Review of Literature
REVIEW OF LITERATURE

Diabetes mellitus, 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 (Zimmert, 2000). It is the most common non-communicable disease worldwide and fourth to fifth leading cause of death in developed countries (Amos et al., 1987). The global figure of people with diabetes mellitus is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025 (King et al., 1998). Developing countries such as India have the maximum increase in the last few years. In India alone the current prevalence of type 2 diabetes mellitus is 2.4 % in rural population and 11.6 % in urban population. It has been estimated that by the year 2025 India will have the largest number of diabetic subjects in the world (King et al., 1998). Diabetes mellitus is a heterogenous group of disorders characterized by high blood glucose levels (World Health Organization, 1999). 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. Some forms of diabetes are characterized by absolute insulin deficiency, or a genetic defect leading to defective insulin secretion, while other forms share insulin resistance as there underlying aetiology.

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 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 common phenotype of hyperglycemia.
Type 1 Diabetes Mellitus

Type 1 diabetes represents a heterogenous and polygenic disorder, with a number of non-HLA loci contributing to disease susceptibility (Lernmark and Ott, 1998). Though this form of diabetes accounts for 5 to 10% of all diabetics yet there is no identified agent substantially capable of preventing this type of disease (Atkinson and Eisenbarth, 2001). American Diabetics Association and WHO (ADA, 2001; WHO, 1999) 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 Mellitus

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 (DeFronzo, 1997). 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 convenience of its microvascular pathology, diabetes is a leading cause of blindness and 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 underutilization of glucose in peripheral tissues (Bergman, 1989).

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 (ADA, 2001). At each end of this spectrum are single gene disorders that affect the obesity of the pancreatic β-cell to secrete insulin (Fajans et al., 2001; Owen and Hattersley, 2001) or the ability of muscle, fat and liver cells to respond to insulin action (Taylor and Arioglu, 1999; Barroso et al., 1999).
INSULIN RESISTANCE AND SYNDROME X

Insulin Sensitivity and Insulin Resistance

The acute metabolic action of insulin and their essential importance for survival are well recognized (Cahill, 1971). 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 (Cheatham and Kahn, 1995). 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 (ADA, 1998), but there is sufficient variability in normal sensitivity to insulin as 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 over expression of actions that retain normal or nominally impaired reactivity to insulin. Also, high concentration 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 (Reaven, 1988; DeFronzo and Ferrannini, 1991).

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 (Reaven, 1988). 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 (Kido et al., 2000). 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 internalisation (Pessin et al., 1999). 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 (Guilherme et al., 2000). It is likely that the actin cytoskeleton is also crucial in insulin stimulated GLUT4 translocation. Insulin causes remodelling 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 tumour necrosis factor-α (TNF-α) is increased in 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 (Hotamisligil et al., 1996).

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 the 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 administrations 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 (Halaas et al., 1995; Shimomura et al., 1999). This cytokine might also have additional direct effects on hepatic cells (Lee et al., 2001).

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 expression of genes involved in fatty acid oxidation and energy expenditure (Yamauchi et al., 2001).

Resistin is the most recently discovered peptide hormone secreted by adipocytes. Initial studies suggest that resistin might cause insulin resistance, as its levels were increased in obese mice and reduced by antidiabetic drugs of the thiazolidinedione class (Steppan et al., 2001). 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 (Nagaev and Smith, 2001).

Whole body insulin-stimulated glucose utilization, measured by the euglycemic-hyperinsulinemic clamp technique, is reduced in obesity and type 2 diabetes (DeFronzo, 1988). The major site of impaired insulin-stimulated glucose utilization is skeletal muscle, which shows reduction in glucose uptake, glycogenesis and glucose oxidation (DeFronzo, 1988; Kelly et al., 1988; Shulman et al., 1990). Insulin-stimulated glucose uptake is impaired and suppression of lipolysis is decreased in adipocytes from type 2 diabetic patients (Olefsky, 1981; Groop et al., 1989) although responsiveness to insulin may vary considerably between different adipocyte depots. Elevated circulatory free fatty acids (FFAs) 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 sufficient marked to make a significant impact on hyperglycemia until the hyperglycemia is severe (Jeng et al., 1994). 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 concentration (Polonsky et al., 1996). Those who cannot sustain sufficient hyperinsulinemia suffer deterioration in glucose homeostasis i.e. impaired glucose tolerance (IGT). An increasing mismatch between escalating insulin resistances 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 (Polonsky et al., 1996).

**Insulin Resistance Syndrome**

The concept of a syndrome linked to insulin resistance and hyperinsulinemia emerged from a realization that obesity and type 2 diabetes are associated with a high prevalence of multiple metabolic abnormalities and on these disturbances that are risk factors for coronary heart disease. These include dyslipidemia, increased triglycerides and small dense LDL-Cholesterol and decreasing HDL-Cholesterol, hypertension, atherosclerosis and a procoagulant state (Reaven, 1995). 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 advance stages. Several features of this syndrome are different to separate from the normal ageing 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 coexistence 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 also can occur quite independently, without the presence of insulin resistance or hyperinsulinemia.

**Obesity**

Obesity is one of the causes 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 mellitus and increased vascular risk (Kopelman and Albon, 1997). 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 (FFAs) 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, down regulates insulin receptors by increasing receptor internalization and degradation. Insulin probably also exerts other negative effects on insulin signalling at the post-receptor level (Kahn, 1997).

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-Cholesterol, which is more atherogenic subclass of LDL-Cholesterol, often is increased in association with insulin resistance and hyperinsulinemia together with a reduction in HDL-Cholesterol (Reaven, 1995).

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 (DeFronzo and Ferrannini, 1991). 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 (DeFronzo and Ferrannini, 1991). It has also been suggested that hyperinsulinemia might enhance atherogenesis via other mechanism such as increased incorporation of cholesterol and FFAs 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 this high incidence of myocardial infarction. Among the procoagulant features of type 2 diabetes is an increased concentration of plasminogen activator inhibitor-1 (PAI-1), reducing the early lysis of clots (Jokl and Colwell, 1997). This has been attributed tentatively to insulin resistance and hyperinsulinemia (Reaven, 1995).

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 (Reaven, 1995).

Justifying a Syndrome

The insulin resistance and compensatory hyperinsulinemia are associated with a collection of risk factors for coronary heart disease, notably obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, atherosclerosis and a pro-coagulant state, and there is justification for assembling them with a definition of a syndrome - a distinct group of syndrome 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 signalling pathways (Cheatham and Kahn, 1995; Kahn, 1994). 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 autophosphorylation of the receptor 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 IRS-2, shc, and various
uncharacterised proteins (White, 1997). The phosphotyrosine residues of these proteins bind to SH2 domains or other signalling 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 elimination of one IRS protein severely impairs but does not completely obliterate any pathway. The phosphoinositol-3-kinase [PI(3)K] 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 (Cheatham and Kahn, 1995). Interaction of IRS proteins with GRB2 and she 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 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 tyrosine kinase activity 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 (Kahn, 1997; Kahn, 1994). Site directed mutagenesis of the β-subunit, which decreases the number of tyrosine residue phosphorylated, carries an approximately proportional decrease of insulin action (Cheatham and Kahn, 1995). 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 (White, 1997), 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 mellitus. Interestingly, IRS-2 knockout causes insulin
resistance and reduced β-cell mass, resulting in severe (often fatal) diabetes mellitus. These observations concur with the possibility that reduced signalling through different IRS proteins could account for the heterogeneity of insulin resistance. In addition to disturbances of insulin signalling, 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 has been noted, and observations at the level of glucose transporters cycling, hexokinases and other key mediators of insulin action remain under suspicion. Adverse effects of chronically raised blood glucose and lipid concentrations (glucotoxicity and lipotoxicity) in diabetes mellitus include the aggravation of insulin resistance (Yki-Jarvinen, 1992; Boden, 1997).

Impaired Glucose Tolerance

Type 2 diabetes is increasingly common indeed epidemic, primarily because of increases in the prevalence of a sedentary life style and obesity (Zimmet, 1995) The possibility of prevailing type 2 diabetes by interventions that affects 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) (Tuomilehto et al., 2001). IGT is defined as hyperglycemia (with glucose values intermediate between normal and diabetes) following a glucose load (WHO, 1999). 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 mellitus (Harris and Zimmet, 1997).

Subjects with IGT also have a heightened risk of macrovascular disease (Harris and Zimmet, 1997). Because of this, and the association with other known CVD risk factors including hypertension, dyslipidemia and central obesity (Zimmet and Albert, 1997), the diagnosis of IGT, particularly in apparently healthy and ambulatory individual have important prognostic implications (Perry and Baron, 1999). Impaired fasting glucose (IFG) was introduced recently as another category of abnormal glucose metabolism (ADA, 1998). It is defined on the basis of fasting glucose concentration and IGT; it is associated with risk of cardiovascular diseases (CVD) and future diabetes mellitus (Table 3).
Table 3: Values for diagnosis of diabetes mellitus and other types of hyperglycemia

<table>
<thead>
<tr>
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<th>Glucose Concentration (mM)</th>
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<tbody>
<tr>
<td></td>
<td>Plasma venous</td>
</tr>
<tr>
<td>Diabetes mellitus fasting</td>
<td>≥ 7.0</td>
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<tr>
<td>2-h post-glucose load</td>
<td>≥ 11.1</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>&lt; 7.0</td>
</tr>
<tr>
<td>fasting</td>
<td>7.8-11.0</td>
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<tr>
<td>2 h post-glucose load</td>
<td>6.1-6.9</td>
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<tr>
<td>Impaired fasting glucose</td>
<td>&lt; 7.8</td>
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<tr>
<td>fasting</td>
<td>6.1-6.9</td>
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</table>

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 (Fagot-Campagna and Narayan, 2001; Rosenbloom et al., 2001). Although type 1 diabetes remains the main form of the disease in children worldwide, it seems possible that type 2 diabetes will be predominant from within ten years in many ethnic groups and potentially in Europid (European descents) groups and reported from several developed countries like US, UK, Australia, Hong Kong and Japan.

The rising prevalence of obesity and type 2 diabetes mellitus in children is symptomatic of the effect of globalisation and industrialization affecting all societies with sedentary life style 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 Paediatrics (ADA, 2000).

Current Diagnostic Criteria of Diabetes Mellitus

Many persons with type 2 diabetes already show the presence of the long term complications associated with diabetes mellitus at the time of diagnosis. It is now widely accepted that if diabetes mellitus 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 the fasting plasma glucose (FPG) is unequivocally elevated, diagnosis of diabetes mellitus does not make any difficulty. When a patient is without clinical symptoms, a diagnosis of diabetes is more difficult. Revised criteria for diagnosing diabetes mellitus have been issued by consensus panel of experts from the National Diabetes Data Group and the WHO. The revised criteria reflect new epidemiologic 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.

According a report of American Diabetes Association (2003) 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.

Impaired fasting glucose (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 impaired glucose tolerance (IGT), which is defined as plasma glucose levels between 7.8 and 11.1 mmol/l (140 and 200 mg/dl) 2 hour after a 75 g oral glucose load. Individuals with IFG or IGT are at substantial risk for developing type 2 diabetes and cardiovascular disease in the future, though they may not meet the criteria for diabetes mellitus.

Thus criteria for diagnosis of diabetes mellitus areas under:

Symptoms of diabetes and 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 (OGTT).
The revised criteria for the diagnosis of diabetes mellitus emphasize the FPG as the most reliable and convenient marker for diagnosing diabetes mellitus in asymptomatic individuals. Oral glucose tolerance testing, although still valid criteria for diagnosis of diabetes mellitus are not recommended as part of routine screening.

Some investigators have advocated the acetylated haemoglobin (HbA1c) as a diagnostic test for diabetes mellitus. Though there is strong correlation between elevations in the plasma glucose and the 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.

**Genetic Aspect of Type 2 Diabetes Mellitus**

The identification and characterization of the genes involved in type 2 diabetes 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 (Pro12Ala) in peroxisome proliferator activated receptor-γ (PPAR-γ) has been associated with type 2 diabetes (Altschuler et al., 2000). People homozygous for the Pro12 allele are more insulin resistant than those having one Ala12 allele and have a 1.25 total increased risk of developing diabetes mellitus. There is also evidence for interaction between this polymorphism and fatty acid, thereby linking this locus with diet (Luan et al., 2001). 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 signalling 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 β-cell dysfunction in type 2 diabetes mellitus. Diabetic islets show reduced insulin gene transcription; this might be due, at least impact, to reduced insulin action in that tissue and indicate that activation of insulin gene transcription is an important effect of insulin-mediated signalling (Leibiger et al., 2001).

Genetic variation in the gene encoding Calpain-10, a ubiquitously expressed cysteine protease, has also been associated with type 2 diabetes mellitus, increasing risk as much as three fold (Horikawa et al., 2000) through effect on both the normal function of the β-cell and insulin action in muscle and fat cells.
Mitochondrial Mutations and Diabetes Mellitus

*Mutations in genes encoding insulin receptor and insulin receptor substrate*

Point mutation or deletions in mitochondrial DNA 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 mutation in the mitochondrial DNA (Ballinger *et al.*, 1992). 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 mellitus (Maassen *et al.*, 2001). 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 mellitus is common and polygenic in nature (Froguel and Velho, 2001). Patients usually display both; resistance to insulin at its target tissues (mainly skeletal muscle) as well as defective insulin secretion (Polonsky *et al.*, 1996). 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 mellitus was observed. Reduced mtDNA content was also reported in peripheral blood cells in such patients even before the onset of the disease (Lee *et al.*, 1998).

UCP-2 is an inner mitochondrial membrane protein that tends to diminish the proton gradient generated by the respiratory chain. Its over expression in β-cells attenuate ATP generation and insulin secretion in response to glucose (Chan *et al.*, 2001). It is of interest that deletion of the UCP-2 gene in mice enhances islet ATP generation and insulin secretion during glucose stimulation (Zhang *et al.*, 2001). 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.
(Unger et al., 1999). Chronic exposure of β-cells to fatty acids induces changes in the expression of numerous genes, among them UCP-2 gene which correlates with reduced glucose-evoked insulin secretion (Lameloise et al., 2001).

**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 (Fajans et al., 2001; Owen and Hattersley, 2001). 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 highest levels in the pancreatic β-cell and in the liver (Lenzen et al., 1988). 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 glycolytic 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 which lead to permanent neonatal diabetes mellitus (Njolstad et al., 2001).

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 (Cereghini, 1996; Rynne, 2001). 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 (Ryffel, 2001). 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 (Fajans et al., 2001; Owen and Hattersley, 2001).

IPF-1 is a homeodomain containing transcription factor involved in pancreatic development (Jonsson et al., 1994; Edlund, 1998), transcriptional regulation of a number of β-cell genes including insulin, glucokinase, islet amyloid polypeptide and glucose transporters 2 [GLUT 2] (Edlund, 1998) and mediation of glucose stimulated insulin gene transcription (Marshak et al., 1996). 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 mellitus.

DIABETIC COMPLICATIONS AND THEIR PATHOGENESIS

1. Acute Complications

These include diabetic keto acidosis (DKA) and non ketotic hyperosmolar state (NKHS). While first one is seen primarily in individuals of type 1 diabetes mellitus, the later is prevalent in individuals of type 2 diabetes mellitus. 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 acids and amino acid delivery from fat and muscle to the liver. Ketosis results from marked increase in free fatty acids release from adipocytes due to increased lipolysis. In DKA, nausea and vomiting are often present. Lethargy and central nervous system depression may evolve into coma in severe DKA. Cerebral oedema, an extremely serious complications are seen most frequently in children.

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

2. Chronic Complications

The chronic complications of diabetes mellitus affect many organ systems and are responsible for majority of morbidity and mortality. Chronic complications can be divided into vascular and non vascular 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 gastroparesis, sexual dysfunction and skin changes. As a consequence of its chronic complications diabetes mellitus is the most common cause of adult blindness, variety of debilitating neuropathies and cardiac and cerebral disorders. Treating complications of diabetes mellitus cost more than controlling the disease.

Early in the course of diabetes mellitus, 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.

Retinopathy

Diabetic retinopathy occurs in 3/4th of all persons, having diabetes mellitus for more than 15 years and is 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. Non-proliferative appears late in the first decade or early in the second decade of disease and is marked by retinal vascular microaneurysms, blot haemorrhages 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 appearance of neovascularisation in response to retinal hypoxia. The newly formed vessels may appear
at the optic nerve and/or macula and rupture easily leading to vitreous haemorrhage, fibrosis and ultimately retinal detachment (Aiello et al., 1998).

**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 macro vascular junction in 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-fibres. It can occur both from direct hyperglycemia induced damage to the nerve parenchyma and from neuronal ischemia leading to abnormalities of micro vessels 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 (Chen et al., 1997).

**Nephropathy**

Nephropathy is the 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 glomerular filtration apparatus is manifested by microalbuminurea and is attributed to changes in synthesis 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 increase in the renal VEGF levels that are observed in preclinical models of diabetes, since VEGF is both, an angiogenic and permeability factor (Ritz and Orth, 1999).

**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, myocardial infarction and 1-5 fold increase in sudden death. The absence of chest pain
(silent ischemia) is common in individuals with diabetes mellitus and a thorough cardiac evaluation is indicated in the 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 profile of the individual in the intensive group (lower total cholesterol, LDL-cholesterol and 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 (3 fold increase in stroke). Individuals with diabetes mellitus have increased incidence of congestive heart failure (diabetic cardiomyopathy). The etiology of this abnormality is probably multifactorial and includes factors such as myocardial ischemia from atherosclerosis, hypertension and myocardial cell dysfunction, secondary to chronic hyperglycemia. Though diabetes mellitus itself does not increase levels of LDL but LDL particles found in type 2 diabetes mellitus are more atherogenic and are more easily glycated and susceptible to oxidation (Grundy et al., 1999).

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 therapeutic agents in the context of an individual patient's risk factor profile. Diabetes mellitus related considerations include the following:

1. α-Adrenergic blockers slightly improve insulin resistance and positively impact the lipid profile. β-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 cardioselective β-1 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 diabetes, 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 vascularisation secondary to long-standing diabetes mellitus. 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. rhino cerebral 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 & soft tissue infections are all more common in diabetes mellitus population. Gram-negative organisms e.g. *Mycobacterium tuberculosis* are more frequent pathogens in patients of diabetes mellitus. Diabetic patients have an increased rate of colonisation of *Staphylococcus aureus* in the skin folds and also have a greater risk of post operative wound infections.

**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: Aldose Reductase theory, Advanced Glycation End Product (AGE) theory; Activation of Protein Kinase C (PKC) isoform theory; Increased Hexosamine Pathway flux and Reactive Oxygen Intermediate theory.

**Aldose Reductase**

It is the first enzyme in the polyol pathway. It is a cytosolic, monomeric oxido-reductase that catalyses the NADPH dependent reduction of a wide variety of carbonyl compounds, including glucose. Increased intracellular glucose in hyperglycemic environment results in its increased enzymatic conversion to the polyalcohol sorbitol, with concomitant decreases in NADPH (Srivastava *et al.*, 1986). In the polyol pathway, sorbitol is oxidized to fructose by the enzyme sorbitol dehydrogenase, with NADH reduced to NADφ. Cataract formation in diabetes mellitus 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 hyperglycaemia 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 (Stitt et al., 1997) and renal glomeruli (Horie et al., 1997). 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 (Nakamura et al., 1997). 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 (Degenhardt et al., 1998). The AGE receptor ligation activates the pleiotropic transcription factors causing pathological changes in gene expression along with other cellular signalling events such as activation of mitogen activated protein kinase (MAP kinase) or PKC which can lead to cellular dysfunction (Ishii et al., 1996).

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

These are critical intracellular signalling molecules that can regulate many vascular functions including permeability, vasodilator release, endothelial activation and growth factor signalling. The PKC family comprises at least eleven isoforms, 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 (Koya et al., 1997). Increased de novo synthesis of DAG leads to activation of β-isoforms of PKC 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 β isoform of PKC significantly reduced PKC activity in the retina and renal glomeruli of diabetic animals (Koya et al., 2000). 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 (Kolm Litty et al., 1998). In this pathway fructose-6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-N-acetylglucosamine, such as proteoglycan 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 increase in the transcription of TGF α, TGF β and PAI-1. This pathway has also important role in hyperglycemia induced and fat induced insulin resistance.

**Reactive Oxygen Intermediate**

Hyperglycemia can increase oxidative stress through both enzymatic and non enzymatic processes. Glucose metabolism through glycolytic pathway and TCA cycle produces reducing equivalents used to drive the synthesis of ATP via oxidative phosphorylation in mitochondria. By-products of mitochondrial oxidation include free radicals like 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 leucocyte 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 mellitus, while levels of some markers of oxidative stress e.g. oxidized LDL-cholesterol increased.
Thus there can be two approaches for designing treatment for 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 signalling 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 recognised 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 recognised that a diet containing 60% carbohydrates even if not including sugar may predispose to the development of dyslipidemia (Garg et al., 1988). Carbohydrates should be predominantly complex and high in soluble fibre; foods with aglycemic index (Jenkins et al., 1989) are preferred although moderate intake of simple sugar such as sucrose does not seem to be detrimental. Protein intake should not exceed daily requirement, since high protein intake appears to have a detrimental effect on renal function (Brenner et al., 1982).

**Dietary Fibres**

Numerous studies recently reviewed by Hoewitz (1990) have shown that addition of certain types of soluble fibre, 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 triglycerides and lipoprotein levels (Axelrod, 1989). However, there is also evidence that in NIDDM
the decrease in plasma triglyceride levels is counterbalanced by adverse effects on blood glucose or LDL-cholesterol (Hendra et al., 1989; Mori et al., 1990; Vessby and Boberg, 1990).

**Physical Activity**

Recent clinical investigations have shed on the mechanism by which exercise may help in controlling excessive blood glucose levels (Berger et al., 1982). 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 mellitus (ADA statement, 1990). 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 (Horton, 1986). Such effects results 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 mellitus 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 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 basis of predicted roles in modulating one or more key aspects of the pathogenesis of the diabetes mellitus and metabolic syndrome. These are: (1) reducing excessive glucose production by liver (2) targeting \( \beta \)-cells (3) targeting insulin signalling pathways (4) targeting lipid metabolism.

**Reducing Excessive Hepatic Glucose Production**

Liver by way of gluconeogenesis and glycogenolysis plays a very important role in regulating endogenous glucose production by the synthesis or break down of glycogen. Increased rates of hepatic glucose production are largely responsible for development of overt hyperglycemia. Glucagon contributes to hyperglycemia through induction of gluconeogenesis and glycogenolytic pathways (Unger, 1971;
Shah et al., 2000) its receptor; a seven transmembrane domain G-protein receptor could be a target for the development of small molecules antagonists (Connell, 1999). Besides, several enzymes that regulate rate-controlling steps in gluconeogenesis or glycogenolytic pathways can also be used as molecular target for therapeutic intervention. One such target is inhibition of hepatic glycogen phosphorylase (Treadway et al., 2001), an enzyme that catalyses the release of glucose from glycogen. Others are fructose-1,6-biphosphatase and glucose-6-phosphatase (Zhang and Moller, 2000). Whereas inhibition of fructose-1,6-biphosphatase would selectively block gluconeogenesis by disrupting the conversion of fructose-1,6-biphosphate to fructose-6-phosphate, inhibition of glucose-6-phosphatase would attenuate final step in hepatic glucose production common to gluconeogenic and glycogenolytic pathways.

**Targeting β-cells**

Two distinct gut derived peptide hormones i.e. 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 (Drucker, 2001). 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 (Marguet et al., 2000). 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 (Drake and Posner, 1998). Over expression of this enzyme prevents insulin receptor kinase activation. A PTP-1B knock out mouse was more insulin sensitive than control
littermates (Table 4). Thus inhibition of PTP-1B represents a good target for drug discovery (Goldstein et al., 1998). 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 phosphatidylinositol-3-OH-kinase play a critical role in insulin action and might be reduced during insulin resistance.

Other putative negative regulators of insulin signalling 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 (Weston and Devis, 2001). Recent results with selected inhibitors of GSK-3 activity in vivo could indeed augment insulin action (Henriksen et al., 2001). SH2 domain containing inositol 5-phosphatase type 2 (SHIP 2) may function to dephosphorylate key phospholipids e.g. phosphatidylinositol phosphate generated by insulin mediated [PI(3)K] activation. Recently heterozygous null mice have been shown to mark enhanced sensitivity to insulin, implicating this enzyme as diabetic target (Clement et al., 2001). Protein kinase C0 could be an additional drug target as increased muscle PKC0 activity has been observed in the context of fatty acid induced insulin resistance (Shulman, 2000).

Table 4: Potential drug targets in the insulin-signaling pathway

<table>
<thead>
<tr>
<th>Target</th>
<th>Insulin, small movement/activators/potentiators</th>
<th>Apparent direct activation of the receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTP-1B Protein</td>
<td>Efficacy of vanadium compounds; PTP-1B⁻ (null) mice (insulin sensitive and obesity resistant); efficacy of PTP-1B anti-sense Oligonucleotide</td>
<td>Mediates dephosphorylation of insulin receptor (and its tyrosyl-phosphorylated substrate)</td>
</tr>
<tr>
<td>Tyrosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHIP-2</td>
<td>SHIP-2⁻/⁻ mice (insulin sensitive)</td>
<td>Dephosphorylation of phosphoinositides [e.g. products of PI(3)K].</td>
</tr>
<tr>
<td>GSK-3</td>
<td>Efficacy of GSK-3 inhibitors in rodent model</td>
<td>Phosphorylation of glycogen synthetase leading to inhibition of glycogen synthesis potential, negative regulating of other insulin signaling events.</td>
</tr>
<tr>
<td>IKB Kinase</td>
<td>Efficacy of high-dose salicylate/inhibits IKB kinase IKB kinase⁻/⁻ mice (insulin sensitive)</td>
<td>Serine threonine phosphorylated insulin signaling intermediate (e.g. IRS proteins)</td>
</tr>
<tr>
<td>PKC0</td>
<td>Activated in muscle in association with fatty acid induced insulin resistance</td>
<td>Negative regulation of insulin signaling; potential threonine phosphorylation of IRS proteins</td>
</tr>
</tbody>
</table>
Targeting Lipid Metabolism

Since obesity plays an important role in 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 knock out of the receptor itself produces a strong phenotype with multiple features of metabolic syndrome (Klebig et al., 1995; Huszar et al., 1997). Appetite reduction through central inhibition of fatty acid synthase also offers a new target (Loftus et al., 2000). 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 (Winder and Hardie, 1999; Abu-Elheiga et al., 2001; Willson et al., 2000).

PPARs are ligand activated transcription factors, which are members of nuclear receptor family offering a promising therapeutic target for metabolic syndrome. PPAR-γ is a predominant molecular target for insulin sensitising thiazolidinediones (TZDs) drugs (Willson et al., 2000; Moller and Greene, 2001). PPAR-γ affect 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 triglycerides and FFAs levels (Moller and Greene, 2001). A closely related nuclear receptor, PPAR-α is the molecular target for fibrate class of lipid modulating drugs (Willson et al., 2000). PPAR-α agonists have an independent insulin sensitising effect arising from reduction in the lipid content of muscle (Ye et al., 2001).

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 diabetes or insulin sensitive type 2 diabetes 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 thiazolidinedione or metformin decrease insulin resistance; α-glucosidase inhibitors decrease postprandial insulin needs; insulin
secretagogues increase endogenous insulin secretion; and insulin and its analogues replace endogenous insulin secretion by exogenous insulin administration.

Drug Therapy of Non-Insulin Dependent Diabetes Mellitus (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 5 lists the types of drugs most commonly used in NIDDM.

Table 5: Drug therapies used in non-insulin dependent diabetes mellitus

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Available drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Chlorpropamide</td>
</tr>
<tr>
<td></td>
<td>Tolbutamide</td>
</tr>
<tr>
<td></td>
<td>Glibenclamide</td>
</tr>
<tr>
<td></td>
<td>Glibornuride</td>
</tr>
<tr>
<td></td>
<td>Gliclazide</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
</tr>
<tr>
<td></td>
<td>Acetohexamide</td>
</tr>
<tr>
<td></td>
<td>Tolazamide</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Roziglitazone</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone</td>
</tr>
</tbody>
</table>

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 mellitus and other components of 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 signalling 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, evertting the desired 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 thus is added risk that excess insulin will precipitate episodes of hypoglycemia, reducing insulin concentrations is a particular problem in type 2 diabetes mellitus.

**Antidiabetic Drugs**

For type 2 diabetes it is clearly a priority to provide effective control of the hyperglycemia to reduce macro and micro vascular complication (Skyler, 1997; UKPDS, 1998). The standard approach begins with dietary advice and exercise and healthy living advice, particularly designed to facilitate weight loss in the obese. These measures are ineffective in more than 80% of newly diagnosed type 2 diabetes patients, and the progressive nature of type 2 diabetes mellitus dictates that most patients required drug therapy. Oral hypoglycemic agents, notably sulphonylureas, metformin and acarbose are instituted as monotherapy and a new class thiazolidinediones has become available recently. If adequate glycemic control is not achieved with oral monotherapy then two different classes of oral drugs are used in combination (Bailey, 1996). Insulin therapy sometimes is supplemented with an oral agent to further improve glycemic control and/or lower drug dosage.

**Sulphonylureas**

Sulphonylureas are widely considered as fine-line drug treatment in NIDDM patients who are not grossly obese (Melander et al., 1990). 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 (Groop, 1992; Bailey, 1998). 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 mellitus. 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 (Galloway, 1990). The major acute problem associated with sulphonylureas is hypoglycemia, the risk of which markedly increased in the elderly and patients with renal insufficiency. Sulphonylureas induced hypoglycemia can be
Review of Literature

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 (Bailey and Turner, 1996). Metformin improves insulin action in tissues that are acutely sensitive to insulin by increasing insulin stimulated insulin receptor phosphorylation and tyrosine kinase A (Stith et al., 1996). 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 (UKPDS, 1998). 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 mellitus that are initiated with metformin show a particularly favourable long-term reduction in morbidity and mortality from micro and macrovascular complications (UKPDS, 1998).

Table 6: Current therapeutic agents and their molecular target for type-2 diabetes mellitus

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Molecular target</th>
<th>Sites of action</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Insulin receptor</td>
<td>Liver, muscle, fat</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Sulphonylureas (e.g. glibenclamide) plus nateglimide and repaglimide</td>
<td>SU receptor/K+ ATP channel</td>
<td>Pancreatic β-cell</td>
<td>Hypoglycemia weight gain</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>Unknown</td>
<td>Liver, muscle</td>
<td>Gastrointestinal disturbance lactic acidosis</td>
</tr>
<tr>
<td>Acarbose</td>
<td>α-glucosidase</td>
<td>Intestine</td>
<td>Gastrointestinal disturbances</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone, rosiglitazone)</td>
<td>PPAR-γ</td>
<td>Fat, muscle, liver</td>
<td>Weight gain, edema, anaemia</td>
</tr>
</tbody>
</table>
\textbf{\textit{\alpha-}}\textit{-Glucosidase Inhibitors}

Acarbose and related compounds delay the intraluminal production of monosaccharides, particularly glucose (Creutzfeldt, 1988). Acarbose competitively inhibits \textit{\alpha-}glucosidases that are associated with the brush border membrane of the small intestine and are responsible for the digestion of complex polysaccharides and sucrose (Lebovitz, 1997). This slows carbohydrates digestion and lowers postprandial hyperglycemia. Although insulin resistance is not addressed directly, the blood glucose lowering effect with reduced glucotoxicity without increasing and possibly decreasing insulin concentrations; thereby reducing at least one part of insulin resistance.

\textbf{Thiazolidinediones (TZDs)}

PPARs (Peroxisome proliferator activated receptors) are ligand activated transcription factors (members of nuclear receptor family), which offer a promising therapeutic approach to the metabolic syndrome. The known beneficial effects of PPAR ligands are largely consistent with mechanism that can ameliorate lipotoxicity. PPAR-\textgamma is the predominant molecular target for insulin sensitising thiazolidinediones (TZDs) drugs (Willson et al., 2000). New compounds with markedly enhanced potency and selectivity for the receptor have recently been discovered (Moller and Greene, 2001). This new class of oral antidiabetic agents targets the nuclear PPAR-\textgamma, which increases transcription of certain insulin sensitive genes. Thus, TZDs provide a new approach to the treatment of insulin resistance (UKPDS, 1998). 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.

The TZDs represented by troglitazone, roziglitazone and pioglitazone, have recently been introduced in the market as insulin sensitizers for the treatment of type 2 diabetes mellitus. These agents improve sensitivity to insulin by binding to the nuclear receptor like peroxisome proliferator activated receptor-\textgamma (PPAR-\textgamma), which acts in conjunction with the retinoid X receptor (RXR) by de-repression to increase transcription of certain insulin sensitive genes (Spiegelman, 1998), like in adipose tissue where
PPAR-γ is highly expressed, lipoprotein lipase (LPL), fatty acid transporter protein (FATP), adipocyte fatty acid binding protein (aP2), fatty acyl CoA synthase, transports uniform GLUT 4. There is preliminary preclinical evidence that TZDs might reduce renal complications and prolong the granulation of functionally impaired β-cells (Buckingham et al., 1998), although the mechanism is undetermined. Troglitazone was effective for type 2 diabetes mellitus, it has been withdrawn from the market as a result of idiosyncratic hepatotoxicity; however, this has not been observed with rosiglitazone or pioglitazone (Saleh, 2000). TZDs are especially effective in combination with insulin to reduce the high insulin dosage and improving glycemic control in type 2 diabetes mellitus and they are also used effectively in combination with other class of antidiabetic agents (Patel et al., 2001).

**Insulin**

The discovery of insulin in 1922 by Banting and Best has been a breakthrough in the treatment of diabetes mellitus. Insulin produces a remarkable life expectancy for diabetics whether of type I or type II. Insulin therapy, however, should be reserved for 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 diabetes mellitus. 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 the diabetes mellitus. 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 insulin detemir) 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 lung using liquid aerosol formulation has benefited from a better understanding of 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 rapid acting analogue provides a good therapy, there is a distinct possibility that the intra pulmonary 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 with whom sulphonylureas 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 (Hermann, 1990).

**Sulphonylureas and Acarbose**

Several placebo-controlled studies have demonstrated improvement in diabetic control in patients with NIDDM treated with sulphonylureas compounds with acarbose (Clissold, 1988). In a study performed by Gerard et al. (1984), a single dose (5 mg) of glibenclamide (glyburide) was administered to 6 NIDDM patients immediately before a standardized breakfast, following one week's treatment with placebo or 100 mg acarbose 3 times daily, in randomised 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 glibenclamide. Significant reductions in the fasting and postprandial blood glucose,
HbA1c and plasma triglycerides levels following additions of acarbose in 12 patients with NIDDM poorly controlled by diet plus sulphonylureas (Reaven et al., 1990).

**Biguanides and Acarbose**

Combination therapy is not common with a biguanides and acarbose, probably because of the risk of gastrointestinal effects associated with these two types of drugs. A preliminary report (Ross *et al.*, 1992) stated that HbA1c levels were significantly reduced in patients treated with metformin plus acarbose. If such a combination is used, it is necessary to recognise that acarbose has been reported to significantly modify the pharmacokinetics of metformin (Scheen and Lefebvre, 1989).

**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 sulphonylureas therapy in NIDDM patients have been published (Bailey and Mezitis, 1990; Groop *et al.*, 1990; Lebovitz and Pasmantier, 1990). Most of the studies investigating the mechanism of action have shown that the beneficial effects (improve 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 (Castillo *et al.*, 1987). However, some of the investigators have suggested that sulphonylureas may also decrease the metabolic clearance rate of insulin (Scheen *et al.*, 1988).

**Insulin and Biguanides**

Biguanides improve diabetic control, despite reducing circulating insulin level, in obese patients with NIDDM (Shafer, 1983). Several studies have shown that metformin improves both peripheral (Hother *et al.*, 1989; Prager *et al.*, 1986) and hepatic (Jackson *et al.*, 1987; Nosadini *et al.*, 1987) 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 mellitus.
Insulin and Acarbose

In many studies performed in patients with type 1 diabetes, insulin requirements decreased during acarbose treatment (Clissold, 1988). 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.

ALCOHOLISM AND DIABETES MELLITUS

Alcohol drinking is an accepted social practice in many societies; it is a common substance of abuse. The regular abuse of alcoholic beverages (ABs) is called "alcoholism". Alcoholism, also known as alcohol dependence, is a disease. Alcoholism is a chronic disease with symptoms that include a strong need to drink despite negative consequences, such as serious job, relationships or health problems. A practical definition of alcoholism is the regular ingestion of ABs sufficient to produce dysfunction or damage at a physical and/or a social economic level. The pathophysiology of drinking covers a wide range of human suffering, illness, social disruption and economic loss. Drinkers develop disease of the liver, pancreas and brain and suffer more strokes than non-drinkers. Alcohol ingestion increases the risk of many types of cancer. Women who drink during pregnancy damage their own children in utero.

There is rapid water loss (diuresis) within the first several hours of AB's ingestion due to decreased secretion of antidiuretic hormone, a pituitary peptide.

Depletion of tissue magnesium occurs very fast (the serum magnesium level may not be reduced). Hypocalcemia may also result from magnesium depletion by reducing parathyroid hormone-induced mobilization of calcium from bone. Reduced serum phosphates may lead to muscle weakness and augmentation.

Folate deficiency occurs in the majority of binge-drinking alcoholics and is a common cause of anaemia. Inadequate dietary intake, intestinal malabsorption, and impaired folate storage in the liver contribute to folate deficiency. Alcohol ingestion also interfere vitamin B₁₂ absorption. Deficiency of the two vitamins causes large-cell (megaloblastic) anaemia. Thiamine deficiency may cause inadequate ingestion and
malabsorption of vitamin. Pyridoxine (B₆) metabolism is disturbed by the process of alcohol oxidation, contributing to anaemia. Pellagra, or niacin deficiency, is common in chronic alcoholics. Pellagra is recognized by the three diseases: diarrhoea, dermatitis and dementia. Vitamin A storage is commonly decreased in alcohol induced liver disease. Liver disease may lead to low blood protein and decreased serum levels of branched chain amino acids.

Trace elements metabolism may be disordered with regular ABs input. Alcohol may increase the urinary loss of zinc and the gastrointestinal absorption of iron. Zinc deficiency aggravates vitamin A deficiency, since zinc is needed in the transformation of vitamin A into its active form. Even low dose of alcohol interfere with memory.

The glucose is the main energy source for all tissues. Glucose is derived from three sources; from food, from synthesis (manufacture) in the body and from the breakdown of glycogen, a form of glucose that the body stores in the liver. Hormones help to maintain a constant concentration of glucose in the blood. This is especially important for the brain because it cannot make or store glucose but depend on glucose supplied by the blood. Two hormones that are secreted by the pancreas and that regulate blood glucose levels are insulin and glucagon. Insulin lowers the glucose concentration in the blood; glucagon raises it.

Alcohol consumption interferes with all three glucose sources and with the actions of regulatory hormones. Chronic heavy drinking has been associated with excessive blood glucose levels (hyperglycemia). Chronic alcohol abuse can reduce the body's responsiveness to insulin and cause glucose intolerance in both healthy individuals (Shah, 1988) and alcoholics with liver cirrhosis (Letlexhe et al., 1993). In fact, 45 to 70 % of patients with alcoholic liver disease are glucose intolerant or are frankly diabetic (Gorden and Lieber, 1992). In animals, chronic alcohol administration also increases secretion of glucagon and other hormones that raise blood glucose levels (Adams and Hirst, 1984).

Alcohol can interfere with the management of diabetes mellitus in different ways. Acute as well as chronic alcohol consumption can alter the effectiveness of hypoglycemic medications (Lewis and Kendall, 1988; Angelini et al., 1992), treatment of diabetes mellitus by tight control of blood glucose levels is difficult in alcoholics, and both hypoglycemic and hyperglycemic episodes are common (Crane and Sereny, 1988).
Metabolism of Alcohol

When alcohol is consumed, it passes from the stomach and intestine into the blood, a process referred to as absorption. In the liver, an enzyme called alcohol dehydrogenase (ADH) mediates the conversion of alcohol to acetaldehyde. Acetaldehyde is rapidly converted to acetate by other enzymes and is eventually metabolized to carbon dioxide and water. Alcohol also metabolized in the liver by the enzyme cytochrome P45011EZ (CYPIEl), which may be increased after chronic drinking (Lieber, 1984). Most of the alcohol consumed is metabolized in the liver, but the small quantities that remain unmetabolized permits alcohol concentration to be measured in breath and urine.

It is widely accepted that alcohol metabolism passes through different mechanisms: alcohol dehydrogenase (ADH) activity in stomach epithelial cells, activity of ADH in the liver, microsomal-ethanol-oxidizing system (MEOS), hepatocyte catalase activity and non-oxidizing metabolic pathway (production of fatty acid ethyl esters). Alcohol causes numerous direct and indirect toxic effects on human organs. The first are directed to epithelial cells of stomach and liver cells, as well as the generation of excessive amount of metabolites: NADH, acetaldehyde and acetate. These amounts of NADH lead to hyperlactacidemia, hypoalbuminemia and fat infiltration to the liver. The activity of MEOS causes drug metabolism changes in the liver and increased rate of hepatotoxic and cancerous substances. Acetaldehyde increases lipid peroxidation, immunity disorders, decrease in enzymatic activities and restoration of nucleoproteins, while acetate decreases lipolytic process in cells (Petrovic et al., 1996). Acetaldehyde (the metabolite produced from ethanol by either ADH or MEOS) impairs hepatic oxygen utilization and forms protein adducts, resulting in antibody production, enzyme inactivation, and decreased DNA repair. It also enhances pyridoxine and perhaps folate degradation and stimulates collagen production by the vitamin A storing cells (lipocytes) and myofibroblasts (Lieber, 1991).

The metabolism of ethanol to acetaldehyde in the liver mainly proceeds via alcohol dehydrogenase (ADH) and the microsomal ethanol-oxydizing system (MEOS), whereas catalase plays no significant role. The ADH pathway which accounts for the bulk of the metabolism, and the MEOS pathway which contributes to the increased rate of ethanol elimination at high alcohol levels (Crabb et al., 1987). ADH is an enzyme of the cytosol, requires NAD⁺ as cofactor and exhibits a pH optimum in the alkaline range.
The Km of ADH is about 2 mM for ethanol (equivalent to 0.1 %). Thus the enzyme is already saturated at low ethanol concentrations. Conversely, MEOS resides in the endoplasmic reticulum, requires NADPH and O₂, is inhibited by CO and exhibits a Km of about 10 mM corresponding to 0.5 % ethanol. This enzyme system is, therefore, primarily the pathway of ethanol metabolism at intermediate to high ethanol concentrations. The product of ethanol oxidation by ADH, MEOS and catalase is acetaldehyde. Acetaldehyde is oxidized in the liver to acetate by NAD dependent aldehyde dehydrogenase. Four clinically significant isozymes have been identified. ALDH I, the most active form, is missing in up to 50 % of Asian people. Lack of isozyme I is responsible for the "flush-syndrome" commonly observed in Asian people following alcohol intake. Ethanol metabolism is affected by the aging process and is decreased with advancing age (Gellert and Teschke, 1988).

Ethanol has variable effects on body weight. It is ketogenic; ketones (like acetaldehyde) may produce a rapid weight loss of several pounds. As cellular toxin, ethanol is catabolic and promotes structural tissues loss. The catabolic effect causes a greater loss of weight than caloric input can replace in the form of fat stores.

Pancreatitis

Chronic relapsing pancreatitis has long been associated with excessive alcohol drinking. Several studies have confirmed the close link between alcohol consumption and pancreatitis (Lake-Bakaar, 1982). Alcohol inhibits pancreatic secretion of digestive enzymes by a direct effect on the pancreas. The deposition of intracellular lipid droplets within the rough endoplasmic reticulum occurs in alcoholic patients with chronic pancreatitis (Bordalo et al., 1977). Long term, heavy alcohol consumption is associated with both acute and chronic pancreatitis. Progression of pancreatitis may lead to multiple co-morbidities including maldigestion, diabetes mellitus and pancreatic cancer (Purohit et al., 2003).

Alcohol Myopathy and Cardiovascular Disease

It has long been known that both acute and chronic abuse can disturb the cardiovascular system in humans, leading to such disorders as high blood pressure, cardiac arrhythmias, and degeneration of the heart muscle, stroke and congestive heart failure. The major functional and structural cardiac abnormalities related to chronic alcohol abuse include hypertrophy, dilatation, fibrosis, cellular swelling, fatty infiltration
and inflammation (Klatsky, 1987). Cardiomyopathy (Alcohol heart muscle disease) has been associated with heavy drinking and chronic alcohol abuse (Klatsky, 1987). Alcohol interferes with activity of many cardiac muscle cell enzymes and also inhibits the binding of actin and myosin. Acetaldehyde is considered to be mainly responsible for the heart damage by affecting the mitochondrial functions and protein synthesis. Chronic alcoholics often suffer from myopathies resulting in elevated serum creatine phosphokinase, aminotransferase, and lactate dehydrogenase (Perkoff et al., 1976).

METABOLIC CHANGES

Carbohydrate Metabolism

Ethanol interferes with carbohydrate energy metabolism. The effects of ethanol on carbohydrate metabolism are complex and various physical, nutritional and hormonal factors may influence the biochemical sequelae. Generally, ethanol affects carbohydrate metabolism via its metabolite acetate, change in NAD+/NADH ratio, and direct action of ethanol and acetaldehyde on the intermediary metabolism of liver. The redox changes associated with the oxidation of ethanol results in a shift of pyruvate to lactate leading to increased lactate level in the blood. The rise in blood lactate decrease urinary uric acid output, resulting in increased serum uric acid concentration. The change in NAD+/NADH ratio alters the tricarboxylic acid cycle, resulting in a number of metabolic disturbances in carbohydrate degradation and synthesis.

Clinically, alcohol-induced hyperglycemia is the major disturbance most frequently observed. Chronic ingestion of ethanol has been found to give rise to glucose intolerance in alcoholics with and without liver disease. Decreased peripheral utilization of glucose and increased breakdown of glycogen in the liver and muscle due to alcohol drinking may be responsible for the increased glucose intolerance. Ethanol abuse is also associated with abnormalities in carbohydrate (as well as lipid) metabolism in skeletal muscle. Ethanol mediated insulin resistance is allied with the inhibitory effects of ethanol on insulin stimulated carbohydrate metabolism. It acutely impairs insulin-stimulated glucose and lipid metabolism, although it is not known whether it has an analogous effect on insulin-stimulated protein synthesis. In alcoholic cirrhosis, insulin resistance occurs with respect to carbohydrate metabolism, although the actions of insulin to suppress protein degradation and stimulate amino acid uptake are unimpaired. Ethanol dosage is associated with the abnormalities in carbohydrate and, to a lesser extent, lipid
metabolism in skeletal muscle (Xu et al., 1996, Klusek et al., 1998). Ethanol is known to acutely reduce the metabolic actions of insulin in several of its target tissues such as skeletal muscle (Spolarics et al., 1994) and adipose tissues (Boden et al., 1993). Ethanol mediated insulin resistance has been the subject of some interest in recent years, particularly with respect to the inhibitory effects of ethanol on insulin-stimulated carbohydrate metabolism (Xu et al., 1996). Studies using the insulin clamp technique, combined with tracer methodologies, have shown that the major tissues in which glucose utilization is reduced by ethanol is skeletal muscle (Spolarics et al., 1994, Xu et al., 1996). 1,2-propanediol and 2,3-butanediol, two novel short chain alcohols whose serum levels are elevated in alcoholism, can impair insulin-stimulated glucose metabolism in vivo (Xu et al., 1998) and in cultured rat adipocytes (Lomeo et al., 1988).

Lipid Metabolism

It is known that chronic alcoholics and type II diabetics show hyperlipidemia, characterised by hypertriglyceridemia and in a minor degree by hypercholesterolemia. The mechanisms underlying the effect of ethanol and carbohydrates on plasma lipids seems to be different; therefore in diabetic subjects, chronic alcohol consumption could produce a more severe hyperlipidemia and to accelerate atherosclerotic events.

One of the major effects of ethanol on lipid metabolism is the inhibition of fatty acid oxidation. Chronic ethanol intake produces fatty liver (steatosis) in man. The accumulation of lipids in the hepatocytes is the most striking initial manifestation of alcoholic liver injury (Baraona and Lieber, 1979). The lipids that accumulate are mainly triglycerols originating from dietary lipids, adipose tissue lipids and lipids synthesized in the liver itself. Many functional disturbances in alcoholism may relate to changes in phospholipid composition of cellular membranes.

Various mechanisms have been implicated in the ethanol oxidation linked disturbances in lipid metabolism. Fatty acids are oxidized via β-oxidation leading to the formation of acetyl-CoA, which in turn is further oxidized by the mitochondrial citric acid cycle. The hydrogen equivalents generated by the oxidation of ethanol are shuttled into the mitochondria to supplant the citric acid cycle as a source of hydrogen. The net result of these transformations is the inhibition of NAD dependent steps of the citric acid cycle promoting accumulation of fatty acids. Partially, they are released as ketone bodies or esterified as glycerolipids or cholesteryl esters.
Hyperlipidemia, as reflected by an increase in serum lipoproteins, may result from increased production and release of hepatic lipoproteins. Large doses of ethanol cause a rise in circulating free fatty acids probably due to enhanced peripheral fat mobilization and decreased breakdown of fatty acids in the liver. Ethanol decreases adipose tissue lipolysis and hence the concentration of plasma free fatty acids through the action of its metabolite acetate. Considerably elevated plasma triglyceride levels have been observed in chronic alcoholics, perhaps due to increased hepatic synthesis of pre-β-lipoproteins and changes in ATP availability. The actions of alcohol on plasma triglycerides depend upon the dose of alcohol administered, the underlying diet, individual susceptibility, the genetic predisposition to hypertriglyceridemia, and the duration of alcohol administration. Ethanol is a powerful inducer of hyperlipidemia in both animals and humans (Avogaro and Cazzolatu, 1975). Ethanol also causes changes in the metabolism of lipoproteins. Chronic alcohol is known to produce hypercholesterolemia, hyperlipidemia and hypertriglyceridemia (Baraona et al., 1983; Baraona and Lieber, 1979).

Ethanol metabolism induces formation of free radicals which are responsible for lipid peroxidation of biological membranes with subsequent aldehyde formation (malondialdehyde, 4-hydroxy-nonenal). These aldehydes are competitive or mixed inhibitors of aldehyde dehydrogenase, and they cause an increase in hepatocellular toxicity of aldehydes. The activity of oxidative systems in human body after chronic as well as acute ethanol intake is being reduced. Interference of ethanol metabolism and gluconeogenesis is caused by inhibition of intake substrates or by decrease NADH/NAD⁺ ratio in hepatocyte. An acute ethanol administration reduces the concentration of most amino acids in plasma by ethanol oxidation impacts on increase of NADH/NAD⁺ ratio or by mechanism mediated by β-adrenergic receptors (Zima, 1993).

Protein Metabolism

Alcohol has been found to enhance the protein synthesis, but also to inhibit it, or be without any significant effect (Poso, 1987). Generally, low levels of albumin and globulins and elevated levels of serum immunoglobulin were found in alcoholics, the low level being attributed to reduce synthesis due to liver damage. The increased immunoglobulin level was related to the severity of liver damage, the highest levels being found in active alcoholic cirrhosis (Wilson et al., 1969). A reduction in the
fractional rate of protein synthesis (i.e. rate of translation) in skeletal muscle in ethanol-fed rats occurs after 2.5 h by approximately 30% (Tieman and Ward, 1986). In ethanol-dosing studies in the rat, the fall in muscle protein synthesis may persist even after the circulating ethanol has been metabolized (Reilly et al., 2000). Ethanol-induced reductions in the protein synthesis in muscle are due to changes in the activation of translation initiation factors involved in the binding of met-tRNA to the 40S ribosomal subunit, i.e. eIF2B and the initiation factors that are involved in the binding of mRNA to the 43S pre-initiation complex eIF4E (Lang et al., 1999; 2000). Insulin is considered to be a potent stimulator of protein synthesis but, in both acute and chronic ethanol administration, insulin levels are increased (Preedy and Garlick, 1988). The paradoxical hyperinsulinemia and decreased rates of muscle protein synthesis are suggestive of insulin resistance.

It has been clearly shown that acetaldehyde covalently binds with a number of proteins, phospholipids and nucleic acids to form more or less stable adducts. The major functional residue on proteins that participate in binding with acetaldehyde is lysine. The adduct formation depends upon the acetaldehyde concentration, the duration of its reaction, and the presence of reducing agents (Tuma and Sorrell, 1985). If acetaldehyde binds at functionally important position of an enzyme, it may lead to a loss in its catalytic properties (Tuma and Sorrell, 1987).

There are also rapid and sustained reductions in total RNA (largely ribosomal) in chronic studies. Loss of RNA appears to be related to increase in the activities of specific muscle RNAses in these long term studies. However, in acute dosing studies, the reductions in muscle protein synthesis are not due to overt loss of total RNA (Preedy et al., 2001).

Biochemical Markers of Alcohol Abuse and Alcoholism

The most obvious method to prove recent drinking is by demonstrating the presence of ethanol in body fluids or breath, but, because ethanol is cleared fairly rapidly from the body, this method is limited to detect only very recent drinking (Helander, 2003). Alcohol abusers may exhibit several clinical and/or biochemical changes. Changes in parameters such as γ-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and mean corpuscular volume (MCV) of erythrocytes may serve as biomarkers of chronic
alcoholism. The main disadvantage with these measures is that they have low sensitivity for recent excessive intake and that raised levels may result from several causes besides heavy drinking, implying a low specificity for alcohol. All available biomarkers have two drawbacks. The first is that they indicate adverse effects in a particular organ, but tell little about their aetiology. The second is that they are not sensitive enough to detect abuse before it results in organic impairment. The 1990s have seen the introduction of a new diagnostic biomarker, carbohydrate-deficient transferrin (CDT). Reduced concentrations of this biomarker are found in serum after regular high alcohol intake (Bilban et al., 2003). Carbohydrate-deficient transferrin (CDT), which refers to changes in the carbohydrate composition of serum transferrin, is a more specific marker for identifying excessive alcohol consumption and monitoring abstinence during outpatient treatment (Helander, 2003). Although no single biochemical marker has shown sufficient diagnostic efficiency, many currently used clinical chemical parameters have proven useful in the diagnosis of alcohol abuse and alcohol-related health problems.

Conventional Markers

\textit{\gamma-\textit{Glutamyl Transferase}}

\gamma-\textit{Glutamyl transferase} (GGT) determination has been the most commonly used as well as the most disputed clinical chemical marker of alcohol abuse. GGT is widely distributed in various organs and is mainly localized in the membranes of cells such as epithelial cells lining the biliary tract, hepatic canaliculi, proximal renal tubules, pancreatic acinar tissue, pancreatic ductules, and intestinal brush border cell (Kokot and Stedzinski, 1974). Most of the GGT activity is found in kidney, liver, prostate, pancreas, spleen, duodenum, and intestine. GGT is synthesized in the endoplasmic reticulum of the liver and transported to the plasma membranes through the Golgi apparatus before being excreted in blood or bile (Nishimura and Teschke, 1983). The serum of healthy adults contains only trace amounts of GGT as compared with its high activity in the kidney. Most studies agree that liver is the source of most of the GGT activity in serum. Serum and liver GGT are identical in kinetic and physical characteristics. The electrophoretic heterogeneity of GGT isozymes in serum results from differences in sialic acid residues, carbohydrate content and hydrophobic domain of the enzyme (Teschke, 1985).

Significantly elevation in serum GGT has been reported in chronic alcoholics and heavy drinkers by a large number of investigators (Chalmers et al., 1981; Garvin et al.,
Abnormally high serum GGT values have been observed in 50-90% of patients with a history of chronic alcohol consumption (Korri et al., 1985). However, serum GGT increase is independent of hepatic GGT activity (Selinger et al., 1982).

Increased serum GGT activity in alcoholism lacks specificity (Salaspuro, 1987). Only 50% of the elevated GGT values were due to alcohol in apparently healthy men (Penn et al., 1981). Drugs like Phenobarbital or phenazone and many forms of non-alcoholic liver disease as well as smoking increase the serum GGT levels (Rosalki and Rau, 1972; Chan-Yeung et al., 1981). The mechanism of increased serum GGT activity following chronic alcohol consumption is not clear completely (Teschke, 1985; Salaspuro, 1986). It has been suggested that a rise in serum GGT following chronic alcohol consumption occurs as a result of hepatic induction of GGT at the site of the endoplasmic reticulum (Teschke et al., 1972).

Mean Corpuscular Volume

A significant incidence of an increased mean corpuscular volume (MCV) of red cells has been found to be an indicator of chronic heavy drinking and alcoholism (Ryback et al., 1982). Although the mechanisms underlying alcohol-related alterations in MCV are still unclear, a direct effect of ethanol on the bone marrow or an underlying folate deficiency may be responsible for the observed increase in MCV in alcoholics (Wu et al., 1974). Among various alcohol-related disorders, elevated MCV values were observed in 82% of patients with alcoholic hepatitis, in 89% of patients with alcoholic cirrhosis and in 100% of alcoholics with normal liver (Buffet et al., 1975). MCV was found to correlate better with alcohol consumption than GGT. Abnormal MCV values have been found to be a better indicator of excessive alcohol consumption and in digestion of alcoholic liver disease. However, elevated MCV values have also been observed in non-alcoholic liver disease, reticulocytosis, vitamin B12 and folic acid deficiency, as well as being dependent upon age, sex and smoking status of the subjects (Papoz et al., 1981; Eckardt et al., 1981)

Aspartate Aminotransferase

Elevated serum aspartate aminotransferase (ASAT) levels have been observed in chronic alcoholics or heavy drinkers. Highest total ASAT (t-ASAT) values have been found in alcoholics with a history of alcoholism exceeding 10 years (Skude and
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Wadstein, 1977). However, there is neither a correlation between total serum ASAT and alcohol consumption nor a correlation with the duration of drinking (Teschke et al., 1980). Consequently elevated ASAT is a general indication of tissue and organ damage caused by alcohol, viral infections, drugs or toxins (McIntyre and Heathcote, 1974). During unspecific hepatic damage, serum levels of s-ASAT (cytoplasmic isozyme) increase significantly, while the m-ASAT (mitochondrial isozyme) level tends to increase to a greater extent in alcoholic liver disease. Thus, determination of the m-ASAT/t-ASAT ratio can be helpful in differentiating alcoholic hepatitis from other disease (Panteghini et al., 1983). Indeed, mean m-ASAT/ASAT ratios were found to be similar in patients with chronic viral hepatitis and healthy controls, whereas the ratio in chronic alcoholics was found to be about four time higher (Nalpas et al., 1984). The sensitivity of the m-ASAT/s-ASAT ratio reached 93% in cases of alcoholic liver disease and 100% in alcoholics without liver disease (Nalpas et al., 1984).

**Alanine Aminotransferase**

Alanine aminotransferase (ALAT) is present mainly in the liver and to a lesser extent in skeletal muscle, kidney and heart. As a consequence of hepatocellular damage, ALAT is released into blood from the liver cytoplasm. Serum ALAT levels are frequently elevated in patients with alcoholic liver disease (Stamm et al., 1984; Matloff et al., 1980). An inverted ALAT/ASAT ratio seems to be the most characteristic indicator of alcoholic liver injury (Cohen and Kaplan, 1979). An ALAT/ASAT ratio of more than two was found to be a reliable indicator of alcoholic liver disease (Correia et al., 1981; Salaspuro, 1987).

**Alkaline Phosphatase**

Alkaline phosphatase (ALP) is located mainly in the bone, liver, placenta, and intestine. Acute alcohol drinking does not affect the serum ALP concentrations but elevated levels of this enzyme have been reported in alcoholics and heavy drinkers (Lal and Singh, 1978). However, the overlap with levels obtained in non-alcoholic liver disease is significant and tends it of limited value in the diagnosis of alcoholic liver disease.

**Glutamate Dehydrogenase**

Abnormally high concentrations of serum glutamate dehydrogenase (GDH) have been noted in patients with hepatic and biliary tract disease (Ellis et al., 1978). GDH is a
reliable marker of liver cell necrosis in the alcoholics. In about 86% of the subjects with heavy alcohol consumption, elevated GDH values were recorded. However, in other recent studies, GDH activity has not been found reliably to reflect the severity of hepatocyte necrosis and a recent alcohol abuse (Jenkins et al., 1982).

**α-Amino-n-Butyric Acid**

A significant increase in plasma α-amino-n-butyric acid (AANB) after chronic alcohol consumption may be due to its increased production as the result of severe disturbances in carbohydrate metabolism. The plasma ratio of AANB to leucine was found to be elevated in alcoholics (Shaw et al., 1976). The measurement of the plasma AANB/leucine ratio has been suggested to be an empirical marker of alcohol-related liver disease.

**High-Density Lipoprotein Cholesterol**

Increased levels of high-density lipoprotein cholesterol (HDL-C) associated with alcohol abuse have been reported (Danielsson et al., 1979; Ernst et al., 1980). Although HDL-Cholesterol elevation may also result from the microsomal system inducing drugs and physical exercise, it is considered as a potential biochemical marker of chronic alcohol consumption (Sanchez-Craig and Annis 1981). Alcohol consumption also increases HDL phospholipids and apolipoproteins A-I and A-II (Johansson and Medhus 1974; Puchois et al., 1984; Taskinen et al., 1982).

**Alcohol Dehydrogenase**

Elevated serum alcohol dehydrogenase (ADH) level has been reported in a number of alcohol-related and unrelated liver disorders (Kato et al., 1984). However, plasma ADH activity in alcoholics and non-alcoholic psychiatric patients was found to be significantly higher only when higher ALAT and GGT values were also observed (Meier-Tackmann et al., 1984). This increase in plasma ADH may be due to a generalized liver damage and therefore plasma ADH determination alone is not a useful diagnostic marker of alcoholism but could be of value when measured in combination with other biochemical parameters such as GGT and MCV.

**Alcoholism and Insulin Resistance**

Epidemiological survey carried out in India reveal that consumption of alcoholic beverages is common in 20-40% subjects aged about 15 years and about 10% of them are regular users (Dube et al., 1978; Mohan, 1981). The prevalence of diabetes mellitus
is very high among people more than 40 years of age and most cases (95%) of diabetes mellitus in India are NIDDM (Das, 1993). Alcohol abuse has also been suggested to be a risk factor for NIDDM. Studies on normal and diabetic subjects have suggested that the low or moderate dose of alcohol improves insulin sensitivity while high dose potentiate insulin resistance (Balkau et al., 1992; Facchini et al., 1994; Bell, 1996). Alcohol abuse is thought to be a risk factor for the cause of liver damage, hyperlipidemia and insulin resistance. The incidence of diabetes mellitus has also been observed to be increased at par with changes in life style in conjunction with dietary pattern. Studies on the link between alcohol consumption and glycoregulation revealed that alcohol consumption might be a target for primary and secondary prevention of impaired glycoregulation and diabetes mellitus (Lombrail et al., 1992; Dhillon et al., 1996). Large intake of alcohol led to the development of frank clinical diabetes with glucose intolerance, which was reversed perfectly to prediabetes condition following abstinence from alcohol (Yoshitsugi, 1992). 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 (Facchini et al., 1994). Moderate alcohol intake reduces the risk of developing NIDDM and protects cardiovascular system while heavy intake acts as a vasoconstrictor resulting in increased systolic and diastolic pressure (Balkau et al., 1992; Rimm et al., 1995; Bell, 1996). Hazard of heavy alcohol intake induces hyperglycemia, glucose intolerance, inhibition of insulin secretion, increased insulin resistance and hypertriglyceridemia (Yki-Jarvinen and Nikkilia, 1985; Avogaro et al., 1987; Lomeo et al., 1988). At relatively low doses, alcohol can cause hypoglycemia in the presence of a low serum insulin and serum glucagon level. In the postprandial state alcohol induces hyperglycemia by inducing glycogenolysis and accelerate the peripheral insulin resistance (Bell, 1996; Ahmed, 1995). The glucose intolerance is not the result of reduced insulin secretion, or circulating insulin antagonists, and does not correlate with the coexisting metabolic acidosis. Glucose intolerance exists because the peripheral insulin-sensitive tissues (muscle, liver, adipose) of the patients with chronic renal failure are insulin resistant (Fiorini et al., 1994). Glucose intolerance and diabetes mellitus are both prevalent not only in alcoholic liver cirrhosis, but also in chronic alcoholics without cirrhosis. Nutritional properties, pharmacological effects and metabolic alterations produced by alcohol intake due to excessive production of reducing equivalents play significant roles in the pathogenesis of
ethanol-induced glucose intolerance. Gluconeogenesis from glycogen, fatty acids, amino acids and lactate are also impaired during ethanol metabolism. Thus, ethanol-induced hypoglycemia is closely related to depressed hepatic gluconeogenesis produced by ethanol, whereas ethanol-induced hyperglycemia or diabetes mellitus is due to hepatic and tissue resistance and impairment of pancreatic endocrine system (Ishii and Ito, 1996).

Moderate amount of alcohol had no effect on diabetic control except for occasional hypoglycaemia while heavy alcohol intake may be associated with an increase in glucose intolerance (Sereny and Enderenyl, 1978). Various studies have shown little or no effect of moderate alcohol intake on diabetes 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 (Ben et al., 1991; Koivisto et al., 1993). A moderate alcohol intake with a meal had no deleterious effect on hypo or hyperglycemia in patient with insulin dependent diabetes mellitus or NIDDM, and if taken outside the context of a meal, can cause hypoglycemia and ultimately increased death from noncardiovascular causes (Christiansen et al., 1994). However, chronic alcohol intake always deteriorates metabolic control persons with NIDDM, and which is reversed after alcohol withdrawal (Swade and Emaneule, 1997).