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# Diabetes mellitus: Complications and therapeutics

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## Summary

Diabetes mellitus has now assumed epidemic proportions in many countries of the world. With the present population of 19.4 million diabetics, and approximately 60 million by the year 2025, India would rank first in its share of the global burden of diabetes. Diabetes mellitus is characterized by derangement in carbohydrate, protein, and fat metabolism caused by complete or relative insufficiency of insulin secretion and/or insulin action. There are two main forms of diabetes, type 1 (insulin-dependent diabetes mellitus) and type 2 (non-insulin-dependent diabetes mellitus). Insulin sensitizers (thiazolidinediones), new-generation insulin secretagogue (glimepiride), acarbose, and designer insulin (lispro and aspart) have enormously helped in achieving better metabolic control. Despite the great strides that have been made in the understanding and management of type 2 diabetes, insulin resistance and diabetes-related complications are increasing unabated. The present review not only updates our knowledge in delineating the molecular mechanism(s) causal to insulin sensitivity or resistance, but also provides clues for the prognosis of diabetes and its better management.

**key words:** **diabetes mellitus • impaired glucose tolerance • insulin resistance • syndrome X • antidiabetic drugs**

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## BACKGROUND

Diabetes mellitus (DM), long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century [1]. It is the most common non-communicable disease worldwide and the fourth to fifth leading cause of death in developed countries [2]. The global figure of people with diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025 [3]. Developing countries such as India have had the maximum increases in the last few years. The current prevalence of type 2 diabetes is 2.4% in the rural population and 11.6% in the urban population of India. It has been estimated that by the year 2025, India will have the largest number of diabetic subjects in the world [3]. Diabetes mellitus is a heterogenous group of disorders characterized by high blood glucose levels [4]. Though the pancreatic β cell and its secretory product insulin are central in the pathophysiology of diabetes, the pathogenic mechanisms by which hyperglycemia arises differ widely. Several distinct forms of diabetes exist which are caused by a complex interaction of genetics, environmental factors, and life-style choices. Some forms are characterized by absolute insulin deficiency or a genetic defect leading to defective insulin secretion, while other forms share insulin resistance as their underlying etiology.

### Types of diabetes mellitus

There are two major forms of diabetes: type 1 and type 2 diabetes mellitus. Type 1A diabetes mellitus is primarily due to autoimmune-mediated destruction of pancreatic β cell islets resulting in absolute insulin deficiency. Type 1B diabetes mellitus is also characterized by insulin deficiency and a tendency to develop ketosis; however, individuals with type 1B diabetes mellitus lack the immunologic marker indicative of an autoimmune destructive process of β cells. People with type 1 diabetes must take exogenous insulin for survival to prevent the development of ketoacidosis. Its frequency is low relative to type 2 diabetes, which accounts for over 90% of cases globally. Type 2 diabetes is characterized by insulin resistance and/or abnormal insulin secretion and increased glucose production. Distinct genetic and metabolic defects in insulin secretion/action give rise to the common phenotype of hyperglycemia.

### Type 1 diabetes

Type 1 diabetes represents a heterogenous and polygenic disorder, with a number of non-HLA loci contributing to disease susceptibility [5]. Though this form of diabetes accounts for 5 to 10% of all diabetics, there is yet no identified agent substantially capable of preventing this type of disease [6]. The WHO and the American Diabetics Association [4,7] have proposed that type 1 diabetes can be divided into autoimmune/immune-mediated diabetes (Type 1A) and idiopathic diabetes with β-cell obstruction (Type 1B). This type of diabetes mellitus requires exogenous insulin to prevent diabetic ketoacidosis.

### Type 2 diabetes

Type 2 diabetes is far more common and results from a combination of defects in insulin secretion and insulin action, either of which may predominate. People with type 2 diabetes are not dependent on exogenous insulin, but may require it for the control of blood glucose levels if this is not achieved with diet alone or with oral hypoglycemic agents. This type of diabetes accounts for 90 to 95% of all diabetic patients [8]. All forms of diabetes are characterized by chronic hyperglycemia and the development of diabetes-specific microvascular pathology in the retina, renal glomerulus, and peripheral nerve. As a consequence of its microvascular pathology, diabetes is a leading cause of blindness, end-stage renal disease, and a variety of debilitating neuropathies. When islet β-cell function is impaired, insulin secretion is inadequate, leading to overproduction of glucose by the liver and under-utilization of glucose in peripheral tissue [9].

Type 2 diabetes is made up of different forms, each of which is characterized by a variable degree of insulin resistance and β-cell dysfunction and which together lead to hyperglycemia [7]. At each end of this spectrum are single gene disorders that affect the ability of the pancreatic β cell to secrete insulin [10,11] or the ability of muscle, fat, and linear cells to respond to insulin action [12,13].

## INSULIN RESISTANCE AND SYNDROME X

### Insulin sensitivity and insulin resistance

The acute metabolic action of insulin and its essential importance for survival are well recognized [14]. Insulin directs the selection of metabolic fuels for energy production and, in doing so, it is the only hormone committed to the prevention of hyperglycemia [15]. Insulin resistance is essentially a condition of reduced insulin sensitivity. Insulin sensitivity is commonly described as the ability of insulin to lower plasma glucose levels, which it does by suppressing hepatic glucose production and stimulating glucose uptake in skeletal muscle and adipose tissue. Insulin resistance describes an impaired biological response to insulin [16], but there is sufficient variability in normal sensitivity to insulin that there is no specific boundary at which sensitivity ends and resistance begins. The need for a flexible interpretation of insulin resistance is emphasized by evidence that insulin resistance affects different tissues and different actions of insulin to different extents. There is no absolute definition of hyperinsulinemia, since an insulin concentration that is raised for an individual is usually still within the wide range of normality. While hyperinsulinemia may compensate for resistance to some actions of insulin, it can result in overexpression of actions that retain normal or nominally impaired reactivity to insulin. Also, high concentrations of insulin might act via receptors for insulin-like growth factors-1. This accentuation of some of the actions of insulin with simultaneous resistance to other actions gives rise to a diversity of clinical presentations and sequelae of insulin resistance [17,18].

### Insulin resistance and type 2 diabetes mellitus

Insulin resistance is a characteristic feature of most patients with type 2 diabetes mellitus and is almost a universal finding in type 2 diabetic obese patients. In obese subjects, insulin levels typically increase to maintain normal glucose tolerance. Basal and total 24-h rates of insulin secretion are

three to four times higher in obese insulin-resistant subjects than in lean controls [17]. The hyperinsulinemia associated with insulin resistance results from a combination of an increase in insulin secretion and a reduction in insulin clearance rates.

The insulin resistance of obesity and type 2 diabetes is characterized by defects at many levels, with decreases in receptor concentration and kinase activity, the concentration and phosphorylation of IRS-1 and IRS-2, PI-3-K activity, glucose transporters translocation, and the activity of intracellular enzymes [19]. Insulin increases glucose transport in fat and muscle cells by stimulating the translocation of the transporter GLUT4 from intracellular sites to the plasma membrane. GLUT4 is found in vesicles that continuously cycle from intracellular stores to the plasma membrane. Insulin increases glucose transport by increasing the rate of GLUT4 vesicle exocytosis and by slightly decreasing the rate of internalization [20]. Although the exact mechanisms are unknown, it is likely that the insulin responsive GLUT4 vesicle is tethered to intracellular sites, perhaps defined by a microtubule network [21]. It is likely that the actin cytoskeleton is also crucial in insulin-stimulated GLUT4 translocation. Insulin causes remodeling of cortical actin filaments just below the plasma membrane and induces membrane ruffling. The docking and fusion of the GLUT4 vesicle at the plasma membrane may also be subject to regulation by insulin. Circulating free fatty acids (FFAs) derived from adipocytes are elevated in many insulin-resistant states and have been suggested to contribute to the insulin resistance of diabetes and obesity by inhibiting glucose uptake, glycogen synthesis, and glucose oxidation and by increasing hepatic glucose output. Elevated FFAs are also associated with a reduction in insulin-stimulated IRS-1 phosphorylation and IRS-1-associated PI-3-K activity. The link between increased circulating FFAs and insulin resistance might involve accumulation of triglycerides and fatty acid-derived metabolites (diacylglycerol, fatty acyl-CoA, and ceramides) in muscle and liver.

In addition to its role as a storage depot for lipid, the fat cell produces and secretes a number of hormones, collectively called adipokines, which may profoundly influence metabolism and energy expenditure. Expression of tumor necrosis factor α (TNF-α) is increased in the fat of obese rodents and humans and has been shown to produce serine phosphorylation of IRS-1, resulting in reduced insulin receptor kinase activity and insulin resistance [22].

Leptin is a member of the cytokine family of hormones that is produced by adipose tissue and acts on receptors in the central nervous system and other sites to inhibit food intake and promote energy expenditure. Insulin resistance characterizes states of severe leptin deficiency or resistance, such as ob/ob or db/db mice, or genetic models of lipoatrophic diabetes. In some of these, administration of exogenous leptin improves glucose tolerance and insulin sensitivity independently of effects on food intake, probably by affecting neuroendocrine pathways that modulate insulin action in the liver [23,24]. This cytokine might also has additional direct effects on hepatic cells [25].

Adiponectin (also called Acrp 30 or adipo Q) is a fat cell-derived peptide. Studies have shown that expression of adiponectin mRNA is decreased in obese humans and mice and some models of lipoatrophic diabetes. Acute treatment of mice with this adipokine decreases insulin resistance, plasma FFAs, and the triglyceride content of muscle and liver and increases the expression of genes involved in fatty acid oxidation and energy expenditure [26].

Resistin is the most recently discovered peptide hormone to be secreted by adipocytes. Initial studies suggested that resistin might cause insulin resistance, as levels were increased in obese mice and reduced by antidiabetic drugs of the thiazolidinedione class [27]. Furthermore, administration of anti-resistin antibody seemed to improve blood sugar and insulin action in mice with diet-induced obesity. Subsequent studies, however, have not confirmed these initial findings [28].

Whole body insulin-stimulated glucose utilization, measured by the euglycemic-hyperinsulinemic clamp technique, is reduced in obesity and type 2 diabetes [29]. The major site of impaired insulin-stimulated glucose utilization is skeletal muscle, which shows reduction in glucose uptake, glycogenesis, and glucose oxidation [29–31]. Insulin-stimulated glucose uptake is impaired and suppression of lipolysis is decreased in adipocytes from type 2 diabetic patients [32,33], although responsiveness to insulin may vary considerably between different adipocyte depots. Elevated circulatory FFAs (free fatty acids) will disrupt the glucose-fatty acids (Randle cycle), aggravating insulin resistance in muscle and liver. Insulin-induced suppression of hepatic glycogenolysis and gluconeogenesis is impaired in type 2 diabetes, but usually this is not sufficiently marked to make a significant impact on hyperglycemia until the hyperglycemia is severe [34]. The ability of insulin-resistant individuals to ward off type 2 diabetes will depend largely upon the adaptive capacity of the pancreatic β cells to maintain increasing insulin concentrations [35]. Those who cannot sustain sufficient hyperinsulinemia suffer deterioration in glucose homeostasis, i.e. impaired glucose tolerance (IGT). An increasing mismatch between escalating insulin resistance and inadequate compensatory hyperinsulinemia causes a progression of IGT into frank type 2 diabetes. By the time type 2 diabetes has developed, insulin resistance appears to be almost fully established. However, hyperglycemia continues to worsen due to increasingly compromised β-cell function. As hyperglycemia becomes severe, β-cell failure is usually clearly evident, with a delayed and diminished insulin response to glucose challenge [35].

**The insulin resistance syndrome**

The concept of a syndrome linked to insulin resistance and hyperinsulinemia emerged from the realization that obesity and type 2 diabetes associated with a high prevalence of multiple metabolic abnormalities, and these disturbances are risk factors for coronary heart disease. These include dyslipidemia, increased triglycerides and small dense LDL-C and decreasing HDL-C, hypertension, atherosclerosis, and a procoagulant state [36]. Insulin resistance may be compensated by hyperinsulinemia, limiting the disturbance of glucose homeostasis to IGT, while other features of the syndrome may range from subclinical to advanced. Several features of this syndrome are difficult to separate from the normal aging process or the consequences of diabetes itself. Many of these events are promoted by insulin resistance and inseparable from raised insulin concentrations, and it is the co-

existence of the two conditions that may provide a significant pathogenic insult to this vascular system. However, it should be remembered that most components of syndrome X can also occur quite independently, without the presence of insulin resistance or hyperinsulinemia.

**Obesity**

Obesity is a cause of insulin resistance. Android obesity, which is characterized by a gross excess of adipose tissue within and around the abdomen, is the main type of obesity associated with type 2 diabetes and increased vascular risk [37]. This adipose depot shows a high rate of turnover, possibly due to increased catecholamine-mediated β-adrenoceptor activity, with high activities of hormone-sensitive lipase as well as lipoprotein lipase. Adipose tissue turnover increases plasma free fatty acids and certain cytokines (e.g. TNF-α and IL-6). Increased nutrient intake and decreased nutrient utilization due to low levels of physical activity will foster the vicious spiral of hyperinsulinemia and insulin resistance.

**Hyperinsulinemia and insulin resistance**

It is presumed that subtle increases in hyperglycemia stimulate extra insulin secretion, e.g. in obesity. Hyperinsulinemia, in turn, downregulates insulin receptors by increasing receptor internalization and degradation. Insulin probably also exerts other negative effects on insulin signaling at the post-receptor level [38].

**Dyslipidemia**

The dyslipidemia of obesity and type 2 diabetes usually features increased VLDL-TG. The production of VLDL-TG is increased by insulin, and this effect appears to persist when other actions of insulin are reduced by insulin resistance. Small dense LDL-C, which is the more atherogenic subclass of LDL-C, often is increased in association with insulin resistance and hyperinsulinemia together with a reduction in HDL-C [36].

**Hypertension**

Raised blood pressure is commonly accompanied by reduced sensitivity to insulin and higher insulin concentration. Also hypotension is highly prevalent in obesity and type 2 diabetes [18]. Since hyperinsulinemia has been implicated as a cause of increased renal sodium reabsorption, increased $Na^+$-$H^+$ exchange in arterial smooth muscle, and increased sympathetic vascular tone, this offers a mechanism to account for the link with hypertension.

**Atherosclerosis**

The dyslipidemia and hypertension of syndrome X are established risk factors for atherosclerosis [18]. It has also been suggested that hyperinsulinemia might enhance atherogenesis via other mechanisms, such as increased incorporation of cholesterol and FFA within the vascular wall and increased proliferation of vascular smooth muscle.

**Pro-coagulant state**

Type 2 diabetes is an atherothrombotic disease. Unstable plaque and clots in the coronary arteries are a major cause of the high incidence of myocardial infarction. Among the pro-coagulant features of type 2 diabetes is an increased concentration of plasminogen activator inhibitor-1 (PAI-1), reducing the early lysis of clots [39]. This has been attributed tentatively to insulin resistance and hyperinsulinemia [36].

**Hyperuricemia**

Several features of syndrome X appear to show more than a causal association with raised serum uric acid concentrations. Since insulin resistance has been reported to reduce urinary clearance of uric acid, hyperuricemia might also shelter beneath the umbrella of syndrome X [36].

**Justifying a syndrome**

Insulin resistance and compensatory hyperinsulinemia are associated with a collection of risk factors for coronary heart disease, notably obesity, T2DM, dyslipidemia, hypertension, atherosclerosis, and a pro-coagulant state, and there is justification for assembling them into a definition of a syndrome: a distinct group of symptoms or sign which, associated together, form a characteristic clinical picture or entity.

**Cellular basis of insulin resistance**

The binding of insulin to its receptor in the plasma membrane instigates an array of intracellular signaling pathways [15,40]. These give rise to the diverse biological actions of insulin on enzymes, transporters and transcription factors.

**Insulin actions**

Insulin binds to the α-subunit of the insulin receptor, causing a conformational change in the β-subunits. This exposes the ATP-binding domain and activates tyrosine kinase A (TKA) and auto-phosphorylation at tyrosine residues of the β-subunit. This, in turn, mediates phosphorylation of tyrosine on a range of protein substrates, notably insulin receptor substrates (IRS) 1 and 2, shc, and various uncharacterized proteins [41]. The phosphotyrosine residue of these proteins binds to SH2 domains or other signaling kinases, which open the multiple pathways of insulin action. Different IRS proteins appear to channel signal transduction preferentially into different pathways. However, there is sufficient overlap that the elimination of one IRS protein severely impairs, but does not completely obliterate, any pathway. The PI-3-K (phosphoinositol-3-kinase) pathway, which signals through protein kinase B (PKB/Akt), is particularly important for this acute metabolic effect of insulin. It stimulates the translocation of GLUT4 glucose transporters into the plasma membrane and, therefore, is crucial for insulin-stimulated glucose transport. The PI-3-K pathway also participates in the acute regulation of glycolysis, lipogenesis, and protein synthesis [15]. Interaction of IRS proteins with GRB2 and shc routes signal transduction into the ras-MAP pathway, which appears to be the main conduit to the nucleus.

**Site of insulin resistance**

Insulin resistance has been studied mainly in muscle, liver, and adipose tissues, where insulin exerts its main acute

**Table 1.** Values for diagnosis of diabetes and other types of hyperglycemia.

| | Glucose concentration (mM) | | | |
|---|---|---|---|---|
| | **Plasma venous** | **Capillary** | **Whole blood venous** | **Capillary** |
| Diabetes mellitus fasting<br>2-h post-glucose load | ≥7.0<br>≥11.1 | ≥7.0<br>≥12.2 | ≥6.1<br>≥10.0 | ≥6.1<br>≥11.1 |
| Impaired glucose tolerance fasting<br>2 h post-glucose load | <7.0<br>7.8–11.0 | <7.0<br>8.9–12.1 | <6.1<br>6.7–9.9 | <6.1<br>7.8–11.0 |
| Impaired fasting glucose fasting<br>2 h post-glucose load | 5.6–6.9<br><7.8 | 5.6–6.9<br><8.9 | 5.6–6.0<br><6.7 | 5.6–6.0<br><7.8 |

metabolic actions. The insulin receptor is structurally normal in type 2 diabetes, and the wealth of 'spare' receptors ensures that a reduced population of insulin receptors in type 2 diabetes does not make a major combination to insulin resistance in most patients. Indeed, decreased phosphorylation and TKA of the insulin receptor, β-subunit, decreased phosphorylation of IRS-1, and decreased activities of PI-3-K have been observed in type 2 diabetes [38,40]. Site-directed mutagenesis of the β-subunit, which decreases the number of tyrosine residues phosphorylated, carries an approximately proportional decrease in insulin action [15]. This emphasizes the detrimental consequences of subtle conformational adjustment to the β-subunit. Since different sites of β-subunit phosphorylation appear to affect the activation of different IRS proteins preferentially [41], it is theoretically possible for changes in the pattern of β-subunit phosphorylation to alter the balance of signal transduction into different post-receptor pathways.

Gene knockout studies in mice have established that the insulin receptor is essential for survival, whereas IRS-1 knockout causes insulin resistance and reduced growth, but not frank diabetes. Interestingly, IRS-2 knockout causes insulin resistance and reduced β-cell mass, resulting in severe (often fatal) diabetes. These observations concur with the possibility that reduced signaling through different IRS proteins could account for the heterogeneity of insulin resistance. In addition to disturbances in insulin signaling, insulin resistance may involve defects in the biological effectors of insulin action in some individuals. Gene polymorphisms associated with glycogen synthase and protein phosphatase 1 have been noted, and observations at the level of glucose transporter cycling, hexokinase, and other key mediators of insulin action remain under suspicion. The adverse effects of chronically raised glucose and lipid concentrations (glucotoxicity and lipotoxicity) in diabetes include the aggravation of insulin resistance [42,43].

**Impaired glucose tolerance**

Type 2 diabetes is increasingly common, indeed epidemic, primarily because of increases in the prevalence of a sedentary lifestyle and obesity [44]. The possibility of preventing type 2 diabetes by interventions that affect the lifestyle of subjects at high risk for the disease is now the subject of a number of studies; these have focused on people with impaired glucose tolerance (IGT) [45]. IGT is defined as hyperglycemia (with glucose values intermediate between normal and diabetic) following a glucose load [4]. It represents a key stage in the natural history of type 2 diabetes as these people are at much higher future risk than the general population for developing diabetes [46]. Subjects with IGT also have a heightened risk of macrovascular disease [46]. Because of this, and the association with other known CVD risk factors including hypertension, dyslipidemia, and central obesity [47], the diagnosis of IGT, particularly in an apparently healthy and ambulatory individual, has important prognostic implications [48]. Impaired fasting glucose (IFG) was introduced recently as another category of abnormal glucose metabolism [49]. It is defined on the basis of fasting glucose concentration and, like IGT, it is associated with risk of CVD and future diabetes (Table 1).

**Type 2 diabetes mellitus in children and youth**

Type 2 diabetes in children, teenagers, and adolescents is a serious new aspect of the epidemic and an emerging public health problem of significant proportions [50,51]. Although type 1 diabetes remains the main form of the disease in children worldwide, it seems possible that type 2 diabetes will be predominant within ten years in many ethnic groups and potentially in Europid (of European descent) groups and reported from several developed countries such as the US, UK, Australia, Hong Kong, and Japan. The rising prevalence of obesity and type 2 diabetes in children is symptomatic of the effect of globalization and industrialization affecting all societies, with sedentary lifestyle and obesity the predominant factors involved. As a result of this new and alarming scenario, a joint consensus statement has been issued recently by the American Diabetes Association and American Academy of Pediatrics [52].

**β-cell dysfunction in type 2 diabetes mellitus**

In type 2 diabetes, more moderate abnormalities of secretion that cause glucose intolerance are present only if insulin resistance is also present. The genetic basis of β-cell dysfunction in this form of diabetes is more complex, involving both multiple interacting genes and environmental factors which determine whether diabetes will develop and at what age. Despite a genetic predisposition, diabetes may never manifest, and hyperglycemia, when it occurs, usually does so later in life (after 50 years of age) [53], although there has been a disturbing increase in the prevalence of type 2 diabetes in children in recent years [54]. The compensatory hypersecretion of insulin in insulin-resistant states is due to an expansion of β-cell mass [55] and alteration in the expression of key enzymes of β-cell glucose metabolism, and

is believed to be a consequence of increased levels of this glycolytic enzyme hexokinase [56]. In normal pancreatic β cells, glucokinase mediates the conversion of glucose to glucose 6-phosphate and determines the threshold at which glucose stimulates insulin secretion [57]. Insulin resistance is associated with increased β-cell hexokinase activity, leading to secretion of insulin at lower glucose concentration. It has been suggested that increased free fatty acids in serum could precipitate β-cell failure [58]. Short-term exposure of pancreatic islets to free fatty acids increases insulin secretion, but long-term exposure inhibits glucose-induced insulin secretion and biosynthesis and may lead to β-cell deaths by apoptosis. These effects may be mediated by increased expressions of proteins which uncouple glucose metabolism from oxidative phosphorylation, a key link between β-cell glucose metabolism and insulin secretion [59].

**Genetic aspect of type 2 diabetes mellitus**

The identification and characterization of the genes involved in type 2 diabetes will add an essential level to our understanding of the pathways regulating β-cell function, including those for β-cell compensation. A common amino-acid polymorphism (Pro 12 Ala) in peroxisome proliferator-activated receptor-γ (PPAR-γ) has been associated with type 2 diabetes [60]. People homozygous for the Pro12 allele are more insulin resistant than those having one Ala12 allele and have a 1.25-fold total increased risk of developing diabetes. There is also evidence for interaction between this polymorphism and fatty acid, thereby linking this locus with diet [61]. The expression of PPAR-γ in insulin-responsive tissues (fat and muscle) and pancreatic β cells provides a link between insulin resistance and insulin secretion. Furthermore, the recent demonstration that insulin-mediated signaling pathways are important in the preservation of normal β-cell function raises the possibility that insulin resistance in the β cell, developing in parallel to insulin resistance in muscle, fat, and liver, could contribute directly to βcell dysfunction in type 2 diabetes. Diabetic islets show reduced insulin gene transcription. This might be due, at least in part, to reduced insulin action in that tissue and indicate that activation of insulin gene transcription is an important effect of insulin-mediated signaling [62].

Genetic variation in the gene encoding Calpain-10, a ubiquitously expressed cysteine protease, has also been associated with type 2 diabetes, increasing risk as much as threefold [63] through affects on both the normal function of the β-cell and insulin action in muscle and fat.

**Mitochondrial mutations and diabetes mutations in genes encoding insulin receptor and insulin receptor substrate**

Point mutation or deletions in mtDNA have been associated with a large spectrum of diseases, with symptoms such as muscle weakness, cardiomyopathy, optic nerve atrophy, retinal dystrophy, impaired hearing, and hyperglycemia (diabetes mellitus). Point mutations in mitochondrial and RNA genes are the primary cause of these pathophysiological manifestations. A specific maternally inherited form of diabetes mellitus was first linked to a mutation in the mtDNA [64]. Often associated with neurosensory deafness, it is also called maternally inherited mitochondrial diabetes and deafness (MIDD). Altogether, mitochondrial diabetes accounts for approximately 1% of all cases of diabetes [65]. The molecular diagnosis of mitochondrial diabetes is complicated by an invariably low degree of heteroplasmy in the peripheral white blood cells usually used for genetic analysis. The mitochondrial diabetes phenotype illustrates the importance of normal respiratory-chain function in the β cell for glucose homeostasis.

In contrast to the above-mentioned rare, monogenic, mitochondrial diabetes, type 2 diabetes is common and polygenic in nature [66]. Patients usually display both resistance to insulin at its target tissues (mainly skeletal muscle) as well as defective insulin secretion [35]. Although the contribution of variations in mtDNA to the development of type 2 diabetes is unknown, a 50% decrease in mtDNA copy number in skeletal muscle of type 2 diabetes was observed. Reduced mtDNA content was also reported in peripheral blood cells in such patients even before the onset of the disease [67].

UCP2 is an inner mitochondrial membrane protein that tends to diminish the proton gradient generated by the respiratory chain. Its overexpression in β cells attenuates ATP generation and insulin secretion in response to glucose [68]. It is of interest that deletion of the UCP-2 gene in mice enhances islet ATP generation and insulin secretion during glucose stimulation [59]. Type 2 diabetics usually have both hyperglycemia and hyperlipidemia. This is thought to induce the phenomenon of 'glucolipotoxicity' in the β cell, leading to lipid accumulation, impaired glucose metabolism, and alterations in mitochondria [69]. Chronic exposure of β cells to fatty acids induces changes in the expressions of numerous genes, among them UCP-2 gene, which correlates with reduced glucose-evoked insulin secretion [70].

**Maturity-onset diabetes of the young (MODY)**

Maturity-onset diabetes of the young (MODY) is a clinically heterogeneous group of disorders characterized by non-ketotic diabetes mellitus, an autosomal dominant mode of inheritance, onset usually before 25 years of age and frequently in childhood or adolescence, and a primary defect in pancreatic β-cell function [10,11]. MODY can result from mutations in any one of at least six different genes that encode the glycolytic enzyme glucokinase and five transcription factors: hepatocyte nuclear factor (HNF) 4α, HNF-1α, insulin promoter factor-1 (IPF-1), HNF-1β, and neurogenic differentiation 1/β cell E box transactivator 2 (Neuro D1/BETA 2). All the genes are expressed in the pancreatic β cell and mutations lead to β-cell dysfunction and diabetes mellitus in the heterozygous state. They are also expressed in other tissues, and abnormalities in liver and kidney function may occur. Non-genetic factors that affect insulin sensitivity, such as infection, puberty, pregnancy and, rarely, obesity, may trigger the onset of diabetes and affect the severity of hyperglycemia in MODY.

Glucokinase is expressed at its highest levels in the pancreatic β cell and the liver [71]. It catalyses the transfer of phosphate from ATP to glucose to generate glucose-6-phosphate: the first rate-limiting step in glucose metabolism. Glucokinase functions as the glucose sensor in the β cell by controlling the rate of entry of glucose into the glycolyt-

ic pathway and its subsequent metabolism. In the liver, glucokinase affects the ability to store glucose as glycogen, particularly in the postprandial state. Heterozygous mutations leading to partial deficiency of glucokinase are associated with MODY, and homozygous mutations resulting in complete deficiency of this enzyme lead to permanent neonatal diabetes mellitus [72].

The transcription factors HNF-1α, HNF-1β, and HNF-4α are involved in the tissue-specific regulation of gene expression in the liver, pancreatic β cells, and other tissues [73,74]. In the pancreatic β cell they regulate the expression of insulin as well as proteins involved in glucose transport, glycolysis, and mitochondrial metabolism, all of which are important in the regulation of insulin secretion [74]. Mutations in these genes produce defects in insulin secretory responses to a variety of factors, particularly glucose, which are present before the onset of hyperglycemia [10,11].

IPF-1 is a homeodomain containing a transcription factor involved in pancreatic development [75,76], transcriptional regulation of a number of β-cell genes including insulin, glucokinase, islet amyloid polypeptide, and glucose transporters 2 (GLUT2) [76], and mediation of glucose-stimulated insulin gene transcription [77]. Mutations in other β-cell transcription factors may also contribute to the development of MODY or a MODY-like disorder. In addition to mutations in the nuclear genome, abnormal mitochondrial function resulting from mutations in the mitochondrial genome can lead to diabetes.

**Alcoholism and insulin resistance**

The incidence of diabetes mellitus has also been observed to be increased at par with changes in lifestyle in conjunction with dietary pattern. Studies on the link between alcohol consumption and glyco-regulation revealed that alcohol consumption might be a target for primary and secondary prevention of impaired glyco-regulation and diabetes mellitus [78,79]. Large intake of alcohol led to the development of frank clinical diabetes with glucose intolerance and insulin deficiency, which were reversed perfectly to the prediabetes condition following abstinence from alcohol [80]. Light to moderate alcohol consumption is shown to be associated with enhanced insulin-mediated glucose uptake, lower incidence of ischemic heart disease, and higher HDL-cholesterol concentration [81]. Moderate alcohol intake reduces the risk of developing NIDDM and protects the cardiovascular system, while heavy intake acts as a vasoconstrictor, resulting in increased systolic and diastolic pressure [82–84]. The hazards of heavy alcohol intake are that it induces hyperglycemia, glucose intolerance, inhibition of insulin secretion, increased insulin resistance, and hypertriglyceridemia [85–87]. At relatively low doses, alcohol can cause hypoglycemia in the presence of a low serum insulin and serum glucagon levels [88]. In the postprandial state, alcohol induces hyperglycemia by inducing glycogenolysis and accelerate the peripheral insulin resistance [84,89,90].

Recent studies in the general population showed a significant reduction in mortality with moderate alcohol intake. The mechanism of the beneficial effects of alcohol includes the positive effect on insulin sensitivity and HDL-cholesterol [91]. A moderate amount of alcohol had no effect on diabetic control except for occasional hypoglycemia, while heavy intake may be associated with an increase in glucose intolerance [92]. Various studies have shown little or no effect of moderate alcohol intake on diabetic control. Heavy alcohol intake is associated with glucose intolerance caused by an inhibition of insulin secretion and increased insulin resistance at both the receptor and post-receptor levels [93–96]. Moderate alcohol intake with a meal had no deleterious effect on hypo- or hyperglycemia in patients with insulin-dependent diabetes mellitus or NIDDM, and if taken outside the context of a meal can cause hypoglycemia and ultimately increased death from non-cardiovascular causes [97]. However, chronic alcohol intake always deteriorates metabolic control in persons with NIDDM, which is reversed after alcohol withdrawal [98].

**Current diagnostic criteria of diabetes mellitus**

Many persons with type 2 diabetes already show the presence of the long-term complications associated with diabetes at the time of diagnosis. It is now widely accepted that if diabetes is detected early and adequate steps are taken, it may be possible to significantly delay the onset and progression of these complications. When a patient is symptomatic and fasting plasma glucose (FPG) is unequivocally elevated, diagnosis of diabetes does not present any difficulty. When a patient is without clinical symptoms, diagnosis of diabetes is more difficult. Revised criteria for diagnosing DM have been issued by a consensus panel of experts from the National Diabetes Data Group and the WHO. The revised criteria reflect new epidemiological and metabolic evidence and are based on the following premises:

1. The spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load varies in normal individuals, and
2. Diabetes mellitus defined as the level of glycemia at which diabetes-specific complications are noted and not on the level of glucose tolerance from a population-based viewpoint.

Glucose tolerance is classified into three categories based on the fasting plasma glucose (FPG):

1. FPG <5.56 mmol/ l (<100 mg/dl) is considered normal,
2. FPG >5.56 mmol/l (>100 mg/dl) but <7.0 mmol/l (<126 mg/dl) is defined as impaired fasting glucose (IFG), and
3. FPG >7.0 mmol/l (>126 mg/dl) warrants the diagnosis of diabetes mellitus.

IFG is a new diagnostic category defined by the expert committee on the diagnosis and classification of diabetes mellitus (American Diabetes Association). It is analogous to IGT, which is defined as plasma glucose levels between 7.8 and 11.1 mmol/l (140 and 200 mg/dl) 2 hours after a 75-gram oral glucose load. Individuals with IFG or IGT are at substantial risk for developing type 2 diabetes mellitus and cardiovascular disease in the future, though they may not meet the criteria for diabetes mellitus.

Thus the criteria for diagnosis of diabetes mellitus are as follows:

- Symptoms of diabetes plus random blood glucose concentrations >11.1 mmol/l (>200 mg/dl) OR

- Fasting plasma glucose >7.0 mmol/l (>126 mg/dl) OR
- Two-hour plasma glucose >11.1 mmol/l (>200 mg/dl) during an oral glucose tolerance test.

The revised criteria for the diagnosis of DM emphasize FPG as the most reliable and convenient test for diagnosing DM in asymptomatic individuals. Oral glucose tolerance testing, although still a valid mechanism for diagnosis of DM, is not recommended as part of routine screening.

Some investigators have advocated acetylated hemoglobin (HbA1c) as a diagnostic test for DM. Though there is strong correlation between elevations in plasma glucose and HbA1c, the relationship between FPG and HbA1c in individuals with normal glucose tolerance or mild glucose intolerance is less clear and the test is not universally standardized or available.

## Diabetic Complications and Their Pathogenesis

### Acute complications

These include diabetic keto acidoses (DKA) and non-ketotic hyper-osmolar state (NKHS). While the first is seen primarily in individuals with type 1 DM, the latter is prevalent in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and altered mental state. In DKA, insulin deficiency is combined with counter-regulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone). The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver and also increases free fatty acid and amino-acid delivery from fat and muscle to the liver. Ketosis results from a marked increase in free fatty acid release from adipocytes due to increased lipolysis. In DKA, nausea and vomiting are often present. Lethargy and CNS depression may evolve into coma in severe DKA. Cerebral edema, an extremely serious complication, is seen most frequently in children.

NKHS is most commonly seen in elderly individuals with type 2 DM. Its most prominent features include polyuria, orthostatic hypotension, and a variety of neurological symptoms including altered mental state, lethargy, obtundation, seizure, and possibly coma. Insulin deficiency and inadequate fluid intake are the underlying causes of NKHS. Insulin deficiency leads to hyperglycemia, which induces an osmotic diuresis leading to profound intravascular volume depletion.

### Chronic complications

The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications are further subdivided into microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease, and cerebrovascular disease). Nonvascular complications include problems such as gastroporesis, sexual dysfunction, and skin changes. As a consequence of its chronic complications, DM is the most common cause of adult blindness, a variety of debilitating neuropathies, and cardiac and cerebral disorders. Treating the complications of diabetes costs more than controlling the disease.

Early in the course of diabetes, intracellular hyperglycemia causes abnormalities in blood flow and increased vascular permeability. This reflects decreased activity of vasodilators such as nitric oxide, increased activity of vasoconstrictors such as angiotensin II and endothelin-1, and elaboration of permeability factors such as vascular endothelial growth factor (VEGF). In diabetic arteries, endothelial dysfunction seems to involve both insulin resistance specific to the phosphotidylinositol–3-OH kinase pathway and hyperglycemia.



### Diabetic retinopathy

Diabetic retinopathy occurs in 3/4 of all persons having diabetes for more than 15 years and is the most common cause of blindness. There is appearance of retinal vascular lesions of increasing severity, culminating in the growth of new vessels. Diabetic retinopathy is classified into two stages: non-proliferative and proliferative. The non-proliferative stage appears late in the first decade or early in the second decade of disease and is marked by retinal vascular microneurisms, blot hemorrhages, and cotton-wool spots and includes loss of retinal pericytes, increased retinal vascular permeability, alterations in regional blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia. In proliferative retinopathy there is the appearance of neovascularization in response to retinal hypoxia. The newly formed vessels may appear at the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment [99].

### Neuropathy

About half of all people with diabetes have some degree of neuropathy, which can be polyneuropathy, mono-neuropathy, and/or autonomic neuropathy. In polyneuropathy there is loss of peripheral sensation which, when coupled with impaired microvascular and macrovascular junction in the periphery, can contribute to non-healing ulcers, the leading cause of non-traumatic amputation. There is thickening of axons, decrease in microfilaments, and capillary narrowing involving small myelinated or non-myelinated C-fibers. It can occur both from direct hyperglycemia-induced damage to the nerve parenchyma and from neuronal ischemia leading to abnormalities of microvessels, such as endothelial cell activation, pericyte degeneration, basement membrane thickening, and monocyte adhesion. Mono-neuropathy is less common than polyneuropathy and includes dysfunction of isolated cranial or peripheral nerves. Autonomic neuropathy can involve multiple systems, including cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems [100].

### Nephropathy

This is a major cause of end-stage renal disease. There are glomerular hemodynamic abnormalities resulting in glomerular hyper-filtration, leading to glomerular damage as evidenced by microalbuminurea. There is overt proteinuria, decreased glomerular filtration rate, and end-stage renal failure. Dysfunction of the glomerular filtration apparatus is manifested by microalbuminurea and is attributed to changes in syn-

thesis and catabolism of various glomerular basement membrane macromolecules such as collagen and proteoglycans, leading to an increase in glomerular basement thickening. Another possible mechanism to explain the increase in permeability of the glomerulus is the increase in renal VEGF levels observed in preclinical models of diabetes, since VEGF is both an angiogenic and a permeability factor [101].

**Cardiovascular morbidity and mortality**

In diabetes mellitus there is marked increase in several cardiovascular diseases, including peripheral vascular disease, congestive heart failure, coronary artery disease, and myocardial infarction, and a one- to fivefold increase in sudden death. The absence of chest pain (silent ischemia) is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures.

Despite proof that improved glycemic control reduces microvascular complications in diabetes mellitus, it is possible that macrovascular complications may be unaffected or even worsened by such therapies. An improvement in the lipid profiles of individuals in the intensive group (lower total and low-density lipoprotein cholesterol, lower triglycerides) suggested that intensive therapy may reduce the risk of cardiac vascular mortality. In addition to coronary artery disease, cerebrovascular disease is increased in individuals with diabetes mellitus (threefold increase in stroke). Individuals with DM have increased incidence of congestive heart failure (diabetic cardiomyopathy). The etiology of this abnormality is probably multifactorial and includes factors such as myocardiac ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia. Though DM itself does not increase levels of LDL, LDL particles found in type 2 DM are more atherogenic and are more easily glycated and susceptible to oxidation [102].

**Hypertension**

Hypertension can accelerate other complications of diabetes mellitus, particularly cardiovascular disease and nephropathy. Antihypertensive agents should be selected based on the advantages and disadvantages of the therapeutic agent in the context of the individual patient's risk-factor profile. DM-related considerations include the following:

1. α-adrenergic blockers slightly improve insulin resistance and positively impact the lipid profile. Â-blockers and thiazide diuretics can increase insulin resistance, negatively impact the lipid profile, and slightly increase the risk of developing type 2 diabetes.
2. β-blockers, because of the potential masking of hypoglycemic symptoms, are effective agents and hypoglycemic events are rare when cardio-selective β1 agents are used.
3. Central adrenergic antagonists and vasodilators are lipid and glucose neutral.
4. Sympathetic inhibitors and α-adrenergic blockers may be associated with orthostatic hypotension in the diabetic individual with autonomic neuropathy.
5. Calcium-channel blockers are glucose and lipid neutral and may reduce cardiovascular morbidity and mortality in type 2 DM, particularly in elderly patients with systolic hypertension.

**Infections**

Individuals with diabetes mellitus exhibit a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia as well as diminished vascularization secondary to long-standing diabetes. Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population (e.g. rhinocerebral mucormycosis and malignant otitis externa, which is usually secondary to *P. aeruginosa* infection in the soft tissue surrounding the external auditory canal). Pneumonia, urinary tract infection, and skin and soft tissue infections are all more common in the DM population. Gram-negative organisms, e.g. *S. aureus* and *Mycobacterium tuberculosis*, are more frequent pathogens in patients of DM. Diabetic patients have an increased rate of colonization of *S. aureus* in skin folds and nares and also have a greater risk of postoperative wound infections [103].

**Mechanisms of hyperglycemia-induced damage**

Many hypotheses about how hyperglycemia causes diabetic complications have generated a large amount of data as well as several clinical trials based on specific inhibitors of these mechanisms. The main hypotheses are: the Aldose Reductase theory, Advanced Glycation End Product (AGE) theory, Activation of Protein Kinase C (PKC) isoform theory, Increased Hexosamine Pathway Flux theory, and the Reactive Oxygen Intermediate theory.

**Aldose reductase**

This is the first enzyme in the polyol pathway. It is a a cytosolic, monomeric oxido-reductase that catalyses the NADPH-dependent reduction of a wide variety of carbonyl compounds, including glucose. Increased intracellular glucose in a hyperglycemic environment results in its increased enzymatic conversion to the polyalcohol sorbitol, with concomitant decreases in NADPH [104]. In the polyol pathway, sorbitol is oxidized to fructose by the enzyme sorbitol dehydrogenase, with $NAD^+$ reduced to NADH. Cataract formation in diabetes and galactosemia result from accumulation in the lens of excessive sorbitol synthesized by the action of aldose reductase on glucose or galactose, respectively. A number of mechanisms have been proposed to explain the potential detrimental effects of hyperglycemia-induced increases in polyol pathway flux. These include sorbitol-induced osmotic stress, decreased ($Na^+ + K^+$) ATPase activity, an increase in cytosolic $NADH/NAD^+$, and a decrease in cytosolic NADPH. Hyperglycemia-induced activation of PKC increases cytosolic phospholipase $A_2$ activity, which increases the production of two inhibitors of $Na^+ K^+$ ATPase, arachidonate and $PGE_2$. It has also been proposed that reduction of glucose to sorbitol by NADPH consumes NADPH. As NADPH is required for regenerating reduced glutathione (GSH), this could induce or exacerbate intracellular oxidative stress.

**Advanced glycation end products**

AGEs are found in increased amounts in diabetic retinal vessels [105] and renal glomeruli [106]. AGE inhibitors partially prevented various functional and structural manifestations of

diabetic microvascular diseases in retina, kidney, and nerve. The AGE inhibitor amino guanidine lowered total urinary protein and slowed progression of neuropathy [107]. Production of intracellular AGE precursors damages target cells by three general mechanisms: intracellular proteins modified by AGEs have altered function; extracellular matrix components modified by AGE precursors interact abnormally with other matrix components and with the receptors for matrix proteins (integrins) on cells; and plasma proteins modified by AGE precursors bind to receptors of AGE (RAGE) on endothelial cells, mesangial cells, and macrophages, inducing receptor-mediated production of reactive oxygen species [108]. The AGE receptor ligation activates the pleiotropic transcription factors, causing pathological changes in gene expression along with other cellular signaling events, such as activation of mitogen-activated protein (MAP) kinase or PKC, which can lead to cellular dysfunction [109].

**Diacylglycerol (DAG) and Protein Kinase C (PKC)**

These are critical intracellular signaling molecules that can regulate many vascular functions, including permeability, vasodilator release, endothelial activation, and growth factor signaling. The PKC family comprises at least eleven isoform, nine of which are activated by the lipid second messenger DAG. Intracellular hyperglycemia increases the amount of DAG in cultured microvascular cells and in the retina and renal glomeruli of diabetic animals [110]. Increased *de novo* synthesis of DAG leads to the activation of PKC β isoforms which have been shown to mediate retinal and renal blood flow abnormalities. Activation of PKC by raised glucose also induces expression of the permeability-enhancing factor VEGF in smooth muscle cells. Treatment with an inhibitor specific for PKC β significantly reduced PKC activity in the retina and renal glomeruli of diabetic animals [111]. Concomitantly, treatment significantly reduced diabetes-induced increases in retinal mean circulation time, normalized increases in glomerular filtration rate, and partially corrected urinary albumin excretion.

**Hexosamine pathway**

Shunting of excess intracellular glucose into the hexosamine pathway might also cause several manifestations of diabetic complications [112]. In this pathway, fructose 6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-N-acetylglucosamine, such as proteoglycans synthesis and the formation of O-linked glycoproteins. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine-glutamine, fructose-6-phosphate amidotransferase (GFAT), blocks hyperglycemia-induced increases in the transcription of TGF α, TGF β, and PAI-1. This pathway has also an important role in hyperglycemia-induced and fat-induced insulin resistance.

**Reactive oxygen intermediate theory**

Hyperglycemia can increased oxidative stress through both enzymatic and non-enzymatic processes. Glucose metabolism through the glycolytic pathway and TCA cycle produces reducing equivalents used to drive the synthesis of ATP via oxidative phosphorylation in mitochondria. Byproducts of mitochondrial oxidation include free radicals such as superoxide anion, whose generation increases with increased glucose levels. Glucose oxidation also produces free radicals which damage cellular proteins as well as mitochondrial DNA. Increased oxidative stress reduces nitric oxide levels, damages cellular proteins, and promotes leukocyte adhesion to the endothelium while inhibiting its barrier function. Levels of antioxidants such as GSH, vitamin C, and vitamin E have been reported to be decreased in patients with diabetes, while the levels of some markers of oxidative stress, e.g. oxidized low-density lipoprotein cholesterol are increased.

Thus there can be two approaches to designing treatment for the prevention of hyperglycemia-induced complications. First, the neutralization of specific glucotoxins such as reactive oxygen species or AGEs, and second, identifying and normalizing the activity of a common signaling pathway used by glucose and glucotoxins to exert their effects. Clinical trials are in progress using both these approaches.

## THERAPEUTICS OF DIABETES MELLITUS

## NON-PHARMACOLOGICAL MANAGEMENT OF DIABETES MELLITUS

**Diet**

***Caloric content***

Most patients with NIDDM are overweight or obese, and it is now well recognized that this is a major factor in insulin resistance. Consequently, reduction of excess weight is a primary component in the management of NIDDM. When extreme caloric restriction and/or rapid weight loss seem desirable, a very low caloric diet or protein-sparing modified fast may be considered.

***Macronutrients***

The ideal balance of carbohydrate, protein, or fat intake in patients with NIDDM is still a matter of discussion. It has recently been recognized that a diet containing 60% carbohydrates, even if not including sugar, may predispose to the development of dyslipidemia [113]. Carbohydrates should be predominantly complex and high in soluble fiber; foods with an aglycemic index [114] are preferred, although moderate intake of simple sugar such as sucrose does not seem to be detrimental [115]. Protein intake should not exceed the daily requirement, since high protein intake appears to have a detrimental effect on renal function [116].

***Dietary fibers***

Numerous studies recently reviewed by Hoewitz [117] have shown that addition of certain types of soluble fiber, particularly guar gum and pectin, may result in significant reduction of postprandial glucose and insulin levels in patients with NIDDM.

***Fish oils***

There is some evidence that fish oils or fish-derived omega-3 fatty acids may play some role in preventing atherosclerotic vascular disease by reducing plasma triglyceride and lipoprotein levels [118]. However, there is also evidence that in NIDDM the decrease in plasma triglyceride levels is counterbalanced by adverse effects on blood glucose or low density lipoprotein (LDL)-cholesterol [119–121].

**Physical activity**

Recent clinical investigations have shed light on the mechanism by which exercise may help in controlling excessive blood glucose levels [122]. Furthermore, there is good evidence that regular exercise has a positive influence via various cardiovascular risk factors that worsen diagnostics in patients with type 2 diabetes [123]. However, in a small proportion of patients exercise may be harmful and, therefore, should not be prescribed. Regular exercise improves insulin sensitivity and, as a consequence, may improve glucose tolerance [124]. Such effects result partly from enzymatic adaptation in skeletal muscles, considered to be responsible for improvement in maximal oxygen uptake, and partly from a decrease in body weight, body fat and, possibly, also cell size. Such effects are beneficial in patients with type 2 diabetes since they enhance work capacity and quality of life and may also help to reduce the requirement for insulin or oral hypoglycemic agents.

## Drug Targets for Diabetes Mellitus and Insulin Resistance

The current therapeutic approaches were largely developed in the absence of the fine molecular targets or understanding of the pathogenesis of the diseases. In last few years a large number of molecular drug targets involving various biochemical pathways have been worked out. These are based on the predicted roles in modulating one or more key aspects of the pathogenesis of the diabetes and metabolic syndrome. These are: 1) reducing excessive glucose production by liver, 2) targeting β cells, 3) targeting insulin-signaling pathways, and 4) targeting lipid metabolism.

**Reducing excessive hepatic glucose production**

The liver, by way of gluconeogenesis and glycogenolysis, plays a very important role in regulating endogenous glucose production by the synthesis or breakdown of glycogen. Increased rates of hepatic glucose production are largely responsible for the development of overt hyperglycemia. Glucagon contributes to hyperglycemia through induction of the gluconeogenesis and glycogenolytic pathways [125,126]. Its receptor, a seven-transmembrane-domain G-protein receptor, could be a target for the development of small-molecule antagonists [127]. Besides, several enzymes that regulate rate-controlling steps in the gluconeogenesis or glycogenolytic pathways can also be used as molecular targets for therapeutic intervention. One such enzyme is inhibition of hepatic glycogen phosphorylase [128], an enzyme that catalyses the release of glucose from glycogen. Others are fructose-1,6-bisphosphatase and glucose-6-biphosphatase [129]. Whereas inhibition of fructose-1,6-bisphosphatase would selectively block gluconeogenesis by disrupting the conversion of fructose-1,6-biphosphate to fructose-6-phosphate, inhibition of glucose-6-phosphatase would attenuate the final step in hepatic glucose production common to the gluconeogenic and glycogenolytic pathways.

**Treating β cells**

Two distinct gut-derived peptide hormones, glucagon-like-peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), act through their respective G protein-coupled receptors on β cells to potentiate glucose-stimulated insulin secretion [130]. Administration of any of these two hormones to humans can potentiate insulin secretion. Since both hormones are subject to rapid amino terminal degradation by dipeptidylpeptidase-IV (DP-IV), use of modified GLP-1 peptide agonists resistant to this enzyme has been recommended. It is observed that DP-IV null mice have increased circulating active GLP-1 along with enhanced insulin secretion, and an otherwise healthy phenotype [131]. Thus, development of GLP-1 analogues and DP-IV inhibitors is likely to yield important new therapeutic approaches that might circumvent the liabilities of hypoglycemia, weight gain, and secondary failures associated with sulphonylureas use.

**Targeting the insulin signaling pathways**

Insulin resistance can be due to multiple defects in signal transduction, such as impaired activation of insulin receptor-tyrosine kinase and reduced activation of insulin-stimulated phosphatidylinositol-3-OH kinase (PI-3-K). A number of molecular targets are now being investigated as ways of enhancing insulin-mediated signal transduction. Elevated expression of PTP 1B has been reported in insulin-resistant patients [132]. Overexpression of this enzyme prevents insulin receptor kinase activation. A PTP 1B knockout mouse was more insulin sensitive than control littermates. Thus inhibition of PTP 1B represents a good target for drug discovery [133]. Serine kinases may phosphorylate and thus inhibit the tyrosine phosphorylation of IRS 1 in experimental paradigms of insulin resistance. Identification of these kinases and specific inhibitors represents another rich area for antidiabetic therapy. Similarly, products of PI-3-kinase play a critical role in insulin action and might be reduced during insulin resistance.

Other putative negative regulators of insulin signaling have recently been implicated as independent drug targets. Glycogen synthase kinase-3 (GSK-3) has a clear role in opposing the effect of insulin by inhibiting the activation of glycogen synthase and the subsequent accumulation of glycogen in muscle [134]. Recent results with selected inhibitors of GSK-3 activity *in vivo* could indeed augment insulin action [135]. The SH2 domain containing inositol 5-phophatase type 2 (SHIP 2) may function to dephosphorylate key phospholipids, e.g. phosphatidyl inositol phosphate generated by insulin-mediated PI-3-K activation. Recently, heterozygous null mice have been shown to display enhanced sensitivity to insulin, implicating this enzyme as a diabetic target [136]. Protein kinase C θ could be an additional drug target, as increased muscle PKC θ activity has been observed in the context of fatty acid-induced insulin resistance [137] (Table 2).

**Targeting lipid metabolism**

Since obesity plays an important role in the development of insulin resistance, attenuating the appetite and/or enhancing energy expenditure will be of great use in treating type 2 diabetes. Melanocortin-4 receptor (MCR-4) offers the prospects of ameliorating obesity and type 2 diabetes. Thus, either an increase in the expression of a natural MCR-4 antagonist or knockout of the receptor itself produces a strong phenotype with multiple features of metabolic syndrome [138,139]. Appetite reduction through central inhi-

**Table 2.** Potential drug targets in the insulin signaling pathway.

| Target | Insulin, small movement/ activators/ potentiators | Apparent direct activation of the receptor |
|---|---|---|
| PTP-IB<br>Protein Tyrosine Phosphatase | Efficacy of vanadium compounds; PTP-IB$^{+}$ (null) mice (insulin sensitive and obesity resistant); efficacy of PTP-1B antisense oligonucleotide | Mediates dephosphorylation of insulin receptor (and its tyrosyl-phosphorylated substrate) |
| SHIP-2 | SHIP-2$^{+/-}$ mice (Insulin sensitive) | Dephosphorylation of phosphoionositides (e.g. products of PI3K) |
| GSK-3 | Efficacy of GSK-3 inhibitors in rodent model | Phosphoxylation of glycogen synthase leading to inhibition of glycogen synthesis potential, negative regulating of other insulin signaling events. |
| IKB Kinase | Efficacy of high-dose salicylate/ inhibits IKB kinase) IKB kinase$^{+/-}$ mice (insulin sensitive) | Serine threonine phosphoxylate of insulin signaling intermediate (e.g. IRS proteins) |
| PKCB | Activated in muscle in association with fatty acid-induced insulin resistance | Negative regulation of insulin signaling; potential threonine phosphorylation of IRS proteins |



bition of fatty acid synthase also offers a new target [140]. cAMP-activated protein kinase, acetyl CoA carboxylase, adipocyte-related complement protein 30, PPAR-γ, and PPAR-α represent some of the mechanisms that could be exploited to reverse or prevent obesity-related lipotoxicity [141–143]. PPARs are ligand-activated transcription factors which are members of a nuclear receptor family offering a promising therapeutic target for metabolic syndrome. PPAR-γ is a predominant molecular target for insulin-sensitizing thiazolidinedione (TZD) drugs [143,144]. PPAR-γ affects the gene transcription in adipose tissues leading to induction of adipocyte genes, such as those for lipoprotein lipase and fatty acid transporter-1, which results in improvement in insulin action along with lowering of triglyceride and FFA levels [144]. A closely related nuclear receptor, PPAR-α, is the molecular target for the fibrate class of lipid-modulating drugs. [143]. PPAR-α agonists have an independent insulin-sensitizing effect arising from reduction in muscle lipid content [145].

## Pharmacological Management of Diabetes Mellitus

Hyperglycemia in patients with diabetes mellitus is always the result of a mismatch between the quantity of insulin necessary to regulate the person's metabolic processes and the amount of insulin being secreted by the person's β cells. Patients with type 1 DM or insulin-sensitive type 2 DM who have normal insulin action have an absolute insulin deficiency. Patients with insulin resistance start with a relative insulin deficiency and with passing years frequently progress to an absolute insulin deficiency. Oral antihyperglycemic agents such as thiazolidinediones or metformin decrease insulin resistance, ∝-glucosidase inhibitors decrease postprandial insulin needs, insulin secretagogues improve and increase endogenous insulin secretion, and insulin and its analogues replace endogenous insulin secretion by exogenous insulin administration.

### Drug therapy of NIDDM

Drug therapy of NIDDM should be considered when diet, patient's education, and increased physical activity have failed to achieve individual treatment goals. Table 4 lists the types of drugs most commonly used in NIDDM.

**Table 3.** Actions of antidiabetic drugs used in non-insulin-dependent diabetes mellitus.

| Drug class | Available drugs | Mode of actions |
|---|---|---|
| Sulphonylureas and Repaglimide | Chlorpropamide<br>Tolbutamide<br>Glibenclamide<br>Glibornuride<br>Gliclazide<br>Glipizide<br>Acetohexamide<br>Tolazamide | Increase insulin secretion |
| Biguanides | Metformin | Counter insulin resistance |
| α-Glucosidase inhibitors | Acarbose | Slow carbohydrate digestion |
| Thiazolidinediones | Roziglitazone<br>Pioglitazone | Selectively increase insulin sensitivity |
| Insulin | Insulin lispro, Insulin aspart<br>Insulin glargine, detemir Insulin | Decrease hepatic glucose production and increase peripheral glucose utilization |

### Antidiabetic drugs

For type 2 diabetes it is clearly a priority to provide effective control of the hyperglycemia to reduce macro- and microvascular complications [146,147]. The standard approach begins with dietary, exercise, and healthy-living advice, particularly designed to facilitate weight loss in the obese. These measures are ineffective in more than four-fifths of newly diagnosed type 2 diabetes patients, and the progressive nature of type 2 diabetes dictates that most patients require drug therapy. Oral agents, notably sulphonylureas, metformin, and acarbose, are instituted as monotherapy, and a new class of TZDs (thiazolidinediones) has recently become available (Table 3). If adequate glycemic control is not achieved with

**Table 4.** Current therapeutic agents and their molecular target for type-2 diabetes.

| Drug class | Molecular target | Sites of action | Adverse events |
|---|---|---|---|
| Insulin | Insulin receptor | Liver, muscle, fat | Hypoglycemia, weight gain |
| Sulphonylureas (e.g. glibenclamide) plus nateglimide and repaglimide | SU receptor/$K^+$ ATP channel | Pancreatic β cell | Hypoglycemia, weight gain |
| Metformin (biguanides) | Unknown | Liver (muscle) | Gastrointestinal disturbance lactic acidosis |
| Acarbose | α-Glucosidase | Intestine | Gastrointestinal disturbances |
| Pioglitazone, Rosiglitazone (Thiazolidinediones) | PPAR-γ | Fat, muscle, liver | Weight gain, edema, anemia |

oral monotherapy, then two different classes of oral drugs are used in combination [148]. Insulin therapy sometimes is supplemented with an oral agent to further improve glycemic control and/or lower insulin dosage.

**Treatment of insulin resistance and type 2 diabetes mellitus**

Given that insulin resistance is an early and pervading feature of typical forms of type 2 diabetes and other components of the syndrome, it may be surprising that insulin resistance is not widely recognized as a clinical entity deserving its own therapeutic attention. Treating insulin resistance is not a simple matter of either giving more insulin to push the signaling pathways harder or reducing insulin concentrations to reduce the consequences of hyperinsulinemia. Either approach carries penalties. Giving more insulin can increase those actions of insulin that are impaired by the bottlenecks of signal transduction. However, everting the desired effect on a severely compromised pathway of insulin (e.g. impaired glucose transport) can result in gross accentuation of other less desirable actions of insulin (e.g. lipogenesis, leading to hypertriglyceridemia and obesity, or sodium retention, promoting hypertension). Indeed, excess insulin exacerbated insulin resistance at the receptor and post-receptor levels. Thus the detrimental effects of hyperinsulinemia can be increased by insulin therapy and the added risk that excess insulin will precipitate episodes of hypoglycemia. Reducing insulin concentrations is a particular problem in type 2 diabetes.

**Sulphonylureas**

Sulphonylureas are widely considered as fine-line drug treatment in NIDDM patients who are not grossly obese [149]. Sulphonylureas and a new short-acting insulin releaser (repaglinide) act directly on the islet β cells to close ATP-sensitive $K^+$ channels, which stimulate insulin secretion [150,151]. The efficacy of these agents depends on the presence of enough β cells with sufficient functional reserve. However, the endogenous insulin response to glucose is usually diminished in advanced states of type 2 diabetes. Thus, small drug-induced increases in insulin secretion, especially post-prandially, are clinically valuable to assist glycemic control. Insulin therapy usually will provide effective glycemic control when oral agents are inadequate [152]. The major acute problem associated with sulphonylureas is hypoglycemia, the risk of which markedly increased in the elderly and patients with renal insufficiency. Sulphonylurea-induced hypoglycemia can be exacerbated by interaction with numerous drugs, including alcohol (ethanol), aspirin, phenylbutazone, and oxidase inhibitors.

**Biguanides**

Metformin is the only established antidiabetic drug that deals with insulin resistance. Its glucose-lowering effect is mainly a consequence of reduced hepatic glucose output (gluconeogenesis and glycogenolysis) and increased insulin-stimulated glucose uptake and glycogenesis in skeletal muscle [153]. Metformin improves insulin action in tissues that are acutely sensitive to insulin by increasing insulin-stimulated insulin-receptor phosphorylation and tyrosine-kinase A [154]. Another action of metformin is to reduce fatty acid oxidation in an apparently insulin-independent manner, which serves to redress the imbalance in the glucose-fatty acid cycle. Thus, metformin improves insulin sensitivity in lined and skeletal muscle without raising insulin concentrations. In fact, insulin concentrations tend to fall during chronic therapy [147]. Metformin also improves insulin action in adipose tissue, but obesity is offset by increased glucose turnover and lower insulin concentration. Metformin offers a range of benefits that combat insulin resistance, and various aspect of syndrome X consistent with the treatment regimens for type 2 diabetes that are initiated with metformin show a particularly favorable long-term reduction in morbidity and mortality from micro- and macrovascular complications [147].

**α-glucosidase inhibitors**

Acarbose and related compounds delay the intraluminal production of monosaccharide, particularly glucose [155]. Acarbose competitively inhibits α-glucosidases that are associated with the brush border membrane of the small intestine and are responsible for the digestion of complex polysaccharides and sucrose [156]. This slows carbohydrates digestion and lowers post-prandial hyperglycemia. Although insulin resistance is not addressed directly, the blood glucose lowering effect with reduced glucotoxicity without increasing, and possibly decreasing, insulin concentrations, thereby reduces at least one part of insulin resistance.

**Thiazolidinediones (TZDs)**

PPARs (peroxisome proliferator-activated receptors) are ligand-activated transcription factors (members of the nuclear re-

ceptor family) which offer a promising therapeutic approach to the metabolic syndrome. The known beneficial effects of PPAR ligands are largely consistent with the mechanism that can ameliorate lipotoxicity. PPAR-γ is the predominant molecular target for insulin-sensitizing thiazolidinedione (TZD) drugs [143]. New compounds with markedly enhanced potency and selectivity for the receptor have recently been discovered [144]. This new class of oral antidiabetic agents targets the nuclear PPAR-γ, which increases transcription of certain insulin-sensitive genes. Thus, TZDs provide a new approach to the treatment of insulin resistance [147]. Although, their long-term clinical efficacy is still under investigation, their blood glucose-lowering activity appears to be increased in the presence of at least normal circulating levels of insulin. Hence, efficacy is greater in combination with insulin therapy or an insulin releaser. Consistent with the different circular mechanisms of TZDs and metformin, preliminary clinical studies have suggested that the two classes of agents can be used in combination to achieve additive blood glucose-lowering activity.

The TZDs, represented by troglitazone, roziglitazone, and pioglitazone, have recently been introduced to the market as insulin sensitizers for the treatment of type 2 diabetes. These agents improve sensitivity to insulin by binding to a nuclear receptor such as peroxisome proliferator-activated receptor-γ (PPAR-γ), which acts in conjunction with the retinoid X receptor (RXR) by de-repression to increase transcription of certain insulin-sensitive genes, like in adipose tissue; lipoprotein lipase (LPL), fatty acid transporter protein (FATP), adipocyte fatty acid binding protein ($aP_2$), fatty acyl CoA synthase, glucose transporter GLUT4 etc. There is preliminary preclinical evidence that TZDs might reduce renal complications and prolong the granulation of functionally impaired β cells [157], although the mechanism is undetermined. Troglitazone was effective in type 2 diabetes, but it has been withdrawn from the market as a result of idiosyncratic hepatotoxicity; however, this has not been observed with rosiglitazone or pioglitazone [158]. TZDs are especially effective in combination with insulin to reduce the high insulin dosage and improving glycemic control in type 2 diabetes, and they are also used effectively in combination with other classes of antidiabetic agents [159].

**Insulin**

The discovery of insulin in 1922 by Banting and Best was a breakthrough in the treatment of diabetes. Insulin produces a remarkable life expectancy for diabetics, whether of type I or type II. Insulin therapy, however, should be reserved to patients who have failed on an adequate trial of diet, exercise, and oral antidiabetics. Insulin therapy can improve or correct many of the metabolic abnormalities present in patients with type 2 DM. Insulin administration significantly reduces glucose concentrations by suppressing hepatic glucose production, increasing postprandial glucose utilization, and improving the abnormal lipoprotein composition commonly seen in patients with insulin resistance. Insulin therapy may also decrease or eliminate the effects of glucose toxicity by reducing hyperglycemia to improve insulin sensitivity and β-cell secretary function. It suppresses ketosis and helps in delaying or arresting diabetic complications.

Initially, injectable bovine or bovine-porcine mixtures were used for treating diabetes. However, it was difficult to replicate the normal pattern of nutrient-related and basal insulin secretion due to high inter- and intra-subject variability in subcutaneous absorption. The advent of recombinant DNA technology provided an opportunity to design insulin analogues in an attempt to overcome these limitations. The subsequent availability of rapid-acting (insulin lispro, insulin aspart) and long-acting (insulin glargine and detemir insulin) insulin analogues for meal and basal requirements offer both individual and collective advantages. The subsequent developments towards insulin delivery led to external continuous subcutaneous insulin infusion pumps, capable of achieving excellent metabolic control and reduced risk of hypoglycemia. Studies have been done, though with limited success due to variable bioavailability, with oral, buccal, rectal, dermal, nasal, and pulmonary routes of delivery. Improvement in delivery of insulin into the alveolar surface of the lung using a liquid aerosol formulation has benefited from a better understanding of the impact of aerosol particle size, inspiratory flow rate, and inhaled volume. The other options include islet cell implantation. Though the recent availability of a new long-acting insulin analogue (insulin glargine) used along with the rapid-acting analogue provides a good therapy, there is a distinct possibility that the intrapulmonary delivery of insulin will become the first widespread non-subcutaneous route of administration. Nevertheless, the advancements in cell biology and genetics may provide the final opportunity for insulin independence.

**Combined oral therapy**

In patients whose condition is not adequately controlled by diet and single-drug hypoglycemic therapy, it may be necessary to consider combination therapy.

**Sulphonylureas and biguanides**

This combination therapy has been used for more than 30 years. In patients in whom sulphonylurea therapy is inadequate, the addition of metformin may provide satisfactory control for several years, while addition of sulphonylureas to metformin monotherapy is used more rarely [160].

**Sulphonylureas and acarbose**

Several placebo-controlled studies have demonstrated improvement in diabetic control in patients with NIDDM treated with sulphonylurea compounds with acarbose [161]. In a study performed by Gerard et al. [162], a single dose of glybenclamide (glyburide) 5 mg was administered to six NIDDM patients immediately before a standardized breakfast, following one week's treatment with placebo or acarbose 100 mg three times daily, in randomized crossover sequence. Acarbose induced a significant improvement in the blood glucose profile together with a significant decrease in plasma insulin levels. Interestingly, acarbose has no significant effect on the pharmacokinetics of glybenclamide. Reaven et al. [163] also demonstrated significant reductions in fasting and postprandial blood glucose, HbA1c, and plasma triglyceride levels following additions of acarbose in 12 patients with NIDDM poorly controlled by diet plus sulphonylureas.

**Biguanides and acarbose**

Combination therapy is not common with a biguanides and acarbose, probably because of the risk of gastrointestinal ef-

fects associated with these two types of drugs. A preliminary report [164] stated that HbA1c levels were significantly reduced in patients treated with metformin plus acarbose. If such a combination is used, it is necessary to recognize that acarbose has been reported to significantly modify the pharmacokinetics of metformin [165].

**Insulin therapy of NIDDM**

When diet and oral therapy (either monotherapy or combined therapy) have failed to achieve adequate glycemic control in patients with NIDDM, it is usual practice to initiate insulin therapy.

**Insulin and sulphonylureas**

A number of reviews on the effectiveness of combined insulin and sulphonylurea therapy in NIDDM patients have been published [166–168]. Most of the studies investigating the mechanism of action have shown that the beneficial effects (improvement in blood glucose control, reduction in HbA1c levels, reduction in daily insulin requirement) are mainly due to stimulation of residual insulin secretion, with minimal or no effect on insulin sensitivity [169]. However, some of the investigators have suggested that sulphonylureas may also decrease the metabolic clearance rate of insulin [170].

**Insulin and biguanides**

Biguanides improve diabetic control, despite reducing circulating insulin level, in obese patients with NIDDM [171]. Several studies have shown that metformin improves both peripheral [172,173] and hepatic [174,175] insulin sensitivity in patients with NIDDM. However, no studies appear to have provided data merely showing the advantages of the combination of insulin and biguanides during chronic treatment in obese patients with type 2 diabetes.

**Insulin and acarbose**

In many studies performed in patients with type 1 diabetes, insulin requirements decreased during acarbose treatment [161]. This has also been observed in NIDDM patients. Improved metabolic control was obtained during acarbose treatment, with a small but significant reduction in insulin requirements. Addition of acarbose to insulin should be considered in insulin-requiring NIDDM patients when an excessive postprandial rise in blood glucose cannot be adequately controlled by rapid-acting insulin given before meals.

## CONCLUSIONS

Hyperglycemia, usually a consequence of insulin resistance and pancreatic β-cell failure, acts in conjunction with other metabolic disturbances of the insulin-resistance syndrome to generate the characteristics chronic complications of type 2 diabetes mellitus. Insulin resistance, often in collusion with hyperinsulinemia, has been identified as a link for the clustering together of obesity, impaired glucose tolerance, type 2 diabetes mellitus, and several other conditions that carry an increased risk of coronary heart disease, notably dyslipidemia, hypertension, atherosclerosis, and a procoagulant state collectively known as syndrome X. Owing to the progressive nature of type 2 diabetes mellitus, currently available oral antidiabetic agents, even when used intensively, are often unable to control the hyperglycemia. Insulin remains the foundation of glycemic control for type 2 diabetic resistant to control with oral agents, based on its demonstrated record of safety and efficacy. Our growing knowledge of insulin resistance at the cellular level is indicating potential new therapeutic targets, and our experience to date suggests that early intervention against insulin resistance should become a primary strategy for the future treatment of type 2 diabetes mellitus. Indeed, advances in genetics, signal transduction, and the neurobiology of energy intake and metabolism should permit a more precise and perhaps individualized approach to therapy, allowing us to focus the attack where the problem lies. This alone is reason for optimism.

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