Introduction
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Diabetes, a metabolic disorder involving high blood sugar levels due to the non-functioning of a key hormone called insulin, has been on the rise across the world, affecting one-fifth or 33 million, of them are Indian, according to the International Diabetes Federation (IDF), resulting in India being dubbed the Diabetes Capital of the world at the recent 2003 IDF conference in Paris. Indian diabetics tend to be younger and are more likely to fall prey to complications ranging from heart attacks and strokes to blindness and sexual dysfunction. Worst, almost 80 percent of them don't even know they suffer from diabetes.

According to the survey, 14 percent of metro residents, most of them below the age of 40, showed a pre-diabetic condition called impaired glucose tolerance (IGT). It is the possible complications that make diabetes a dreaded disease. People with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney diseases, 30-40 times more likely to undergo a major amputation, 2-4 times as likely to suffer a heart attack and twice as likely to get a stroke than a normal individual. It is because diabetes forms part of the larger Insulin Resistance Syndrome (IRS) in Indian, which includes hypertension, thinner arteries and hypercholesterol levels.

Simply put, glucose, obtained from our diet, is our body's fuel. It is crucial. Cells grab it from the blood and burn it for energy. The gate through which glucose enters cells is controlled by insulin, a pancreatic hormone, which acts as the key. Diabetes mellitus happens when the body's insulin does not work. So glucose cannot enter the cells and its levels in the blood increases. The disease is of two types. In Type 1, insulin cannot be produced by the pancreas, and manifests itself in early childhood. In type 2, or adult onset diabetes, insulin is produced but cannot function as efficiently a condition known as insulin resistance. Starving and desperate, the brain then directs the pancreas to churn out higher amounts of insulin, not realizing that the cells are blind to the hormone. Worse, high insulin levels increase the transport of fatty acids, also obtained from the diet, into fat cells. It leads to fatty acids floating about in blood vessels too, causing cardiovascular horrors. The glucose, meanwhile, chokes other crucial proteins with a sugar layer, rendering them in effective. The eye, brain, kidneys, heart even the healing properties of the body are adversely affected.
20 percent or 33 million of the world’s diabetics are Indians.

- 12 percent of the people living in India metros suffer from diabetes.
- 14 percent more are in a pre-diabetic stage and many get it late.
- 30 percent of diabetics in urban India are below the age of 40 (India Today, 2003)

Complications associated with uncontrolled diabetes

1. Heart attack and stroke

Heart attack is the leading cause of death in people with diabetes. The risk of heart disease and stroke is two to four times higher for people with diabetes, according to the American Heart Association. Women with diabetes are at a greater risk, with a study showing that men over 55 years with diabetes are seven times more likely to have heart disease. “People with diabetes are often over-eight, have high blood pressure, high triglycerides, high bad cholesterol and low good cholesterol, all factors that increase their heart risk.”

Diabetes makes arteries more prone to clogging. “Heart disease is more diffused in diabetics, who are also more prone to silent heart attacks because of neuropathy.”

Research suggests that arterial inflammation is possible reason for insulin resistance and increased risk of heart disease among diabetics. “The American Diabetes Association recommends aspirin to reduce inflammation and block thromboxane production to reduce the risk of heart disease and stroke in diabetics.

2. Diabetic neuropathy

If uncontrolled, diabetes can cause damage to nerves throughout body. Symptoms include numbness, pain or weakness in the extremities such as the hands, feet ad legs. “Diabetic neuropathy is more common in people who have had problems controlling their blood glucose level, in those with high levels of blood fat and blood pressure, in overweight people and in people over the age of 40”. The most common type is peripheral neuropathy, also called distal symmetric neuropathy, which affects the arms and legs. Symptoms include a burning sensation or tingling in the feet due to nerve damage and the resultant lack of blood supply.
3. Kidney failure

"Diabetes is the most common cause of kidney failure, accounting for more than 40 percent of new cases." People with kidney failure undergo either dialysis, which substitutes for some of the filtering functions of the kidneys or transplantation.

4. Impotence

Apart from kidney disease, chronic alcoholism, multiple sclerosis and vascular disease, uncontrolled diabetes is a leading cause of impotence.

5. Diabetic retinopathy

If one has uncontrolled diabetes there are 2-5 percent chances of going blind. Still, only 5.5 percent of all diabetics know it.

A potentially blinding complication that damages the retina, diabetic retinopathy is irreversible. While surgery can stabilize vision of people with retinopathy, it cannot improve it, so it is vital to detect retinopathy in the early stages by going for annual eye check-ups.

6. Hypoglycaemia

It can happen suddenly, but it can be treated equally quickly by eating something with carbohydrate and bringing the blood glucose level back to normal. Its symptoms include hunger, nervousness, perspiration, dizziness, confusion and anxiety.

Hypoglycaemia is usually caused by delayed or skipped meals, excessive doses of diabetes medications—including sulphonylureas and meglitinides— or having excessive alcohol. Some relief is now being offered by basal insulin products such as Aventis’ Lantus, which is insulin that needs to be taken once a day yet offers a 24-hour blood glucose lowering activity.

Indians are predisposed to diabetes, no doubt, but obesity and lack of exercise play an equally important causative role, as confirmed by the six-city national urban diabetes survey. "The bottom line is that people who are overweight, don’t exercise and have a family history of diabetes should get the blood glucose tested every year to detect and control the disease in time" (The Hindustan Times, 2004).
India tops the heap

A list of top 10 countries with most cases of diabetes (in millions) in 2000 and those that are expected to have the most cases in the year 2030 are given below in the table.

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(The Week, 2004)

Why Indians are more prone:

**In the Genes:** Indians are prone to the Insulin Resistance Syndrome, which is caused by abdominal fat, thin arteries and high blood pressure.

**Store House of fat:** One theory says, Indians have ‘thrifty’ genes, which enabled survival during famine by storing fat in the abdomen. Now, this tendency to store can lead to diabetes.

**Changing life style:** Rapid life style changes and lack of physical exercise has led to a spurt in the incidence of diabetes in urban India (India Today, 2003).

**Symptoms**

- Frequent hunger and thirst are common signs of diabetes.
- Weight loss, irritability and lack of energy are other symptoms.
- Frequent urination is also a sign.
- A common sign is when wounds don’t heal, cramps and pain in legs.

**The whole body is affected**

Diabetic foot: Foot ulceration, caused by nerve damage and lack of blood supply, makes diabetics 30 times more likely to undergo limb amputation.
Prolonged healing: High blood glucose affects crucial proteins, so wounds take long to heal.

Sexual dysfunction: A common problem among diabetics because blood supply to organ is affected.

Brain: Diabetics are 2-5 times more likely to suffer strokes than non-diabetics, especially if they have high blood pressure as well. Strokes are also more severe in diabetics. This is because prolonged high blood glucose levels weaken the blood vessels in the brain.

Eyes: Diabetics are 25 times more likely to go blind than non-diabetics. Retinopathy, caused by damage to the eye capillaries, is most common. So are cataract and glaucoma.

Heart: High blood sugar levels and increased amounts of fatty acids due to insulin, thicken the arteries. Diabetics are at greater risk of heart attacks.

Kidney failure: High blood glucose, and blood pressure damage kidney vessels. So diabetics are 17 times more likely to suffer kidney failure (India Today, 2003).

**DEFINITION, INSULIN, GLUCAGON, PHYSIOLOGY, PATHOPHYSIOLOGY**

Diabetes mellitus (DM) may be defined as a metabolic disorder of which chronic hyperglycaemia (with or without glycosuria) is the essential feature. The prevalence varies from 2-5% in developing countries to 5-10% in developed countries. Carbohydrates, an important energy source, are ingested as sugars, starch and glycogen and are partially digested by salivary amylase to form intermediate dextrins and maltose. Maltose, dextrins and other disaccharides are digested further to form the monosaccharides glucose, galactose and fructose, which are absorbed and transported via the portal vein to the liver, where fructose and galactose are converted to glucose.

In the tissues, glucose is broken down (glycolysis) by a series of enzymes constituting the Embden-Meyerhof pathway, and the products undergo oxidative metabolism in the Krebs cycle. One of the enzymes in the glycolytic pathway is hexokinase, which catalyses the phosphorylation of glucose to glucose-6-phosphate. Hexokinase has a very high affinity for glucose and dominates other enzymes, which also act on glucose. Thus the glycolytic pathway is the physiological metabolic channel. If, however, carbohydrate metabolism is
disordered, the glycolytic pathway may be so overwhelmed by glucose that an alternative pathway must be used, i.e. the polyol pathway.

In this pathway glucose is converted by aldose reductase to sorbitol, which is then oxidized to fructose. Diversion of glucose to this abnormal pathway may be important in the pathogenesis of the specific complication, which may occur in DM. It is postulated that the sorbitol and fructose, which accumulate intracellularly, cause water retention and destroy the cells. This hypothesis is supported by studies of cataract formation in rats exposed to experimental hyperglycaemia or galactosaemia. The hyperglycaemic mouse does not form cataracts because it has very low levels of aldose reductase in the lens.

In DM the blood glucose (BG) is abnormally high because of defective insulin action at cell level. Although the definition emphasizes hyperglycemia, there are related and consequential distortions of intermediate metabolism, and of protein and fat metabolism. To some extent our preoccupation with hyperglycemia stems from the historical evolution of our understanding of DM, in that glycosuria was the first objective finding to be recorded. It is possible that chronic hyperglycaemia represents only the full-blown clinical picture. Thus, a middle-aged woman presenting with classical symptoms of DM may describe a characteristic reproductive history. Similarly, the skin lesion, necrobiosis lipoidica diabeticorum (NLD) may appear many years before hyperglycaemia develops, islet cell antibodies (ICA), elevated levels of activated T-lymphocytes, and a reduction in the normal initial rapid secretion of insulin (i.e. first-phase secretion) in response to i.v. dextrose may be demonstrable many years before hyperglycaemia appears. Although a caveat has been entered about regarding DM as primarily and fundamentally a disorder of carbohydrate metabolism, current pathophysiological concepts assign a central role to the defective action of insulin. This may be due to beta cell-B-cell) malfunction, resulting in partial or total failure of insulin synthesis and/or secretion, as in insulin-dependent DM (IDDM or type 1 DM), or to a combination of a sluggish secretion of insulin by the B-cell with an associated reduction in the cellular response to insulin, as in non-insulin dependent DM (NIDDM or type 2 DM). The impaired response at cell level may be due to a reduction either in affinity or in numbers of insulin receptors (binding defect) and/or a failure of insulin to trigger the normal intracellular biochemical process (post-binding defect).
Normal insulin synthesis and secretion

Insulin is formed in the B-cells of the islets of Langerhans, which number about one million and form 3% of the mass of the pancreas, being most numerous in the tail. The daily output is 30-40 units. Human insulin has a molecular weight of 6000 and contains 51 amino acids arranged as an A-chain (21) and a B-chain (30) linked by two disulphide bridges. There is also a disulphide bridge within the A-chain. In the fasting state the B-cell secretes 20 μg of insulin per hour into the portal vein where the concentration is 50-100 microm units per ml, in contrast to the peripheral circulation in which it is only 12 microm units per ml. The liver removes 50-60% of portal vein insulin in one ‘pass’, and this extraction may be as high as 90% after a meal.

Proinsulin, the precursor of insulin, is relatively inactive and contains the A- and B-chains linked by a connecting peptide made up of 35 amino acids-C-peptide—which is important in biosynthesis because it ensures that the proinsulin molecule folds properly to produce the correct alignment of the disulphide bridges.

The B-cell synthesizes proinsulin at a constant slow rate, but the process accelerates in response to rising levels of BG. Arginine, leucine, mannose and glucagon also stimulate proinsulin biosynthesis, which is inhibited by adrenaline. Biosynthesis occurs in the ribosomes of the rough endoplasmic reticulum of the B-cell whence the proinsulin is transferred to the Golgi apparatus, where it is packaged into secretory granules and converted to insulin by proteolytic cleavage. On cleavage, the secretory granules move from the Golgi apparatus to the general cytoplasm of the B-cell where they are stored. The basic unit of secretion is the storage granule, which contains insulin, C-peptide, zinc, calcium, etc. Glucose increases the concentration of free calcium within the B-cell, and as a result the insulin granule is transported by a tubular-microfilamentous system to the membrane of the cell, with which it fuses, after which secretion takes place by exocytosis.

The secretory product consists of equimolar amounts of insulin and C-peptide, together with a small amount of uncleaved proinsulin, which has only 5% of the biological activity of insulin. Rare cases of DM have been documented in which proteolytic cleavage is defective, so that most of the circulating insulin is in the form of biologically ineffective proinsulin. High levels of circulating proinsulin are also found in association with islet cell tumours, the levels being highest if the tumour is malignant. Although
insulin and C-peptide are secreted in equimolar amounts, this relationship is not maintained in the peripheral blood because of different clearance rates. As a result of hepatic extraction (50%) and receptor-mediated catabolism the half-life of insulin, at 4 minutes, is much shorter than that of C-peptide, which is not extracted by the liver but is cleared by the kidney and has a half-life of 20 minutes. The normal fasting concentration of C-peptide in peripheral blood is 0.18-0.63 pmol/ml, which, on a molecular basis, is four to five times that of insulin (0.086-0.17 pmol/ml). Nevertheless, peptide levels are a useful measure of residual B-cell function in insulin-treated patients in whom direct measurement of insulin levels is not informative. B-cell damage in IDDM (type 1 DM) is not an all or none phenomenon, and some residual function indicated by some preservation of C-peptide secretion may persist for years. In such cases, metabolic control tends to be more stable, episodes of ketoacidosis are fewer, and degenerative complications may develop later and be less severe. The possibility of preserving some residual B-cell mass and function is an argument for early diagnosis, and the introduction of insulin therapy before B-cell exhaustion has occurred. It is also the basis of current therapeutic experiments with immunosuppressants.

**Insulin release**

The release of stored insulin by the B-cell is determined by the circulating levels of nutrients such as glucose, amino acids, fatty acids and ketone bodies. Glucose and protein taken together induce a greater release of insulin than either alone. The release of insulin is also increased by other hormones, e.g. gastrin, secretin, glucagon and cholecystokinin, and is inhibited by somatostatin and adrenaline. In addition, there is some neurological control via the vagus nerve. This meal-induced insulin boost is designed to anticipate absorption of nutrients, thereby preventing post-prandial hyperglycaemia. Such a variety of stimulators and suppressors predicate a number of sensor system, which can trigger or inhibit the release mechanism. Within the B-cell, changes in the concentration of calcium and of cyclic AMP appear to activate the contractile microtubular system, which actively expels insulin from the B-cell into the circulation. A rise in BG above 5 mmol/L stimulates the release of insulin in two phases, a sharp initial response being followed by a slow plateau-like second phase. The ability of the B-cell to respond so rapidly to such a minor change in BG implies the presence of a specific and extremely sensitive sensor,
which may be an enzyme within the cell, since glucose must be broken down within the cell to stimulate insulin release.

The B-cell system can also adapt to a more chronic change in the metabolic milieu by altering the 'set' of the system, e.g. its action is enhanced during pregnancy and is reduced in chronic malnutrition.

**Insulin action**

When insulin has been synthesized and secreted by the B-cell it is transported via the circulation throughout the body. All cells except the retina, brain cells and kidney medulla depends on insulin for metabolic needs, but its action on liver, muscle and adipose cells is especially important. The circulating insulin is bound to receptors on the plasma membrane of cells. These receptors have a high specificity and affinity for insulin. There is a local control mechanism at the level of the cell membrane whereby, in the presence of persistently increased concentration of insulin, the number of receptors available for insulin binding is reduced, thereby controlling the action of insulin on the cell. This phenomenon, called down-regulation, prevents excessive insulin action at the cell level.

Receptors are also present within the cell on membranes of its nucleus and Golgi apparatus. Insulin, bound to its receptor, may enter the cell and activate therein a number of molecular events (post-binding action), or it may initiate a signal, which sets in train a cascade of metabolic events within the cell. Cyclic AMP, cyclic GMP and calcium may be important at this point.

In summary, the fundamental action of insulin takes place within the cell and is the culmination of a series of events: the B-cell, through its glucose sensor, recognize a rising BG, and in response secretes and synthesize insulin in appropriate amounts; circulating insulin becomes attached to specific receptors on cell membranes and is then internalized to facilitate metabolic processes within the cell. A break at any link in this chain will have the same effect, i.e., faulty cell metabolism, of which hyperglycemia is the most recognizable consequence, but there are profound effects on protein and lipid metabolism also. As insulin plays an essential part in controlling the storage and utilization of fuels (food) it may be termed the hormone of the fed state. It also promotes cell growth and division. After meals, insulin is secreted to control the post-absorptive rise in blood
glucose and amino acids by promoting their storage in muscle and liver as glycogen, and in adipose tissue as triglycerides. In the fasting state the normal level of BG is sustained by glycogenolysis and gluconeogenesis in the liver under the influence of glucagons.

The action of the liver in functioning either as a store for glycogen or as a provider of glucose (gluconeogenesis and glycogenolysis) depends on the relative proportion of opposing hormones. Insulin (regulator), and glucagons, catecholamines, corticosteroids and growth hormone (counter-regulators). In the fed state insulin levels are relatively high and glucagons levels are low, so that glucose output from the liver is switched off (i.e. insulin inhibits gluconeogenesis). In the fasting state insulin levels are low and glucagons levels are high, so that gluconeogenesis is switched on not only because of the stimulatory effect of glucagons, but also because of the removal of the inhibitory effect of insulin.

Clearly, a normal metabolism depends on a balanced reciprocal relationship between insulin, the product of the B-cell, and glucagons, the product of the alpha-(a) cell. This normal reciprocity is maintained by responses to the changes in nutrient supply governed by feeding and fasting. However, the close anatomical relationship between B- and A-cells may have a purpose, and there is evidence of a communication between these cells within the islet-an example of a paracrine system.

It is implicit in this metabolic scenario that protein and fat metabolism are inextricably bound up with carbohydrate metabolism.

Insulin not only favours the conversion of glucose, amino acids and fatty acids into triglycerides, which are stored in adipose tissue, but as a separate action inhibits the breakdown of triglycerides (TG). It also controls the level of ketone production by the liver. Therefore, when insulin levels are low, as in the normal short-term fasting state, there is a controlled release of TG from fat stores and a controlled formation of ketones by the liver. If there is a little or no insulin (type 1 DM), fat breakdown and ketone formation are not controlled. Decontrolled lipolysis and ketogenesis may also occur if an excess of counterregulatory hormones (stress-induced) occurs in the presence of a low level of insulin production (type 2 DM).

Similarly, insulin favours the formation of protein from amino acids and inhibits protein breakdown. In the fasting state the low level of insulin permits a controlled amount of protein breakdown, thereby making amino acids available to the liver for physiological

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gluconeogenesis. If, however, insulin is absent (IDDM), protein breakdown is decontrolled, so that excessive hepatic gluconeogenesis contributes to the hyperglycaemia, which is therefore due to a combination of underutilization of glucose at cell level and overproduction of glucose in the liver.

**Action of insulin within the cell**

The precise way in which insulin acts is not clear. It is specifically bound to cell membrane by a glycoprotein made up of at least two kinds of polypeptides—subunit A and subunit B. The A subunit binds insulin and the B subunit is associated with the activation of insulin by phosphorylation. It was thought that after binding to the cell membrane insulin generated a signal for transmission within the cell by means of a second messenger, e.g., cyclic nucleotides, calcium, or hydrogen peroxide. This concept has not been proven and it is now considered that bound insulin passes into the cell and is conveyed by the Golgi apparatus to the lysosomes (internalization). Within the cell, the action of insulin may be mediated by a polypeptide derived from the plasma membrane, which acts on protein kinases and on phosphoprotein phosphatases.

The internalization of bound insulin reduces the number of its receptors on the membrane, i.e., down-regulation. Their number is restored by re-externalization of those, which have not been destroyed within the cell, and by reassembly.

Up and down regulation of receptors is not the only ‘local’ control of insulin action. When insulin becomes bound to a receptor on a plasma membrane the configuration of neighbouring receptors is altered so that their affinity for insulin is reduced—this local on-site modulation is called negative cooperativity. By these mechanisms binding is increased when levels of circulating insulin are low, and conversely is reduced when insulin levels are high. Insulin resistance at tissue level will arise if there is a defect in the binding of insulin, because of a reduction in either the number (usual) or the affinity (rare) of receptors. Alternatively, the internalized bound insulin may fail to initiate or to complete the intracellular metabolic cascade.

**Termination of insulin action**

Within the cell, insulin is destroyed by proteases, which break down the disulphide bridges and the A- and B-chains. The enzyme glutathione insulin transdehydrogenase
(insulinase), which splits the disulphide bridges, is present in all tissues, but especially in liver and kidneys.

**Insulin antagonists**

Within the wonderful economy of the body, normality is often dependent on a balance between opposing forces, and this is well exemplified by the maintenance of normal carbohydrate hormones. Thus, insulin lowers blood glucose (regulator) whilst other hormones, e.g. glucagons, catecholamines, cortisol, growth hormone and thyroxine, elevate it. In this sense this group may be regarded as insulin antagonists or counter-regulators. If any one of them is present in excess, the B-cells respond by producing extra insulin, thus restoring the balance of forces. If, however, the B-cell reserve is inadequate, biochemical or clinical diabetes develops, as in acromegaly or Cushing's syndrome. In acromegaly there is an increase in the affinity of insulin receptors but a reduction in their number, whilst steroid excess (iatrogenic or pathological) reduces receptor affinity.

**Insulin and growth**

In the past, when diabetic control in young children was often poor, growth retardation was common, and indeed the combination of growth retardation with enlargement of the liver from fatty infiltration was dignified with a specific name- Mauriac syndromes. It is consoling that this term has almost disappeared from the literature, but minor deficiencies in growth still occur in association with poor metabolic control because insulinopenia, by permitting, excessive gluconeogenesis, diverts amino acids from protein synthesis. For this reason growth charts should be maintained for every diabetic child. These effects of insulin on growth and development are indirect via the general metabolic milieu. There is, however, a specific growth-promoting effect of insulin, which is apparent at high concentrations. The explanation of this effect seems to be that there are specific growth-promoting peptides, which resemble insulin, and are therefore called insulin- like growth factors 1 and 2 (IGF). These peptides, which have powerful growth-promoting effects and weak insulin-like metabolic effects, are bound by specific receptors on plasma membranes of cells. However, although insulin and IGF are immunologically distinct, they are structurally similar and cross-react with their individual specific receptors. As the actions of IGF are not inhibited by anti-insulin antibodies they account for the so-called non-suppressible insulin-like activity demonstrated by the earlier insulin assays.
The short stature of pygmies is due to a selective deficiency of IGF 1, which is the more active growth factor.

It appears that insulin growth factor 1 is important in mediating the somatotropic, effects of growth hormone-hence although circulating growth hormone levels are high in poorly controlled DM, the coexisting deficiency of IGF 1 nullifies its effect growth may be impaired. Insulin, therefore, promotes growth not only indirectly by maintenance of a normal metabolic milieu, but also directly, albeit in a subsidiary role.

**Glucagon**

As insulin is the hormone of the fed state, glucagon is the hormone of the fasting state, because its main function is to maintain the supply of the fuel between meals. A polypeptide made up of 29 amino acids, glucagon is produced in the A-cells of the pancreas. These cells were discovered in 1907 by Lane of Chicago who named them A-cells because they contained granules, which were precipitated by alcohol. Glucagon, which is degraded in the kidney, has a half-life of 5 minutes.

Cells in the small intestine produce a substance, which has the same immunoreactivity as pancreatic glucagons- this substance, known as enteroglucagon, may be convertible to true glucagons.

An arterial BG of about 3 mmol/l is required to deliver glucose to the brain, which uses glucose at a rate of 6 g/h. At rest, other tissues require 4 g/h, so that the whole-body requirement is about 10 g/h. There must, therefore, be a mechanism to sustain BG levels during fasting, and glucagon is the prime hormone for this purpose. The relationship between insulin and glucagon in the circulation is a reciprocal one. In the fed state insulin levels are high and glucagon levels are low, whilst the converse applies in the fasting state. Glucose, fatty acids and ketones, gastrointestinal polypeptide (GIP). Gastrin and secretin in the portal vein inhibit glucagon secretion, whilst amino acids, hypoglycaemia, stress and exercise stimulate it.

As with B-cells, A-cell activity is also influenced by the ventral hypothalamus via the autonomic system and probably by a local control system within the islet itself, whereby A- and B-cells communicate- the paracrine system

The action of glucagon as a provider of circulating nutrients between meals is mediated in the liver, where it promotes glycogenolysis (by activating phosphorylase and inhibiting
glycogen synthetase), gluconeogenesis and ketogenesis. It provides the necessary substrates for this by activating triglyceride lipase, thereby causing the breakdown of triglycerides to glycerol and fatty acids (lipolysis). Glycerol is used by the liver in gluconeogenesis, whilst fatty acids are either burned as a source of energy or used by the liver for ketogenesis. Glucagon also breaks down muscle protein (proteolysis) to provide amino acids, especially alanine, for gluconeogenesis in the liver. These actions of glucagons are most effective when the level of circulating insulin is low—hence the importance of the reciprocal relationship between these two hormones.

During an overnight fast, levels of insulin fall whilst those of glycogen rise, and BG levels are maintained mainly by glycogenolysis in the liver. The available glycogen in the liver is not more than 150 g, and if the fast is prolonged glycogenolysis as a source of glucose is replaced by gluconeogenesis in liver and in the cortex of the kidney.

Unger (1985) has proposed a hypothesis that disordered function of the A-cell may be an integral part of the diabetic syndrome. In all types of DM there is a relative hyperglucagonaemia, but this may be secondary to insulin deficiency, i.e. in the absence of the physiologically appropriate insulin response to hyperglycaemia the normal inhibition of glucagon does not occur. Unger suggests that this simple disturbance of reciprocal circulating hormone relationship is not the complete answer and postulates that there is an inherent disturbance of both A-cell and B-cell functions, i.e. the bihormonal hypothesis. In his view the full expression of insulin deficiency is only apparent in the presence of glucagons. If this hypothesis could be established, there might be a therapeutic role for somatostatin.

A-cell tumours (glucagonoma) lead to glucagons excess and mild hyperglycemia, whilst the rare A-cell failure syndrome leads to fatal neonatal hypoglycaemia.

**Somatostatin-14 or growth hormone release inhibitory hormone (GHR14)**

This regulatory hormone is a 14-amino acid peptide produced in the hypothalamus and in the D-cells of the pancreas. It is so named because it was originally shown to inhibit the secretion of growth hormone. Infusions of somatostatin-14 also inhibit the secretion of insulin, glucagons, TSH, and gut enzymes, and reduce gastric motility, splanchnic blood flow and portal venous pressure. A synthesized view of its many actions would be that it...
is a regulator of nutrient absorption and nutrient disposal designed to prevent flooding of
the carburetor. Experimentally, infusions of somatostatin have been shown to slow the
rate of metabolic derangements when insulin is withdrawn in cases of IDDM, presumably
due to its action in inhibiting the secretion of glucagons.

The pathological counterpart is the D-cell tumour, and such patients have high levels of
somatostatin and low levels of glucagons and insulin. The associated DM is mild adding
weight to Unger's hypothesis that the full expression of DM requires not only insulin
deficiency, but also the presence of glucagons.

Analogues of somatostatin have been used in the treatment of a variety of endocrine
tumours, e.g. insulinomas, and attempts are being made to produce analogues with
specific effects.

The dawn phenomenon

In normal people, tissue sensitivity to insulin is maximal between 2 a.m. and 4 a.m.,
declining thereafter to reach its nadir about noon. Correspondingly, the BG is lowest at
about 3 a.m., rising thereafter to a peak at noon whether or not food is eaten. Circadian
rhythms of insulin antagonists, i.e. cortisol, adrenergic hormones, and particularly growth
hormone, may explain this biological rhythm of glucose. The rising tide of BG at about 6
a.m., called the dawn phenomenon, causes special difficulty in the treatment of DM.

Pathophysiology and classification

As there are many links in the chain of events which maintain euglycaemia, there are
correspondingly many points at which a link may be weakened or broken with a common
end result, i.e. hyperglycaemia. In fact, we should really think of DM as the diabetic
syndrome, and although there are two main types there are also many others, which do
not readily fit into these major categories. Whilst it is not easy to devise a classification
system which will take into account variables such as aetiology, clinical pattern, mode of
therapy, prognosis, etc. It helps our understanding to do so. An attempt to write a
classification based on therapeutic modality illustrates some of these difficulties, for
example.

Insulin-dependent DM (IDDM)

Patients in this group usually develop DM before the age of 30 and are truly dependent
on insulin in the sense that without it they develop diabetic ketoacidosis (DKA) more or

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less rapidly. Within this group the degree of insulin deficiency and therefore the degree of insulin dependence (and proneness to DKA) is variable.

**Non-insulin dependent DM (NIDDM)**

Patients in this group usually develop DM in middle or late life. Many are overweight and respond to calorie restriction; others need oral hypoglycaemics, whilst, in a few, acceptable levels of BG can only be achieved with insulin. These patients are not truly insulin-dependent, as they do not normally develop ketoacidosis when insulin is withdrawn. Strictly speaking, they are insulin requiring non-insulin dependent diabetics. The prevalence of NIDDM shows marked geographical and ethnic variations. In Eskimos the rate is less than 2%, whilst in the Pima Indians of the U.S.A. it is at least 35%. In the Micronesian population of Nauru, 83% of full-blooded Nauruans over 60 have NIDDM. Alternative terms for the main categories of DM are:

Type 1=IDDM
Type 2=NIDDM

Based as it is on age of onset and therapeutic modality, this classification ignores other factors, e.g. aetiology, and within the types specified there are subgroup which can be distinguished on this basis, e.g. DM may be secondary to pancreatectomy or pancreatitis, or may be due to increased circulating levels of insulin antagonist, as in steroid therapy. Cushing’s syndrome, acromegaly, etc.

In spite of these difficulties a standard classification system is essential not only for understanding but also for communication, so that workers may know which type of diabetic syndrome is under consideration when results of treatment, complication rates, etc, are being discussed (Drury MLA, 1986).

**PATHOGENESIS, CLASSIFICATION, PRESENTATION, DIAGNOSIS AND NATURAL HISTORY**

Diabetes mellitus is estimated to affect about 40 million people throughout the world including all races and age groups and both sexes. In Australia 2% of our community is known to be diabetic with four new cases being diagnosed every hour. The detection of new cases is increasing because of more widespread routine urine and blood testing, the
increased incidence of obesity and the advancing age of the community. The diagnosis of diabetes carries with it the imposition of a daily treatment regimen and the high probability of the development of premature and severe atherosclerosis and of the tissue damage caused by disease of small blood vessels, which characterizes the condition.

1. Pathogenesis and Classification

When it was first demonstrated that insulin lowered blood glucose levels it was natural to assume that all diabetes was due to insulin deficiency. While all syndromes of diabetes are associated with hyperglycemia in the untreated state and are due to insufficient insulin action, it is now apparent that, in general, diabetes in younger age groups is associated with deficient insulin secretion, but in the more frequent form seen in older patients, plasma insulin levels are usually high initially implying some resistance to insulin action.

1.1 Primary (Idiopathic) Diabetes Mellitus

These patients are those in whom there is no obvious cause for the development of diabetes. While a family history of the condition is common in diabetes, there are differences in genetic patterns in the two clinically distinct types. In insulin-dependent diabetes mellitus (IDDM) fewer than 10% of first-degree relatives are diabetic and there is less than 50% concordance in identical twins where one develops diabetes. On the other hand, in non-insulin-dependent diabetes mellitus (NIDDM) more than 20% of first-degree relatives are affected and there is a high concordance (>80%) in identical twins after the development of diabetes in one. With certain HLA haplotypes common in IDDM but not in NIDDM and with characteristic clinical differences between the two types of diabetes it seems likely that there are different aetiological factors. Above all, these differences emphasize the fact that diabetes as it is expressed clinically is the end result of many causes, which are becoming better understood with advancing knowledge. Although many features are common to all diabetics whatever the causative factors, the clinical presentation and course are variable and call for different treatment strategies.

1.1.1 IDDM. Insulin-dependent Diabetes Mellitus or Type I Diabetes

This condition is so named because insulin is required to normalize blood glucose levels and prevent progression of the metabolic disorder to ketoacidosis. It has been called
juvenile-onset diabetes in the past because it is the common form of diabetes occurring early in life with a peak at puberty, most cases developing before the age of 45 years. The patient is usually at or below ideal body weight at diagnosis, which commonly follows a few weeks of severe symptoms. Ketonuria is usual at presentation. If the patient is untreated, diabetic ketoacidosis occurs and this is the reason for the alternative nomenclature of ‘ketosis-prone diabetes’. Hence early recognition and institution of insulin treatment are essential.

1.1.2 NIDDM, Non-insulin-dependent Diabetes or Type II Diabetes
This is the commonest form of diabetes, its incidence increasing with advancing years. Most cases occur after the age of 45 years hence the previously used name maturity-onset diabetes. It may be asymptomatic or insidious in onset with symptoms occurring for months before diagnosis. In retrospect after diagnosis, clinical features in the past history may have identified patients as having the potential to develop NIDDM, or there may have been transient biochemical or clinical evidence of diabetes resulting from the stress of associated illness.

Insulin is not indicated for initial control of this type of diabetes, euglycaemia usually being obtained by treatment with diet and oral hypoglycaemic agents. However, in many patients such treatment may fail to maintain control, which can then be restored by insulin. This does not, however, represent a conversion to IDDM, these patients being ‘insulin requiring’ rather than ‘insulin dependent’. Furthermore, patients with NIDDM do not spontaneously become ketoacidosis without adequate treatment even if insulin is later found necessary to maintain euglycaemia (although they may become so with severe intercurrent illness). Because of this, NIDDM is sometimes referred to as ‘non-ketosis-prone diabetes’.

The incidence of NIDDM varies widely in different communities but is usually common in obese, physically inactive population and uncommon in lean, active populations regardless of race. Over 80% of all NIDDM patients are more than 15% in excess of their ideal body weight, with the risk of developing NIDDM increased four-fold in moderate obesity and thirty-fold in severe obesity, the risk depending on the duration as well as the degree of obesity.
A readily recognized but uncommon subgroup of NIDDM occurring in younger patients with dominant Mendelian inheritance has been described and is called maturity-onset diabetes of youth (MODY). Despite the early age of diagnosis (usually in the second or third decade), these patients are not insulin dependent or ketosis prone, nor are obesity a factor. Early suggestions that these patients are less prone to tissue complications have not been substantiated.

1.1.3 Special Forms of Primary (Idiopathic) Diabetes

Development of molecular and cellular investigative techniques have led to the recognition of rare forms of diabetes associated with the formation of insulin with abnormal amino acid sequences, with insulin receptor deficiency or with the presence of antibodies directed against the insulin receptor.

There is a small number families described with clusters of autoimmune diseases including thyroid disease, pernicious anemia, Addison’s disease, hypoparathyroidism and hypopituitarism, who also develop diabetes with islet cell antibodies present. There are other rare genetic syndromes associated with diabetes such as that where diabetes insipidus, optic atrophy and deafness are also present.

1.2 Secondary Diabetes Mellitus

This small group includes patients in whom there is a clear-cut factor associated with the development of diabetes. Depending on the severity of the insulin deficiency or antagonism, the patient may require insulin, although most patients are not ketosis prone. In general, the long-term outcome of the diabetic state is the same as for primary diabetes. It is possible that many of these patients have primary or idiopathic NIDDM, the condition being precipitated by the causative factor.

1.2.1 Pancreatic Disease

Diabetes may result from pancreatitis, appearing occasionally in the acute phase, more often after repeated attacks. It is being seen increasingly often in fibrocystic disease with increasing duration of survival. Surgical pancreatectomy does not cause diabetes unless about 90% of the pancreas is removed. Diabetes is often present with pancreatic
carcinoma, the cause being unclear when it occurs in the absence of extensive pancreatic destruction.

Haemochromatosis is associated with diabetes (bronze diabetes) in two-thirds of such patients, where it is generally considered to be due to beta-cell damage.

1.2.2 Diabetes and Endocrine Diseases

Excessive production of the insulin antagonistic hormones (growth hormone, glucocorticoids, glucagon and catecholamines) occurs in acromegaly, Cushing's syndrome, glucagonoma and phaeochromocytoma, and is responsible for the high incidence of diabetes in these conditions. Additionally, diabetes is more commonly associated with thyrotoxicosis than by chance, an autoimmune aetiology being common to each disease and with the increased metabolic rate of thyrotoxicosis being an additional contributory factor.

1.2.3 Stress Diabetes

Hyperglycaemia seen in predisposed individuals subject to a variety of stresses (traumatic, metabolic and physiological) is in part due to increased secretion of insulin antagonistic hormones and usually resolves when the stress is withdrawn. Myocardial infarction, severe peripheral vascular disease with ischaemic gangrene and severe infections are clinical states where hyperglycemia at levels consistent with diabetes may develop, to return to normal after the precipitating illness remits. Such patients are predisposed to the later spontaneous development of diabetes.

1.2.4 Gestational Diabetes

Pregnancy is a diabetogenic stress since hormones which are secreted in increased amounts in pregnancy (oestrogen, progesterone, human chorionic gonadotrophin, somatomammotrophin and corticosteroids), may antagonize the action of insulin and promote hyperglycemia. Consequently many patients manifest diabetes for the first time during pregnancy (gestational diabetes) and pre-existing diabetes usually requires increased insulin dosage. Most patients return to the pre-pregnancy state after delivery, but many women with gestational diabetes subsequently become permanently diabetic.
1.2.5 Drug-associated Diabetes

Thiazide diuretics and phenytoin may impair insulin secretion and oestrogen induces a state of insulin resistance. These drugs, together with glucocorticoids, are the most common drug precipitants of diabetes, but they are uncommon causes. Cessation of the drug may allow return to the pretreatment state.

2. Clinical Presentation

The classical symptoms of diabetes are thirst, polyuria, tiredness, weight loss, blurred vision, and skin and genital infection particularly carbuncles and monilial vaginitis. They are widely known, easily recognized and when associated with glycosuria are virtually diagnostic. However, particularly in NIDDM, they may not be present or may be gradual in onset, or masked by other factors such as diuretic therapy or prostatism, and one symptom may be predominant. Routine urine testing increases the recognition rate of diabetes in such patients.

The absence of symptoms may allow the persistence of significant hyperglycemia for long periods exposing the patient to possible tissue damage. Hence, the absence of symptoms at diagnosis does not indicate ‘mild’ or ‘benign’ diabetes. Many patients with NIDDM have ischaemic heart disease, peripheral vascular disease and retinopathy at the time of diagnosis and, although other factors may be involved, long-standing asymptomatic diabetes or unrecognized diabetes are probably important. While IDDM usually presents with classical symptoms of short duration, it may present with the severe metabolic disorder of ketosis and acidosis should earlier symptoms remain unrecognized and untreated.

Although NIDDM does not progress spontaneously to diabetic ketoacidosis, as does IDDM, the long-continued osmotic diuresis of diabetes, if not balanced by appropriate fluid intake and particularly if associated with severe intercurrent illness or infection, may lead to the development of hyperosmolar non-ketosis coma which carries a very high mortality rate.

As well as these common presentations of diabetes other cases will be diagnosed because of the recognition of typical complications, such as cataracts, gangrene, mononeuropathy or impotence.
Clinical assessment including a detailed history and physical examination will detect secondary diabetes and associated disorders. Further investigation is determined by the physical findings.

It is estimated that approximately one per cent of the population has undiagnosed diabetes. Many of these people are completely asymptomatic. Routine urine and (where indicated) blood glucose estimations at all clinical examinations are recommended. These will result in an increasing proportion of asymptomatic patients being diagnosed.

3. Diagnosis of Diabetes Mellitus

Laboratory diagnosis of diabetes is based on plasma glucose measurements in conjunction with clinical assessment. The diagnostic criteria have been re-evaluated in recent years and the figures quoted and accepted throughout Australia are very similar to those carrying the imprimatur of a WHO Expert Committees on Diabetes.

In a patient with symptoms suggestive of diabetes mellitus, the finding of either a fasting plasma glucose level of 8.0 mmol/L or more on two occasions or a random plasma glucose level of 11.0 mmol/L or above two hours or more after a meal is diagnostic. With symptoms and diagnostic glucose levels, particularly where ketonuria is present, glucose tolerance testing introduces an unnecessary delay in initiation of urgent treatment. Figures below 6.0 mmol/L fasting or 8.0 mmol/L after food exclude the diagnosis, although such findings in children in whom the clinical evidence is strong must be viewed with suspicion. Intermediate levels call for glucose tolerance testing.

In an asymptomatic patient with glycosuria, a glucose tolerance test should be performed using a 75g glucose load with plasma glucose levels as the standard (these are around 15% higher than whole blood levels). Thus, knowledge of the specimen tested (plasma or whole blood) is important in the interpretation of results.

The criteria for plasma glucose levels are as follows.

<table>
<thead>
<tr>
<th>Plasma glucose level (mmol/L)</th>
<th>Fasting</th>
<th>1 hour</th>
<th>2 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance</td>
<td>&lt; 6.0</td>
<td></td>
<td>&lt; 8.0</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>6.0-8.0</td>
<td>8.1-10.9</td>
<td>8.1-10.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&gt; 8.0</td>
<td>&gt; 11.0</td>
<td>&gt; 11.0</td>
</tr>
</tbody>
</table>
Although progression from impaired glucose tolerance to diabetes is the exception rather than the rule, female patients with impaired glucose tolerance are at risk of developing large vessel disease. Thus the diagnosis of impaired glucose tolerance (IGT) avoids the need for the label 'diabetes' but carries with it the need to treat risk factors for diabetes and vascular disease.

Gestational diabetes is that which occurs de novo during pregnancy. Although a clear nexus between the WHO criteria for categorization as IGT and fetal morbidity has not been established, patients with IGT should be managed as diabetic since there is evidence of increased fetal morbidity and mortality in such women if the condition is not treated as diabetes.

Standard criteria are applicable in the diagnosis in children, with the glucose load adjusted by weight.

4. Natural History

The natural history of diabetes is very variable and although many surveys point to the gradual and progressive development of tissue complications, it is unwise to extrapolate from these statistics when counseling an individual patient. For reasons, which are not yet fully apparent, diabetics of an outwardly similar disposition may live a normal life span with little evidence of complications, or may die prematurely with extensive microvascular or macrovascular disease.

In most countries diabetes features prominently as a cause of blindness, renal failure, peripheral vascular disease, ischaemic heart disease and stroke. Because of these life-threatening complications the average life span is reduced by up to one-third of its potential from the time of diagnosis, particularly in younger patients.

It is rare for IDDM patients to have clinically recognizable tissue changes at the time of diagnosis, such changes beginning to appear after 10 to 15 years. In NIDDM, on the other hand, tissue changes may be present at diagnosis and tend to occur sooner in patients initially unaffected.

As well as this progression of the underlying disease, many patients with IDDM will experience fluctuations in the control of diabetes or complications of therapy, particularly
hypoglycaemia. Episodes of symptomatic glycosuria are common in poorly controlled patients, often because such patients are afraid to increase the insulin dose for fear of hypoglycaemia. Some patients experience few problems in maintaining euglycaemia, requiring little modification of treatment, others may need to monitor their response closely and constantly adjust treatment. While ketoacidosis and coma are not common their occurrence is always possible in IDDM patients (Taft P, 1920).

MODALITIES AND AIMS OF TREATMENT

The short-term aims of treatment in diabetes are to achieve maximal reversal of the metabolic abnormalities and minimal interference with the desired lifestyle of the patient. These two aims are not mutually exclusive; one of the major advances in the management of diabetes in the last decade has been the realization that greater participation of the diabetic in his own management can increase the chances of achieving both goals. The long-term aim of treatment is prevention of the vascular and neuropathic complication of diabetes. There is a widely held belief that control of hyperglycaemia may reduce the risk of development of microvascular complication, and that smoking, hypertension, and abnormalities of serum lipids also contribute to macrovascular risks. Thus attention is directed towards control of these risk factors.

The therapeutic modalities available include diet, oral hypoglycaemic agents and insulin. Integrated with these specific therapeutic measures are a programme involving exercise, surveillance of blood pressure with control of hypertension, and encouragement to cease smoking. Such a programme should be advocated for the community at large, but it is of particular importance for diabetic subjects. Education of the diabetic subject increases the effectiveness of management, both by giving the patient knowledge of the appropriate therapeutic response to unforeseen circumstances and by improving treatment compliance.

1. Diet

The general aims of dietary treatment are; achievement and maintenance of ideal body weight; prevention of excessive glycaemic excursions; and provision of a balanced, nutritionally correct diet, with the least potential to cause atherosclerosis or hypertension.

*Jamia Hamdard* 24 *Ph. D. Thesis*
Although rapidly absorbed highly refined carbohydrate should be avoided (except in emergency situations), the proportion of carbohydrate in the diet need not be as strictly limited as it has been, since it has been shown that insulin sensitivity and glucose tolerance suffer if the intake of carbohydrate is severely restricted. On the other hand, there is ample evidence that unrefined carbohydrate exceeding 50% of total calories does not render diabetic control more difficult. Inherent in this contemporary approach to diet is the constraint on total caloric intake limited to the patient’s needs; this implies reduction in the number of calories from fat and protein to accommodate the increased number of carbohydrate calories.

Thus, the major constraints on carbohydrate intake are the use of unrefined carbohydrate, the distribution of the carbohydrate intake in relation to insulin administration and exercise and regulation of caloric intake.

2. Oral Hypoglycaemic Agents

The unnecessary use of pharmacological agents will be avoided if the use of these drugs is reserved for patients with NIDDM who fail to respond adequately to a trial of appropriate dietary treatment.

2.1 Sulphonylureas

Included in this group are a variety of drugs differing from one another in their relative hypoglycaemic potency, duration of action and frequency of administration. While glymidine is included in this list, it is chemically sufficiently different not cross-react in drug sensitivity caused by other sulphonylureas. No drug possesses unique hypoglycaemic properties, which make it preferable to others, and selection is based on experience. As a general rule it is wise to avoid the use of potent long-lasting agents in elderly patients whose diet may be erratic and in whom protracted hypoglycaemia would be dangerous.

An added stated indication for the use of gliclazide is its platelet antiaggregation properties, potentially improving capillary blood flow in critical areas such as the retina and the glomerulus. Dermatological, gastrointestinal, haematological and hepatotoxic side effects have been described with the use of sulphonylureas, but are rare. Since metabolism of all these drugs occurs to a variable extent in the liver and they are excreted...
in the urine they should be prescribed with caution in the presence of liver disease and in states of renal insufficiency where drug accumulation may result in overdosage.

2.2 Biguanides

Metformin is the only biguanide in clinical use. The tablet is 0.5 g and is given in divided dosage with a maximum dose of 3 g. Gastrointestinal symptoms such as anorexia, nausea, abdominal discomfort and diarrhoea are the only side effects of this drug and are uncommonly experienced when slow-release preparations are used except in large doses. While lactic acidosis is an extremely uncommon toxic effect, the risk of its occurrence can be limited by avoiding the use of metformin in patients with impaired hepatic or renal function (a serum creatinine level greater than 0.11 mmol/L excludes its use), since drug levels will rise with impaired metabolism or excretion. States of anoxia due to heart or lung disease also add to the risks of development of lactic acidosis and are contraindications.

Metformin can be used alone or in combination with a sulphonylurea. It may be chosen as the first oral agent after failure of diet to control hyperglycaemia in NIDDM, or in patients where blood and urine sugar levels remain high despite treatment with diet and a sulphonylurea.

3. Insulin

3.1 Indications for the use of Insulin

Insulin is required in IDDM, in NIDDM where diet and oral therapy fail to achieve adequate metabolic control, or in circumstances where the use of oral agents may be hazardous, such as hepatic or renal failure. In symptomatic patients with high blood sugar levels where categorization as IDDM or NIDDM is difficult, it is safer to initiate treatment with insulin, withdrawing it later if appropriate. Insulin may be used temporarily in pregnancy or in patients on oral hypoglycaemic agents where control is disturbed by surgery, intercurrent illness or drugs exacerbating hyperglycaemia (such as corticosteroids).

3.2 Insulin Preparations

In general, the insulins in common use can be considered in three groups, based on their action profiles.
3.2.1 Short-acting Insulin Preparations

Examples are regular or soluble, neutral (Actrapid, Nuralin, Velosulin) and semilente. These begin to act within an hour of subcutaneous administration, have their maximal effect by about four hours after administration, and cease to act after eight hours (slightly longer for semilente insulin). It should be noted that these action profiles are only guides, as considerable variation is observed between individuals.

These insulin (particularly regular or neutral) are used in the management of hyperglycaemic emergencies. Where rapid action is required, as bolus injections before meals, or in combination with longer-acting insulin. Regular insulin and semilente insulin have been used in the past in a twice-daily regimen, but their short duration of action make them less than ideal for twice-daily administration in most subjects.

3.2.2 Intermediate-acting Insulin Preparations

Examples are NPH or isophane, lente, Rapitard, Monotard, Mixtard, Bitard. These insulins have a slower onset of action (although Bitard, Mixtard and Rapitard have a component of rapidly acting insulin), have their maximal action eight to 12 hours after administration, and can have a hypoglycaemic effect lasting 18 to 24 hours. They can be used alone or in combination with a short-acting insulin in once or twice daily regimens.

3.2.3 Long-acting Insulin Preparations

Examples are ultralente and protamine zinc insulin (PZI). These insulins have a slow onset of action, a maximum action at 12 to 18 hours, and a duration of about 36 hours.

3.3 Insulin Regimens used for Maintenance

Some diabetic subjects are well controlled with a single daily injection of insulin (usually an intermediate-acting insulin, alone or given together with a short-acting insulin) given about 10 to 15 minutes before breakfast.

There is an increasing trend to the use of a twice-daily regimen, particularly in younger subjects. This provides better glycaemic control with less risk of hypoglycaemia. It also allows greater flexibility in relation to the evening mealtime, and the amount of exercise taken late in the day. A versatile regimen which can be modified to fit most requirements is a twice-daily injection (before breakfast and before the evening meal) of a mixture of short and medium acting insulin. Using this regimen, the diabetic or his doctor can...
respond to consistently high or low glucose levels before lunch by altering the morning short-acting insulin, in the afternoon by altering the morning intermediate-acting insulin, at suppertime by adjusting the evening short-acting insulin, or during the night or before breakfast by adjusting the evening intermediate insulin. As a rough starting guide, about two-thirds of the total dose can be given in the morning, and about one-third in the evening, with two-thirds of each dose as intermediate-acting insulin. Home blood glucose monitoring aids greatly in optimizing the regimen for each individual.

Other regimens, such as a background dose of long-acting insulin with short-acting insulin before each meal, are favoured in some centres. Administration of short-acting insulin by continuous subcutaneous infusion is undergoing intensive evaluation, but at present the use of this technique should be restricted to specialized centres.

The range of porcine and bovine insulins with different profiles of action includes also a range of purities with respect to the presence of small amounts of non-insulin protein. While insulins now contain less non-insulin protein than those produced a few years ago, there are some which are more highly purified (Rare Immunogenic insulins, Nordisk: Monocomponent, Nova; insulin 2 range, CSL). There is no consensus regarding the need for the use of porcine insulins of high purity. However, on the grounds of lesser antibody production, fewer injection site problems, lower dose requirement and fewer immunological consequences in the event of interrupted treatment, there is a body of opinion which recommends the use of these highly purified insulins particularly in young IDDM patients.

4. Exercise

Regular exercise has favourable effects on body weight, plasma lipids and insulin sensitivity and is a recommended part of the diabetic’s lifestyle. The form of exercise varies according to the age and preference of the individual. In general, regular moderate rather than sporadic violent exercise is advocated, just as it in nondiabetics. No particular activity need be barred except where potentially hazardous sports (such as scuba diving, hang gliding, rock climbing) may become exceedingly dangerous in the event of hypoglycaemia.

Exercise in an insulin-treated diabetic tends to lower the plasma glucose level; thus extra carbohydrate should be taken before exercise, which is outside the range of normal
activities. Experience soon determines the requirement for supplementary carbohydrate in circumstances where regular repeated exercise is undertaken, such as tennis, squash, swimming and jogging. Twenty grams of carbohydrate before exercise is a reasonable starting point, the result of which can be assessed preferably by blood glucose estimation.

5. Education

Education in self-management is a central part of the treatment of every diabetic subject. Education should occur at every contact between the diabetic and those involved in his management. Enthusiasm for organized group teaching should not obscure the need for individual discussion and instruction. The aim should be to develop self-reliant, confident diabetics who are able to meditate good control, to cope with every eventuality with a minimum of trouble and to recognize circumstances, which require medical assistance (Taft P, 1920).

ORAL HYPOGLYCAEMIC AGENTS

Oral hypoglycaemic agents (OHA) are only effective in NIDDM patients who retain some β-cell function. If hyperglycaemia is not adequately controlled when OHA are first prescribed the failure is described as primary. In those who respond initially there is an annual secondary failure rate of about 5%. Some secondary failures are due to neglect of the nutrition plan, but most are examples of true drug failure. Within the group of secondary failures are some patients who were not NIDDM at all but slowly evolving IDDM culminating in total loss of β-cell function.

Sulphonylureas

In 1941 Janbon, a French physician noted that some typhoid patients on treatment with a sulphonamide developed hypoglycaemia. Loubatières showed that this effect was mediated through the pancreas and this led to the introduction in 1954 of sulphonylureas especially for the treatment of DM. Their general structural formula is:
but there are many variations on this basic structural theme. By the introduction of an
acylaminoalkyl group at position 4 in the benzene ring preparations were developed
which were much more efficacious on a weight-to-weight comparison—these are called
second-generation sulphonylureas. There is no evidence that they are superior.

Mode of action of sulphonylureas

As the hypoglycaemic action of sulphonylureas depends on the presence of some β-cell
function they are ineffective after pancreatectomy and in fully developed IDDM, i.e.,
those with severe insulinopenia. The actions of sulphonylureas include the following:
1. An increase in the basal output of insulin and in the nutrient-stimulated secretion of
insulin from the β-cell. This action may be mediated by a decline in cell membrane
potassium permeability.
2. A reduction in hepatic glycogenolysis and gluconeogenesis so that the basal output of
glucose from the liver is reduced.
3. A reduction in the release of glucagon from the α-cells.
4. A reduction in the absorption of glucose from the gut.
5. An increase in the production of the insulinotrophic hormones in the gut, i.e., secretin
and gastrointestinal polypeptide.
6. An increase in the number and affinity of insulin receptors on the cell membranes.
7. This effect is most pronounced with second-generation sulphonylureas.
8. Improvement in post-receptor response within the cell.
9. An inhibition of the release of catecholamines, diminishing their negative effect on
insulin secretin.
10. Some correction of the haemotological malfunctions, which may play an aetiological
role in microangiopathy.
Some of these responses may be indirect, i.e., due to the direct effect of sulphonylureas in increasing the output of insulin. The stimulating effect on β-cell function does not appear to last for more than a year. Although this has been interpreted to mean that the short and long term effects of sulphonylureas are different, it is more likely that the apparent reduction of effect of β-cells is due to the lower levels of BG which by then pertain. If BG levels are artificially elevated the stimulant effect of the drugs on β-cell function is again demonstrable. Furthermore, as hyperglycaemia itself may disturb normal metabolic processes, the restoration of normoglycaemia by any means diminishes the hepatic output of glucose and improves the peripheral action of insulin.

**Pharmacokinetics**

As sulphonylureas are highly protein-bound they may interact with many other drugs. Most are metabolized in the liver, but in some cases the metabolites are so active that the hypoglycaemic action is prolonged. Others are excreted unchanged via kidney. Hence it is important to be conscious that hepatic or renal impairment will influence the Pharmacokinetics of these drugs, e.g., the action of chlorpropamide which has a long half-life will be very prolonged indeed in the presence of hepatic and/or renal disease.

**Chlorpropamide**

As chlorpropamide is very potent and has a long half-life it should be used with caution in the elderly who, if they miss a meal, may become hypoglycaemic. This is especially likely if there is any defect of hepatic or renal function because there is variable hepatic metabolism to active metabolites and the renal excretion of the unchanged drug averages 6-60% of the administered dose. Hypoglycaemia in association with chlorpropamide is profound and prolonged because of its long half-life. Dialysis is not helpful because it is not dialyzable.

**Gliclazide**

It has been suggested that this drug has certain advantages over and above its hypoglycaemic role, e.g., that it does not cause weight gain and that it protects against retinopathy by reducing platelet adhesiveness and aggregation, by increasing thrombus formation. However, these effects may be due to control of hyperglycaemia rather than to any direct effect of the drug. In animals it delayed the appearance and hastened the clearance of experimentally induced thrombi. As it is not eliminated by the kidney and
has a relatively short duration of action it may be useful in elderly subjects and in the presence of renal failure.

The varying potency and duration of action within the group provides a wide choice. Chlorpropamide is very potent and its long half-life permits a once-daily regime. For these very reasons it is not the wisest choice in the elderly, who at times may not eat adequately and thereby run the risk of profound hypoglycaemia. It is metabolized in the liver and excreted by the kidney, and if there is any suggestion of impairment of function in these organs it should not be used.

Gliclazide is potent and if the claim that it does not promote weight gain and protects against retinopathy can be confirmed it could be the drug of choice. In the elderly or in the presence of renal impairment, tolbutamide is safe because it is not very potent and has a short half-life. Gliquidone may also be useful in this situation because it is extensively metabolized and its metabolites are inactive.

**Adverse effects of the sulphonylureas**

Hypoglycaemia is most likely with the long-acting drugs and may be profound, prolonged and relapsing, especially in the elderly. The response to glucagon may be blunted because sulphonylureas inhibit glycogenolysis in the liver. Allergic skin rashes, photosensitization, antithyroid activity, nausea, vomiting and diarrhoea occasionally occur. Patients who are allergic to sulphonylureas may not show a cross-reaction to the sulphapyrimidine drug glymidine, which may thus be useful as a fallback.

The disulfiram (Antabuse) reaction with alcohol, whilst seen especially with chlorpropamide, may also occur with tolbutamide. If bothersome, an alternative sulphonylurea may be tried, but if the patient has an alcohol problem, this adverse reaction may be useful fringe benefit. Rare reactions include cholestatic jaundice and bone marrow depression. The occasional occurrence of an ADH syndrome has already been described.

Coexisting renal or hepatic disease demands careful drug selection. In the elderly, impaired renal function and/or hepatic detoxification mechanisms result in prolonged action with increased risk of hypoglycaemia. Less potent short-acting preparations should be used in such cases. Although there has been no evidence of teratogenesis the author does not prescribe these drugs if conception is possible. Withdrawal of the drugs when a period has been missed is of no value, as embryogenesis is by then well advanced.
Furthermore, OHA may not provide the optimal control, which is essential for the developing fetus.

**Drugs which augment action of sulphonylureas**

*Alcohol  
Anabolic steroids  
Bishydrocoumarin  
Guanethidine  
Methotrexate  
MAO inhibitors  
Phenylbutazone

*Acute intake of alcohol may cause hypoglycaemia by interfering with gluconeogenesis.

**Drugs, which antagonize action of sulphonylureas**

Corticosteroids  
Frusemide  
Thiazides  
Anovulants  
Rifampicin

*Chronic alcohol intake may reduce the duration of action of OHA by enzyme induction.

**Biguanides**

Biguanides are derivatives of guanidine with a common chemical core

\[
\text{NH} \quad \text{NH} \\
\text{C-NH-C-NH}_2
\]

Phenethylbiguanide or phenformin was withdrawn because of a tendency to cause lactic acidosis. Buformin (1-butyl-biguanide hydrochloride) is used in some European countries as a sustained-release preparation in a dose of 100-300 mg daily.

**Dimethylbiguanide or metformin**

This is the only biguanide now in use in the UK and Ireland. It is not metabolized but is eliminated via the kidneys by glomerular filtration and active secretion and has a half-life of four hours. The maximum daily dose is 2 g.
Mode of action
As biguanides do not stimulate insulin secretion they do not lower BG in normals and rarely cause hypoglycaemia in diabetics. Nevertheless, some residual β-cell activity is necessary for their action. They are concentrated in the intestinal wall, and they alter the tolerance to oral dextrose more than to intravenous dextrose. They diminish the absorption of glucose and amino acids, possibility by inhibiting active transport mechanisms. By an effect on insulin receptors they increase peripheral glucose uptake in muscle but not in fat. At high dosage levels they decrease gluconeogenesis in the liver and the consequential increase in blood lactate becomes important in certain circumstances, e.g., in the presence of renal or hepatic disease, anoxia, or heavy alcohol intake. Malabsorption of amino acids, B₁₂ and folate has been reported after long-term use, but it is doubtful if this ever reaches clinical significance. Biguanides cause significant weight loss and are therefore the drug of choice in overweight patients who do not respond to dietary restriction.

Adverse reactions
These include metallic taste, nausea, vomiting, abdominal cramps and diarrhoea, offensive flatulence, weight loss and a general lack of well being.

Although lactic acidosis is very uncommon with metformin, it should not be used in patients with impaired renal function and ideally it should be avoided in alcohol abusers or when there is a special risk of anoxia as in patients with cor pulmonale.

Use and misuse of oral hypoglycaemics
The correct use of OHA depends on the realization that they are of two separate families with differing modes of action. Combinations of drugs from different families may result in synergism, but combinations from within the same family have no merit. Clinicians should be familiar with the pharmacodynamics of chosen agents, as their metabolic pathways differ; e.g., tolbutamide has a short action because it is carboxylated in the liver to carboxytolbutamide, which is metabolically inert. On the other hand, chlorpropamide is very firmly bound to protein and metabolized slowly so that it has a long action. Acetohexamide is changed rapidly in the liver to the more potent L-hydroxyhexamide, which is then excreted by the kidney.
Patients vary considerably in their handling of these drugs and the half-life times commonly cited should only be regarded as guides. Obviously, choice of drug should be related to integrity of hepatic and renal function.

Common errors in the use of oral hypoglycaemics include the following:

1. Use without establishing the correct clinical diagnosis
When insulin was the sole therapeutic agent, treatment was initiated in hospital after the diagnosis of DM had been confirmed by blood glucose analyses. Since the oral agents became available, it is not unusual to see patients who have been placed on OHA without appropriate confirmation of the diagnosis.

2. Use when contraindicated
In general, OHA are ineffective in those who have developed diabetes before the age of 30 years. There is no evidence that the use of biguanides in combination with insulin has any value.

3. Unnecessary use
Many maturity-onset diabetics, especially if overweight, can and should be controlled by dietary restriction alone. In such patients, OHA should not be prescribed until a determined effort at calorie restriction has been made.

4. Use incorrect dosage
It should be understood that there is a point of no return beyond which increments of dosage result in little improvement and that toxic effects are often dose-related.

5. Incorrect combinations
It is often helpful to seek a synergistic effect by combining a member of the sulphonylurea family with a biguanide. There is, however, no merit in combining two members of the same family, e.g. chlorpropamide and tolbutamide.

6. Initial use without supervision
Even when circumstances seem propitious, it should be assumed that OHA will be successful. On initiation of treatment, the patient should be seen frequently to detect primary failure, which occurs in 10-30%, depending on case selection.

7. Continuing usage during stress
During stress, e.g. infection, trauma, surgery, metabolic control may deteriorate so that a temporary transfer to insulin becomes necessary.
Initiation of oral hypoglycaemic therapy

The treatment should not begin until the diagnosis has been firmly established by clearly abnormal blood glucose levels or by OGTT. In overweight patients the initial approach should be by dietary restriction and this should continue for at least four weeks before concluding that the regimen has failed or that the patient cannot or will not cooperate. The uncooperative cannot be permitted to continue out of control, and OHA should be used, albeit reluctantly.

It is not possible to predict the response to oral agents even when circumstances seem most favourable, and 10-30% of apparently suitable cases fail to respond adequately (primary failure). In some cases a partial response to a sulphonylurea may be made completely by the addition of a biguanide or vice versa. This is a matter of trial and error. Contrary to expectations, modest Ketonuria does not necessarily preclude a response, nor does absence of Ketonuria guarantee one, but a history of full-blown ketoacidosis is a contraindication to OHA. A high fasting blood glucose suggests, but does not necessarily guarantee, failure. In some cases of NIDDM, especially if the diagnosis has been delayed, the β-cells may be temporarily exhausted and therefore unresponsive to oral agents. After a period on insulin, enough β-cell function may return to permit the use of tablets for some time at least.

The therapeutic programme should be planned in the following sequence:

A. Non-insulin dependent diabetes (NIDDM)-overweight
1. Nutrition plan (low-calorie) for 4-6 weeks with increased exercise.
2. If BG levels are unacceptable at that stage metformin, beginning with 500 mg per day and working up gradually as required to the maximum dosage of 1 g t.i.d. over a further 4-6 week period.
3. If hyperglycaemia continues, add a sulphonylurea in full dosage for two weeks.
4. If hyperglycaemia persists although compliance is assured, and if no interacting drug is being used, OHA should be replaced by insulin.

B. NIDDM-normal body weight
1. Nutrition plan for 4-6 weeks.
2. If BG is still too high add a potent sulphonylurea in full dosage for two weeks.
3. If BG levels are still unacceptable add metformin working up slowly to maximum dosage.

4. If control is still inadequate-use insulin.

C. NIDDM with significant loss of body weight

Insulin is used until body weight is acceptable-then proceed as in B.

Patients on OHA may lose control during any stressful illness or during a phase of dietary neglect. In such cases responsiveness may return after a short spell on insulin. In others, control is permanently lost (secondary failure), and in such cases insulin is required permanently. The rate of secondary failure is about 5% per year.

Secondary failure is sometimes explainable by the fact that the case was not a NIDDM but a slowly evolving IDDM in whom, total β-cell failure ultimately occurs.

As always, the target depends on many considerations, e.g., age, but ideally the FBG should be 6-7 mmol/l and the post-prandial 8-10 mmol/l. in patients under 60 with a prospective life-span of 15-20 years during which complications may develop, criteria of control should be more strict than in those aged 70 or more in whom the aim may be to control symptoms.

Primary and secondary failure rates are to some extent determined by case selection to diet and by the clinician’s view of what constitutes adequate control.

In patients who have been well controlled for some time on OHA, the dose should gradually be reduced, as some cases may then be controllable by diet alone. When tablets are withdrawn strict adherence to diet and close surveillance with frequent monitoring are essential (Drury Ml b, 1986).
### TYPES OF ORAL HYPOGLYCAEMIC AGENTS

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Daily per day</th>
<th>Frequency of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. SULPHONYLUREAS (SU)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First generation Chlorpropamide</td>
<td>100-500 mg</td>
<td>1</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500-2500 mg</td>
<td>2-3</td>
</tr>
<tr>
<td>Second generation Glibinclamide</td>
<td>2.5-20 mg</td>
<td>1-2</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5-20 mg</td>
<td>1-3</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>80-320 mg</td>
<td>1-2</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1-8 mg</td>
<td>1</td>
</tr>
<tr>
<td>Lipizide XL</td>
<td>5-20 mg</td>
<td>1</td>
</tr>
<tr>
<td>Gliclazid MR</td>
<td>30-120 mg</td>
<td>1</td>
</tr>
<tr>
<td><strong>2. NON-SULPHONYLUREA AGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Meglitinide analog Repaglinide</td>
<td>1.5-10 mg</td>
<td>3</td>
</tr>
<tr>
<td>b. Biguanides Metformin</td>
<td>25-2500 mg</td>
<td>2-3</td>
</tr>
<tr>
<td>c. Alpha glucosidase inhibitors Acarbose</td>
<td>25-300 mg</td>
<td>3</td>
</tr>
<tr>
<td>d. Thiazolidinediones Rosiglitazone</td>
<td>2-8 mg</td>
<td>1-2</td>
</tr>
<tr>
<td>Piozitazone</td>
<td>15-45 mg</td>
<td>1</td>
</tr>
</tbody>
</table>

(The Week, 2003)

### INDIGENOUS PLANTS USED IN THE CONTROL OF DIABETES

Many herbal remedies, individually or in combination with different formulations such as leaf-powder, pastes, decoctions and infusions, pills etc. have been recommended in various medical treatises. Indian Materia Medica has also recorded many drug items not necessarily of tried value but collected from the folklore and traditional practices. No medicine capable of giving radical cure of diabetes has yet been discovered. Insulin therapy has made great strides in the past five decades but with certain limitations. In the recent years attention is, however, paid to study the biochemical modus operandi of the diabetic syndrome and connected factors. This knowledge on insulin antagonists, bound insulin degradation and other aspects of carbohydrate metabolism has now widened the spectrum of the possible mechanism of drug action in diabetes mellitus (with sugar in urine).

-- Jamia Hamdard

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Ph. D. Thesis
Some of the earlier workers mentioned the use of herbal and mineral preparations for the treatment of this disease. Nadkarni’s Indian Materia Medica gives the names of 42 plants, which are considered to be useful in diabetes. Mukherji has given a detailed account of about a dozen of the important indigenous plants with regard to their pharmacognosy, chemistry, pharmacology and therapeutic uses. Ajgaonkar also describes potential plants for similar uses. Aiman listed 35 plants, which have been tested clinically for the curative properties in the last two decades. Chaudhury and Vohora have reviewed the work done on 21 plants for their antidiabetic activity. Karnck enumerates some aspects of 16 crude India drug plants, frequently used as a cure for diabetes in Ayurvedic system of medicine. Israili gives a detailed account of diabetes with reference to Unani system of medicine and lists drugs with hypoglycaemic antidiabetic activity. Among other sources this list includes 100 plants, which have been known to possess specific property to control diabetes.

In the recent years the emphasis has been to identify as many plants as possible which could have effective control of the disease, if not able to completely cure the same. Pharmacological screening and clinical trials, as reported by subsequent and recent workers, reveal the presence of hypoglycaemic activity in a large number of plants, hitherto not reported.

It has been found that about 75 Indian plants have been known to possess the hypoglycaemic activity. Of these plants tried, only ten, viz., *Allium cepa*, *Coccinia indica*, *Ficus bengalensis*, *F. glomerata*, *Gymnema sylvestre*, *Momordica charantia*, *Pterocarpus marsupium*, *Rauwolfia serpentina*, *Scoparia dulcis* and *Syzygium cumini* have been studied in detail. Some of these plants are being used by practitioners of indigenous systems of medicine either singly or in combinations with other plants. Fourteen plants, viz., *Allium cepa*, *Anacardium occidentale*, *Clerodendrum phlomidis* (Crude drug Arani), *Dolichos lablab*, *Enicostemma littorale*, *Ficus bengalensis*, *gymnema sylvestre*, *Momordica charantia*, *Olea europea*, *Orthosiphon spiralis*, *Pterocarpus marsupium*, *Rauwolfia serpentina*, *Scoparia dulcis* and *Syzygium cumini* have been tried on human beings, though not to the extent where they can be taken as drugs.

Conflicting reports on the hypoglycaemic activity of some of the plants may be attributed to a number of variables such as botanical identity of the drugs, time and place of
collection of plant material, mode of administration of the drug and the type of experimental animal.

The drugs, which have consistently shown significant hypoglycaemic activity and have low toxicity, need intensive screening. It is important to note that these drugs be investigated under the conditions similar to those followed by the practitioners of indigenous system of medicine. Undue emphasis should not, however, be laid on the pure hypoglycaemic principles from the crude drugs as they may have some adverse side effects (Nagarajan et al., 1982).

There may be several possible mechanisms of action of the active principles from plant sources. They may;

1. Act on $\beta$-cells of the pancreas and stimulate the secretion of insulin,
2. Inhibit $\alpha$-cells or hyperglycaemic factor,
3. Enhance the effect of insulin and adrenaline,
4. Assist in inhibiting the synthesis of glucose-6-phosphate phosphatase, fructose diphosphatase, pyruvate carboxylase or phosphoenol pyruvate carboxylase and stimulate the synthesis of glukokinase.

A review of the chemistry and other related work on the uses of ergot alkaloids, which may possess hypoglycaemic activity has been published. Baender emphasized the significance of sulphonylureas as a hypoglycaemic antidiabetic drugs. Bever has presented a discourse on oral hypoglycaemic plants in West Africa while a review on antidiabetic drugs by Wishner was published in 1982. In 1984, Petrack reported approaches to novel antidiabetic therapy with non-insulin-dependent diabetes.

Hypoglycaemic activity has been reported in many plants during the last 20 years. A survey of the literature has showed that large variety of compounds obtained from several plant families are found to be responsible for the hypoglycaemic action. For instance, glycosides isolated from the families Caesalpinaceae, Compositae, Convolvulaceae, Ericaceae, Moraceae, Myrtaceae, Papavaraecae, Ranunculaceae, Rhamnaceae and Scrophulariaceae afforded active principles, which lowered blood sugar in test animals. Similarly, glycans of Ranunculaceae and Graminae exhibited similar activity. Certain triterpenes from plants belonging to the family Ranunculaceae also showed hypoglycaemic effects. In Liliaceae, this property was attributed to various types of
sulfide molecules. Polysaccharides, oils and vitamins from the family Graminae also showed pharmacological activity by decreasing blood sugar level in animals. Alkaloids of Apocynaceae, Papavraceae, Rhamnaceae and Zygophylaceae were particularly effective in diabetes. Saponins from Araliaceae, glycoproteins from Malvaceae, peptides, amino acids and proteins from Papilionaceae and Rubiaceae families also showed beneficial effects in reducing the blood sugar.

Thus, aqueous extracts of *Bambusa dendrocalamat* leaves caused significant lowering of blood sugar in both normal and alloxan-treated rabbits. The effect persisted for about 96 h. The alcoholic extract of *Kurleria cristata* was found to have hypoglycaemic activity in albino rats. A glycoside isolated from the bark of *Ficus bengalensis* produced a hypoglycaemic effect in normal rabbits but not in diabetic animals. The aqueous extract exerted no significant effect on the fasting blood sugar level of normal diabetic rabbit. The aqueous extract showed no hypoglycaemic action on normal human beings although it showed slight hypoglycaemic activity in diabetic patients. On oral administration to normal fasting rabbits, flavonoids A, B, C were active as hypoglycaemic agents, of which compound B showed maximum activity. The milky sap of the same plant caused a lowering of blood sugar. β-sitosterol-D-glucoside isolated from the bark of *F. religiosa* showed hypoglycaemic activity.

The alcoholic extract of the leaves of *Gymnema syvestre* and *Tribang shila* caused insignificant reduction in blood sugar in normal rats but produced marked and significant reduction in anterior pituitary-treated hyperglycaemic animals. Aqueous extract of the crude drug “byakujutsu”, *Atractylodes japonica* rhizomes, showed hypoglycaemic activity in mice. Quinquefolan A, B and C (glycans) of *Panax quinquefolium* roots exerted significant hypoglycaemic activity in mice. Quinquefolium A exhibited prominent effects. Intraperitoneal injection A to alloxan-induced hyperglycaemic mice also lowered blood glucose level. Combined aqueous methanol extracts of the rhizophores of *Dioscorea japonica* and *D. batatus* exerted variable hypoglycaemic effects on i.p. dosing of normal mice. Glycans A, B, C, D, E and F all exhibited remarkable hypoglycaemic effects on normal and alloxan-induced hyperglycaemic rats. Oryzarans A, B, C and D of *Oryza sativa* roots significantly lowered the sugar levels in normal and alloxan-induced diabetic mice. An aqueous extract of rice bran (*O. sativa*).
exhibited significant hypoglycaemic effects on i.p. administration to normal and alloxan-induced hyperglycaemic mice.

Glycans (aconitans A, B, C and D) of Aconitum carmichaeli exhibited hypoglycaemic effects in normal and alloxan-induced hyperglycaemic mice. Mucilages and the deacetylated product of Plantago mucilage showed marked hypoglycaemic activity. The decoction of Artemisia abyssinica significantly decreased the blood glucose level in alloxanized mice over a period of 6 h, however, the decoction produced a significant increase in blood glucose level after 2 h and 4 h of drug administration in normal mice. The same increase has been observed in mice treated with normal saline. Effect of powdered Cuminum nigrum seeds on blood glucose of normal and alloxan-treated hyperglycaemic rabbits has been observed. Anamerans A, B, C and D from Anemarrhena asphodeloides rhizome afford significant hypoglycaemic effects in normal and alloxan-induced hyperglycaemic rats. Recently the effect of Eriobotrya japonica leaves on blood glucose level of normal and alloxan-diabetic rabbits has been reported. Extracts of leaves and flowers of Centaurea corubionensis reduced sugar levels in rats with glucose-induced hyperglycaemia, but had no effect on alloxan diabetic animals.

It is an all too common misconception that “all that is natural is good and a number of highly toxic compounds have been isolated from plants for instance many of the tannin-containing plant extracts are toxic to the liver while many extracts containing alkaloids have side effects on a number of different parts of the body. The fact that most of the plant materials have been used for generations for the treatment is, however, convincing evidence that many of the herbal prescriptions are reasonably safe but scientific toxicological trials are still necessary. This will involve detailed toxicological tests both on crude plant extracts as well as on the purified substances, which show hypoglycaemic activity. At the same time, the synergistic actions of different compounds in a crude extract cannot be ignored. Extensive studies in animals cannot entirely eliminate the possibility of unanticipated injurious effects of plant-derived drugs. Care must therefore be exercised before herbal extracts can be used either in indigenous or modern systems of medicine. Moreover, while many of the plants show only very weak activity, which may not be of therapeutic utility (Atta-Ur-Rahman & Khurshid Zaman, 1989).
So, no doubt many plant drugs have been employed for treating diabetes, the following plants were investigated pharmacognostically as well as pharmacologically for antidiabetic activity;

<table>
<thead>
<tr>
<th>Botanical Name</th>
<th>Common Name</th>
<th>Family</th>
<th>Part used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyamopsis tetragonoloba</td>
<td>Guar</td>
<td>Leguminosae</td>
<td>Beans</td>
</tr>
<tr>
<td>Grewia asiatica</td>
<td>Phalsa</td>
<td>Tiliaceae</td>
<td>Fruits</td>
</tr>
<tr>
<td>Psidium guajava</td>
<td>Amrud</td>
<td>Myristaceae</td>
<td>Stem bark</td>
</tr>
<tr>
<td>Pterocarpus marsupium</td>
<td>Vijasar</td>
<td>Leguminosae</td>
<td>Heart wood</td>
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</tbody>
</table>

REFERENCES