Insulin Resistance & Metabolic Syndrome.

Learning Objectives :

On completion of this course you should be able to :

1. **understand the process of insulin production and it's role in glucose uptake by cells;**
2. **give a definition of insulin resistance, and discuss the main mechanisms by which it is though to occur;**
3. **appreciate the role of obesity in the development of insulin resistance;**
4. **understand the contribution of beta cell dysfunction;**
5. **describe the contributing factors which are thought to contribute to metabolic syndrome;**
6. **discuss the aetiology and consequences of metabolic syndrome.**

Insulin Action.

Insulin is synthesised in the β-cells of the islets of Langerhans in the endocrine pancreas. It is a 51 amino acid peptide hormone comprising two polypeptide chains, the A and B chains, which are linked by disulphide bridges. Other main cell types of the islets are the α-cells producing glucagon, the δ-cells (delta cells) producing somatostatin, and the PP cells producing pancreatic polypeptide. The β-cells are the most numerous and are mainly located at the centre of the islets whilst the other cells are located around the periphery.

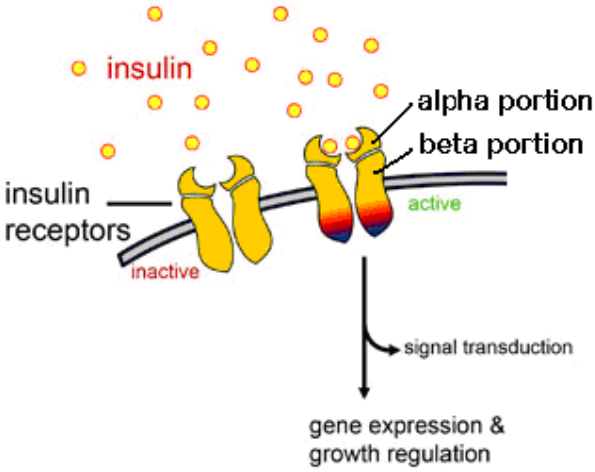
Insulin is synthesised in the ribosomes of the rough endoplasmic reticulum (RER) as a single amino acid chain precursor molecule called preproinsulin. The proinsulin part is transferred from the RER to the Golgi apparatus,

where soluble zinc-containing proinsulin hexamers are formed. The prohormone convertase enzyme finally acts outside the Golgi apparatus to produce the mature insulin and connecting peptide (C peptide). Both insulin and C peptide are released simultaneously in response to a number of stimuli, including glucose and amino acids.

Insulin is secreted in a co-ordinated fashion from the islet cells into the portal vein in a characteristic, biphasic pattern; first there is an acute, rapid first phase release of insulin lasting for a few minutes followed by a less intense, more sustained second phase. Pancreatic β-cells secrete 0.25 to 1.5 units of insulin per hour during the fasting state and this accounts for over 50% of total daily insulin secretion. Meal-related insulin secretion accounts for the remaining fraction of the total daily output. Glucose is the principal stimulus for insulin secretion, though other macronutrients, hormonal, and neuronal factors may alter this response.

When glucose is taken up by the β-cells, it undergoes phosphorylation and metabolism by glycolysis to produce ATP. The rise in ATP closes potassium channels leading to depolarisation of the cell membrane. This is followed by an influx of calcium ions which triggers insulin granule translocation to the cell surface and exocytosis. The mechanism of action of sulphonylureas, a class of oral hypoglycaemic agents, is by binding to a receptor in close apposition to the potassium channels and results in their closure, thereby increasing the release of insulin.

Insulin exerts its biological actions by binding to the insulin receptor on the surface of a target cell. The insulin receptor consists of two α and two β glycoprotein subunits linked by disulphide bonds. Insulin binds to the extracellular α subunits, resulting in change in shape, allowing ATP to bind to the intracellular component of the β subunit and triggers phosphorylation of that subunit, conferring tyrosine kinase activity. This enables tyrosine phosphorylation of intracellular substrate proteins known as insulin responsive substrates (IRS), which can then bind other signalling molecules and so mediate further cellular actions of insulin.



Between meals, insulin is secreted at a low basal level but concentrations rise rapidly following meals. As such, insulin may be considered as a hormone that signals the 'fed' state and as the pivotal hormone regulating cellular energy supply and macronutrient balance and directing anabolic processes of the fed state. Insulin has major anabolic actions on intermediate metabolism, affecting glucose, lipid and protein metabolism. The major insulin-sensitive tissues are the liver, skeletal muscle and adipose tissue. Following secretion of insulin, 60% is subsequently removed by the liver; thus portal vein insulin concentrations reaching the liver are almost threefold higher than in the peripheral circulation.

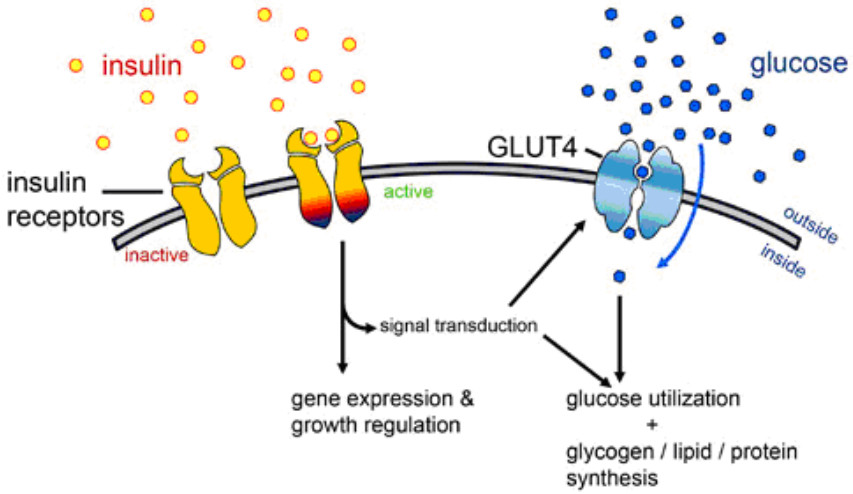
Insulin plays a major role in regulating hepatic glucose output by inhibiting gluconeogenesis and promoting glycogen storage. Similarly in muscle cells, insulin-mediated glucose uptake enables glycogen to be synthesised and stored, and for carbohydrates rather than fatty acids or amino acids, to be utilised as the immediately available energy source for muscle contraction. Adipose tissue fat breakdown is suppressed and its synthesis promoted.

Intracellular actions of insulin

Glucose metabolism - Normally plasma glucose concentration is maintained within a narrow range despite wide fluctuations in nutrient supply and demand. Under normal physiological conditions, insulin, together with its principal counter-regulatory hormone glucagon, is the prime regulator of glucose metabolism.

Insulin is involved in the regulation of carbohydrate metabolism at many steps. Insulin increases glucose uptake into key insulin-sensitive tissues. Glucose is carried into cells across the cell membrane by a family of specialised transporter proteins called glucose transporters:

- GLUT-1 is involved in basal and non-insulin-mediated glucose uptake in cells
- GLUT-2 is important in the β-cells for glucose sensing.
- GLUT-3 is involved in non-insulin-mediated glucose uptake into the brain.
- GLUT-4 is responsible for insulin-stimulated glucose uptake into muscle and adipose tissue. GLUT-4 is normally located within the vesicles in the cytoplasm and following binding of insulin to its receptor, these transporters are moved to the cell surface where they act as a portal for glucose entry.



Insulin acts to increase glycogen synthesis and inhibit glycogen breakdown (glycogenolysis). The control of glycogen metabolism is dependent on the phosphorylation and dephosphorylation of the enzymes controlling glycogenolysis to glycogen synthesis; the rate-limiting enzymes are the catabolic enzyme phosphorylase and the anabolic enzyme glycogen synthase. Insulin increases glycogen synthesis through its action to activate glycogen synthase while inhibiting glycogenolysis by dephosphorylating glycogen phosphorylase kinase.

Glycolysis is stimulated and gluconeogenesis inhibited by dephosphorylation of pyruvate kinase (PK) and 2,6 biphosphate kinase. Insulin also enhances the irreversible conversion of pyruvate to acetyl CoA by activation of the intra mitochondrial enzyme complex pyruvate dehydrogenase. Acetyl CoA may then be directly oxidised via the Krebs' cycle, or used for fatty acid synthesis.

Lipid metabolism - Insulin increases the rate of lipogenesis in several ways in adipose tissue and liver, and controls the formation and storage of triglyceride. The critical step in lipogenesis is the activation of the insulin-sensitive lipoprotein lipase in the capillaries. Fatty acids are then released from circulating chylomicrons or very low-density lipoproteins and taken up into the adipose tissue. Fatty acid synthesis is increased by activation and increased phosphorylation of acetyl CoA carboxylase, while fat oxidation is suppressed by inhibition of carnitine acyltransferase.

Triglyceride synthesis is stimulated by esterification of glycerol phosphate, while triglyceride breakdown is suppressed by dephosphorylation of hormone-sensitive lipase.

Protein metabolism - Insulin stimulates the uptake of amino acid into cells and promotes protein synthesis in a range of tissues. There are effects on transcription of specific mRNA, as well as translation of mRNA into proteins in the ribosomes. Examples of enhanced mRNA transcription include the mRNA for glucokinase and fatty acid synthase, while insulin action decreases mRNA for liver enzymes such as carbamoyl phosphate synthetase, a key enzyme in the urea cycle. However the major action of insulin is to inhibit the breakdown of proteins. In this way it acts synergistically with growth hormone and insulin like growth factor-l to increase protein anabolism.

Glucagon

Glucagon is a polypeptide with a molecular weight of around 3.5 kD. It is synthesised as a large precursor, preproglucagon, and is split within the α-cells into the active hormone. Its secretion is stimulated by a fall in blood glucose and by amino acids. Release of glucagon is also under neurological control, and

sympathetic adrenergic activation increases glucagon release.

Glucagon plays an important part in preventing significant hypoglycaemia during fasting by antagonising the actions of insulin. Its primary site of action is the liver where it binds to specific glucagon receptors that are linked to adenylate cyclase. It leads to the mobilisation of glycogen and to the production of glucose from non-carbohydrate precursors by gluconeogenesis.

KEY LEARNING POINTS.

1. **Insulin is synthesised by the beta-cells in the islets of Langerhans in the pancreas.**
2. **Insulin release is mediated by blood glucose levels, picked up by the beta-cells. A rise in blood glucose levels leads to a release of active insulin.**
3. **Insulin binds to the extra-cellular portion of the glucose receptor on the target cell, which begins a signal transduction process, moving the GLUT-4 receptor to the surface membrane of the cell.**
4. **Insulin also increases lipogenesis in the liver, and controls the formation and storage of triglycerides.**
5. **insulin stimulates the uptake of amino acids, promoting protein synthesis.**
6. **Insulin is antagonised by glucagon, produced by the alpha-cells in the islets of Langerhans.**

Insulin Resistance

Insulin resistance is defined as resistance to the effects of insulin on glucose uptake, metabolism, or storage. Insulin resistance is a characteristic feature of most individuals with Type 2 diabetes and is an almost universal finding in diabetic individuals who are obese. An additional characteristic is the impaired ability to inhibit hepatic glucose secretion, and an inability to stimulate uptake of glucose by skeletal muscle cells (via GLUT-4 receptor loss). Where there is insulin resistance there is also an inability to suppress lipolysis in adipose cells. Other features include impaired vascular endothelial function, increase in stiffness of the basement membrane in the arterial tree, and a reduction in coagulation time. Due to the action of insulin on the hypothalamus there is also increased sympathetic tone.

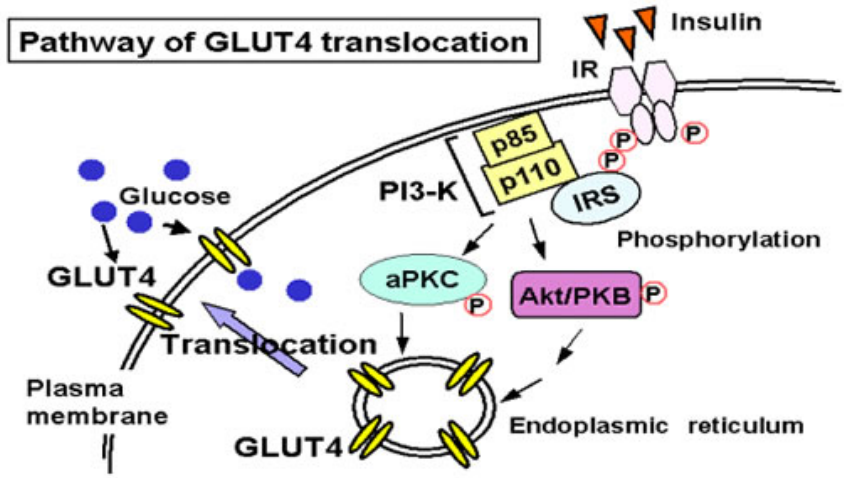
The process by which insulin resistance occurs is not yet fully mapped, and defects can occur at many points in the production or signalling pathway, but most evidence suggests that in Type 2 Diabetes, the majority of insulin resistance occurs via a defect in post-receptor signalling, i.e. after the insulin has bound to the receptor site on a target cell.

The evidence that insulin resistance has a major role in the pathogenesis of Type 2 diabetes can be gauged from the findings that;
(1) insulin resistance is often detected 10 to 20 years before the onset of diabetes in predisposed individuals, and;
(2) in prospective studies, insulin resistance is the best predictor for subsequent progression to diabetes.

It is recognized that insulin resistance is a complex phenomenon, influenced by a variety of genetic and environmental factors.

Contribution of GLUT-4 Receptor action

The uptake of glucose into a skeletal muscle cells and lipocytes is dependent on the presence of a population of activated GLUT-4 receptors situated on the cell membrane. These receptors are activated in the presence of insulin, which allows glucose to be transported, via the GLUT-4 receptor, into the cell. When insulin is not present the GLUT-4 receptors are stored in an inactive form within the Golgi apparatus, and are therefore unavailable on the cell membrane. At this point no glucose is able to cross the cell membrane and enter the cell.



Once a cell's insulin receptors are activated by the attachment of insulin, intra-cellular signalling pathways causes the GLUT-4 receptors to be released, allowing them to locate themselves on the cell membrane, and therefore allow glucose to enter the cell. The movement of GLUT-4 to the cell surface requires the presence of ATP, and also requires an intact microtubular system. Some drugs can affect this, such as cholchicine, which binds to microtubular proteins and destroys them, explaining why the use of cholchicine can increase blood glucose levels – if the cell microtubular system does not work, GLUT-4 receptors cannot be activated, therefore no glucose is taken up by the cell.

In cases where there is a high level of plasma insulin, insulin receptors on muscle cells will be activated, resulting in a population of GLUT-4 receptors on cell membranes. This allows glucose to be taken into the muscle cells, but when the cell is saturated with glucose, the GLUT-4 receptors are inactivated, and no further glucose is taken into the cell. Unless that cell utilises all of the glucose, the GLUT-4 receptors will stay inactive, and the cell takes in no further glucose, no matter whether there is insulin action. This leads to a situation of higher plasma glucose levels, and hyperglycaemia.

Obesity and Insulin Resistance

The association of obesity with Type 2 diabetes has been recognized for decades, with visceral obesity being common in the majority of Type 2 diabetics. Insulin resistance appears to be the link between obesity and diabetes. The risk of diabetes developing increases as the body mass index increases, suggesting a dose-response relationship between body fat and insulin resistance. Although many details of the "adipo-insulin axis" are still unclear, some of the mechanisms which are known to lead to insulin resistance have been clarified.

1. Role of free fatty acids (FFAs): an inverse correlation between fasting plasma FFAs and insulin sensitivity has been demonstrated in cross-sectional studies. The level of intracellular triglycerides is often markedly increased in muscle and liver tissues in obese individuals, presumably because excess circulating FFAs are deposited in these organs. Intracellular triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state. These lipotoxic effects of FFAs are most likely mediated through a decrease in activity of key insulin-signaling proteins.

2. Role of adipocytokines: Adipose tissue is not a passive storage depot for fat, but operates as a functional endocrine organ, releasing hormones in response to extracellular stimuli or changes in the metabolic status. A variety of proteins released into the systemic circulation by adipose tissue have been identified, and these are collectively termed adipocytokines. Among these are leptin,

adiponectin, and resistin, and relative changes in their levels are associated with insulin resistance. Adiponectin levels are reduced in states of obesity and insulin resistance, suggesting that, under physiological conditions, this cytokine contributes to insulin sensitivity in peripheral tissues. Conversely, levels of resistin are increased in obesity, and this cytokine contributes to insulin resistance.

3. Role of the PPARγ and thiazolidinediones (TZD): TZDs are a class of antidiabetic compounds that were first developed in the early 1980s as antioxidants. The target receptor for TZDs has been identified as PPARγ, a nuclear receptor and transcription factor. PPARγ is most highly expressed in adipose tissue, and its activation by TZDs results in modulation of gene expression in adipocytes, eventually leading to reduction of insulin resistance. The targets of PPARγ activation include several of the adipocytokines discussed above. PPARγ activation also decreases concentrations of FFAs. A family of proteins called sirtuins, which were identified as being involved in ageing, have also been implicated in diabetes. The best-studied mammalian sirtuin, called Sirt-1, has been shown to improve glucose tolerance, enhance β cell insulin secretion, and increase production of adiponectin. It remains to be seen if sirtuin abnormalities are involved in the pathogenesis of type 2 diabetes.

β-Cell Dysfunction

β-cell dysfunction in Type 2 diabetes reflects the inability of these cells to adapt themselves to the long-term demands of peripheral insulin resistance and increased insulin secretion. In states of insulin resistance, insulin secretion is initially higher and this hyper-insulinaemic state is a compensation for peripheral resistance, and can often maintain normal plasma glucose for years. Although the data in humans are scant, studies from animal models of diabetes support the hypothesis of β-cell hyperplasia in the pre-diabetic state followed by decrease in β-cell mass that coincides with clinical progression to diabetes. Eventually, however, β-cell compensation becomes inadequate, and there is progression to overt diabetes. The underlying bases for failure of β-cell adaptation is not known, although it is postulated that several mechanisms, including adverse effects of high circulating FFAs (lipotoxicity) or chronic hyperglycemia (glucotoxicity),

may have a role. β-cell dysfunction in Type 2 diabetes encompasses both qualitative and quantitative aspects.

Qualitative β-cell dysfunction is initially manifest as subtle abnormalities, such as loss in the normal pulsatile, oscillating pattern of insulin secretion, and attenuation of the rapid first phase of insulin secretion triggered by elevation in plasma glucose. Over time, the secretory defect progresses to encompass all phases of insulin secretion, and even though some basal insulin secretion persists in Type 2 diabetes, it is inadequate for overcoming insulin resistance.

Quantitative β-cell dysfunction is manifest as a decrease in β-cell mass, islet degeneration, and deposition of islet amyloid. Islet amyloid protein (amylin) is a characteristic finding in individuals with Type 2 diabetes, and it is present in more than 90% of diabetic islets examined. Islet amyloidosis is associated with a decrease in β-cell mass, although it is uncertain whether the amyloid is a cause or consequence of cell damage in Type 2 diabetes. In this context, it is important to note that even a "normal" β-cell mass in diabetic individuals may, in fact, indicate a relative reduction as compared with the expected hyperplasia needed to compensate for insulin resistance. β-cell numbers are typically reduced by 20-30% in Type 2 Diabetes, but α-cell mass remains unchanged, and glucagon secretion increases, potentially contributing to a hyperglycaemic state.

KEY LEARNING POINTS.

1. **Insulin resistance is the resistance to the effects of insulin on glucose uptake, metabolism, and storage.**
2. **It is a characteristic feature of Type 2 Diabetes, but also occurs in obese individuals.**
3. **Inactivation of GLUT4 receptors prevents uptake of glucose, thereby resisting the effects of insulin.**
4. **Obesity plays a major role in the development of insulin resistance, where adipose tissue acts as an endocrine organ.**

KEY LEARNING POINTS (continued)

5. Beta-cell dysfunction is linked to a decrease in beta-cell mass, leading to a decrease in insulin output.

Metabolic Syndrome (Syndrome X, Reaven Syndrome)

The metabolic syndrome describes the clustering of cardiovascular risk factors including dyslipidaemia, glucose intolerance and hypertension with central adiposity. The syndrome is increasing in prevalence worldwide as a consequence of increasing obesity prevalence. Metabolic syndrome is likely to have a marked impact on the prevalence of cardiovascular disease and type 2 diabetes worldwide in the next two decades. There is uncertainty as to whether all patients with the syndrome are indeed insulin resistant, so the aetiology has been broadened to include concepts of obesity, adipose tissue disorders and other factors.

The clustering of CVD risk factors with type 2 diabetes, hyperlipidaemia, hypertension and obesity was first noted in the 1960s-70s. The concept of the metabolic syndrome was proposed in 1988, when G.M. Reaven published a landmark paper describing Syndrome X.
(Reaven GM; Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988 Dec;37(12):1595-607.)

Reaven postulated that insulin resistance was the cause of glucose intolerance, hyperinsulinaemia, increased VLDL, decreased HDL and hypertension, but he did not include obesity in his original description. It has since been realised that obesity is often the cause of the insulin resistance that leads to metabolic abnormalities. Subsequently, the term metabolic syndrome was coined to reflect the range of metabolic features involved. Various definitions of the syndrome have been created. More recently, some have questioned the usefulness of the metabolic syndrome as a clinical diagnosis.

There have been several definitions of the syndrome but the most commonly used

at present are the World Health Organisation (WHO), and the ATP III definition.

The WHO criteria are:

1. central obesity with a waist: hip ratio above 0.9 for men and 0.85 for women and/or a body mass index (BMI) above 30 kg/m2;
2. blood pressure above 140/90;
3. triglycerides above 1.7 mmol/L;
4. HDL cholesterol <0.9 mmol/L in men and <1 mmol/L in women;
5. a blood glucose level above 7.8 mmol/L after glucose fasting, or 2 hours after a glucose load.

The ATP III* definition requires 3 of:

1. waist circumference ≥102 cm (men) or ≥88 cm (women);
2. blood pressure ≥130/85;
3. HDL-cholesterol <40 mg/dL (men) or <50 mg/dL (women);
4. triglycerides ≥150 mg/dL;
5. fasting glucose ≥110 mg/dL.

*National Cholesterol Education Program Adult Treatment Panel III, 2001

In April 2005, the International Diabetes Federation produced a consensus on the definition of the metabolic syndrome which includes central obesity and 2 metabolic sequaelae. Central obesity is defined by waist circumference and differs between ethnic groups with limits of 94 and 80 cm respectively for white European men and women, but 90 and 80 cm for South Asian or Chinese individuals. Triglycerides, HDL and blood pressure have the same limits as the ATP III definition but glucose intolerance is defined as a fasting plasma glucose ≥5.6 mmol/L (100 mg/dL) or a pre-existing diagnosis of impaired glucose tolerance or diabetes. This classification is still relatively new, and is not yet in common usage.

The prevalence of the metabolic syndrome varies with country, race and the definition used, but in one study in the USA using the ATP III criteria there was

a prevalence of 24%, increasing to 44% in the over-60s (http://pmj.bmj.com/cgi/content/full/81/956/358). It is likely that the prevalence of metabolic syndrome will increase together with the rising rates of obesity which have been observed, both in the West and in the developing world.

Aetiology

The underlying aetiology of the metabolic syndrome is still under discussion, but there is a consensus that many factors are involved:

1. Insulin resistance – together with consequent hyperinsulinaemia, insulin resistance is recognised as an important or even essential factor in the metabolic syndrome. Originally, Reaven proposed that insulin resistance is central to the syndrome's aetiology and is the unifying pathological feature, but some authors are less certain.

Insulin resistance itself seems to be due to a combination of genetic factors, physical activity and obesity. Genetic factors predispose to the metabolic syndrome, but are insufficient to create it without the contributing lifestyle factors. There are also ethnic differences in predisposition to insulin resistance and CVD, with south Asians being at greater risk. In addition, hypertension and insulin resistance are closely linked.

2. Lifestyle factors -

- Obesity- BMI, abdominal obesity and upper body obesity are all linked to the metabolic syndrome; some experts suggest that abdominal obesity or upper body obesity are more closely linked than BMI. Adipose tissue in obese people is insulin resistant, and adversely affects lipids, inflammatory mediators and other mediators which influence insulin resistance and CVD.
- Physical inactivity - thought to interact with genetic factors and obesity to produce the metabolic syndrome. Increased physical activity helps control body weight and blood pressure, improves lipid profiles and reduces cardiovascular risk and the risk of diabetes.

- Atherogenic diet - modern Western diets are very different in composition from traditional human diets. Notably, they are high in refined carbohydrates and refined vegetable oils, but low in omega-3 fatty acids, fresh fruit and vegetables. All these have a role in obesity, adverse lipid profiles and the metabolic syndrome.

3. A pro-inflammatory state - Obesity, inflammation and cardiovascular risk seem to be connected. CRP (C-reactive protein) levels and white cell counts both seem to increase with obesity or the metabolic syndrome, and there is some evidence linking them to CVD risk. The mechanism may again be related to the behaviour of adipose tissue which, in the presence of obesity, produces excess proinflammatory cytokines and less of the protective adiponectin.

4. A pro-thrombotic state - There is evidence for high circulating levels of prothrombotic factors in the metabolic syndrome, which could contribute to CVD.

5. Atherogenic dyslipidaemia - The metabolic syndrome and insulin resistance are linked to an atherogenic lipid profile, which includes:

- Raised triglycerides, including the atherogenic remnant lipoproteins
- Increased LDL and small LDL particles
- Increased apoB-containing lipoproteins
- Reduced HDL-C

Possible consequences of metabolic syndrome.

The metabolic syndrome and insulin resistance are associated with:

- Cardiovascular disease - the cardiovascular risk approaches that of full diabetes
- Diabetes mellitus - the natural progression of metabolic syndrome is to develop overt Type 2 diabetes.

- Chronic kidney disease (CKD) - patients with the metabolic syndrome are at significantly higher risk for microalbuminuria and/or CKD, and the level of risk is related to the number of components of the syndrome itself. It is currently unclear how much of the risk is due to individual metabolic syndrome components such as hypertension and impaired glucose metabolism, and how much may be due to aspects of the metabolic syndrome itself, such as abdominal obesity.
- Non-alcoholic fatty liver disease
- Polycystic ovary syndrome
- Cholesterol gallstones
- Obstructive sleep apnoea
- Lipodystrophies

The management of the metabolic syndrome is not specific to the syndrome, but consists of management of the underlying risk factors for CVD and diabetes, and treatment of any established disease such as hypertension, heart disease or diabetes. Recommendations are that clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the metabolic syndrome.

Treatment may involve the use of low dose aspirin, anti-hypertensives, statins and/or fibrates, and anti-diabetic drugs. There is no specific drug treatment for the metabolic syndrome itself. Metformin, glitazones and acarbarose have been suggested as either improving the syndrome or delaying progression to Type 2 diabetes, though recent safety concerns do not favour glitazones. Metformin may have a role in the development of polycystic ovary syndrome.

There still remain areas of controversy around metabolic syndrome, particularly in whether or not it represents a true ‘syndrome’. A cluster of factors is usually defined as a syndrome either if it predicts future events, or if it identifies a unifying pathological process. In the case of metabolic syndrome, it is not clear that either of these apply. There is no conclusive evidence that the metabolic syndrome itself increases CVD risk above that of the existing individual risk

factors. The syndrome is predictive of diabetes, but this is unsurprising given the definitions involving abnormal glucose values or insulin resistance.

Additionally, some have begin to question whether a diagnosis of metabolic syndrome is clinically useful as it is recommended that doctors should evaluate and treat all CVD risk factors regardless of whether or not the patient has metabolic syndrome, and this concords with the Joint British Societies' Guidelines and current UK targets for primary care (http://heart.bmj.com/cgi/content/full/91/suppl_5/v1).

Reaven, the American Diabetes Association, and the European Association for the Study of Diabetes, eventually concluded that identifying metabolic syndrome is not useful clinically (http://care.diabetesjournals.org/content/28/9/2289). Other authors and recent SIGN guidelines, on the contrary, suggest that it is still a useful concept to identify people at high CVD risk who need primary prevention and risk monitoring. Some argue that a diagnosis of metabolic syndrome is a medicalisation of Western lifestyle and will label large numbers of people as diseased.

KEY LEARNING POINTS.

1. **Metabolic syndrome was first proposed in 1988, although the clustering of factors had been noted as early as the 1960's.**
2. **It is a combination of insulin resistance, hyperinsulinaemia, increased VLDL, decreased HDL, hypertension, with visceral adiposity.**
3. **The underlying causes are thought to include obesity, physical inactivity, high fat diets, and raised triglycerides.**
4. **Possible consequences of metabolic syndrome include CV disease, diabetes, chronic kidney disease, liver disease, gallstones, and polycystic ovary syndrome.**
5. **Management involves the usual treatment of cardio-vascular risk factors, and possibly the use of certain anti-diabetic drugs.**