INTRODUCTION

1.0 Introduction :

Diabetes mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycaemia. Though it is difficult to ascertain the real frequency in population because of the large number of persons affected, the initial asymptomatic nature of disease, different standards of diagnosis used by clinicians but probably in between 1-2% if fasting hyperglycaemia is accepted as the criterion for diagnosis. Fasting venous plasma glucose is at present accepted as the most reliable and convenient test for diagnosis of Diabetes Mellitus and is strongly recommended as a screening test by W.H.O. and National Diabetes Data Group of U.S.A. The metabolic dysregulation associated with D.M. causes pathophysiologic changes in multiple organ systems like eyes, kidneys, nerve and blood vessels. Several distinct clinical syndromes can be described under the heading of Diabetes Mellitus as a result of its heterogeneous nature [1].

Diabetes is one of the leading causes of morbidity worldwide. Major causes of prolonged morbidity in Diabetes include coronary heart disease, glomerulosclerosis, retinopathy, gangrene of lower extremity, stroke and cataract. In fact Diabetes Mellitus is one of the leading causes of end-stage renal disease, non-traumatic lower limb amputations and blindness in adults. With increasing incidence globally, it will likely to continue as a major cause of morbidity and mortality [2].

1.1 Etiological classification of diabetes :

I. Type 1 Diabetes (β cell destruction usually leading to absolute insulin deficiency).

   (a) Immune mediated

   (b) Idiopathic

II. Type 2 Diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance.)

III. Other specific types of Diabetes

(A) Genetic defects of β cell function characterised by mutations in.

   (1) Hepatocyte Nuclear Transcription Factor (HNF) 4α (MODY 1)

   (2) Glucokinase (MODY 2)

   (3) HNF-1α (MODY 3)

   (4) Insulin Promoter Factor (IPF) 1 (MODY 4)

   (5) HNF-1β (MODY 5)

(6) Mitochondrial DNA

(7) Proinsulin or insulin conversion

(B) Genetic defects in insulin action

(i) Type A insulin resistance

(ii) Leprechaunism

(iii) Rabson Mendenhall Syndrome

(iv) Lipoatrophic Diabetes

(C) Disease of the exocrine pancreas : Pancreatitis, Pancreatectomy, Neoplasia, Cystic fibrosis, Haemochromatosis, Fibrocalculous Pancreatopathy.

(D) Endocrinopathies : Acromegaly, Cushing's Syndrome, Glucagonoma, Phaeochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma.

(E) Drug or chemical induced : Vacor, Pentamidine, Nicotinic acid, Glucocorticoids, Thyroid hormone, Diazoxide, β adrenergic agonists, Thiazides, Phenytoin, α interferon, Protease inhibitors, Clozapine, β blockers.

(F) Infectious : Congenital rubella, Cytomegalo virus, Coxsackie.

(G) Uncommon forms of immune mediated diabetes : "stiff-man" syndrome, Anti insulin receptor antibodies.

(H) Other genetic syndromes sometimes associated with diabetes : Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, Myotonic dystrophy, Porphyria, Prader-Willi syndrome.

IV. Gestational Diabetes Mellitus (GDM) [3].

1.2 Epidemiology :

Worldwide prevalence of Diabetes has risen dramatically over two decades. It is projected that diabetes will increase in frequency in near future. Although the prevalence of both type 1 and Type 2 DM is increasing, the prevalence of Type 2 DM is likely to increase more as a result of increase in obesity and reduction of physical activity level. Considerable geographic variations exist in prevalence and seem to be due to variation in both genetic and environmental factors. Considerable variation in prevalence of DM exists between different ethnic populations within a given country [4].

1.3 Pathogenesis :

The exact etiopathogenesis of both type 1 and type 2 diabetes remain uncertain. Genetic predisposition alongwith environmental factors determine which persons are going to develop the clinical syndrome of diabetes. The pathogenetic pattern differs in type 1 and type 2 diabetes.

1.3.1 Pathogenesis of type 1 DM

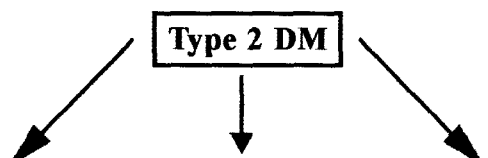
Step	Event	Agent or Response
1.	Genetic Susceptibility	HLA D region genes
	↓	
2.	Environmental Event	Infection or Food
	↓	
3.	Insulitis	Infiltration of activated T lymphocytes in pancreatic islets.
	↓	
4.	Activation of auto immunity	Self-nonself transition
	↓	
5.	Immune destruction of β cells [5]	Islet cell autoantibodies, activated T lymphocytes.
	↓	
6.	β cell death	Tonic effect of cytokines like TNF, α interferon or IL. Apoptosis of β cells, formation of nitric oxide metabolites. at Direct CD8+ T cell Cytotoxicity.
	↓	
7.	Gradual decline in β cell mass at variable rate, differing from one to other.	Progressive impairment of insulin release over a period of months to years.
	↓	
8.	80% or more β cells destroyed.	Diabetes mellitus [6].

1.3.2. Pathogenesis of Type 2 DM :

Type 2 DM is not HLA linked and no evidence of auto immunity or viruses have anything to do with its development. Although it occurs with a strong familial associations, the definition

of genetic abnormalities remain a challenge. Insulin resistance and abnormal insulin secretion remain central to the development of type 2 diabetes. Although controversy exists but most evidence points to insulin resistance precedes insulin secretory defects [7].

Type 2 DM is characterised by 3 pathophysiologic abnormalities (i) impaired insulin secretion, (ii) peripheral insulin resistance [8], (iii) excessive hepatic glucose production. Obesity augments the genetically determined. insulin resistance of type 2 DM. Adipocytes secrete a number of biologic products (leptin, TNFα, FFA) that modulate processes such as insulin secretion, insulin action, body weight and may contribute to insulin resistance. In early stage glucose tolerance remains normal despite insulin resistance as pancreatic β cells compensate by increasing insulin output. An insulin resistance and compensatory hyperinsulinemia progress, impaired glucose tolerance develops. With further decline in insulin secretion and concomittant increase in hepatic glucose release, overt diabetes supervenes. Ultimately β cells may fail to secrete insulin [9].



Insulin Resistance

Decreased ability of insulin to act effectively on peripheral tissues (muscle + liver) [post-receptor abnormality as main cause postulated e.g., polymorphism in IRS1 and PI3 kinase signalling defect with reduced translocation of GLUT4 to plasma membrane. ↑FFA may also contribute to ↓glucose utilization in skeletal muscle, ↑glucose production in liver and ↓β cell function [10].]

Impaired Insulin secretion

Insulin secretion and sensitivity are correlated. Initially insulin secretory defect is mild and selectively involves glucose with sparing of other secretagogues e.g., arginine. Eventually gross deficiency in insulin secretion supervenes and endogenous insulin secretion is grossly inadequate. [Cause is not known with intense genetic investigations exclude mutation of genes as a cause. Islet amyloid polypeptide, amylin is co-secreted with insulin and deposited in islets but significance is unknown. However, chronic hyperglycaemia and elevation of FFA impairs β cell function]

Increased Production of glucose from liver

Liver maintains blood glucose levels during fasting by glycogenolysis and gluconeogenesis. Insulin suppress glycogenolysis and gluconeogenesis. Type 2 DM insulin resistance in liver causes failure of supression of glycogenolysis and gluconeogenesis in post prandial state causing hyperglycaemia.

Risk factors associated with development of type 2 DM includes :

(i) Family history of diabetes (i.e., parent or sibling with type 2 DM).

(ii) Obesity (≥20% desired body weight).

(iii) Age ≥ 45 years.

(iv) Race/Ethnicity (African, Asian especially Indian, Native American).

(v) Previously identified IFG or IGT.

(vi) History of GDM or of delivery of a large baby.

(vii) Hypertension (B.P. ≥ 140/90 mm Hg.).

(viii) HDL cholesterol level ≤ 35 mg/dl and/or triglyceride level ≥ 250 mg/dl.

(ix) Polycystic ovary syndrome.

1.3.3 Mody (Maturity onset Diabetes of young; monogenic form of DM) :

Mody constitutes phenotypically and genetically heterogenous subtypes of DM. Five different forms of MODY have been described owing to mutations in genes encoding Islets cell transcription factors or glucokinase. All are transmitted as autosomal dominant disorder. MODY 2 is the commonest one involving mutation in glucokinase gene MODY1, MODY 3, MODY 5 are results of mutation in hepatocyte nuclear transcription factor HNF-4α, HNF-1α and HNF-1β respectively. MODY 4 is a rare variant caused by mutation in Insulin Promoter Factor Gene (IPF1). Pathogenesis of diabetic states in MODY are not well known [11].

1.4 Clinical Features :

Symptoms of hyperglycaemia includes polyuria, polyphagia and polydipsia.

No specific sign is attributed to DM and a complete assesment of diabetic state, presence of complications and associated disease should be attempted from history and physical examination. Body weight, orthostatic hypotension, hypertension, foot examination, peripheral pulses, retinal examination, examination of deep reflexes and posterior column sensation, etc. are done to assess the type severity and complication of DM. Mental confusion, coma, severe dehydration, acidotic breathing may accompany diabetic ketoacidosis. Severe dehydration, vomiting and altered mental state may be features of non-ketotic hyperosmolar state [12].

Potential Diabetics :

An individual with a first degree relative with DM is a potential diabetes with increased risk to develop DM or IFG in later life.

Latent Diabetics :

They are persons with normal GTT but shows abnormality under conditions like pregnancy, steriod therapy, therapy with other diabetogenic drugs like thiazide diuretic.

1.5 Diagnosis :

Criteria of diagnosis of diabetes mellitus :

(i) Symptoms of diabetes and a random blood glucose > 250 mg/dl

(ii) Fasting plasma glucose ⩾ 126 mg/dl. (Fasting is defined as no calorie intake for 8 hours.)

(iii) 2 hour plasma glucose ⩾ 200 mg/dl during an oral GTT. (The test is performed by using a glucose load containing the equivalent of 75 gm of anhydrous glucose, dissolved in water; not recommended for routine clinical use). In the absence of unequivocal hyperglycaemia and acute metabolic decompensation, these criteria should be confirmed on a repeat testing on a different day (Adopted from American Diabetes Association 2000)

1.6 Management :

The goal of therapy in diabetes includes :

(i) Fredom from symptom of hyperglycaemia

(ii) Reduction or elimination of complications of diabetes.

(iii) To achieve as normal life-style as possible

Ways of achievement of goal

(1) Identification of target level of glycaemic control in each patient	(2) Provision of educational, non-pharmacological and pharmacological resources to establish the glycaemic control	(3) Monitor, Treatment of complications

Comprehensive diabetic case means more than establishment of glycaemic control though it is central to optimal management of diabetes. Symptoms usually subside at or around 2 hours plasma glucose < 200 mg/dl and the mainstem of therapy revolves around detection and management of diabetic complication and risk modification for DM associated diseases [13].

Patient education is an important part of daibetic care and it involves training regarding (i) self monitoring of blood/urine glucose, (ii) monitoring of urine ketones (type 1 DM), (iii) insulin administration, (iv) guidelines of diabetic management during illness, (v) recognition and management of hypoglycaemia, (vi) foot and skin care, (vii) risk factor modifying activity [14].

1.6.1 Nutrition :

Medical Nutrition Therapy is a term used by ADA to describe the optimal co-ordination of calorie intake with other aspects of diabetes therapy. Though imparted with some flexibility in recent time (like provision of calorie sweeteners like sucrose), diabetic diet remains a complicated, restrictive, and stoic one. MNT must be adjusted in accordance with individual needs [15].

Nutritional recommendations for all diabetics :

(1) Proteins to provide ~ 10-20% of KCal/d (~10% for those with nephropathy).

(2) Saturated fats to provide ~ 10% of KCal/d (~ 7% for those with ↑ LDL cholesterol).

(3) Polyunsaturated fats to provide ~ 10% of KCal/d.

(4) Remaining calories to be distributed between carbohydrate and monounsaturated fat based on medical needs and individual tolerence.

(5) Use of calorie sweeteners like sucrose is permissible provided the insulin demand they create is matched by available insulin.

(6) Fibres (20-35 gm/d) and sodium (≤3000 mg/d) levels as recommended for normal persons.

(7) Cholesterol intake ↟ 300 mg/d.

(8) Same precaution regarding alcohol as applicable in general population. As alcohol increases the risk of hypoglycaemia it should be taken with food.

Goal of MNT in type 1 DM is to match the calorie intake, temporarily and quantitatively with the appropriate amount of insulin. MNT in type 1 DM and self monitoring of glucose must be integrated to deduce the optimal insulin regimen. MNT must be flexible to account of exercise and insulin therapy must allow for deviation in calorie intake. MNT in type 1 DM must also minimize the weight gain often encountered in intensive diabetic management [16].

The goal of MNT in type 2 diabetes address the reduction in body wt. and reduction in increased frequency of cardiovascular disease like hypertension or dyslipidemia. MNT in type 2 diabetes includes modest calorie reduction, increased physical activity and reduction of hypertension and hyperlipemia [17]. Reduction in weight with hypocaloric diets sometimes result

in marked improvement of glycaemic control. About 50% of patients respond to MNT alone without pharmacological intervention (type 2 DM). All type 1 DM patients require exogenous insulin in addition to MNT, exercise and risk factor modification. The target glycaemic control and HbA1c level are individualised but a general guideline as adopted from ADA 2000 is given [18].

	Normal	Goal	Additional action suggested
Average Pre-prandial glucose	< 100 mgm/dl	80-120 mgm/dl	< 80 mgm/dl > 140 mgm/dl
Average bedtime glucose	< 110 mgm/dl	100-140 mgm/dl	< 100 mgm/dl > 160 mgm/dl
HbA1c %	< 6	< 7	>8

Normoglycaemia or near normal glycaemia is the goal of therapy. However, it is elusive in most cases. Sometimes it is required to achieve near normal glycaemia and there intensive diabetes management by techniques like multi component insulin, multiple daily injections (MDI) or continuous subcutaneous insulin infusions (CSII). Benefits of intensive management with improved glycaemic control include a reduction/delay in occurence of micro and macrovascular complications of DM, a sense of well-being, greater flexibility in diet and exercise. Intensive management in pregnancy reduces the frequency of foetal malformations and morbidity. However, intensive management require frequent interaction with health care professionals, excellent patient education, self monitoring of blood glucose (8 times per day minimally) and entails heavy financial cost. It is not suitable for most patients [19].

1.6.2 Indications for intensive management :

(1) Otherwise healthy adults with type 1 or type 2 DM (selected adolescents or older children).

(2) All pregnant women with diabetes, all women planning pregnancy.

(3) Management of labile diabetes.

(4) Patients who have had kidney transplantation for diabetic nephropathy [20].

1.6.3 Pharmacological Management of Type 2 DM :

Besides MNT (as described above) and an exercise program to induce weightloss, if glycaemic control is not achieved after 4 weeks, pharmacologic approach is needed. Oral glucose-lowering agents are used [21,22].

Depending on mechanism of action oral glucose lowering agents are divided into 3 categories.

(1) Insulin secretagogues like sulfonylureas of 1st and 2nd generation, effective in type 2 DM of < 5 years of duration, obese patients with some residual endogenous insulin secretion.

(2) (a) Biguanides (Metformin) reduce blood glucose by reducing hepatic glucose production, increasing peripheral glucose utilisation and inducing modest weightloss.

(b) α glucosidase inhibitors (Acarbose, Miglitol) reduce post-prandial hyperglycaemia by inhibiting glucose absorption from gut by inhibiting the enzyme which cleaves oligosaccharides to monosaccharides.

(3) Thiazolidinediones (Rosiglitazone, Pioglitazone) : They reduce insulin resistance. They reduce hyperglycaemia by improving peripheral glucose utilisation and insulin sensitivity.

All failures in treatment by oral agents or severely ill patients of type 2 DM are treated with exogenous insulin [23, 24, 25, 26, 27, 28, 29, 30].

Factors associated with increased morbidity in diabetes are :

(i) Duration (ii) early onset (iii) high HbA1c (iv) hypertension (v) proteinuria (vi) obesity (vii) hyperlipemia.

1.7 Complication :

Complications can be divided into two groups : Acute complications are (i) diabetic ketoacedosis (ii) non-ketotic hyperosmolar state (iii) Lactic acidosis (iv) Hypoglycaemia (Ketoogenic in most cases).

Chronic complications are : (i) Diabetic retinopathy (ii) Diabetic foot (iii) Diabetic neuropathy (iv) Diabetic nephropathy [31, 32, 33, 34, 35, 36, 37, 38].

1.8 Selenium and its role in human metabolism :

Globally selenium (Se) is an important element because it has wide application. Selenium was discovered by Berzelius in 1817. The Se atomic number is 34 and it is in the Group VI (A) elements of the Periodic Table. The Se atomic weight is 78.96. Selenium is a required micronutrient for animals and humans; excessive Se, however, can be toxic. Its requirement for plants is not clearly understood. The range between Se toxicity and deficiency for animals is rather narrow. Selenium toxicity problems have been documented as early as the twelfth century.

For example, Marco Polo travelling in China in 1295 was probably describing toxicity symptoms of Se in livestock. In 1560, Father Simon Pedro described what was probably Se toxicity symptoms in humans in Colombia. In 1857, T.W. Madison, U.S. Army Surgeon, described the suspected Se toxicity symptoms in horses near Fort Randall, South Dakota. In China, two types of Se endemic human diseases, cardiomyopathy (Se deficiency) and selenosis (Se toxicity) were reported [39].

Selenium occurs naturally in soils and groundwaters. The main geological source of Se in soils is derived from cretaceous age snales. However, soils derived from igneous rocks are expected to contain low Se. Selenium is expected to be found in higher concentrations in semiarid and arid environments of western United States, China, Mexico and Colombia. In some humid environments of eastern United States, China, United Kingdom, Japan, India and New Zealand, Se concentration is expected to be lower. The common range of total Se concentrations in most soils is between 0.01 and 2 mgm/kg. However, in some soils of the world, total Se concentrations can be as high as 1200 mgm/kg [40]. Such soils are commonly known as seleniferous soils.

Very limited information regarding the dissolved Se concentrations in natural waters is available. Dissolved Se concentrations in fresh water may range between 0.1 and 400 μg/L [41]. Dissolved Se concentrations between 16 and 231 ng/L for river waters in Japan have been reported [42]. Dissolved Se concentrations ranging between 60-70 ng/L in Finnish groundwaters, rivers and lakes have also been reported [43].

Human activities may introduce Se into soil-water systems. Burning fossil fuels (coal), disposal of coal residues, mining activities and application of fertilizers put Se into soil-water systems. Anthropogenic activities such as coal burning power plants and smelting and refining industries are the main sources of Se [44]. Worldwide total Se input to, fresh waters from coal burning power plants is 6-30 x 10^4 metric tones of Se per year. Smelting and refining industries contribute 3-20 x 10^4 metric tons of Se per year to fresh waters.

Se in natural waters (e.g., soil water, groundwater) exist in the form of free ionic species (e.g., selenate SeO_4^{2-}) and Selenite (SeO_3^{2-}), inorganic complexes (e.g., $CaSeO_4^6$, $MgSeO_3^6$), and dissolved organic carbon complexes (DOC-Se) [45].

Se levels in blood appear to reflect the large body Se pools of nutritional interest during static long-term intakes of Se, because erythrocyte and plasma Se levels were good indicators of muscle and liver Se content in rats fed constant amounts of dietary selenium for 8 weeks or

more [46]. Skeletal muscle and liver are important because these tissues contained the largest body pools of Se. The skeletal muscle appears to contain the largest body pool of Se in humans. If a person who weighs 70 kg has a skeletal muscle mass of 28 kg [47] with Se level of 0.24 mgm/kg [48], then this tissue contains about 6.7 mgm, or 46% of the total body Se content. In humans, the liver apparently has a smaller Se pool relative to muscle than in rats. A liver of 1.8 kg with a Se content of 0.54 mgm/kg would contain only about 1 mg of Se. Sodium selenite was less effective than selenomethionine in elevating blood Se levels in New Zealand subjects of low Se status [49]. Hair Se levels were better correlated with muscle or liver Se content than either plasma or red cell Se levels in rats. Toe nails have recently been suggested as a useful indicator of human Se status [50].

The use of urinary Se levels to assess Se status in humans has recently been reviewed [51]. Se exposure in industrial workers has been monitered by measuring Se in urine [52] and a good correlation between blood Se levels and urinary excretion was observed in New Zealand residents [53]. However, random urine samples are strongly affected by current dietary Se intake and also suffer from dilution effects, whereas 24 hrs samples are difficult to obtain. The excretion of trimethyl Selenonium ion may be influenced by dietary Se intake [54] and quantification of urinary Se metabolites may lead to a convenient way of assessing Se status in humans.

Arsenic, cadmium, lead and mercury have metabolic interaction with Selenium [55].

Keshan Disease - Keshan disease, a childhood cardiomyophy endemic in some regions of the People's Republic of China, has been attributed to selenium deficiency.

Kaschin-Beck disease has also been attributed to selenium deficiency.

Gallagher et al have found hair analysis to be a valuable tool for assessing selenium status. They found dietary supplementation with selenium enriched yeast was reflected by significant increase in hair selenium levels. While the supplementation resulted in increased hair levels, it was not reflected in blood selenium levels and there was no correlation between blood and hair selenium levels [56].

Selenium intoxication may result in Kidney and liver damage, as well as damage to the CNS and brain. Reports on selenium intoxication in China also show elevated selenium levels in the hair, blood and urine. The source of selenium in this case was the food crops from soils rich in this element [57, 58].