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Review Article

A COMPLETE REVIEW ON DIABETES MELLITUS AND ITS COMPLICATIONS

Siva Rami Reddy E*

Faculty of Homoeopathy, Tantia University, Sri Ganganagar, Rajasthan, India – 335002

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ABSTRACT

Diabetes Mellitus (DM) is a clinical syndrome characterized by hyperglycaemia due to absolute or relative deficiency of insulin. This can arise in many different ways. Lack of insulin affects the metabolism of carbohydrate, protein and fat and causes a significant disturbance of water and electrolyte homeostasis. Death may result from acute metabolic decompensation while long standing metabolic derangement is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, with those of the vascular system being particularly susceptible.

INTRODUCTION

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of Diabetes mellitus exist and are caused by a complex interaction of genetics, environmental factors, and life style choices [1-6]. Depending on the etiology of the Diabetes Mellitus, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with Diabetes mellitus causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, Diabetes Mellitus is the leading cause of end stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness [7-10]. With an increasing incidence worldwide, Diabetes Mellitus will be a leading cause of morbidity and mortality for the foreseeable future[11].

Epidemiology

The worldwide prevalence of Diabetes Mellitus has risen dramatically over the past two decades. Likewise, prevalence rates of IFG are also increasing. Although the prevalence of both type $_1$ and type $_2$ Diabetes mellitus is increasing worldwide, the prevalence of type $_2$ Diabetes mellitus is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels. Diabetes Mellitus increases with aging. In 2000, the prevalence of Diabetes mellitus was estimated to be 0.19% in people 20 years old and 8.6% in people 20 years old. In individuals 65 years the prevalence of Diabetes Mellitus was 20.1%. The prevalence is similar in men and women throughout most age ranges but is slightly greater in men 60 years. There is considerable geographic variation in the incidence of both type $_1$ and type $_2$ Diabetes Mellitus. Scandinavia has the highest incidence of type 1 Diabetes Mellitus (e.g., in Finland, the incidence is 35/100,000 per year). The Pacific Rim has a much lower rate (in Japan and China, the incidence is 1 to 3/100,000 per year) of type $_1$ Diabetes Mellitus; Northern Europe and the United States share an intermediate rate (8 to 17/100,000 per year). Much of the increased risk of type $_1$ Diabetes Mellitus is believed to reflect the frequency of high risk HLA alleles among ethnic groups in different geographic locations. The prevalence of type $_2$ Diabetes Mellitus and its harbinger, IGT, is highest in certain Pacific islands, intermediate in countries such as India and the United States, and relatively low in Russia and China. This variability is likely due to genetic, behavioural, and environmental factors. Diabetes Mellitus prevalence also varies among different ethnic populations within a given country. In 2000, the prevalence of Diabetes Mellitus in the United States was 13% in African Americans, 10.2% in Hispanic Americans, 15.5% in Native Americans (American Indians and Alaska natives), and 7.8% in non

Corresponding author:* **Siva Rami Reddy E
Faculty of Homoeopathy, Tantia University, Sri Ganganagar, Rajasthan, India – 335002

Hispanic whites. The onset of type $_2$ Diabetes Mellitus occurs, on average, at an earlier age in ethnic groups other than non Hispanic whites.

Insulin Biosynthesis, Secretion and Action

Biosynthesis

Insulin is produced in the beta cells of the pancreatic islets. It is initially synthesized as a single chain 86 aminoacid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the aminoterminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin ike growth factors I and II, which bind weakly to the insulin receptor[12]. Cleavage of an internal 31 residue fragment from proinsulin generates the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and cosecreted from secretory granules in the beta cells. Because the C peptide is less susceptible than insulin to hepatic degradation, it is a useful marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia[13-15]. Human insulin is now produced by recombinant DNA technology; structural alterations at one or more residues are useful for modifying its physical and pharmacologic characteristics[16].

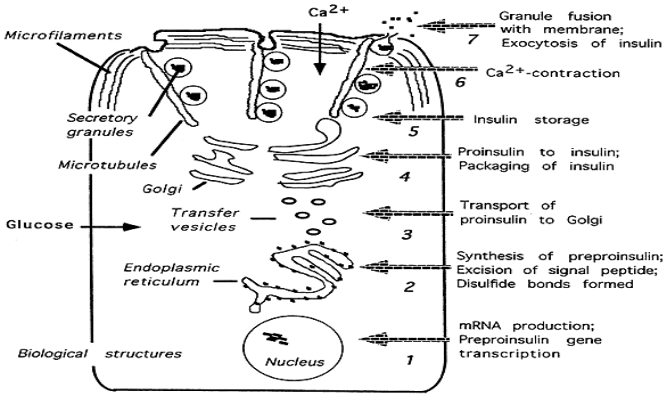

Fig 1 Insulin Biosynthesis

Secretion

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion. Glucose levels 3.9 mmol/L (70 mg/dL) stimulates insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by the GLUT2 glucose transporter. Glucose phosphorylation by glucokinase is the rate limiting step that controls glucose regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibits the activity of an ATP sensitive K channel. This channel consists of two separate proteins: one is the receptor for certain oral hypoglycemics (e.g., sulfonylureas, meglitinides); the other is an inwardly rectifying K channel protein. Inhibition of this K channel induces beta cell membrane depolarization, which opens voltage dependent calcium channels (leading to an influx of calcium), and stimulates insulin secretion. Insulin secretary profiles reveal a pulsatile pattern of hormone release, with small secretary bursts occurring about every 10 min, superimposed upon greater amplitude oscillations of about 80 to 150 min. Meals or other major stimuli of insulin secretion induce large (four to fivefold increase versus baseline) bursts of insulin secretion that usually last for 2 to 3 h before returning to baseline. Derangements in these normal secretory patterns are one of the earliest signs of beta cell dysfunction in Diabetes Mellitus.

Action

Once insulin is secreted into the portal venous system, 50% is degraded by the liver. Unextracted insulin enters the systemic circulation where it binds to receptors in target sites. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signalling molecules, such as insulin receptor substrates (IRS). These and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin.

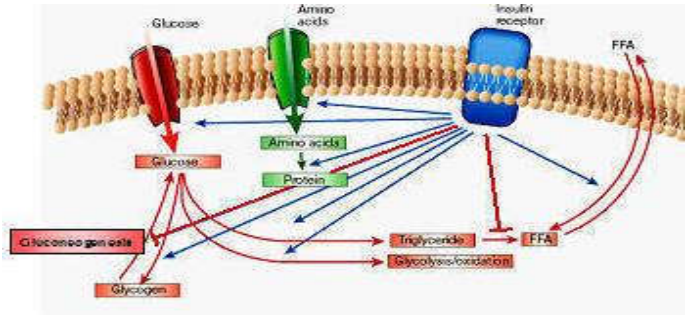

Fig 2 Insulin Action

As an example, activation of the phosphatidylinositol-3-kinase (PI-3-kinase) pathway stimulates translocation of glucose transporters (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signalling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin responsive cells. Glucose homeostasis reflects a precise balance between hepatic glucose production and peripheral glucose uptake and utilization. Insulin is the most important regulator of this metabolic equilibrium, but neural input, metabolic signals, and hormones (e.g., glucagon) result in integrated control of glucose supply and utilization. In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis.

Pathophysiology

Type 2 Diabetes mellitus is characterized by three pathophysiologic abnormalities: impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production. Obesity, particularly visceral or central (as evidenced by the hip waist ratio), is very common in type 2 Diabetes mellitus. Adipocytes secrete a number of biologic products (leptin, TNF free fatty acids, resistin, and adiponectin) that modulate insulin secretion, insulin action, and body weight and may contribute to the insulin resistance.

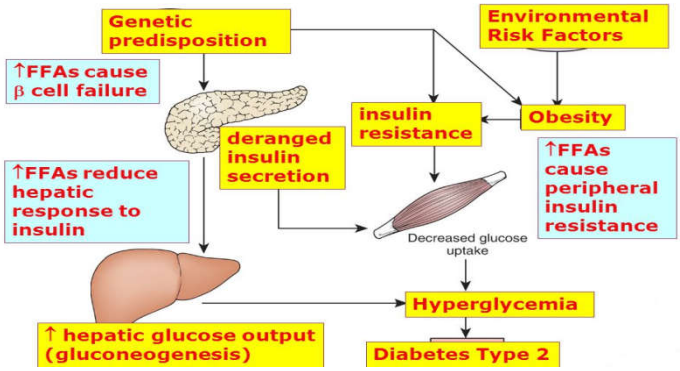

Fig 3 Pathophysiology of Diabetes Mellitus

In the early stages of the disorder, glucose tolerance remains normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue. Markers of inflammation such as IL 6 and C-reactive protein are often elevated in type 2 diabetes.

Insulin Resistance

The decreased ability of insulin to act effectively on peripheral target tissues (especially muscle and liver) is a prominent feature of type $_2$ Diabetes mellitus and results from a combination of genetic susceptibility and obesity. Insulin resistance is relative, however, since supernormal levels of circulating insulin will normalize the plasma glucose. Insulin dose response curves exhibit a rightward shift, indicating reduced sensitivity, and a reduced maximal response, indicating an overall decrease in maximum glucose utilization (30 to 60% lower than normal individuals). Insulin resistance impairs glucose utilization by insulin sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia. Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose usage results in postprandial hyperglycemia. In skeletal muscle, there is a greater impairment in nonoxidative glucose usage (glycogen formation) than in oxidative glucose metabolism through glycolysis. Glucose metabolism in insulin independent tissues is not altered in type $_2$ Diabetes mellitus.

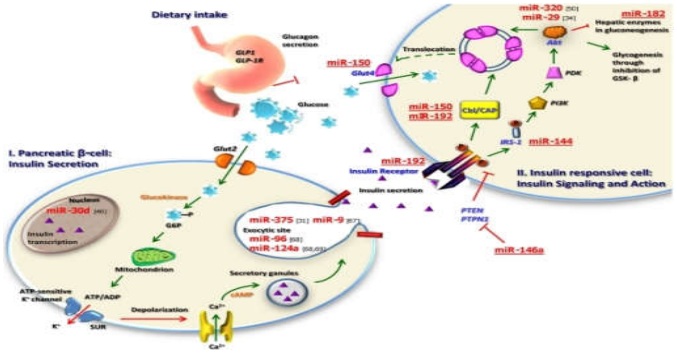

Fig 4 Insulin Resistance

The precise molecular mechanism of insulin resistance in type $_2$ Diabetes mellitus has not been elucidated. Insulin receptor levels and tyrosine kinase activity in skeletal muscle are reduced, but these alterations are most likely secondary to hyperinsulinemia and are not a primary defect. Therefore, postreceptor defects are believed to play the predominant role in insulin resistance. Polymorphisms in IRS-1 may be associated with glucose intolerance, raising the possibility that polymorphisms in various postreceptor molecules may combine to create an insulin resistant state. The pathogenesis of insulin resistance is currently focused on a PI-3-kinase signaling defect, which reduces translocation of GLUT4 to the plasma membrane, among other abnormalities of note, not all insulin signal transduction pathways are resistant to the effects of insulin [e.g., those controlling cell growth and differentiation and using the mitogen activated protein (MAP) kinase pathway. Consequently, hyperinsulinemia may increase the insulin action through these pathways, potentially accelerating diabetes related conditions such as atherosclerosis. Another emerging theory proposes that elevated levels of free fatty acids, a common feature of obesity, may contribute to the pathogenesis of type 2 Diabetes mellitus. Free fatty acids can impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function.

Impaired Insulin Secretion

Insulin secretion and sensitivity are interrelated. In type $_2$ Diabetes mellitus, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves Glucose stimulated insulin secretion. The response to other nonglucose secretagogues, such as arginine, is preserved. Eventually, the insulin secretory defect progresses to a state of grossly inadequate insulin secretion.

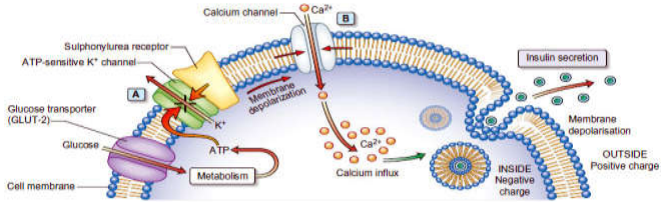

Fig 5 Insulin Secretion

The reason(s) for the decline in insulin secretary capacity in type $_2$ Diabetes mellitus is unclear. Despite the assumption that a second genetic defect-superimposed upon insulin resistance leads to beta cell failure, intense genetic investigation has so far excluded mutations in islet candidate genes. Islet amyloid polypeptide or amylin is cosecreted by the beta cell and likely forms the amyloid fibrillar deposit found in the islets of individuals with long standing type 2 Diabetes mellitus. Whether such islet amyloid deposits are a primary or secondary event is not known. The metabolic environment of diabetes may also negatively impact islet function. For example, chronic hyperglycemia paradoxically impairs islet function ("glucose toxicity") and leads to a worsening of hyperglycemia. Improvement in glycemic control is often associated with improved islet function. In addition, elevation of free fatty acid levels ("lipotoxicity") and dietary fat may also worsen islet function.

Acute Complications of Diabetes Mellitus

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 Diabetes mellitus, but it also occurs in individuals who lack immunologic features of type 1A Diabetes mellitus and who can subsequently be treated with oral glucose lowering agents (these individuals with type 2 Diabetes mellitus are often of Hispanic or African American descent). HHS is primarily seen in individuals with type 2 Diabetes mellitus. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid base abnormalities. Diabetic ketoacidosis and HHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in Diabetic ketoacidosis. Both disorders are associated with potentially serious complications if not promptly diagnosed and treated.

Diabetic Ketoacidosis (DKA)

Clinical Features

The symptoms and physical signs of Diabetic ketoacidosis are usually developed over 24 hours. Diabetic ketoacidosis may be the initial symptom complex that leads to a diagnosis of type 1 Diabetes mellitus, but more frequently it occurs in individuals with established diabetes. Nausea and vomiting are often prominent, and their presence in an individual with diabetes warrants laboratory evaluation for Diabetic ketoacidosis. Abdominal pain may be severe and can resemble acute pancreatitis or ruptured viscous. Hyperglycemia leads to glucosuria, volume depletion, and tachycardia. Hypotension can occur because of volume depletion in combination with peripheral vasodilatation. Kussmaul respirations and a fruity odour on the patient's breath (secondary to metabolic acidosis and increased acetone) are classic signs of the disorder. Lethargy and central nervous system depression may evolve into coma with severe Diabetic ketoacidosis but should also prompt evaluation for other reasons for altered mental status (infection, hypoxia, etc.). Cerebral oedema, an extremely serious complication of Diabetic ketoacidosis, is seen most frequently in children. Signs of infection, which may precipitate Diabetic ketoacidosis, should be sought on physical examination, even in the absence of fever. Tissue ischemia (heart, brain) can also be a precipitating factor

Laboratory Abnormalities and Diagnosis

The timely diagnosis of Diabetic ketoacidosis is crucial and allows for prompt initiation of therapy. Diabetic ketoacidosis is characterized by hyperglycemia, ketosis, and metabolic acidosis (increased anion gap) along with a number of secondary metabolic derangements. Occasionally, the serum glucose is only minimally elevated. Serum bicarbonate is frequently 10 mmol/L, and arterial pH ranges between 6.8 and 7.3, depending on the severity of the acidosis. Despite a total body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis. Total body stores of sodium, chloride, phosphorous, and magnesium are also reduced in Diabetic ketoacidosis but are not accurately reflected by their levels in the serum because of dehydration and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well. Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in Diabetic ketoacidosis the amylase is usually of salivary origin and thus is not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected. The measured serum sodium is reduced as a consequence of the hyperglycemia [1.6 mmol/L (1.6 meq) reduction in serum sodium for each 5.6 mmol/L (100 mg/dL) rise in the serum glucose]. Normal serum sodium in the setting of Diabetic ketoacidosis indicates a more profound water deficit. In "conventional" units, the calculated serum osmolality [2 (serum sodium serum potassium) plasma glucose (mg/dL)/18 BUN/2.8] is mildly to moderately elevated, though to a lesser degree than that found in HHS.

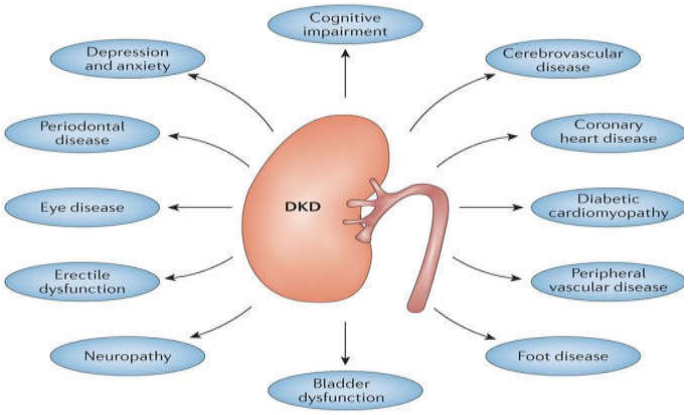

Fig 6 Diabetic ketoacidosis

In Diabetic ketoacidosis, the ketone body, hydroxybutyrate, is synthesized at a threefold greater rate than acetoacetate; however, acetoacetate is preferentially detected by a commonly used ketosis detection reagent (nitroprusside). Serum ketones are present at significant levels (usually positive at serum dilution of 1:8 or greater). The nitroprusside tablet, or stick, is often used to detect urine ketones; certain medications such as captopril or penicillamine may cause false positive reactions. Serum or plasma assays for hydroxybutyrate more accurately reflect the true ketone body level. The metabolic derangements of Diabetic ketoacidosis exist along a spectrum, beginning with mild acidosis with moderate hyperglycemia evolving into more severe findings. The degree of acidosis and hyperglycemia do not necessarily correlate closely since a variety of factors determine the level of hyperglycemia (oral intake, urinary glucose loss). Ketonemia is a consistent finding in DKA and distinguishes it from simple hyperglycemia. The differential diagnosis of Diabetic ketoacidosis includes starvation ketosis, alcoholic ketoacidosis (bicarbonate 15 meq/L) and other increased anion gap acidosis.

Treatment

After initiating intravenous fluid replacement and insulin therapy, the agent or event that precipitated the episode of Diabetic ketoacidosis should be sought and aggressively treated. If the patient is vomiting or has altered mental status, a nasogastric tube should be inserted to prevent aspiration of gastric contents. Central to successful treatment of Diabetic ketoacidosis is careful monitoring and frequent reassessment to ensure that the patient and the metabolic derangements are improving. A comprehensive flow sheet should record chronologic changes in vital signs, fluid intake and output, and

laboratory values as a function of insulin administered. After the initial bolus of normal saline, replacement of the sodium and free water deficit is carried out over the next 24 h (fluid deficit is often 3 to 5 L). When hemodynamic stability and adequate urine output are achieved, intravenous fluids should be switched to 0.45% saline at a rate of 200 to 300 mL/h, depending on the calculated volume deficit. The change to 0.45% saline helps to reduce the trend toward hyperchloremia later in the course of DKA. Alternatively, initial use of lactated Ringer's intravenous solution may reduce the hyperchloremia that commonly occurs with normal saline. A bolus of intravenous (0.15 units/kg) or intramuscular (0.4 units/ kg) regular insulin should be administered immediately, and subsequent treatment should provide continuous and adequate levels of circulating insulin. Intravenous administration is preferred (0.1 units/kg per hour), because it assures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. Intravenous regular insulin should be continued until the acidosis resolves and the patient is metabolically stable. As the acidosis and insulin resistance associated with Diabetic ketoacidosis resolve, the insulin infusion rate can be decreased (to 0.05 to 0.1 units/kg per hour). Intermediate or long acting insulin, in combination with subcutaneous regular insulin, should be administered as soon as the patient resumes eating, as this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay. It is crucial to continue the insulin infusion until adequate insulin levels are achieved by the subcutaneous route. Even relatively brief periods of inadequate insulin administration in this transition phase may result in Diabetic ketoacidosis relapse. Hyperglycemia usually improves at a rate of 4.2 to 5.6 mmol/L (75 to 100 mg/dL) per hour as a result of insulin mediated glucose disposal, reduced hepatic glucose release, and rehydration. The latter reduces catecholamines, increases urinary glucose loss, and expands the intravascular volume. The decline in the plasma glucose within the first 1 to 2 h may be more rapid and is mostly related to volume expansion. When the plasma glucose reaches 13.9 mmol/L (250 mg/ dL), glucose should be added to the 0.45% saline infusion to maintain the plasma glucose in the 11.1 to 13.9 mmol/L (200 to 250 mg/dL) range, and the insulin infusion should be continued. Ketoacidosis begins to resolve as insulin reduces lipolysis, increases peripheral ketone body use, suppresses hepatic ketone body formation, and promotes bicarbonate regeneration. However, the acidosis and ketosis resolve more slowly than hyperglycemia. As ketoacidosis improves, hydroxybutyrate is converted to acetoacetate. Ketone body levels may appear to increase if measured by laboratory assays that use the nitroprusside reaction, which only detects acetoacetate and acetone.

The improvement in acidosis and anion gap, a result of bicarbonate regeneration and decline in ketone bodies, is reflected by a rise in the serum bicarbonate level and the arterial pH. Depending on the rise of serum chloride, the anion gap (but not bicarbonate) will normalize. A hyperchloremic acidosis [serum bicarbonate of 15 to 18 mmol/L (15 to 18 meq/L)] often follows successful treatment and gradually resolves as the kidneys regenerate bicarbonate and excretes chloride. Potassium stores are depleted in Diabetic ketoacidosis [estimated deficit 3 to 5 mmol/kg (3 to 5 meq/kg)]. During treatment with insulin and fluids, various factors contribute to the development of hypokalemia. These include insulin mediated potassium transport into cells, resolution of the acidosis (which also promotes potassium entry into cells), and urinary loss of potassium salts of organic acids. Thus, potassium repletion should commence as soon as adequate urine output and normal serum potassium are documented. If the initial serum potassium level is elevated, then potassium repletion should be delayed until the potassium falls into the normal range. Inclusion of 20 to 40 meq of potassium in each liter of intravenous fluid is reasonable, but additional potassium supplements may also be required. To reduce the amount of chloride administered, potassium phosphate or acetate can be substituted for the chloride salt. The goal is to maintain the serum potassium 3.5 mmol/L (3.5 meq/L). If the initial serum potassium is less than 3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is supplemented to 3.3 mmol/L (3.3 meq/L). Despite a bicarbonate deficit, bicarbonate replacement is not usually necessary. In fact, theoretical arguments suggest that bicarbonate administration and rapid reversal of acidosis may impair cardiac function, reduce tissue oxygenation, and promote hypokalemia.

The results of most clinical trials do not support the routine use of bicarbonate replacement, and one study in children found that bicarbonate use was associated with an increased risk of cerebral edema. However, in the presence of severe acidosis (arterial pH 7.0 after initial hydration), the ADA advises bicarbonate [50 mmol/L (meq/L) of sodium bicarbonate in 200 mL of 0.45% saline over 1 h if pH 6.9 to 7.0;or 100 mmol/L (meq/L) of sodium bicarbonate in 400 mL of 0.45% saline over 2 h if pH 7 6.9]. Hypophosphatemia may result from increased glucose usage, but randomized clinical trials have not demonstrated that phosphate replacement is beneficial in Diabetic ketoacidosis. If the serum phosphate is 0.32 mmol/L (1.0 mg/dL), then phosphate supplement should be considered and the serum calcium monitored. Hypomagnesemia may develop during Diabetic ketoacidosis therapy and may also require supplementation. With appropriate therapy, the mortality of Diabetic ketoacidosis is low (5%) and is related more to the underlying or precipitating event, such as infection or myocardial infarction. The major non metabolic complication of Diabetic ketoacidosis therapy is cerebral edema, which most often develops in children as Diabetic ketoacidosis is resolving. The etiology and optimal therapy for cerebral edema are not well established, but over replacement of free water should be avoided. Venous thrombosis, upper gastrointestinal bleeding, and acute respiratory distress syndrome occasionally complicate Diabetic ketoacidosis.

Following treatment, the physician and patient should review the sequence of events that led to Diabetic ketoacidosis to prevent future recurrences. Foremost is patient education about the symptoms of Diabetic ketoacidosis, its precipitating factors, and the management of diabetes during a concurrent illness. During illness or when oral intake is compromised, patients should: (1) frequently measure the capillary blood glucose;(2) measure urinary ketones when the serum glucose 16.5 mmol/L (300 mg/ dL);(3) drink fluids to maintain hydration;(4) continue or increase insulin and (5) seek medical attention if dehydration, persistent vomiting, or uncontrolled hyperglycemia develop. Using these strategies, early Diabetic

ketoacidosis can be prevented or detected and treated appropriately on an outpatient basis.

Hyperglycemic Hyperosmolar State

Clinical Features

The prototypicalpatient with HHS is an elderly individual with type 2 Diabetes mellitus, with a several week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma. The physical examination reflects profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of Diabetic ketoacidosis. HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or stroke. Sepsis, pneumonia, and other serious infections are frequent precipitants and should be sought. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake may contribute to the development of the disorder.

Pathophysiology

Relative insulin deficiency and inadequate fluid intake are the underlying causes of HHS. Insulin deficiency increases hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilization in skeletal muscle (see above discussion of Diabetic ketoacidosis). Hyperglycemia induces an osmotic diuresis that leads to intravascular volume depletion, which is exacerbated by inadequate fluid replacement. The absence of ketosis in HHS is not completely understood. Presumably, the insulin deficiency is only relative and less severe than in Diabetic ketoacidosis. Lower levels of counterregulatory hormones and free fatty acids have been found in HHS than in Diabetic ketoacidosis in some studies. It is also possible that the liver is less capable of ketone body synthesis or that the insulin/glucagon ratio does not favor ketogenesis.

Laboratory Abnormalities and Diagnosis

Most notable are the marked hyperglycemia [plasma glucose may be 55.5 mmol/L (1000 mg/dL)], hyperosmolality (350 mosmol/L), and prerenal azotemia. The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased [add 1.6 meq to measured sodium for each 5.6 mmol/L (100 mg/dL) rise in the serum glucose]. In contrast to Diabetic ketoacidosis, acidosis and ketonemia are absent or mild. A small anion gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation. Several elements. In both disorders, careful monitoring of the patient's fluid status, laboratory values, and insulin infusion rate is crucial. Underlying or precipitating problems should be aggressively sought and treated. In HHS, fluid losses and dehydration are usually more pronounced than in Diabetic ketoacidosis due to the longer duration of the illness. The patient with HHS is usually older, more likely to have mental status changes, and more likely to have a life threatening precipitating event with accompanying comorbidities. Even with proper treatment, HHS has a substantially higher mortality than Diabetic ketoacidosis (up to 15% in some clinical series). Fluid replacement should initially stabilize the hemodynamic status of the patient (1 to 3 L of 0.9% normal saline over the first 2 to 3 h). Because the fluid deficit in HHS is accumulated over a period of days to weeks, the rapidity of reversal of the hyperosmolar state must balance the need for free water repletion with the risk that too rapid a reversal may worsen neurologic function. If the serum sodium is 150 mmol/L (150 meq/L), 0.45% saline should be used. After hemodynamic stability is achieved, the intravenous fluid administration is directed at reversing the free water deficit using hypotonic fluids (0.45% saline initially then 5% dextrose in water, D5W). The calculated free water deficit (which averages 9 to 10 L) should be reversed over the next 1 to 2 days (infusion rates of 200 to 300 mL/h of hypotonic solution). Potassium repletion is usually necessary and should be dictated by repeated measurements of the serum potassium. In patients taking diuretics, the potassium deficit can be quite large and may be accompanied by magnesium deficiency. Hypophosphatemia may occur during therapy and can be improved by using KPO4 and beginning nutrition.

As in Diabetic ketoacidosis, rehydration and volume expansion lower the plasma glucose initially, but insulin is also required. A reasonable regimen for HHS begins with an intravenous insulin bolus of 5 to 10 units followed by intravenous insulin at a constant infusion rate (3 to 7 units/h). As in Diabetic ketoacidosis, glucose should be added to intravenous fluid when the plasma glucose falls to 13.9 mmol/L (250 mg/dL), and the insulin infusion rate should be decreased to 1 to 2 units/h. The insulin infusion should be continued until the patient has resumed eating and can be transferred to a subcutaneous insulin regimen. The patient should be discharged from the hospital on insulin, though some patients can later switch to oral glucose lowering agents.

Chronic Complications of Diabetes Mellitus

The chronic complications of Diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of Diabetes mellitus are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease). Nonvascular complications include problems such as gastroparesis, infections, and skin changes. The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type 2 Diabetes mellitus often has a long asymptomatic period of hyperglycemia, many individuals with type 2 Diabetes mellitus have complications at the time of diagnosis. The microvascular complications of both type 1 and type 2 Diabetes mellitus result from chronic hyperglycemia.

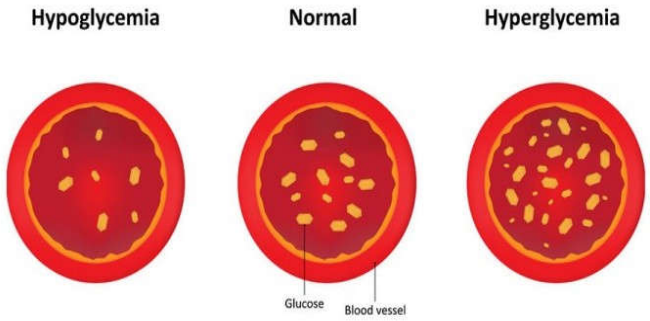

Fig 7 Glucose in the Blood

Large, randomized clinical trials of individuals with type 1 or type 2 Diabetes mellitus have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy. Other incompletely defined factors may modulate the development of complications. For example, despite long standing Diabetes mellitus, some individuals never develop nephropathy or retinopathy. Many of these patients have glycemic control that is indistinguishable from those who develop microvascular complications, suggesting that there is a genetic susceptibility for developing particular complications. Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease events and mortality are two to four times greater in patients with type 2 Diabetes mellitus. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

Mechanisms of Complications

Although chronic hyperglycemia is an important etiologic factor leading to complications of Diabetes mellitus, the mechanism by which it leads to such diverse cellular and organ dysfunction is unknown. Four prominent theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of Diabetes mellitus. One theory is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylaton of intra and extracellular proteins. Nonennenzymatic glycosylation results from the interaction of glucose with amino groups on proteins. AGEs have been shown to cross link proteins (e.g., collagen, extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with the level of glycemia, and these products accumulate as glomerular filtration rate declines.

A second theory is based on the observation that hyperglycemia increases glucose metabolism via the sorbitol pathway. Intracellular glucose is predominantly metabolized by phosphorylation and subsequent glycolysis, but when increased, some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentration alters redox potential, increases cellular osmolality, generates reactive oxygen species, and likely leads to other types of cellular dysfunction. However, testing of this theory in humans, using aldose reductase inhibitors, has not demonstrated significant beneficial effects on clinical endpoints of retinopathy, neuropathy, or nephropathy. A third hypothesis proposes that hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C (PKC). Among other actions, PKC alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons. A fourth theory proposes that hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O linked glycosylation and proteoglycan production. The hexosamine pathway may alter function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in gene expression of transforming growth factor (TGF) or plasminogen activator inhibitor-1 (PAI-1).

Growth factors appear to play an important role in Diabetes mellitus related complications, and their production is increased by most of these proposed pathways. Vascular endothelial growth factor (VEGF) is increased locally in diabetic proliferative retinopathy and decreases after laser photocoagulation. TGF is increased in diabetic nephropathy and stimulates basement membrane production of collagen and fibronectin by mesangial cells. Other growth factors, such as platelet derived growth factor, epidermal growth factor, insulin like growth factor I, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in Diabetes mellitus related complications. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria; these compounds may activate all for of the pathways described above. Although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.

Glycemic Control and Complications

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 Diabetes mellitus. This large multicenter clinical trial randomized over 1400 individuals with type 1 Diabetes mellitus to either intensive or conventional diabetes management, and prospectively evaluated the development of retinopathy, nephropathy, and neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support. Individuals in the conventional diabetes management group received twice daily insulin injections and quarterly nutritional, educational, and clinical evaluation. The goal in the former group was normoglycemia; the goal in the latter group was prevention of symptoms of diabetes. Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (A1C;7.3%) than individuals in the conventional diabetes management group (A1C;9.1%). The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also

slowed the progression of early diabetic complications. There was a nonsignificant trend in reduction of macrovascular events. The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from ESRD, and 5.6 years free from lower extremity amputations. If all complications of Diabetes mellitus were combined, individuals in the intensive diabetes management group would experience 15.3 more years of life without significant microvascular or neurologic complications of Diabetes mellitus, compared to individuals who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group. The benefit of the improved glycemic control during the DCCT persisted even after the study concluded and glycemic control worsened. The benefits of an improvement in glycemic control occurred over the entire range of A1C values, suggesting that at any A1C level, an improvement in glycemic control is beneficial. Therefore, there is no threshold beneath which the A1C can be reduced and the complications of Diabetes mellitus prevented. The clinical implication of this finding is that the goal of therapy is to achieve an A1C level as close to normal as possible without subjecting the patient to excessive risk of hypoglycemia.

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of 5000 individuals with type 2 Diabetes mellitus for 10 years. This study utilized multiple treatment regimens and monitored the effect of intensive glycemic control and risk factor treatment on the development of diabetic complications. Newly diagnosed individuals with type 2 Diabetes mellitus were randomized to (1) intensive management using various combinations of insulin, a sulfonylurea, or metformin;or (2) conventional therapy using dietary modification and pharmacotherapy with the goal of symptom prevention. In addition, individuals were randomly assigned to different antihypertensive regimens. Individuals in the intensive treatment arm achieved an A1C of 7.0%, compared to a 7.9% A1C in the standard treatment group. The UKPDS demonstrated that each percentage point reduction in A1C was associated with a 35% reduction in microvascular complications. One of the major findings of the UKPDS was that strict blood pressure control significantly reduced both macro and microvascular complications. In fact, the beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to moderate goals (144/82 mmHg) reduced the risk of DM related death, stroke, microvascular end points, retinopathy, and heart failure (risk reductions between 32 and 56%). Despite concerns that insulin therapy is associated with weight gain and may worsen underlying insulin resistance and hyperinsulinemia, most available data support strict glycemic control in individuals with type 2 Diabetes mellitus. Similar reductions in the risks of retinopathy and nephropathy were also seen in a small trial of lean Japanese individuals with type 2 Diabetes mellitus randomized to either intensive glycemic control or standard therapy with insulin (Kumamoto study).

These results demonstrate the effectiveness of improved glycemic control in individuals of different ethnicity, and, presumably a different etiology of Diabetes mellitus (i.e., phenotypically different from those in the DCCT and UKPDS). The findings of the DCCT, UKPDS, and Kumamoto study support the idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications. These landmark studies prove the value of metabolic control and emphasize the importance of (1) intensive glycemic control in all forms of Diabetes mellitus, and (2) early diagnosis and strict blood pressure control in type 2 Diabetes mellitus.

Ophthalmologic Complications of Diabetes Mellitus

DM is the leading cause of blindness between the ages of 20 and 74 in the United States [17-21]. The gravity of this problem is highlighted by the finding that individuals with Diabetes mellitus are 25 times more likely to become legally blind than individuals without Diabetes mellitus. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular edema. Diabetic retinopathy is classified into two stages: non proliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton wool spots[22-24]. Mild nonproliferative retinopathy progresses to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia. The appearance of neovascularization in response to retinal hypoxia is the hallmark of proliferative diabetic retinopathy. These newly formed vessels appear near the optic nerve and macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment[25].

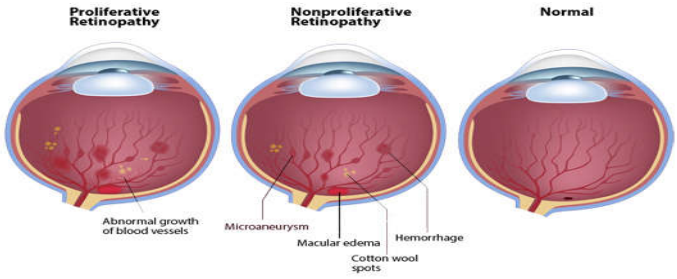

Fig 8 Diabetic Retinopathy

Not all individuals with nonproliferative retinopathy develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years. This creates an important opportunity for early detection and treatment of diabetic retinopathy. Clinically significant macular edema can occur when only nonproliferative retinopathy is present. Fluorescein angiography is useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next 3 years. Duration of Diabetes mellitus and degree of glycemic control are the best predictors of the development of retinopathy hypertension is also a risk factor. Nonproliferative retinopathy is found in almost all individuals who have had Diabetes mellitus for 20 years (25% incidence with 5 years, and 80% incidence with 15 years of type 1 Diabetes mellitus). Although there is genetic susceptibility for

retinopathy, it confers less influence than either the duration of Diabetes mellitus or the degree of glycemic control.

Treatment

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and blood pressure control will delay the development or slow the progression of retinopathy in individuals with either type 1 or type 2 Diabetes mellitus. Paradoxically, during the first 6 to 12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term, improved glycemic control is associated with less diabetic retinopathy. Individuals with known retinopathy are candidates for prophylactic photocoagulation when initiating intensive therapy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, though adequate ophthalmologic care can prevent most blindness. Regular, comprehensive eye examinations are essential for all individuals with Diabetes mellitus. Most diabetic eye disease can be successfully treated if detected early. Routine, nondilated eye examinations by the primary care provider or diabetes specialist are inadequate to detect diabetic eye disease, which requires an ophthalmologist for optimal care of these disorders. Laser photocoagulation is very successful in preserving vision. Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation. Although exercise has not been conclusively shown to worsen proliferative diabetic retinopathy, most ophthalmologists advice individuals with advanced diabetic eye disease to limit physical activities associated with repeated Valsalva maneuvers. Aspirin therapy (650 mg/d) does not appear to influence the natural history of diabetic retinopathy, but studies of other antiplatelet agents are under way.

Renal Complications of Diabetes Mellitus

Diabetic nephropathy is the leading cause of ESRD in the United States and a leading cause of Diabetes mellitus related morbidity and mortality. Proteinuria in individuals with Diabetes mellitus is associated with markedly reduced survival and increased risk of cardiovascular disease. Individuals with diabetic nephropathy almost always have diabetic retinopathy. Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia[26]. The mechanisms by which chronic hyperglycemia leads to ESRD, though incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II receptors[27-31]. Smoking accelerates the decline in renal function. The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 Diabetes mellitus but appears to be similar in type 2 Diabetes mellitus. Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of Diabetes mellitus and cause an increase of the glomerular filtration rate (GFR). During the first 5 years of Diabetes mellitus, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5 to 10 years of type 1 Diabetes mellitus,_40% of individuals begin to excrete small amounts of albumin in the urine. Microalbuminuria is defined as 30 to 300 mg/d in a 24 h collection or 30 to 300 g/mg Creatinine in a spot collection (preferred method). The appearance of Microalbuminuria (incipient nephropathy) in type 1 Diabetes mellitus is an important predictor of progression to overt proteinuria (300 mg/d) or overt nephropathy. Blood pressure may rise slightly at this point but usually remains in the normal range [32,33]. Once overt proteinuria is present, there is a steady decline in GFR, and 50% of individuals reach ESRD in 7 to 10 years. The early pathologic changes and albumin excretion abnormalities are reversible with normalization of plasma glucose.

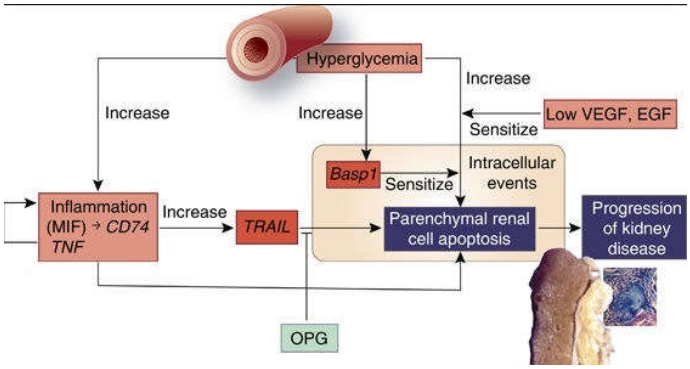

Fig 9 Diabetic Nephropathy

However, once overt nephropathy develops, the pathologic changes are likely irreversible. The nephropathy that develops in type 2 Diabetes mellitus differs from that of type 1 Diabetes mellitus in the following respects: (1) microalbuminuria or overt nephropathy may be present when type 2 Diabetes mellitus is diagnosed, reflecting its long asymptomatic period;(2) hypertension more commonly accompanies microalbuminuria or overt nephropathy in type 2 Diabetes mellitus and (3) microalbuminuria may be less predictive of diabetic nephropathy and progression to overt nephropathy in type 2 Diabetes mellitus. Finally, it should be noted that albuminuria in type 2 Diabetes mellitus may be secondary to factors unrelated to Diabetes mellitus, such as hypertension, congestive heart failure, prostate disease, or infection. Diabetic nephropathy and ESRD secondary to this develop more commonly in African Americans, Native Americans, and Hispanic individuals than in Caucasians with type 2 Diabetes mellitus.

Treatment

The optimal therapy for diabetic nephropathy is prevention. As part of comprehensive diabetes care, microalbuminuria should be detected at an early stage when effective therapies can be instituted. The recommended strategy for detecting microalbuminuria is outlined. Interventions effective in slowing progression from Microalbuminuria to overt nephropathy include: (1) near normalization of glycemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors or ARBs, and (4) treatment of dyslipidemia.

Improved glycemic control reduces the rate at which Microalbuminuria appears and progresses in type 1 and type 2

Diabetes mellitus. However, once overt nephropathy exists, it is unclear whether improved glycemic control will slow progression of renal disease. During the phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. Furthermore, glucose lowering medications (sulfonylureas and metformin) are contraindicated in advanced renal insufficiency. Many individuals with type 1 or type 2 Diabetes mellitus develop hypertension. Numerous studies in both type 1 and type 2 Diabetes mellitus demonstrate the effectiveness of strict blood pressure control in reducing albumin excretion and slowing the decline in renal function. Blood pressure should be maintained at 130/80 mmHg in diabetic individuals without proteinuria. A slightly lower blood pressure (125/75) should be considered for individuals with microalbuminuria or overt nephropathy.

Neuropathy and Diabetes Mellitus

Diabetic neuropathy occurs in approximately 50% of individuals with long standing type 1 and type 2 Diabetes mellitus[34-37]. It may manifest as polyneuropathy, mononeuropathy or autonomic neuropathy. As with other complications of Diabetes mellitus, the development of neuropathy correlates with the duration of diabetes and glycemic control; both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded[38-40].

Polyneuropathy/Mononeuropathy

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss. Hyperesthesia, paresthesia, and dysesthesia also occur. Any combination of these symptoms may develop as neuropathy progresses. Symptoms include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting 12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense.

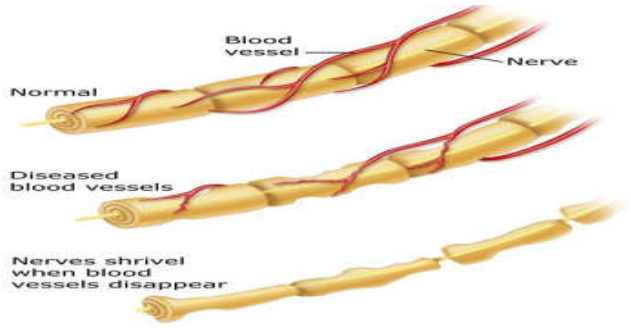

Fig 10 Diabetic Neuropathy

Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately, diabetic polyradiculopathies are usually self limited and resolve over 6 to 12 months. Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve. A vascular etiology has been suggested, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and opthalmoplegia with normal pupillary constriction to light. Sometimes cranial nerves IV, VI, or VII (Bell's palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

Treatment

Treatment of diabetic neuropathy is less than satisfactory. Improved glycemic control should be pursued and will improve nerve conduction velocity, but the symptoms of diabetic neuropathy may not necessarily improve. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Avoidance of neurotoxins (alcohol), supplementation with vitamins for possible deficiencies (B12, B6, folat and symptomatic treatment are the mainstays of therapy. Aldose reductase inhibitors do not offer significant symptomatic relief. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae; consequently, prevention of such problems is of paramount importance. Since the pain of acute diabetic neuropathy may resolve over the first year, analgesics may be discontinued as progressive neuronal damage from Diabetes mellitus occurs. Chronic, painful diabetic neuropathy is difficult to treat but may respond to tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, nonsteroidal anti inflammatory agents (avoid in renal dysfunction), and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream). Referral to a pain management center may be necessary. Therapy of orthostatic hypotension secondary to autonomic neuropathy is challenging. A variety of agents have limited success (fludrocortisone, midodrine, clonidine, octreotide, and yohimbine) but each has significant side effects. Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose) may offer some benefit.

Gastrointestinal/Genitourinary Dysfunction

Long standing type 1 and 2 Diabetes mellitus may affect the motility and function of gastrointestinal (GI) and genitourinary systems. The most prominent GI symptoms are delayed gastric emptying (gastroparesis) and altered small and largebowel motility (constipation or diarrhea). Gastroparesis may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal is the best study to document delayed gastric emptying, but noninvasive "breath tests" following ingestion of a radiolabeled meal are under development.

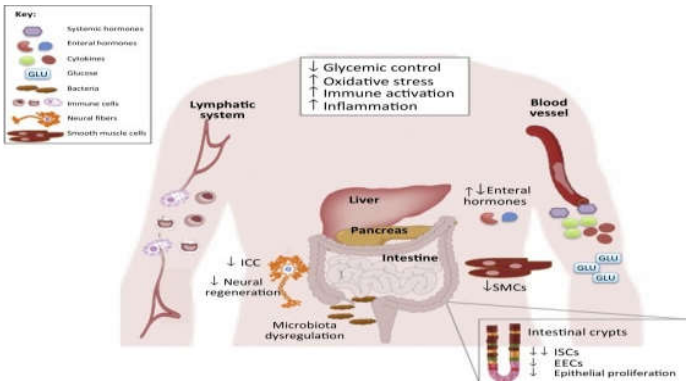

Fig 11 Diabetes Mellitus in Gastrointestinal

Though parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhoea, alternating with constipation, is a common feature of Diabetes mellitus related GI autonomic neuropathy. In type 1 Diabetes mellitus, these symptoms should also prompt evaluation for celiac sprue because of its increased frequency. Esophageal dysfunction in longstanding Diabetes mellitus is common but usually asymptomatic. Diabetic autonomic neuropathy may lead to genitourinary dysfunction including cystopathy, erectile dysfunction, and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely. As bladder contractility worsens, bladder capacity and the post void residual increase, leading to symptoms of urinary hesitancy, decreased voiding frequency, incontinence, and recurrent urinary tract infections. Diagnostic evaluation includes cystometry and urodynamic studies. Erectile dysfunction and retrograde ejaculation are very common in Diabetes mellitus and may be one of the earliest signs of diabetic neuropathy. Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy.

Treatment

Current treatments for these complications of Diabetes mellitus are inadequate. Improved glycemic control should be a primary goal, as some aspects (neuropathy, gastric function) may improve. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Cisapride (10 to 20 mg before each meal) is probably the most effective medication but has been removed from use in the United States except under special circumstances. Other agents with some efficacy include dopamine agonists (metoclopramide, 5 to 10 mg, and domperidone, 10 to 20 mg, before each meal) and bethanechol (10 to 20 mg before each meal). Erythromycin interacts with the motilin receptor and may promote gastric emptying. Diabetic diarrhoea in the absence of bacterial overgrowth is treated symptomatically with loperamide but may respond to clonidine at higher doses (0.6 mg tid) or octreotide (50 to 75 g tid subcutaneously).

Treatment of bacterial overgrowth with antibiotics is sometimes useful. Diabetic cystopathy should be treated with timed voiding or selfcatherization. Medications (bethanechol) are inconsistently effective. The drug of choice for erectile dysfunction is sildenafil, but the efficacy in individuals with Diabetes mellitus is slightly lower than in the nondiabetic population. Sexual dysfunction in women may be improved with use of vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement.

Cardiovascular Morbidity and Mortality

Cardiovascular disease is increased in individuals with type 1 or type 2 Diabetes mellitus. The Framingham Heart Study revealed a marked increase in peripheral arterial disease, congestive heart failure, coronary artery disease, myocardial infarction (MI) and sudden death (risk increase from one to fivefold) in Diabetes mellitus. The American Heart Association recently designated Diabetes mellitus as a major risk factor for cardiovascular disease (same category as smoking, hypertension, and hyperlipidemia). Type 2 diabetes patients without a prior MI have a similar risk for coronary artery related events as non diabetic individuals who have had a prior myocardial infarction[41-44]. Because of the extremely high prevalence of underlying cardiovascular disease in individuals with diabetes (especially in type 2 Diabetes mellitus), evidence of atherosclerotic vascular disease should be sought in an individual with diabetes who has symptoms suggestive of cardiac ischemia, peripheral or carotid arterial disease, a resting electrocardiogram indicative of prior infarction, plans to initiate an exercise program, proteinuria, or two other cardiac risk factors (ADA recommendations). The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures[45]. The prognosis for individuals with diabetes who have coronary artery disease or myocardial infarction is worse than for non diabetics. Coronary artery disease is more likely to involve multiple vessels in individuals with Diabetes mellitus.

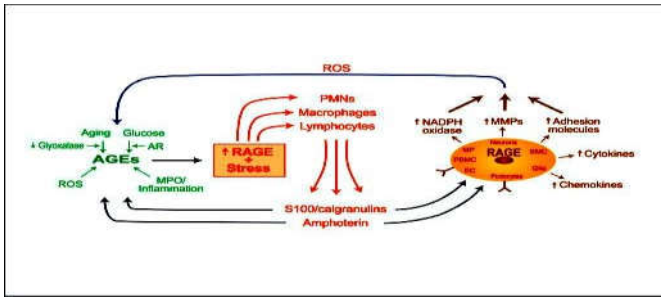

Fig 12 Described advanced glycation end product receptor for advanced glycation end products and a vicious cycle of cellular perturbation and tissue injury: implications for diabetic complications

The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. For example, after controlling for all known cardiovascular risk factors, type 2 Diabetes mellitus increases the cardiovascular death rate two fold in men and fourfold in women. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors specific to the diabetic population include microalbuminuria, gross proteinuria, an elevation of serum creatinine, and abnormal platelet function. Insulin resistance, as reflected by elevated serum insulin levels, is associated with an increased risk of cardiovascular

complications in individuals with and without Diabetes mellitus. Individuals with insulin resistance and type 2 Diabetes mellitus have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis. Diabetes is also associated with endothelial, vascular smooth muscle, and platelet dysfunction. Proof that improved glycemic control reduces cardiovascular complications in Diabetes mellitus is lacking; in fact, it is possible that macrovascular complications may be unaffected or even worsened by such therapy. Concerns about the atherogenic potential of insulin remain, since in nondiabetic individuals, higher serum insulin levels (indicative of insulin resistance) are associated with a greater risk of cardiovascular morbidity and mortality. In the DCCT, the number of cardiovascular events did not differ between the standard and intensively treated groups. However, the duration of Diabetes mellitus in these individuals was relatively short, and the total number of events was very low. An improvement in the lipid profile of individuals in the intensive group [lower total and low density lipoprotein (LDL) cholesterol, lower triglycerides] suggested that intensive therapy may reduce the risk of cardiovascular morbidity and mortality associated with Diabetes mellitus. In the UKPDS, improved glycemic control did not conclusively reduce cardiovascular mortality. Importantly, treatment with insulin and the sulfonylureas did not appear to increase the risk of cardiovascular disease in individuals with type 2 Diabetes mellitus, refuting prior claims about the atherogenic potential of these agents.

Treatment

In general, the treatment of coronary disease is no different in the diabetic individual. Revascularization procedures for coronary artery disease, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), are less efficacious in the diabetic individual. Initial success rates of PCI in diabetic individuals are similar to those in the non diabetic population, but diabetic patients have higher rates of restenosis and lower long term patency and survival rates. The use of stents and a GPIIb/IIIa platelet inhibitor has improved the outcome in diabetic patients. Perioperative mortality from CABG is not altered in DM, but both short and long term survival is reduced. Recent trials indicate that diabetic individuals with multivessel coronary artery disease or recent Q wave MI have better long term survival with CABG than PCI. The ADA has emphasized the importance of glycemic control and aggressive cardiovascular risk modification in all individuals with Diabetes mellitus. Past trepidation about using beta blockers in individuals who have diabetes should not prevent use of these agents since they clearly benefit diabetic patients after MI. ACE inhibitors may also be particularly beneficial and should be considered in individuals with type 2 Diabetes mellitus and other risk factors (smoking, dyslipidemia, history of cardiovascular disease, microalbuminuria). Antiplatelet therapy reduces cardiovascular events in individuals with Diabetes mellitus who have coronary artery disease. Current recommendations by the ADA include the use of aspirin for secondary prevention of coronary events. Although data demonstrating efficacy in primary prevention of coronary events in Diabetes mellitus are lacking, antiplatelet therapy should be strongly considered, especially in diabetic individuals with other coronary risk factors such as hypertension, smoking, or dyslipidemia. The aspirin dose (81 to 325 mg) is the same as that in nondiabetic individuals. Aspirin therapy does not have detrimental effects on renal function or hypertension, nor does it influence the course of diabetic retinopathy.

Cardiovascular Risk Factors

Dyslipidemia

Individuals with Diabetes mellitus may have several forms of dyslipidemia. Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be aggressively detected and treated as part of comprehensive diabetes care[46]. The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. Diabetes mellitus itself does not increase levels of LDL, but the small dense LDL particles found in type 2 Diabetes mellitus are more atherogenic because they are more easily glycated and susceptible to oxidation. According to guidelines of the ADA and the American Heart Association, the target lipid values in diabetic individuals without cardiovascular disease should be: LDL 2.6 mmol/L (100 mg/dL); HDL 1.1 mmol/L (40 mg/dL) in men and 1.38 mmol/L (50 mg/dL) in women and triglycerides 1.7 mmol/L (150 mg/dL). The National Cholesterol Education Program Adult Treatment Panel III also recommends lowering the LDL to 2.6 mmol/L (100 mg/dL) in diabetics. This is because the incidence of MI in type 2 Diabetes mellitus is the same as that in patients without diabetes who have had a prior MI[47].

Hypertension

Hypertension can accelerate other complications of Diabetes mellitus, particularly cardiovascular disease and nephropathy[48]. Hypertension therapy should first emphasize life style modifications such as weight loss, exercise, stress management, and sodium restriction. Antihypertensive agents should be selected based on the advantages and disadvantages of the therapeutic agent in the context of an individual patient's risk factor profile. Diabetes mellitus related considerations include the following:

1. ACE inhibitors are either glucose and lipineutral or glucoseand lipid beneficial and thus positively impact the cardiovascular risk profile. For example, captopril improves insulin resistance, reduces LDL slightly, and increases HDL slightly. Adrenergic blockers slightly improve insulin resistance and positively impact the lipid profile, whereas beta blockers and thiazide diuretics can increase insulin resistance and negatively impact the lipid profile. Calcium channel blockers, central adrenergic antagonists, and vasodilators are lipid and glucose neutral.
2. Beta blockers may slightly increase the risk of developing type 2 Diabetes mellitus. Although often questioned because of the potential masking of hypoglycemic symptoms, beta blockers are safe in most patients with diabetes and reduce cardiovascular events. In one study of nondiabetic individuals, the ACE inhibitor ramipril reduced the risk of developing type 2 Diabetes mellitus.
3. Sympathetic inhibitors and adrenergic blockers may worsen orthostatic hypotension in the diabetic individual with autonomic neuropathy.

Lower Extremity Complications

Diabetes mellitus is the leading cause of nontraumatic lower extremity amputation in the United States. Foot ulcers and infections are also a major source of morbidity in individuals with Diabetes mellitus. The reasons for the increased incidence of these disorders in Diabetes mellitus involve the interaction of several pathogenic factors: neuropathy, abnormal foot biomechanics, peripheral arterial disease, and poor wound healing. The peripheral sensory neuropathy interferes with normal protective mechanisms and allows the patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury. Disordered proprioception causes abnormal weight bearing while walking and subsequent formation of callus or ulceration. Motor and sensory neuropathy lead to abnormal foot muscle mechanics and to structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint).

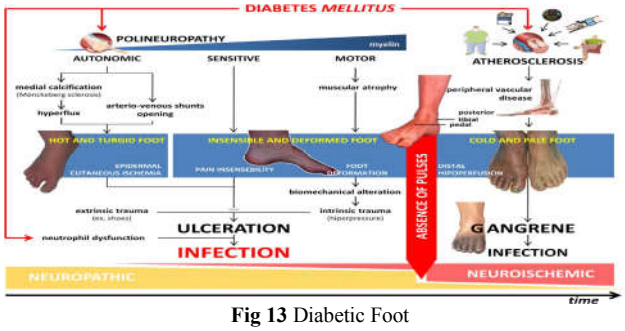

Fig 13 Diabetic Foot

Autonomic neuropathy results in anhidrosis and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation[49-51]. Peripheral arterial disease and poor wound healing impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected.

Treatment

The optimal therapy for foot ulcers and amputations is prevention through identification of high risk patients, education of the patient, and institution of measures to prevent ulceration. High risk patients should be identified during the routine foot examination performed on all patients with Diabetes mellitus[52-57]. Patient education should emphasize: (1) careful selection of footwear, (2) daily inspection of the feet to detect early signs of poor fitting footwear or minor trauma, (3) daily foot hygiene to keep the skin clean and moist, (4) avoidance of self treatment of foot abnormalities and high risk behavior (e.g., walking barefoot), and (5) prompt consultation with a health care provider if an abnormality arises. Patients at high risk for ulceration or amputation may benefit from evaluation by a foot care specialist. Interventions directed at risk factor modification include orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin pressure from abnormal bony architecture. Attention to other risk factors for vascular disease (smoking, dyslipidemia, hypertension) and improved glycemic control are also important[58-60].

Infections

Individuals with Diabetes mellitus have a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization. Hyperglycemia aids the colonization and growth of a variety of organisms (Candida and other fungal species). Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population. Examples of this latter category includes rhinocerebral mucormycosis, emphysematous infections of the gall bladder and urinary tract, and "malignant" or invasive otitis externa. Invasive otitis externa is usually secondary to P. aeruginosa infection in the soft tissue surrounding the external auditory canal, usually begins with pain and discharge, and may rapidly progress to osteomyelitis and meningitis. These infections should be sought, in particular, in patients presenting with HHS. Pneumonia, urinary tract infections, and skin and soft tissue infections are all more common in the diabetic population. In general, the organisms that cause pulmonary infections are similar to those found in the nondiabetic population; however, gram negative organisms, S. aureus, and Mycobacterium tuberculosis are more frequent pathogens. Urinary tract infections (either lower tract or pyelonephritis) are the result of common bacterial agents such as Escherichia coli, though several yeast species (Candida and Torulopsis glabrata) are commonly observed. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Bacteriuria occurs frequently in individuals with diabetic cystopathy. Susceptibility to furunculosis, superficial candidal infections, and vulvovaginitis are increased. Poor glycemic control is a common denominator in individuals with these infections. Diabetic individuals have an increased rate of colonization of S. aureus in the skin folds and nares. Diabetic patients also have a greater risk of postoperative wound infections. Strict glycemic control reduces postoperative infections in diabetic individuals undergoing CABG and should be the goal in all diabetic patients with an infection.

Dermatologic Manifestations

The most common skin manifestations of Diabetes mellitus are protracted wound healing and skin ulcerations. Diabetic dermopathy, sometimes termed pigmented pretibial papules, or "diabetic skin spots," begins as an erythematous area and evolves into an area of circular hyperpigmentation. These lesions result from minor mechanical trauma in the pretibial region and are more common in elderly men with Diabetes mellitus. Bullous diseases (shallow ulcerations or erosions in the pretibial region) are also seen. Necrobiosis lipoidica diabeticorum is a rare disorder of Diabetes mellitus that predominantly affects young women with type 1 Diabetes mellitus, neuropathy, and retinopathy. It usually begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration.

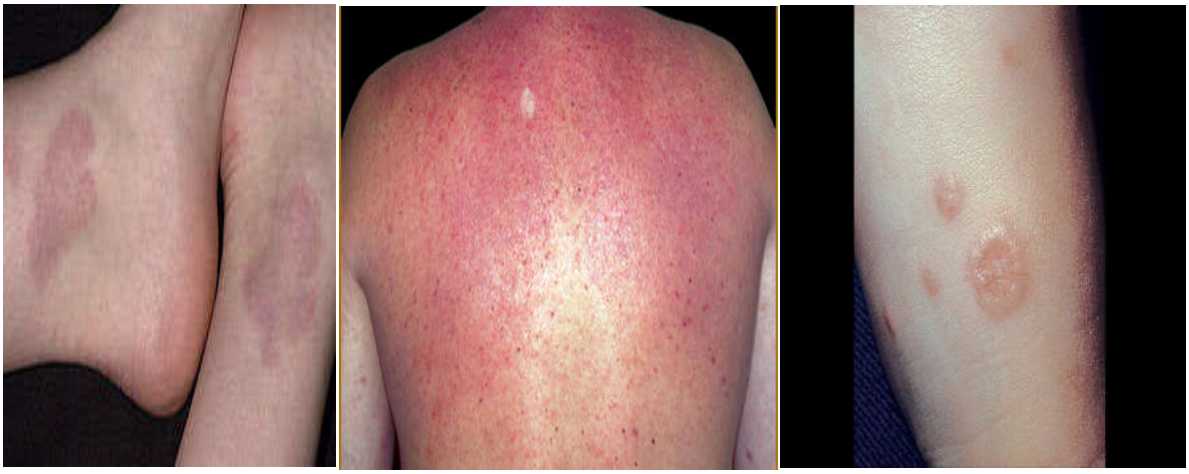

Fig 14 Diabetic Dermopathy

They may be painful. Acanthosis nigricans (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes. Generalized or localized granuloma annulare (erythematous plaques on the extremities or trunk) and scleredema (areas of skin thickening on the back or neck at the site of previous superficial infections) are more common in the diabetic population. Lipoatrophy and lipohypertrophy can occur at insulin injection sites but are unusual with the use of human insulin. Xerosis and pruritus are common and are relieved by skin moisturizers.

CONCLUSION

Diabetes Mellitus is a costly disease for developing economies of the global. It is necessary to have an improved understanding of its epidemiology, synthesis, acute complications, chronic complication and management (treatment). Supports from government authorities, scientists, clinical practitioners and nongovernmental organizations can be reduce the incidence of Diabetes mellitus and its complications significantly.

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Conflicts of Interest

None declared

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