

DIABETES MELLITUS.

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OVERVIEW

Diabetes is a huge subject, which occupies the working life of several thousand health workers in this country alone; to expect to cover it all in one module is therefore unrealistic. The module has been designed to be all-inclusive, so although it is long, there should be no need to resort to any literature searches, unless of course you wish to.

Our objectives for this module are that by the end of it you will be able to:

- * Understand normal glucose metabolism and homeostasis
- * Explain how this process goes wrong in diabetes
- * Appreciate the importance of diabetes care to patients, the health care systems and society
- * Describe the classification of diabetes and how it is diagnosed
- * Understand how diabetes gives rise to microvascular and macrovascular complications.
- * Discuss the treatment options, which are available in diabetes.

THE DEFINITION AND CLASSIFICATION OF DIABETES:

Diabetes Mellitus is a disorder caused by the total (or relative) absence of insulin, which manifests clinically as an elevated blood glucose. The classification of diabetes mellitus has been a major discussion point over the last few years. It has been increasingly recognised that the old classification system based upon a patients' dependence on insulin was misleading; under the old system patients were either classified as either Insulin Dependent Diabetes Mellitus (IDDM) or Non Insulin

Dependent Diabetes Mellitus (NIDDM). In 1998, a new classification system based upon the aetiological factors at work in diabetes was proposed by the WHO and we have listed it below: this has now become the accepted system for classifying diabetes mellitus (1).

Type 1 diabetes: immune mediated and idiopathic forms of β cell dysfunction, which lead to absolute insulin deficiency. This is an autoimmune mediated disease process which gives rise to absolute deficiency of insulin and therefore total dependency upon insulin for survival.

Type 2 diabetes: disease of adult onset, which may originate from insulin resistance and relative insulin deficiency or from a secretory defect. This is a disease, which appears to have a very strong genetic predisposition and is caused by a combination of inadequate insulin secretion and an insensitivity of the body tissues to insulin so leaving patients with this condition relatively deficient in insulin.

Type 3 diabetes: this covers a wide range of specific types of diabetes including various genetic defects in insulin action, and diseases of the exocrine pancreas.

Type 4 diabetes is gestational diabetes.

THE EPIDEMIOLOGY OF DIABETES.

The prevalence of diabetes of all types is approximately 3% in the UK. It is estimated that there may be a further 2% of the population with undiagnosed diabetes.

The relative prevalence of diabetic patients in the UK by classification is:

Type 1 DM	25% of cases
Type 2 DM	70% of cases
Types 3&4 DM	5% of cases

Morbidity

Diabetes places a huge burden of illness on sufferers and society. People with diabetes in the age group 45-64 years are 23 times more likely to be registered blind than the non diabetic population of the same age. Diabetic retinopathy is the lead cause of blindness in this age group. Diabetes often affects the kidneys and up to 40% of people who develop Type 1 diabetes before the age of 30 years can expect to develop diabetes related nephropathy. A significant number of these will progress to renal failure requiring long term renal dialysis treatment. 30% of people with diabetes develop diabetic neuropathy leading to a range of problems including from foot ulceration, sexual difficulties, cardiac arrhythmias and sudden death.

Mortality

It is thought that 20 000 people per year die prematurely because of diabetes associated disease. Most of these deaths are from the macrovascular complications of diabetes such as myocardial infarcts and cerebrovascular accidents. The number of people dying prematurely in the diabetic population is double that of the non diabetic population.

Clinical Features and Aetiology

Type 1 diabetes typically presents in the teens with a short history of weight loss, incredible thirst and polyuria (passing lots of urine). Such patients are often thin, there is very often no family history of diabetes and although the cause of the illness is not known, it is thought to be triggered by a viral infection.

Type 2 diabetes typically presents later in life. Such patients are often overweight at diagnosis and there is often a strong family history of the disease. It is not known why the disease develops but it may be related to over-eating. In contrast to type 1 diabetes, patients with type 2 diabetes are often asymptomatic when it is diagnosed and the diagnosis is often made whilst a doctor is investigating some other complaint.

NORMAL CARBOHYDRATE METABOLISM

Diabetes Mellitus is a condition characterized by defective insulin utilisation by the body, which manifests itself as raised blood glucose. To understand Diabetes Mellitus it is first essential to have an understanding of how the body normally deals with glucose, which is the most important sugar in human metabolism. You have been supplied with a supplement, which briefly describes glucose homeostasis and in particular the role and importance insulin within it. We suggest you read this now and work through the questions in the supplement too. Once you have done so it may be helpful to write yourself a brief summary of the actions of insulin before you proceed with the remainder of this module, as a thorough understanding of the role of insulin is key to understanding diabetes.

THE DIAGNOSIS OF DIABETES MELLITUS

Diagnosis and diagnostic tests

The body usually is able to keep glucose concentrations stable. The normal fasting blood sugar is usually between 3.5-6.7mmol/l. After a meal it would rarely exceed

8mmol/l. Normally there is no glucose in urine since the normal threshold above which glucose would appear in the urine would be 10mmol/l. Below a concentration of 10mmol/l the kidneys reabsorb glucose back into the blood stream and so glucose does not appear in the urine unless the blood concentration of glucose is high. Dip-sticking urine for the presence of glucose is therefore often used as a screening test for diabetes mellitus.

The diagnosis of diabetes mellitus is made by finding a fasting blood glucose of over 6.7mmol/l or a random glucose of >10mmol/l. If a patient presents with symptoms of diabetes and is found to have a single very high glucose measurement eg >15mmol/l then this can be diagnostic. More commonly it would be appropriate to ask the patient to fast overnight and attend for a fasting blood glucose to be taken the next morning. Ideally this should be performed on two occasions before diagnosing diabetes.

If there is any doubt about the diagnosis then a further test can be performed. This test is called the oral glucose tolerance test and it measures how the body responds to a glucose load. The patient is asked to fast overnight and then attends for the test. The patient has a blood glucose level taken and is then given a drink, which contains 75gm of glucose. After two hours another blood sample is taken. From the results of the glucose tolerance test the patient can be either diagnosed as having diabetes, impaired glucose tolerance or no abnormality of glucose handling.

Pause for thought.

Before you move on be sure you can answer the following questions:

1. What is diabetes mellitus?
2. According to the new classification, what are the two commonest types of diabetes mellitus in the UK?
3. A 14 year old boy is taken by his mother to the doctor with a 2 week history of being unwell, losing weight and drinking pints and pints of water. He also admits

to going to the loo very frequently. He is found to have glucose in his urine and the blood glucose is also high. The doctor diagnoses diabetes. Based on the new classification, which type of diabetes do you think he has?

4. A 70 year old man attends his eye casualty with a sixth nerve palsy. The gentleman himself is overweight but otherwise proclaims himself fit and well. Urine dipstick suggests diabetes, which is confirmed by a blood test. What type of diabetes is this gentleman likely to have? Whilst doing his fundus photography he asks you if his type of diabetes runs in the family as he wonders if he should tell his sister to get checked. What is your answer?

THE COMPLICATIONS OF DIABETES:

The complications of diabetes can be classified as:

1. ACUTE PROBLEMS: (Otherwise termed the diabetic medical emergencies)

Diabetic ketoacidosis.

Hypoglycaemia.

2. THE CHRONIC COMPLICATIONS OF DIABETES:

Microvascula complications.

Macrovascular complications.

1. THE ACUTE COMPLICATIONS OF DIABETES.

These are beyond what you are expected to know for this module but because there is sometimes confusion about how to deal with a diabetic patient who becomes unwell in the clinic setting we have included a short description of the two most important acute emergencies, diabetic ketoacidosis and hypoglycaemia. The acute diabetic emergencies can be found in supplement 2.

2. THE CHRONIC COMPLICATIONS OF DIABETES.

These are the complications that occur because of the chronic exposure of the body's tissues to hyperglycaemia, hypoinsulinaemia or their associated metabolic disturbances. The potential chronic complications of diabetes are those that most people with diabetes fear; however over 40% of patients with type 1 diabetes survive for over 40 years after the disease has been diagnosed, half of them without developing significant complications.

The chronic complications of diabetes are classified as follows:

1. MICROVASCULAR (microangiopathic)

- *Diabetic Retinopathy.
- *Diabetic Neuropathy.
- *Diabetic Nephropathy.
- *Diabetic skin problems (the “Diabetic foot”)

2. MACROVASCULAR.

- *Accelerated propensity to atherosclerosis/atheroma
 - Peripheral vascular disease/ coronary heart disease.
 - Myocardial infarction.
- * Arteriosclerosis.
 - Hypertension and cerebrovascular disease.

3. OTHER ASSOCIATED METABOLIC ABNORMALITIES.

- *Hypercholesterolaemia.

4. INCREASED SUSCEPTIBILITY TO INFECTION.

For reasons not totally understood people with diabetes have an increased susceptibility to bacterial infection. This is an important factor in the development of diabetic foot ulceration and explains why people with diabetes have a much higher risk of limb amputation compared to the normal population.

1. MICROVASCULAR (Microangiopathic) disease.

This disease is characteristic of and specific to diabetes. It is a disease which leads to damage of the capillary wall and its principle clinical manifestations are;

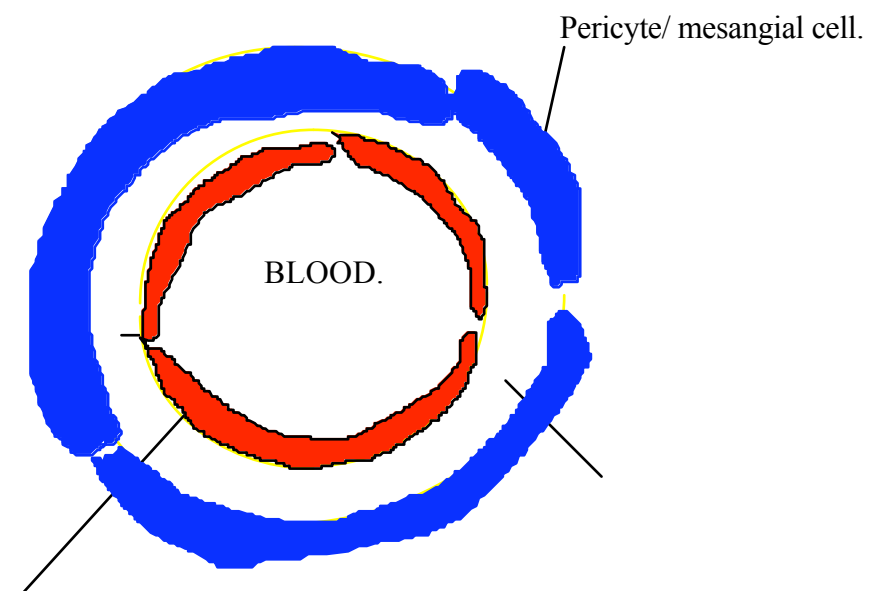
1. Diabetic retinopathy.
2. Diabetic neuropathy.
3. Diabetic nephropathy.
4. It also has a significant impact on the development of diabetic foot ulcers.

Before discussing these, it is worth reviewing the structure of the capillary wall as an understanding of how it functions in health helps understand how it goes wrong in diabetes.

The normal capillary wall.

The normal capillary wall comprises the basement membrane, which is sandwiched between the endothelial cells, which lie on the inside and specialized supporting cells (pericytes or mesangial cells) on the outside. The capillary wall functions as a highly specialized filter, which regulates the transfer of a variety of substances between the blood stream and the tissues immediately surrounding it. This filter has two principle components, the specialized supporting cells and the basement membrane. The supporting cells surrounding the capillary basement membrane have tiny pores in them, which form a mechanical filter. The basement acts both as a mechanical filter augmenting that of the supporting cells but in addition it also has an intrinsic electric potential which acts as an electrical barrier to particles of the same electrical polarity.

Diagram 1. The normal capillary wall.

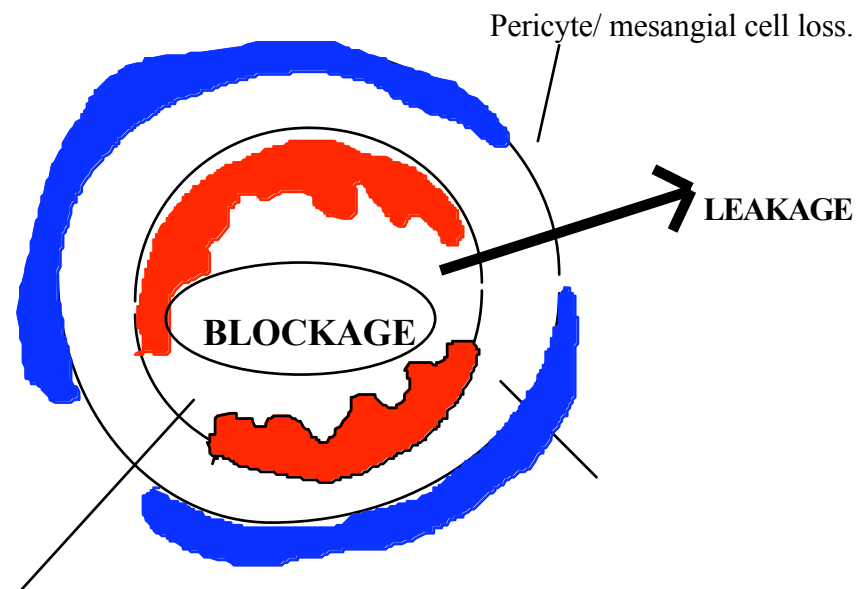


Endothelial cell.

With time we know that the capillary wall of people with diabetes is structurally altered in 3 ways (see diagram 2):

1. Pericyte/ mesangial cells die and are lost effectively opening up holes in the previously tight physical filter.
2. The basement membrane becomes thickened and ceases to work either as an effective physical or electrical barrier.
3. Endothelial cell changes occur: The endothelial cells lining the inside of the capillary start to express receptors, which encourage elements of the bodies clotting system to stick to them. The blood of people with diabetes also becomes more sticky and as a consequence of these two processes the capillaries get clogged up with small blood clots and are effectively destroyed; this process is sometimes termed “capillary drop out”.

Diagram 2. The capillary wall changes in diabetes.



Basement Membrane thickening

Endothelial cell loss and endothelial changes which makes platelets in blood more likely to stick to them leading to blockage of the vessel.

How do these changes cause disease? (see diagram 2)

1. The combination of the basement membrane changes and the loss of pericytes/ mesangial cells mean the capillaries **leak** profusely and substances that previously were held in the circulation spill into the surrounding tissues. In the retina this process manifests as retinal *oedema*; if this occurs at the macula it can lead to profound visual disturbance and is one manifestation of diabetic maculopathy. In the kidney the renal glomeruli leak proteins and cease to filter waste products of metabolism effectively.
2. Progressive loss of capillaries as they get **blocked** off with small blood clots “capillary drop” out means that the tissues which they are supposed to supply slowly get starved of blood; the tissues are said to be *ischaemic*. As the tissues become more ischaemic they cease to function normally and this is the mechanism underlying proliferative retinopathy, ischaemic maculopathy and diabetic neuropathy.

What causes these microvascular changes in diabetics?

The cause of the structural and functional changes outlined above is complex and not fully understood. However, we are able to conclude with certainty that hyperglycaemia does play a significant role as there good evidence from two large epidemiological studies; the Diabetes chronic complications trial (DCCT) and the UK Prospective Diabetes study (UKPDS); (2,3), that the prevalence of microvascular complications in both type 1 and type 2 diabetics falls dramatically with tight glycaemic control. These two studies have been hugely influential in the management

of diabetes as they have shown a relationship between hyperglycaemia, microvascular disease and the potential benefits of treatment. We will revisit these papers later! Hyperglycaemia alone, however cannot be the whole story because a significant number of diabetic patients never develop severe microvascular disease. Inherited susceptibility must therefore also be very important in determining who develops what.

1. DIABETIC RETINOPATHY.

Retinopathy is a readily visible sign of widespread microvascular disease. After 20 years of diabetic life virtually all patients will have evidence of background retinopathy, but by contrast proliferative changes only ever develop in approximately 30% of people with diabetes, and they may represent a subset with a specific inherited susceptibility to the disease. Diabetes may threaten sight by one of two mechanisms:

1. Macular oedema:

As detailed earlier, increased vascular permeability is a feature of microvascular disease. Certain individuals appear to be predisposed to developing capillary leakage at the macular and this leads to tissue oedema, structural disruption of the photoreceptors and ultimately to visual disturbance. These leaking capillaries can be identified by fluorescein angiography and photocoagulated with focal laser. Once the leaking areas have been successfully treated the oedema resolves with usually some improvement in vision.

2. Retinal ischaemia:

Retinal ischaemia can impact on vision in one of two ways

1. The retina's response to ischaemia is to generate angiogenic factors, which stimulate new vessel formation with the intention of reperfusing the ischaemic areas.

Unfortunately these new vessels are unsupported and therefore have a propensity

to bleed. Visual loss due to preretinal or vitreous haemorrhage is the immediate consequence of this; the long term sequelae includes the proliferation of fibroblasts, the formation of fibrotic membranes, retinal traction and ultimately retinal detachment. Ischaemic changes are also responsible for one of the late and very serious conditions seen in people with diabetes; rubeosis iridis. Pan-retinal photocoagulation (PRP) laser therapy is intended to reduce the propensity to new vessel formation by destroying the ischaemic retina rendering it incapable of synthesizing the angiogenic factors that drive the whole process.

2. Retinal ischaemia at the central macula leads to loss of neural elements at the fovea. This manifests clinically as the loss of central vision; ischaemic diabetic maculopathy. Unlike macular oedema, ischaemic maculopathy is untreatable.

The classification of Diabetic retinopathy is beyond the scope of this discussion and the reader is directed to the chapter on diabetic retinopathy in: JJ. Kanski: Clinical Ophthalmology (4th Edition 1999); publ: Butterworth/ Heinmann.

2. DIABETIC NEUROPATHY.

Diabetes may affect both the somatosensory system causing a variable sensory and motor deficits and the autonomic nervous system. About 30% of diabetic patients have evidence of neuropathy on formal testing but in the vast majority it is asymptomatic. Diabetic neuropathy may manifest clinically in one of two ways. A focal (or occasionally multifocal) acute neuropathy in which individual nerves are picked off by discrete, presumably, vascular insults; an acute sixth nerve palsy would be an example. The other clinical manifestation is that of a diffuse, often symmetrical pattern of sensory loss in which the longest nerves are often the most susceptible. This explains why the characteristic pattern of sensory loss seen in people with diabetes is that of a “glove and stocking” distribution. This type of neuropathy is insidious in its onset, gradually progressive and with time leads to the loss of cutaneous and proprioceptive sensation in a glove and stocking pattern.

Causative factors in diabetic neuropathy are thought to include hyperglycaemia and vascular damage. Why hyperglycaemia should cause and exacerbate neuropathy is not fully understood but glycosylation of proteins, a structural change which has profound functional consequences, has been implicated. Vascular damage appears to occur by two mechanisms both of which are manifestations of microvascular disease. Diffuse occlusion of the capillaries supplying the nerves; the vasa nervorum, may lead to its progressive ischaemia and loss of function; (this is thought to be the pathophysiological process behind the slowly progressive glove and stocking neuropathies). The acute palsies of the larger peripheral and cranial nerves may be due to sudden occlusion of larger vessels causing localised infarction of the nerve.

3. DIABETIC NEPHROPATHY.

Diabetic nephropathy is the commonest cause of premature death in type 1 diabetes and in the UK it accounts for a quarter of all patients with end stage renal failure requiring dialysis. Diabetic nephropathy is a specific microvascular disease affecting the renal *glomerulus*. Nephropathy is one facet of generalised microvascular damage and it is almost always associated with retinopathy.

The kidneys are the bodies purifying system and our entire blood volume passes through them many times a day. The kidneys role is to filter the waste products of metabolism out of the blood, excreting them in the form of urine, whilst at the same time retaining potentially useful substances such as proteins. The principle site of this filtration is a highly specialised capillary structure called the renal glomerulus and as described above its filter is comprised of the glomerular basement membrane and mesangial cells. In diabetes this filter becomes seriously disrupted with two consequences; it starts to let proteins through which are lost in the urine (proteinuria), and it fails to excrete waste products efficiently. This microvascular disruption of the kidneys renal glomeruli is known as diabetic nephropathy, and the most reliable

clinical indicator of diabetic kidney damage is whether or not the kidneys are constantly leaking proteins. Typically once diabetic nephropathy is established the picture is one of a slow decline of progressive protein leakage (as more mesangial cells are lost) and eventually “renal failure” when the kidneys are no longer able to excrete the bodies waste products.

End stage diabetic nephropathy can have a profound effect on vision. Patients with diabetes who are in renal failure, tend to progress rapidly to proliferative retinopathy, and once this is established it is often very resistant to treatment. Patients with diabetic nephropathy also have a peculiar propensity to macular oedema and this too often proves refractory to treatment.

There are now numerous large epidemiological studies, which show that the speed of progression of renal failure in those patients who are going to develop it can be slowed by aggressively treating high blood pressure (2-5). This probably represent one of the biggest advances in diabetic care of the last decade and it is now standard practice within the diabetic clinics to measure patients blood pressure regularly.

Once end stage renal failure has intervened patients have to be maintained on renal dialysis treatment; often requiring hospital treatment every 2 or 3 days, to clear the bodies waste products. Renal transplant surgery can be very successful in selected patients, but typically premature death is 10 times higher in diabetic than non-diabetic patients receiving renal transplant therapy.

4. SKIN AND THE DIABETIC FOOT.

The microvascular changes within the skin deserve brief mention. Capillary closure within the skin mean that injuries often heal very slowly if at all and this has profound implications for the care of foot ulcers. Foot care is an important part of the care of the diabetic patient as a small ulcer may rapidly progress and threaten the viability of

the foot itself. Peripheral neuropathy means patients are often unaware of skin trauma making foot ulceration more common. Their loss of pain sensation may be compounded by poor eye sight, if the patients can't see the ulcers it goes unnoticed and untreated. As people with diabetes have an increased propensity to bacterial infection, any untreated skin wound can rapidly get infected and because of poor circulation once infection has set in it often spreads very rapidly and responds slowly if at all to treatment. To put this into perspective a patient with a diabetic foot ulcer requiring antibiotic treatment may be hospitalised for months waiting for a relatively small ulcer to heal and in many cases amputation is often the only way of dealing with the infected tissue. This explains why the rate of limb amputation in diabetics is so much greater than in the general population.

Pause for thought:

Before moving on, be sure you can answer the following questions.

1. In diabetic microvascular disease what are the three structural changes that are seen in the capillary wall that means the capillaries leak and get clogged up?
2. An old gentleman who you are photographing has been given a diagnosis of *macular ischaemia* with a vision of just 1/60. Just as you are nearing the end of your assessment he happens to say that his diabetic friend recently lost some vision in his left eye, which was successfully treated with laser treatment. It transpires that his friend had diabetic *macular oedema*. The gentleman you are assessing then asks why we cannot treat his eye in the same way. How do you answer his question?
3. A 60 year old, diabetic lady presents to eye casualty with an acute 3rd nerve palsy. Her daughter unfortunately was trying to find somewhere to park and therefore missed her mother's consultation with the doctor. She is desperate to find out why her mum has suffered this problem and therefore asks you. What is your response, what is the aetiology of such nerve palsies?

4. You are assessing a young man with type 1 diabetes, who you see from their records is known to have renal impairment. He happens to mention that he has a bit of blood pressure but he doesn't feel ill and therefore doesn't bother to take his tablets. Does tight blood pressure control in patients with diabetic kidney disease make any difference to the long-term outcome of the disease?
5. Whilst examining an elderly patient who is known to have type 2 diabetes you cannot but notice a large bandage wrapped around her right foot. When you ask what happened she says she stood on a nail the previous week and a kindly neighbor put the bandage on. The bandage has not been changed since but she is adamant that every thing is OK because she cannot feel any pain. You note her visual acuity is 6/36 either eye. Why may she feel no pain? Why are people with diabetes prone to getting problems with their feet? If the foot is infected do you think it will respond quickly to treatment?

2. MACROVASCULAR DISEASE.

Although microvascular disease is only seen in people with diabetes, they are also predisposed to developing atherosclerosis and arteriosclerosis, diseases of the large blood vessels that affect the general population. Compared to the general population, people with diabetes get both these diseases at a younger age and when they do they are often more severely affected. This explains why they are at least twice as likely to develop complications associated with macrovascular disease, such as heart attacks, than non diabetics.

ATHEROSCLEROSIS.

Atherosclerosis is the deposition of plaques of a mixture of lipid, and fibrovascular tissue (atheroma) on the inside of the vessel wall of the large blood vessels. Once

established these plaques usually slowly increase in size with two important clinical consequences:

1. Chronic ischaemia. (Coronary heart disease and peripheral vascular disease)

As the atheromatous plaques get bigger the lumen of the blood vessel gets narrower. Over time the total blood flow along the affected vessel is gradually reduced leading to ischaemia of the tissue it supplies. This is the pathological process behind the development of coronary heart disease and peripheral vascular disease.

eg.

Coronary heart disease. At rest the narrowed blood vessel may be able to deliver enough blood to satisfy the requirements of the myocardium (muscle of the heart), but as soon as the patient starts to exercise the narrowed blood vessel can no longer supply the myocardium all the blood it demands and the myocardium becomes ischaemic. The patient experiences this process as chest pain “angina”.

2. Acute vessel ischaemia (Myocardial infarction).

Atheromatous plaques may rupture. Plaque rupture activates the body's intrinsic clotting system, which forms a blood clot over the rupture site. This clot may completely block the affected vessel leading to acute ischaemia and cell death of all the tissues supplied by that vessel. Plaque rupture in the coronary vessels is the commonest cause of acute myocardial infarction (heart attack).

ARTERIOSCLEROSIS.

Arteriosclerosis is a histological term meaning the loss of elastic tissue from the walls of the medium and large arteries (arterio-), which consequently become rigid (-sclerosis). As elastic tissue is lost the arteries become increasingly less able to absorb the pressure wave, which is pumped into the circulation with every heart beat, the

pressure within the system therefore rises and the blood pressure goes up. Diabetes and untreated hypertension are a particularly bad combination for patients. High blood pressure appears to hasten the slide to kidney failure; it accelerates the process the process of atherosclerosis, and is also associated with an increased mortality from strokes and heart attacks.

3. OTHER METABOLIC DISTURBANCES ASSOCIATED WITH DIABETES.

Although the most profound metabolic disturbance in diabetes is hyperglycaemia, other metabolic disturbances also occur. The most important of these is hyperlipidaemia or hypercholesterolaemia. It is now accepted that high cholesterol is a significant risk factor for heart disease because it probably accelerates the formation of atheroma. It is now therefore routine for doctors to check the cholesterol level in all patients with diabetes.

Pause for thought.

1. What is atherosclerosis and why are people with diabetes more prone to heart disease?
2. Why are people with diabetes more likely to suffer from high blood pressure, and why does this matter?

THE MANAGEMENT OF DIABETES.

This is a huge topic encompassing many disciplines. Essentially the management of diabetes can be classified into 4 areas:

1. Psychological/ social support for patients who may have many specific needs arising from a range of disabilities.
2. Treatment of the primary disturbance of blood sugar, this encompasses ways in how the treatment is monitored.
3. Address other cardiovascular risk factors, particularly hypertension, hypercholesterolaemia, smoking.
4. Treatment of diabetic complications.

In this module we shall review only the treatments available for correcting the primary disturbance of glucose metabolism and how the effectiveness of this treatment may be monitored.

THE TREATMENT OF DIABETES.

The treatment of diabetes with medication is complex and largely beyond the scope of this module but we hope that this short discussion will however give you an insight into some of the treatments your patients may be taking.

It is worth taking a few moments to dismiss the myth of the “diabetic diet”. A person with diabetes should eat a healthy balanced diet; this advice is applicable to all of us! The old ideas of a diabetic sugar restricted diet with a certain proportion of carbohydrates etc has been abandoned.

The aim and purpose of treating a patient with type 1 diabetes is fundamentally different to that of a patient with type 2 diabetes.

The treatment of patients with type 1 diabetes.

The patient with type 1 diabetes has lost the ability to produce insulin and is therefore dependent upon externally administered insulin without which they would

die. The treatment of type 1 diabetes is therefore relatively straight forward; insulin. Each individual's daily insulin requirements are different and will depend upon such diverse factors as their age, sex, build and physical activity, but an average daily requirement is about 1 unit of insulin per Kg weight per day. Patients are often being treated with a confusing array of different insulin's; long acting, short acting, medium acting or a mixture of all three but the choice of insulin is largely dictated by a patient's life style. A teenager with erratic eating habits and irregular meal times will need the flexibility to give themselves a variable dose of short acting insulin before every meal enabling them to titrate the insulin dose to the size of the meal. As the short acting insulin's only last 3 to 4 hours they will then have to supplement this regimen with an evening dose of a longer acting insulin to cover them over night. Another patient with a more predictable lifestyle may be able to control their diabetes with a mixture of short and medium acting insulin's just twice a day; in the morning before breakfast and in the evening at teatime.

The treatment of patients with type 2 diabetes.

Patients with type 2 diabetes have some residual insulin production of their own and therefore will survive, at least a short time without insulin. The underlying problem with patients who have type 2 diabetes is that they don't produce enough insulin for their needs. The patient with type 2 diabetes is in a state of relative insulin deficiency.

The shortfall in insulin production can be made up in one of two ways, tablets or insulin. In treating type 2 diabetes, you start with one type of tablet, if that fails to control the blood sugar adequately add the other type of tablet. If the blood sugar is still not controlled one has to resort to insulin.

1. Tablets (Oral hypoglycaemics)

There are two principle types of oral hypoglycaemics; the sulphonylureas and metformin. The *sulphonylureas*; of which gliclazide, glibenclamide, and tolbutamide are commonly used examples, work by stimulating the pancreas to produce more

insulin than it otherwise would at a particular blood sugar level. This has the effect of driving the blood sugar level down to normal limits. Note if you do not have any insulin production at all (as in type 1 diabetes) these tablets will have no effect because they can only stimulate the pancreas to produce more insulin if it is already producing some already ! *Metformin*, the other type of oral hypoglycaemic acts by making the insulin the body has produced more effective. It achieves this by assisting insulin drive glucose into the peripheral cells, which thereby reduces the blood glucose level.

2. Insulin.

Some type 2 diabetics cannot achieve an acceptable blood sugar level by tablets alone and therefore require insulin therapy instead. The choice of which type of insulin is used and how frequently it should be taken is determined by the same factors as in type 1 diabetics.

MONITORING TREATMENT.

If you remember, we now have good evidence from the DCCT and UKPDS trials that tight glycaemic control does significantly reduce the rate of microvascular and macrovascular complications. Effective glycaemic control can only be achieved by effective monitoring of the effectiveness of treatment.

Day to day glycaemic monitoring can be achieved by measuring capillary blood sugar; the so called BM stick. This gives an instantaneous, snapshot reading of the blood sugar and it allows the patient to decide how much insulin to give themselves before a meal. It is also helpful in the emergency situation when you are trying to decide if a diabetic patient who has become unwell may simply be hypoglycaemic.

Longer term monitoring of the blood sugar can be achieved by a formal blood test looking at what percentage of a particular protein in the red blood cell (HBA₁C) has been glycosylated. The HBA₁C percentage acts as a very accurate barometer of what the ambient blood sugar level has been over the month prior to the test and it therefore serves as a very useful indicator to patients and doctor as to whether the blood sugar has been adequately controlled over this period.

SUMMARY.

Diabetes Mellitus is a metabolic disturbance characterised by hyperglycaemia and a relative lack, or complete absence of, insulin. It is a disease, which by virtue of its complications may affect all organ systems in the body and people with diabetes are exposed to two principle sets of problems. 1 the “*acute diabetic emergencies*” which arise from an acute imbalance between the concentrations of glucose and insulin in the blood, and 2 the more slowly developing “*chronic complications*” that arise from the prolonged exposure of the body’s tissues to hyperglycaemia. It is the chronic complications, microvascular and macrovascular, that gives rise to most of the morbidity that is associated with diabetes. It is now apparent that the key to preventing the long term complications of diabetes is tight glycaemic and blood pressure control. The mainstay of treatment for the underlying metabolic disturbance that occurs in diabetes is currently the oral hypoglycaemics or insulin.

SUGGESTIONS FOR FURTHER READING

1. Chapter 78: Insulin, Glucagon and Diabetes Mellitus. In TEXTBOOK OF MEDICAL PHYSIOLOGY (9th Edition) Editors: A Guyton and J Hall.

- Publishers WB Saunders London 1996. A comprehensive description of the role of insulin in diabetes.
2. Diabetic retinopathy. A short chapter in JJ Kanski's excellent book CLINICAL OPHTHALMOLOGY (4 th Edition) Publishers Butterworth/Heinmann London 1999. Unsurpassed as a short, succinct description of the aetiology, classification and management of diabetic retinopathy.
 3. The section on Diabetes Mellitus in chapter 19 "Diabetes Mellitus and disorders of lipid and intermediary metabolism" from TEXTBOOK OF MEDICINE Editors R. Souhami, J Moxham. Publishers: Churchill Livingstone London 1994. A very thorough but readable text which expands upon many of the sections we have covered in the module, and many more besides.

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SUPPLEMENT 1. NORMAL GLUCOSE HOMEOSTASIS.

Glucose is one of two key energy substrates used by cells to fuel cellular metabolism; thinking simplistically if the cell were a car, glucose is its petrol and consequently if the cell runs out of glucose it rapidly ceases to function and dies. The body therefore has been designed with very complex and elaborate systems that carefully regulate the use, production and storage of glucose and the key player in this system is the hormone insulin. In the next few pages we shall first explore the mechanisms that control the use, synthesis and storage of glucose and its fellow energy substrate the ketone bodies. We shall then introduce insulin and attempt to explain how it coordinates these processes.

1. Introducing glucose and the ketone bodies, the fuels of cellular metabolism.

The body has two principle energy substrates that are used to fuel cellular metabolism; glucose and ketone bodies (see diagram 1). Thinking simplistically, glucose is a clean higher energy fuel compared to the ketone bodies, therefore whilst all cells can use glucose for their energy requirements only some can use ketone bodies. There are therefore certain cells, principally those with very high metabolic requirements eg the brain, which can only use glucose. Such cells are therefore *utterly* dependant on glucose and consequently the body does its utmost to reserve glucose for these tissues. As the remaining tissues can use ketone bodies to fuel their metabolic needs they are programmed to use ketone bodies instead of glucose whenever possible. Very complex systems have therefore evolved which both hold the concentration of glucose in blood at a constant level and reserve it for those tissues that are absolutely dependant on it. We do not need to know how these systems work in any detail but suffice to say that insulin plays a key role.

2. Where does glucose and the ketone bodies come from?

(Please refer to diagram 1 during this discussion).

1. Glucose.

Glucose can be obtained from food, or it can be synthesised by the body from its own energy stores. The relationship between glucose and its energy stores are complex and there exists a very delicate and constantly changing balance between glucose storage and production which is dependant upon whether you have just eaten or not. For example, immediately after a meal there is an excess of glucose in the blood and the body therefore swings the balance of this system into storing the excess glucose. Some hours later however when the body's blood glucose level starts to drop and the balance swings back; the body now starts to synthesize glucose from the energy stores and the level of glucose in the blood is therefore maintained.

Glucose may be stored in 1 of 2 ways; as glycogen (a carbohydrate) or protein. When these stores are full the body then converts any excess glucose into fat. Interestingly, although in times of glucose excess the body can make turn glucose into fat, it cannot do the process in reverse during times of hypoglycaemia (glucose deficiency in the blood). The body cannot therefore turn fat back into glucose and the only way the body can utilize the energy in fat is to turn it into ketone bodies.

2. Ketone bodies.

Ketone bodies are synthesised from fat. Whilst glucose is very important for driving the metabolic processes in a few highly metabolic tissues, the ketone bodies are used as fuel by most tissues of our bodies. Fat is the most abundant energy store in man and even in thin people the stores are often considerable. The body's potential supply of ketone bodies is therefore huge in comparison to that of glucose and it is for this reason that glucose is so carefully reserved only for those tissues that are utterly

dependant on it. If all our tissues were allowed to use glucose at will, its stores would rapidly be depleted leading to starvation of important tissues like the brain.

Where does insulin fit into all this?

Insulin plays a pivotal role in how the body controls and regulates the use and distribution of glucose. Insulin is produced in the pancreatic β cells in response to rising blood glucose levels. Insulin has therefore been dubbed the “hormone of plenty” as it is produced in response to plentiful supplies of glucose. Although its functions are many we can, for our discussion assume them to be just three fold.

1. Insulin encourages the uptake and hence storage of glucose into the tissues as either glycogen, protein and fat.
2. Insulin inhibits the reverse of this process, i.e. it prevents the synthesis of glucose and ketone bodies from these very same energy stores.
3. Insulin is a vital component of the glucose transport system in all cells. In the absence of insulin cells are therefore unable to take glucose from the blood and they will effectively starve. Thus, with the exception of people with type1 diabetes, insulin production is never allowed to fall to zero. (see table 1)

Table 1: Insulin, glucose levels and the balance between glucose storage and synthesis.

GLUCOSE EXCESS.		GLUCOSE DEFICIENCY.	
High.	INSULIN PRODUCTION.	Low.	
Promoted.	GLUCOSE STORAGE.	Inhibited.	
Inhibited	GLUCOSE SYNTHESIS.	Stimulated.	

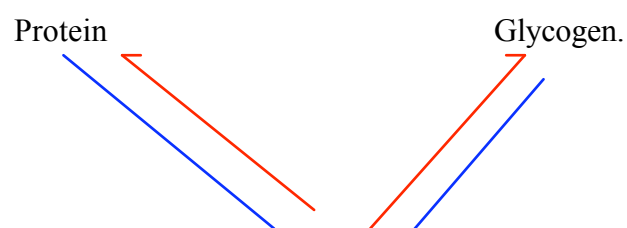
In summary during times of glucose excess insulin encourages the body to store glucose in any way it can until all the excess glucose has been used up. Once the excess glucose has all been stored the glucose concentration in blood starts to fall and insulin production is turned down. If the concentration of glucose in the blood continues to fall such that a state of glucose deficiency is created, insulin production is reduced still further allowing the reverse of the process detailed above to occur. The peripheral stores are now stimulated to synthesise glucose which is released back into the blood resulting in the blood glucose level returning to normal.

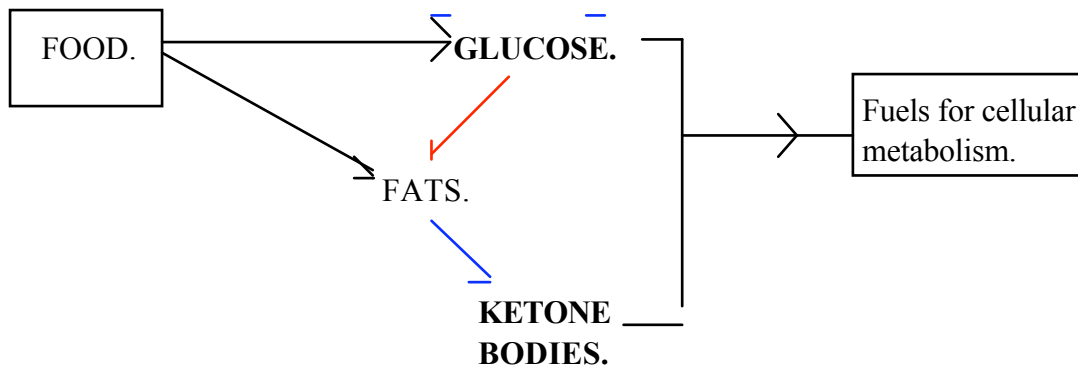
Do any other hormones influence glucose homeostasis ?

The inevitable answer is yes, lots do. All the other hormones involved in glucose homeostasis (cortisol, adrenaline and glucagon) oppose the actions of insulin, and are thus released when the glucose level falls. They all act by stimulating the energy storage areas to synthesise glucose for release into the blood. Thus as glucose levels fall, these hormones are released, glucose is synthesised and the blood glucose level goes up. The only one of these hormones worth remembering is glucagon which can be injected into patients who become hypoglycaemic (see the section on acute complications of diabetes) to help raise their blood sugar.

Before we leave carbohydrate metabolism altogether we have to emphasise that this discussion is a huge simplification of what really goes on but if you understand this you can gain a handle on some of the problems that people with diabetes may suffer.

Figure1: The relationship between the energy substrates glucose and ketone bodies and their corresponding fuel stores.





Key:

— Movement during times of glucose excess.
(ie = processes driven by insulin).

— Movement during times of glucose deficiency.

Exercise

Pause for thought

Once you have read the basic physiology answer the following questions before proceeding.

With regard to insulin answer true or false:

- | | |
|--|-----|
| a) Insulin promotes glycogen formation | T/F |
| b) Insulin promotes glucose formation | T/F |
| c) Insulin lowers blood glucose concentration | T/F |
| d) Insulin stimulates uptake of glucose into muscle and fat stores | T/F |
| e) Insulin is produced in response to low glucose levels. | T/F |

(Ans: TFTTF)

SUPPLEMENT 2; THE ACUTE DIABETIC EMERGENCIES.

Diabetic Ketoacidosis; (DKA).

This is caused by the sudden and *complete* lack of insulin in the body. Glucose entry into cells is *utterly* dependant on insulin and therefore without insulin the cells cannot take up glucose from the blood stream and they effectively start to starve. If cells starve they die and if cells die the organism dies. So at the first hint of cells starving the body starts to mobilise all its available energy stores (fats, carbohydrates and proteins) converting them into glucose and ketone bodies; the energy substrates which cells normally feed on. To summarise then, the bodies normal and only response to cellular starvation is to increase the concentration of glucose and ketone bodies in blood. However, without insulin the body's cells cannot use the glucose or ketone bodies and the cells therefore continue to starve. [It is for this reason that diabetic ketoacidosis was known in the last century as "starvation in the midst of plenty"]. The body is now in real trouble, its cells are starving and without insulin they will continue to do so. The body's only response to cellular starvation is to raise the blood levels of glucose and ketone bodies and the patient therefore is in a vicious cycle of ever accelerating hyperglycaemia.

To compound matters further the very high levels of glucose and ketone bodies in the blood generated by this process lead to their own catastrophic problems. The kidneys cannot handle such a high level of glucose and they start to leak massive amounts of glucose into the urine. (At the turn of the century it was common for physicians to diagnose diabetes by tasting their patients urine, if it was sweet the patient had diabetes!). As the kidneys cannot excrete glucose without water these patients therefore start to pass large volumes of urine (POLYURIA). The consequence of this is that the patients get very dehydrated and start to drink gallons of water in a vain attempt to replace the water they are constantly losing (POLYDYPسيا). The final nail in the coffin is that the ketone bodies which are also produced in this process are acids and as their concentration rises the patient gets more acidotic with serious consequences for the brain.

Diabetic ketoacidosis is a life-threatening disease which develops over days whose treatment necessitates emergency hospital admission. A diabetic patient who suddenly becomes unwell over the space of a few minutes in your clinic will not usually have diabetic ketoacidosis, they are much, much more likely to have suffered hypoglycaemia; "a hypo". The treatment of diabetic ketoacidosis is insulin and rehydration, if the insulin is not replaced the patient may die as the cells continue to starve driving the whole process remorselessly onwards. Diabetic ketoacidosis only affects patients with type 1 diabetes. Even patients with type 2 diabetes on insulin treatment produce enough insulin (although admittedly a feeble amount) to prevent most of what happens above.

Hypoglycaemia.

Hypoglycaemia is by far the commonest of the acute diabetic emergencies and is the one most people will be familiar with. Patients who suffer an episode of hypoglycaemia can be quite well one minute and alarmingly unwell the next as they become clammy, pale and confused. If it is a severe episode they may even become unconscious. Unlike diabetic ketoacidosis, the fundamental problem is a sudden shortage of circulating glucose. As the glucose level falls the cells become starved of energy and stop working properly and because the cells of the brain are the most metabolically active they are the ones that are affected first; hence patients with hypoglycaemia become confused, sometimes aggressive and unconscious etc.

Knowing what the fundamental problem is it is then easy to work out why people with diabetes become hypoglycaemic. In health because your body will accurately balance its insulin production with the glucose you eat, if you don't eat all day you may feel hungry but the amount of glucose in your blood stream won't actually change very much as the body simply lowers its production of insulin. The blood glucose level therefore remains stable and your cells don't starve. By comparison, people with diabetes have only very gross control of this balance between blood glucose and insulin levels. Once they have given themselves their morning dose of insulin, or a tablet which augments the effects of insulin; (please refer to the section on treatment) they have to eat a certain amount of glucose to balance it. If, for example, the patient has not had a chance to eat lunch at their accustomed time (eg because clinic has overrun) they may effectively run out of glucose and are then at risk of becoming hypoglycaemic.

Hypoglycaemia is usually very easy to recognise because the patients become unwell so quickly. If you suspect the patient is hypoglycaemic one can quickly check their capillary blood glucose level (The so called BM test) which will be very low. The treatment is to give the patient anything that may contain glucose, sweets, lucozade etc. (Very rarely if the patient is unconscious and cannot swallow they have to be given an injection of glucagon, a hormone which has the opposite effect of insulin and which therefore has the effect of raising the level of blood glucose). As the blood glucose level rises the patient makes a miraculous and rapid recovery.

Practical exercise:

From the above descriptions you should now be able to tackle the scenario played out below.

You are coming towards the end of a busy morning clinic when a lady from the waiting room asks you for help because her friend is feeling faint. Her friend is a 76 year old lady who is waiting to be assessed because of her recent onset of diplopia which the casualty doctor thinks is due to a sixth nerve palsy. You quickly find out that this lady has diabetes and was recently changed from tablets to insulin. The lady is pale and when questioned appears very disorientated and confused. She is usually well.

What questions would you like to ask her or her friend?

What would you do?

What is the most likely problem?

How could you confirm this?

What can you do?

What advice would you give the lady before she leaves the clinic?