people lose a great deal of weight because of anorexia. Malnutrition is a potent predictor of mortality and its presence indicates the need to begin kidney replacement therapy early. Dietary assessment and advice from a dietician with specialist knowledge of diabetes and kidney disease is essential to obtain a balanced diet.

Acute Chronic Renal Failure

When people with diabetes with end-stage kidney disease become unwell for another reason, they are at risk of a sudden further fall in kidney function - "acute chronic renal failure". The most common causes are emergency cardiovascular investigations using x-ray dyes, severe infections with blood poisoning (septicaemia) and heart failure with low cardiac output or shock. Not infrequently, this acute deterioration in kidney function is severe enough to require emergency dialysis. Often, the kidneys do not recover and long-term dialysis is required. This irreversible acute kidney failure has a particularly poor outlook for the person.

Anaemia

One of the great advances of the past decade has been the recognition that anaemia is an important complication of advanced kidney disease and that treating the anaemia improves quality of life and reduces cardiovascular risk and the risk of many other complications. It is interesting that at any given degree of kidney failure, the effects of the anaemia are more severe in people with diabetes compared to people without diabetes.

Fact

Anaemia is an important complication of advanced kidney disease.

Normally, the kidneys make the chemical hormone erythropoietin which stimulates the bone marrow to make red blood cells. In people with diabetes (particularly type 1 diabetes) and even very early kidney failure, the bone marrow responds less well to erythropoietin. This may be related to, and perhaps caused by, autonomic neuropathy. As kidney function fails further, less and less

erythropoietin is made and the anaemia becomes more severe. Individuals with anaemia and low blood levels of erythropoietin lose kidney function more quickly. However, it is not known whether treating the anaemia slows down the rate of loss of kidney function.

In the microvascular complications of diabetes (eye and nerve disease), there is poor blood supply to the tissues and thus low levels of oxygen in the tissues (hypoxia). Oxygen in the blood is carried in red blood cells. In anaemia there are less red blood cells and thus less oxygen is carried to the tissues. This may worsen the microvascular complications of diabetes. Several studies are currently underway to test whether giving erythropoietin is beneficial to diabetic eye and nerve damage.

People with end-stage kidney disease and anaemia should be given appropriate treatment. This might include iron tablets or injections of erythropoietin.

Kidney Bone Disease (Renal Osteodystrophy)

As the kidneys fail, they stimulate other glands in the body called the parathyroid glands. The parathyroid glands make a chemical hormone called parathyroid, which acts on bones to increase bone breakdown. However, this complication is relatively rare in people with diabetes: it takes a long time for the parathyroid glands to become overactive and kidney failure develops relatively quickly in diabetes. In addition, blood glucose and insulin levels may help protect the parathyroid gland. However, it may be necessary occasionally to treat kidney bone disease with calcium or Vitamin D.

Initiation of Renal Replacement Therapy

Most kidney specialists (nephrologists) would agree that kidney replacement therapy should be started earlier in people with diabetes rather than in people without diabetes, when the glomerular filtration rate is approximately 15 ml/min. An even earlier start may be justified in individual cases if fluid overload (hypervolaemia) and blood pressure are very difficult to control, if the person is anorexic and if vomiting due to kidney failure or delayed emptying of the stomach (gastroparesis) is severe. It is important to make an individual decision as to when to begin dialysis based on the person as a whole and not to rely simply on levels of kidney function.

Treatment options for the person with diabetes in end-stage kidney disease:

- Haemodialysis
- Continuous anbulatory peritoneal dialysis (CAPD)
- Transplantation

There is no doubt that kidney transplantation, particularly combined with pancreas transplantation, provides optimal survival and the best quality of life. It is certainly the optimum procedure for young people with type 1 diabetes. If transplantation is performed in older people with type 2 diabetes, it is usually kidney transplant alone. Provided macrovascular disease is investigated and treated aggressively before transplantation, the outcome of transplantation in people with diabetes is good. If this is not done, people are likely to die of vascular disease very quickly. Unfortunately, because of limited availability of organs, the great majority of people with type 2 diabetes are not given transplants but treated by either haemodialysis or CAPD.

Haemodialysis

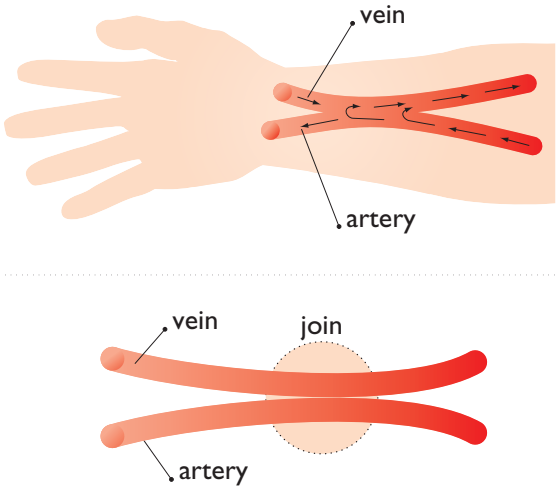
In haemodialysis, the person is attached to a blood dialysis machine for several hours 2 or 3 times each week. The blood circulates round an artificial filter in the dialysis machine, so that waste products and toxins are removed and the "cleaned" blood returned to the person. Most people attend hospital for this but a few have dialysis machines at home. [See figure 6-2]

Haemodialysis requires good access to the circulation, with the creation of a "shunt" or

fistula. In this procedure, an artery and vein are connected directly together to create a blood vessel of relatively high pressure. This blood vessel is then used to connect the circulation to the blood dialysis machine. It is important that this access is created in advance of the person needing dialysis, usually when the glomerular filtration rate is 20-25 ml/min.

Figure 6-1 : A fistula

A fistula is created surgically by a minor operation. The surgeon joins a vein to an artery usually in the area of the wrist. This greatly increases blood flow and pressure in the vein, which grows much larger. This means needles can then be easily placed in to allow dialysis.

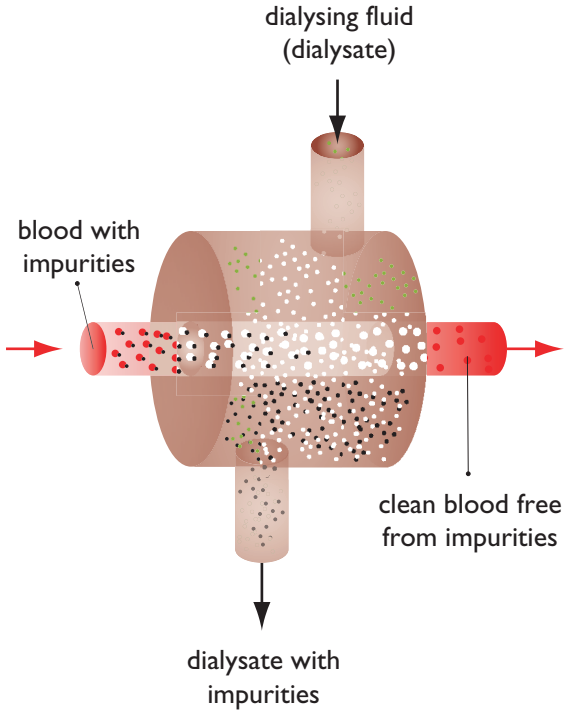


Adapted from: Australian Kidney Foundation

This shunt is usually fashioned from the veins in the forearm or upper arm, so it is important that arm veins are not damaged in frequent blood sampling. Generally, as someone approaches end-stage kidney failure, blood samples should be taken from the veins on the back of the hand. Creation of the shunt requires a skilled, dedicated surgeon. Shunts may not perform as well in people with diabetes compared to people without diabetes. If the artery is damaged because of vascular disease, blood flow through the shunt may be

Figure 6-2

An artificial kidney (dialyser)



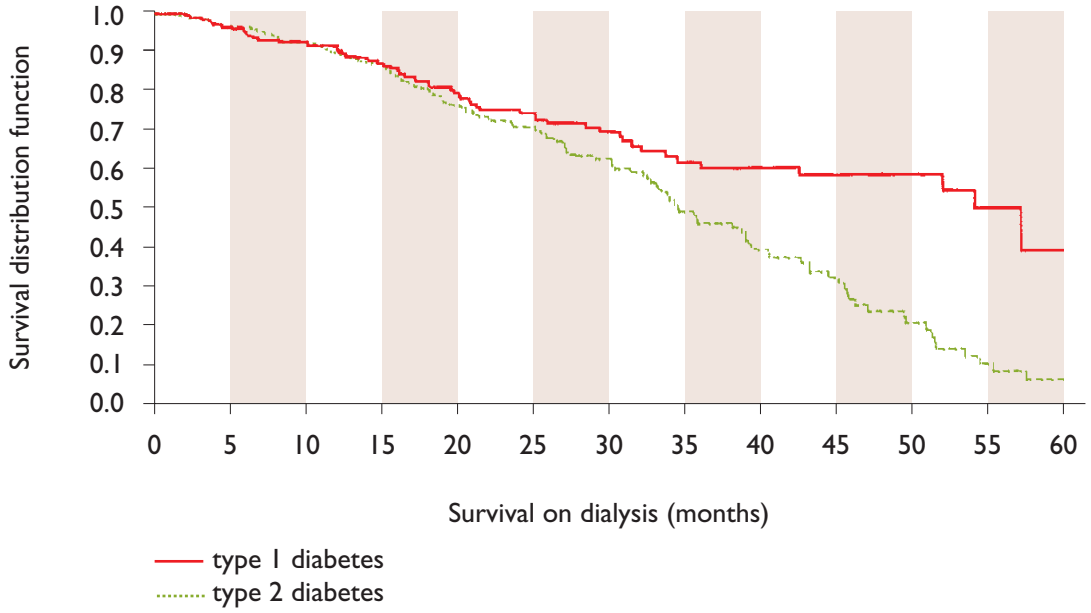
Adapted from: Australian Kidney Foundation

inadequate. If this is the case, another shunt, higher up in the arm, may need to be created.

Survival of haemodialysed people varies widely between different countries. It is particularly poor in the USA and in Northern Europe, better in the Mediterranean countries and particularly high in Asian countries. This difference reflects different cardiovascular risk in the background population and points to cardiovascular disease as the major cause of death. The most frequent mode of death is **sudden death**, followed by myocardial infarction and congestive **heart failure**. In 1998, Kock reported that 5 year survival in people with type 2 diabetes was 5% and in type 1 only 30%, figures which correspond to the survival of people with gastric cancer which has spread through the body. In more recent reports, patient survival has improved but it remains poorer than in people without diabetes on haemodialysis.

Figure 6-3

Survival distribution function of 412 people with diabetes (181 type 1 and 231 type 2) with end-stage kidney disease



Adapted from: Koch et al, 1998

For people requiring haemodialysis, the main problems relate to vascular access for dialysis, blood pressure control and complications of macrovascular disease, particularly amputation of the leg and stroke. It may be extremely difficult to obtain good blood pressure control when the person is upright without episodes of too low blood pressure (hypotension) during dialysis.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

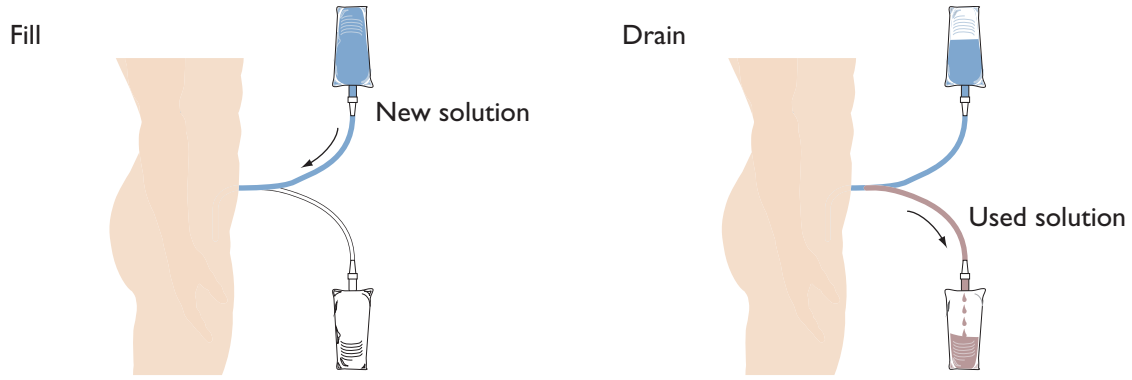
In CAPD, a tube is inserted though the abdominal wall into the space around the internal organs, the peritoneal space. Fluid can then be introduced into this peritoneal space. The membrane lining the abdominal cavity acts as a filter, so that waste products and toxins in the blood are drawn across the membrane into the fluid. After several hours, the fluid is then drained out, bringing with it toxins and waste products. This procedure is performed 3-4 times each day, generally by the person themselves at home.

Currently only a minority of people with diabetes undergo CAPD. According to the US Renal Data System, 7.1% of people with diabetes perform CAPD, 75.4% receive maintenance haemodialysis and 17.5% undergo transplantation. The advantages of CAPD are that no access to the circulation is required and that removal of fluid and waste products occurs in a continuous fashion, reducing the risk of large swings in blood pressure and in the levels of waste products and toxins in the blood. The main disadvantage is the risk of infection being introduced into the abdominal cavity (peritonitis). A recent report suggested that the risk of death was 23% higher in people with diabetes on CAPD compared to those on haemodialysis, particularly in people with evidence of coronary heart disease. However, this may be because people with severe coronary heart disease are less likely to be suitable for haemodialysis because of vascular access problems.

Figure 6-4: CAPD Dialysis

Dialysis solution flows through a tube into the peritoneal cavity. The solution collects waste products and excess fluid from the blood and instils fresh dialysis solution back, so that the cleansing process can begin again

The used dialysis solution is drained from the peritoneal cavity, carrying away waste products and excess fluid from the blood out of the body

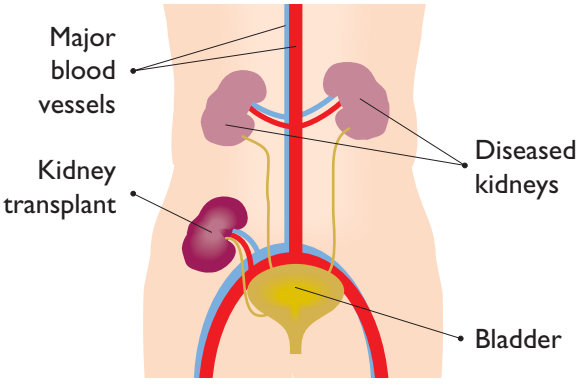


Adapted from: Renal Resource Centre, Australia

Transplantation

The survival rate of people with diabetes who receive transplants is not as good as people without diabetes who receive transplants. However, this is not an argument against transplantation. In fact, the benefits of kidney transplantation are greater in the person with diabetes compared to the person without diabetes. Reports have shown that the percent survival benefit of people with diabetes who receive transplants compared to haemodialysed people on the waiting list for transplantation is better than the respective survival advantage in those without diabetes.

Figure 6-5
Kidney transplant



Adapted from: Australian Kidney Foundation

In principle there are four transplant options:

- Kidney transplantation alone
- Combined kidney and pancreas transplantation
- Pancreas transplantation after kidney transplantation
- Kidney transplantation plus islet cell transplantation

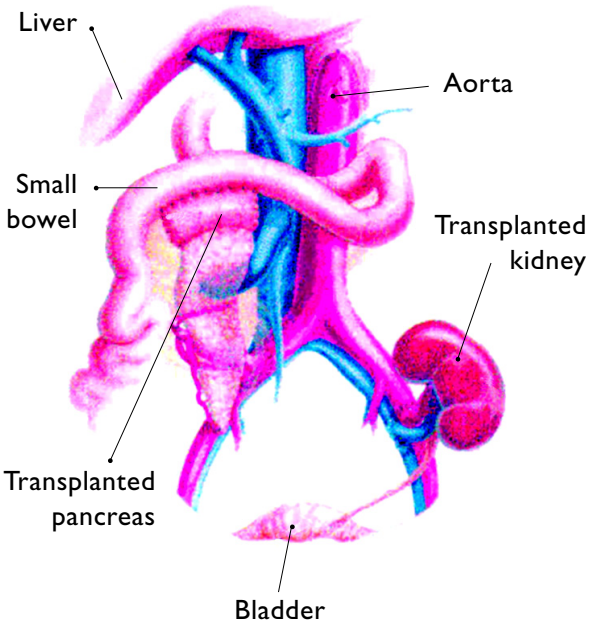
The last procedure is still experimental. One study compared patient survival and kidney graft survival in different transplant strategies and showed that combined kidney and pancreas transplantation provided the best results, almost comparable to those in people without diabetes. An alternative is to transplant a kidney first, usually from a live donor and then at a later stage perform pancreas transplantation.

Because of the very high risk of vascular disease in people with end-stage kidney

disease, prior to transplantation it is important to perform extensive investigations for coronary artery disease, stroke disease and peripheral vascular disease. An X ray dye study to directly visualise the arteries carrying blood to the heart is usually necessary. Vascular disease must be treated aggressively as necessary, including bypass surgery if indicated, before transplantation.

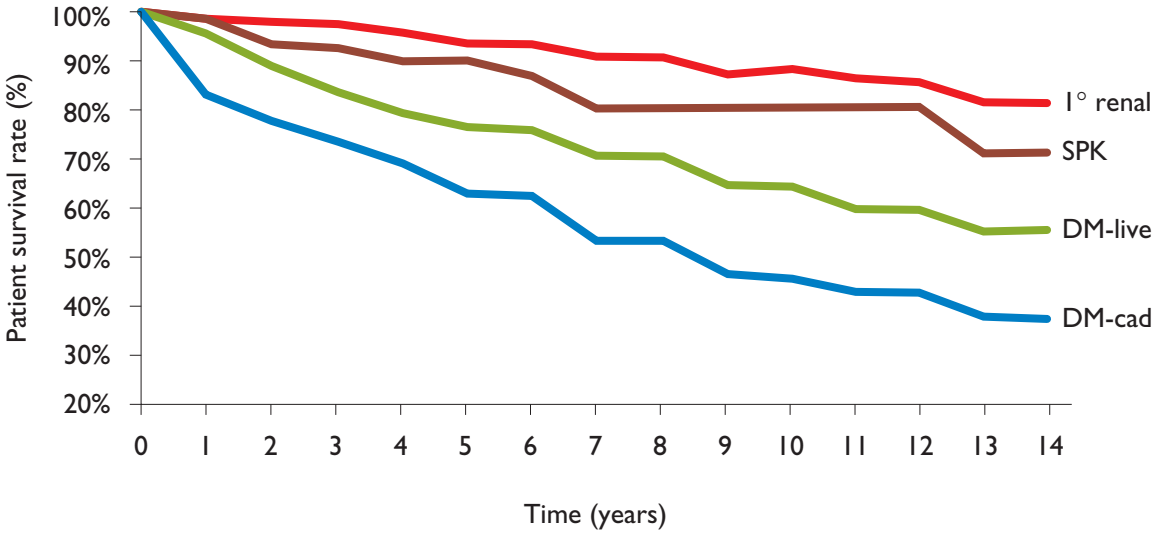
A transplanted organ will be recognized as "foreign" and attacked by the body's immune system, leading to organ rejection and failure. Large doses of drugs which suppress the body's immune system (immunosuppressants) are needed to prevent rejection. Previously, immunosuppressive treatments included large doses of **steroid** hormones. These steroid hormones gave rise to a number of complications including higher blood glucose levels and infections. In recent years, the outcome of transplantation in people with diabetes has been improved greatly by the use of novel low steroid or steroid free immunosuppressive drug regimens.

Figure 6-7
Image of the transplanted pancreas and the kidney



Courtesy of the University of Maryland Medical System

Figure 6-6
Estimates of the survival of the patient after simultaneous pancreas-kidney transplantation, (SPK) cadaveric, (DM-cad) or living donated kidney transplantation (DM-live) in people with diabetes compared to first cadaveric kidney transplantations (1° renal) in people without diabetes.



Adapted from Becker et al, 2000

The results of **islet** transplantation are still not good, although the Edmonton group has reported on successful islet transplantation achieving insulin independence in 7 consecutive people using a steroid free immunosuppressive regimen consisting of the drugs sirolimus, tacrolimus and taclizumab. This procedure is currently being evaluated in a multi-centre trial.

The Costs of Treating End-Stage Kidney Disease

The costs of dialysis or transplantation are high. Dialysis costs around $35,000 per person per year. Figures for a kidney transplant are $15,000 for the first year and then $6,000 per year thereafter. For a combined kidney-pancreas transplant the figure is higher. Thus efforts to prevent the development of end-stage kidney disease are extremely important.

Fact

Dialysis costs around $35,000 per person per year.

CONCLUSION

The Way Forward

Conclusion

The contents of this publication can leave the reader in no doubt as to the magnitude of the problems posed by diabetic nephropathy, which is a major cause of illness, death and healthcare costs. It is also clear that these problems are global in perspective and are worsening rapidly. The good news is that it is now possible to take action to slow or stop the development of diabetic nephropathy. However, there can be no doubt that now is the time to act.

Action must be taken on four levels:

1. **Prevention**
2. **Treatment**
3. **Education/Awareness**
4. **Research**

Prevention

Investment in primary and secondary prevention strategies is possibly the most effective measure in the long term, in both human and economic terms.

It is necessary to adopt an uncompromising multi-factorial approach to prevent or slow the progression of diabetic nephropathy. Fundamental aspects of prevention include:

Promoting a healthy lifestyle
Primary prevention of diabetes by lifestyle modification has the advantage that it will simultaneously help to reduce other risk factors for diabetic nephropathy such as hypertension and dyslipidaemia. The lifestyle changes required can be summarized simply by the IDF slogan "Eat Less, Walk More".

Early screening for diabetes and for diabetic nephropathy
This will enable intervention in the early stages of diabetic nephropathy, with prevention or slowing of progression to end-stage disease. However, it must be recognized that this may lead to a short-term rise in the use of resources as a result of an increased identification of new cases. This should be viewed as an advantage rather than a disadvantage, since early detection has obvious long-term benefits.

Investment in national programmes
National programmes aimed at primary and secondary prevention of diabetes and diabetic nephropathy can be integrated or linked with other health or environmental programmes.

Treatment

Adequate healthcare resources need to be made available not only for prevention, but also for the treatment of established diabetes and diabetic nephropathy. This means the provision of essential medical treatment so that the best possible prognosis can be ensured. At the very least we should aim for a significant decline in the numbers of people with diabetes reaching end-stage kidney disease. Access to dialysis or kidney transplantation should be available for all, with pancreas or islet cell transplantation as appropriate.

Education/Awareness

Education and awareness at all levels and strata of society is the key to success.

Governments
Decision makers need to be made aware of the importance of diabetic nephropathy. If measures are not taken to prevent diabetes and diabetic nephropathy, a global explosion of end-stage kidney failure due to diabetes is waiting to happen. Given the scope for prevention of both diabetes and diabetic nephropathy, investment in prevention can yield a high return.

Healthcare professionals
As reported in this book, the risk factors for diabetic nephropathy have been identified by many recent studies. A number of these risk factors are modifiable and it has been proven possible to reduce their impact dramatically. Healthcare professionals must be made aware of the importance of systematically and aggressively implementing these findings in clinical practice.

Public
People with diabetes in particular need to be aware of the risk factors for diabetic nephropathy and the measures that can be taken to decrease or delay their chance of developing diabetic nephropathy.

Research

Expanded basic and clinical research is needed in order to gain a better understanding of the factors that contribute to the development of diabetic nephropathy. In the future, new strategies should aim to identify those people with diabetes most at risk of diabetic nephropathy, with new therapies aiming to prevent the development of the condition.

Conclusion

It is hoped that *Diabetes and Kidney Disease: Time to Act* will prompt action on all these planes. Success can only be achieved through teamwork and collaboration. IDF and its member associations must continue to work together with organizations such as the International Society of Nephrology and WHO to halt the catastrophe of diabetic nephropathy and to make governments aware that action must be taken urgently.

ANNEX I

Studies of Diabetes and Kidney Disease

Studies

United Kingdom Prospective Diabetes Study (UKPDS)

This is one of the largest studies ever in type 2 diabetes. When blood glucose was aggressively lowered (obtaininig a HbA_{1c} level around 7%), the risk of retinopathy and nephropathy was 25% less. When high blood pressure was aggressively lowered there were major reductions in the risk of stroke, heart failure, blindness and kidney damage.

The Collaborative Study Group

The effect of angiotensin-converting-enzyme inhibition with captopril was evaluated in 207 people with type 1 diabetes and diabetic nephropathy as compared with 202 people given other drugs to lower blood pressure to the same degree. Captopril treatment was associated with a 50% reduction in the risk of death, dialysis, and transplantation that was independent of the small disparity in blood pressure between the groups.

EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID)

530 people with type 1 diabetes and normo or microalbuminuria were treated with an ACE inhibitor, (lisinopril) or with placebo. Lisinopril slowed the progression of kidney disease in people with no or little albuminuria, but the greatest effect was in those with microalbuminuria.

Heart Outcome Prevention Evaluation (HOPE) – MicroHOPE substudy

This study considered 3577 people enrolled in the HOPE study who had diabetes, previous heart problems but no kidney disease. People were given the ACE inhibitor ramipril or a placebo. Ramipril was beneficial for cardiovascular events and also reduced the risk of development of nephropathy by 25%. This treatment therefore provides cardiovascular and renal protective effect.

Appropriate Blood Pressure Control in Diabetes Study (ABCD)

The effects of intensive versus moderate blood pressure control on the incidence and progression of type 2 diabetic complications was evaluated in 470 people with diabetes with high blood pressure, treated with enalapril or nisoldipine. In this particular setting, both drugs obtained a stabilization of renal function, and intensive blood pressure control slowed the progression to incipient and overt diabetic nephropathy.

Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA)

This study of 590 hypertensive people with type 2 diabetes and microalbuminuria evaluated the protective effect on the kidney of the angiotensin II receptor antagonist irbesartan. The study demonstrated that treatment with irbesartan reduced the rate of progression to

macroalbuminuria, the hallmark of overt diabetic nephropathy.

Irbesartan Diabetic Nephropathy Trial (IDNT)

The study compared the effect of angiotensin II receptor antagonist irbesartan with a calcium channel blocker amlodipine and with placebo in 1715 hypertensive people with overt diabetic nephropathy. When a composite end point (deterioration of kidney function, need of dialysis or death) was considered, irbesartan reduced the risk by 20% in comparison with the placebo and 23% in comparison with amlodipine, even though all groups had their blood pressure controlled to the same degree.

Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL)

1513 people were involved in this study comparing losartan with placebo, both taken in addition to conventional antihypertensive treatment. The primary outcome was the composite of a doubling of the base-line serum creatinine concentration, end-stage kidney disease, or death. Losartan reduced the incidence of a doubling of the serum creatinine concentration by 25% and end-stage kidney disease by 28%, but had no effect on the rate of death.

MicroAlbuminuria Reduction with Valsartan Study (MARVAL)

This study involved 352 people with type 2 diabetes, microalbuminuria, with or without high blood pressure. Two drugs were compared: an angiotensin II receptor blocker, valsartan, and a calcium channel blocker, amlodipine. In 24 weeks, valsartan lowered the albumin excretion more effectively than amlodipine, and its effect was independent from the reduction of blood pressure.

The Diabetes Control and Complications Trial (DCCT)

In this study, the effects of tight blood glucose control on the development of the long-term complications of diabetes in type 1 diabetes were examined. In individuals with tight blood glucose control (HbA_{1c} approximately 7.5%), the risk of developing microalbuminuria was reduced by 39% and of proteinuria by 54% compared to individuals with less good control (HbA_{1c} approximately 9.0%), over 6.5 years.

ACE Inhibitors in Diabetic Nephropathy Trialist Group

In this paper, the results of all good-quality studies examining the effect of ACE inhibitors in individuals with microalbuminuria and type 1 diabetes were pooled and analysed together. The paper concludes that treatment with ACE inhibitors significantly reduced the numbers of people with microalbuminuria who progress to proteinuria and increased the number of people who return to normal albumin excretion.

The Steno 2 Study

Individuals with type 2 diabetes and microalbuminuria received either "multifactorial" management, with tight blood pressure, blood lipid and blood glucose control and intensive dietary and lifestyle education or routine diabetes care. Over 7.8 years, the risks of suffering a cardiovascular problem were reduced by 53% and of progressing from microalbuminuria to proteinuria by 60% in those having maultifactorial management compared to those receiving standard diabetes care.

Glossary

Glossary

ALBUMINURIA
A condition where albumin, a protein normally present in the blood, is secreted into the urine. Tiny amounts of albumin in the urine are called "microalbuminuria". Albuminuiria is a marker of kidney damage.

ALPHA BLOCKERS
Drugs which help lower blood pressure by dilating blood vessels

ANAEMIA
A deficiency of red blood cells and/or haemoglobin in the blood.

ANGINA
A condition marked by severe pain in the chest, often also spreading to the shoulders, arms and neck, caused by an inadequate blood supply to the heart.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR
ACE stands for angiotensin-converting enzyme. This oral medicine is used to lower blood pressure and to treat heart failure. It works by blocking the production of an enzyme that helps convert the protein angiotensin 1 into angiotensin 2, a protein that raises blood pressure by constricting blood vessels and promoting the retention of fluid. ACE-inhibitors make it easier for the heart to pump blood around the body. Studies have indicated that, particularly for people with protein (albumin) in the urine, ACE-inhibitors can help prevent or slow the progression of kidney disease even in the absence of hypertension.

ANGIOTENSIN II RECEPTOR ANTAGONISTS
A class of drugs used to treat high blood pressure, such as Losartan

ANGIOTENSIN II RECEPTOR BLOCKERS
A class of drugs used to treat high blood pressure, which shows similar properties as ACE inhibitors in protecting the kidney

ARTERY
A vessel carrying blood from the heart to the various part of the body

ATHEROSCLEROSIS
The process of thickening of the walls of arteries due to build up of fatty material (cholesterol), which can lead to slowing or blocking of blood flow.

AUTONOMIC NEUROPATHY
Disease of the nerves that are not under the person's conscious control. These nerves are present in all internal organs; autonomic neuropathy results in bad function of these organs

BETA BLOCKER
A class of drugs that lower high blood pressure and slow the heart rate. They have protective effects on the heart.

BLOOD PRESSURE
A measure of the force exerted by the blood upon the walls of the arteries as it is pushed around the body by the heart. This pressure is created when the heart beats, forcing blood around the body and also by the elastic resistance of the arteries themselves. The blood pressure is measured with an instrument called sphygmomanometer, which reports two numbers. The high number (systolic) shows the pressure created by the heart contracting or pumping out the blood. The lower number (diastolic) indicates the pressure between heartbeats. The blood pressure is measured in millimetres of mercury (mm Hg).

BLOOD VESSEL
An artery, vein, or capillary

CALCIUM CHANNEL BLOCKER
A drug used to lower high blood pressure. These can either be dihydropyridine or nondihydropyridine, depending on their exact chemical structure.

CAPILLARY
A very small blood vessel that joins an artery with a vein

CARDIOVASCULAR DISEASE
Cardiovascular diseases are diseases and injuries of the circulatory system: the heart, the blood vessels of the heart, and the system of blood vessels throughout the body as well as to (and in) the brain.

CEREBROVASCULAR DISEASE
Damage to the blood vessels of the brain, which may results in a stroke.

CHOLESTEROL
A fat of the body. It is absorbed from animal fat we eat and is also produced by the liver. Cholesterol circulates in the blood in form of particles called lipoproteins. Two main types of lipoproteins carrying cholesterol are called **HIGH DENSITY LIPOPROTEINS (HDL)** and **LOW DENSITY LIPOPROTEINS (LDH).** All these elements can be measured in the blood.

CIRCULATORY SYSTEM
The system formed by the heart and the blood vessels.

CLEARANCE
A measure of how well the kidneys are able to filter the blood and excrete waste and toxic products. It is determined by measuring the level of creatinine in the blood and the amount excreted in the urine over a period of time. The normal clearance is about 100 mls/min. When it falls to about 10 mls/min dialysis is needed. It is a more reliable indicator of kidney function than simple blood tests. The clearance of a substance varies with gender, age and body size. When comparing clearance values between individuals, results must be adjusted for gender, age and body size.

CLINICAL TRIAL
A study in which people are given (usually) a potentially innovative drug, to be tested against another innovative drug, or a well-known drug or a placebo.

CORONARY ARTERY
The blood vessels that bring oxygen and nutrients to the heart.

CORONARY ARTERY DISEASE
Damage to the heart caused by the narrowing or blockage of the coronary arteries. It often results in angina and heart attack.

CREATININE
A waste product which is filtered and excreted by the kidney

DIABETES MELLITUS
Diabetes mellitus is a chronic condition that arises when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin produced. This causes hyperglycaemia, which seriously damages many of the body's systems, especially the blood vessels and nerves. There are two main types of diabetes: type 1 diabetes and type 2 diabetes.

DIALYSIS
The process of cleaning wastes from the blood artificially - a job normally done by the kidneys. If the kidneys fail, the blood must be cleaned artificially with special equipment.

DIASTOLIC PRESSURE
see **BLOOD PRESSURE**

DIURETIC
A class of drugs that increases the urine output and helps the body to get rid of excess water and salt. They are very effective in lowering blood pressure, either alone or in conjunction with other drugs.

DYSLIPIDAEMIA

This term refers to abnormal levels of lipids (fats) in the blood.

END-STAGE KIDNEY DISEASE

When the kidneys no longer perform their function and dialysis or transplantation is needed. See also **KIDNEY FAILURE**.

GLOMERULUS

A small corpuscle of the kidney where the filtration of water, salts and other small molecules takes place. There are approximately 2 million glomeruli in both kidneys.

GLUCOSE

A specific form of sugar present in the bloodstream. "Blood sugar" always refers to blood glucose.

GLYCAEMIA

The presence of glucose in the blood

HAEMOGLOBIN A_1C (HBA_{1C})

Haemoglobin is the protein in the red cells that carries the oxygen to the cells. HbA_{1c} corresponds to a small part of haemoglobin which joins with glucose in the blood. The measure of HbA_{1c} reflects the average blood glucose level during the last three months.

HAEMODIALYSIS

A modality of renal replacement therapy, so called "washing" of the blood by pumping a persons' blood through an apparatus where blood is separated from the washing fluid by a membrane that permits the transfer of "toxic" substances but prevents the transit of proteins and blood cells (semi-permeable membranes).

HEART FAILURE

Heart failure occurs when the heart muscles become overworked from the strain of pushing blood through narrow, hard blood vessels.

HIGH DENSITY LIPOPROTEIN (HDL)

One of the forms of cholesterol circulating the blood. HDL protects against cardiovascular disease, so that low levels of HDL increase cardiovascular disease. Also see **CHOLESTROL**

HORMONE

Synthesized in glands, hormones are chemical signaling molecules which have a specific regulatory effect upon the activity of body tissues. Hormones are transported around the body in the blood so that they can act on tissues at a distance from the gland in which they were produced.

HYPERGLYCAEMIA

A raised level of glucose in the blood.

HYPERTENSION

Persistently elevated blood pressure. In adults, a systolic blood pressure greater than 140 mm Hg of mercury or a diastolic blood pressure greater than 90 mm Hg of mercury is indicative of hypertension.

HYPOGLYCAEMIA

A low level of glucose in the blood.

IMPAIRED FASTING GLYCAEMIA (IFG)

Raised fasting levels of glucose

IMPAIRED GLUCOSE TOLERANCE (IGT)

Blood glucose levels that are higher than normal but below the level of a person with diabetes

INCIDENCE

The number of people newly found to have a disease, usually per year, in a given population.

INSULIN

A hormone which enables the body cells to absorb glucose from the blood and use it for energy. It is produced by the beta cells of the pancreas. It also regulates lipid and protein metabolism.

ISLET

A portion of tissue structurally distinct from surrounding tissues

KIDNEY FAILURE

Inability of the kidneys to perform all their tasks. At its last stage, called end-stage renal or kidney disease, people require a kidney replacement therapy, i.e. dialysis or transplantation.

LACTIC ACID
Acid produced in the muscle tissues during strenuous exercise.

LOW DENSITY LIPOPROTEIN (LDL)
see **CHOLESTEROL**

MACROALBUMINURIA
Large amounts of the protein albumin in the urine

MACROVASCULAR DISEASE
Disease of the large blood vessels. It is called also macroangiopathy.

MALNUTRITION
Lack of proper nutrition (see **NUTRITION**)

METAFORMIN
Drug used to lower blood glucose

MICROALBUMINURIA
In the initial stages of renal damage, albumin, i.e. a specific serum protein, is excreted in small (micros = small) amounts which are not detected by routine measurements of urinary protein, but can be assessed by using specific assays for urinary albumin. Detection of microalbuminuria is important because it is a powerful predictor of future cardiovascular events and kidney disease.

MICROVASCULAR DISEASE
Disease of the small blood vessels. It is also called microangiopathy.

MORBIDITY
The condition of having a disease. The morbidity rate is the number of cases of disease occurring within a particular number of the population.

MORTALITY
The state of being subject to death. The mortality rate is the number of deaths in a given area or period, or from a particular cause

MYOCARDIAL INFARCTION
Also known as heart attack; results from permanent damage to an area of the heart muscle. This happens when the blood supply to the area of the heart is interrupted because of narrowed or blocked blood vessels. In the majority of cases this is due to **CORONARY ARTERY DISEASE**.

NEPHROPATHY
Disease caused by damage to the small vessels of the kidneys. It results in loss of protein in the urine, high blood pressure and progressive kidney failure.

NEPHROTIC SYNDROME
Leaking of very large amounts of proteins through the kidney into the urine. So much protein is lost in the urine that the protein level in the blood falls below normal and the person develops ankle and leg swelling.

NEUROPATHY
Diabetic neuropathy refers to damage to the nerve fibres caused by diabetes. Long nerves are most affected and so the process is usually first noticed in the feet with a numbness and loss of sensation.

NORMOALBUMINURIA
Having a regular amount of the protein albumin in the urine

NORMOTENSIVE
Having a blood pressure within the normal range for an individual's age and sex. (See **BLOOD PRESSURE**)

NUTRITION
The process by which the body uses food necessary for growth, energy production and repair of tissues.

OBESITY
When people have 20 percent (or more) extra body fat for their age, height, sex, and bone structure. Fat works against the action of insulin. Extra body fat is a risk factor for diabetes.

ORAL HYPOGLYCAEMIC AGENTS
Drugs that lower the level of glucose in the blood. They cause the cells of pancreas to release more insulin. They work in some people with type 2 diabetes if their pancreas still produces some insulin. They can help the body

in several ways such as causing the cells in the pancreas to release more insulin.

OVERT

When a disease is plainly or readily apparent.

PANCREAS

An organ which produces insulin. The pancreas is situated behind the lower part of the stomach.

PERIPHERAL NEUROPATHY

Inflammation of the nerves in the outlying parts of the body.

PERIPHERAL VASCULAR DISEASE

Disease of the arteries. Usually the most affected are the arteries of the legs, and the symptom is pain while walking. It may cause such a severe reduction of blood supply to the lower limbs to cause gangrene, i.e. death of tissue, which requires amputation of the limb.

PLACEBO

A substance that has no therapeutic effect and is used as a control in testing new drugs.

PREVALENCE

The number of all people with a disease in a given population.

PRIMARY PREVENTION

Protecting susceptible individuals from developing diabetes. It therefore has an impact by reducing both the need for diabetes care and the need to treat diabetic complications. While there is yet no conclusive evidence to suggest that type 1 diabetes can be prevented, primary prevention of type 2 diabetes is potentially possible.

PROTEINURIA

Loss of proteins in the urine. It is often used interchangeably with **ALBUMINURIA**, although proteinuria means that not only albumin but also other proteins are lost in the urine

RENAL BIOPSY

In order to correctly assess the type of lesions within the kidney, a small kidney sample is taken using puncture with a needle under ultrasonographic control. Renal biopsy is not regularly needed in the person with diabetes, but may be useful if renal disease other than diabetic nephropathy is suspected.

RENAL TRACT

This is the means by which urine is formed and excreted. It begins in the glomerulus-where urine is formed by filtration of the blood, collected by small tubules (which concentrate the urine) and which join to form the pelvis of the kidney. The urine drains from each kidney by a tube called the ureter, which carries urine into the bladder to be expelled via the urethra.

RENIN-ANGIOTENSIN SYSTEM

This is the hormone or messenger system which helps control blood pressure and the pressure inside the kidney.

RETINOPATHY

Changes in the retina of the eye which may cause visual impairment and blindness. Both type 1 and type 2 diabetes can lead to damage to the small blood vessels that supply blood to the retina. Early stages of diabetic retinopathy are known as nonproliferative or background retinopathy. At a more advanced stage of the complication, called proliferative retinopathy, the retina grows new blood vessels to replace those that are damaged. Vision can seriously deteriorate if scar tissue develops as a response to the growth of new blood vessels and consequent bleeding. This process can cause the retina to become detached, resulting in blindness.

SERUM CREATININE

The amount of the substance creatinine circulating the blood. Creatinine is a waste product which is filtered and excreted by the kidney. As the kidneys fail, less creatinine is excreted and the level in the blood rises. In general, the higher the level of creatinine, the greater degree of kidney failure. However, a more accurate test to assess the severity of kidney failure is the rate at which creatinine is cleared from the blood by the kidney. This is called **clearance**.

STATIN

A drug that lowers blood cholesterol.

STEROID

A large class of compound with a characteristic structure. They have many functions in the body. Some act as chemical messengers or hormones, being made by one organ in the body and carried in the blood stream to another part of the body where they have specific effects.

STROKE

A sudden loss of function of the brain caused by interruption of blood flow because of obstructed artery

SUDDEN DEATH

This term refers to the death of a person from an abrupt loss in heart function

SYSTOLIC PRESSURE

See **BLOOD PRESSURE**

TRANSPLANTATION

In the person with diabetes either the kidney or the kidney plus the pancreas may be transplanted. Kidneys can be obtained from life donors or cadaveric donors. A pancreas can be obtained usually only from a cadaveric donor. The major problem is the differences in tissue type (HLA antigens), i.e. that the body recognizes the transplant as "foreign", so that it launches a rejection reaction which must be suppressed by immunosuppressive treatment.

TRIGLYCERIDE

The major form of fat made in the liver. Most of the fat we eat is composed of triglycerides. The rest is **CHOLESTEROL**.

TYPE 1 DIABETES

Type 1 diabetes occurs most frequently in children and adolescents, but is also found in adults. About 10% of people with diabetes have type 1. The symptoms vary in intensity and include excessive thirst, excessive passing of urine, weight loss and lack of energy. Insulin is a life sustaining medication for people with type 1 diabetes, who require daily insulin injections for survival.

TYPE 2 DIABETES

Type 2 diabetes occurs most frequently in adults, but it is increasingly being diagnosed in children. Some people with this type of diabetes have no early symptoms and are only diagnosed several years after the onset of the condition, when various diabetic complications are already present. Type 2 diabetes is usually controlled by diet, exercise and oral hypoglycaemic agents. Insulin injections may also be required.

ULTRASOUND EXAMINATION

A simple scan test which is used to visualise the kidneys and bladder.

URINE ALBUMIN EXCRETION

The amount of the protein albumin which leaks through the kidney into the urine.

VASCULAR DISEASE

Disease relating to or affecting the blood vessels. (See also **MICROVASCULAR DISEASE** and **MACROVASCULAR DISEASE**)

VEIN

A vessel carrying blood back from various parts of the body to the heart.

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