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Review Paper

Diabetes: Mechanism, Pathophysiology and Management-A Review

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Abstract

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Over the last three decades, the status of diabetes has been changed, earlier it was considered as a mild disorder of the elderly people. Now it becomes a major cause of morbidity and mortality affecting the youth and middle aged people. According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. The main force of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population. The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years. This could have long lasting adverse effects on nation's health and economy. Therefore, it is necessary to identify the diabetic patients at the earliest and provide appropriate lifestyle intervention in preventing or postponing the onset of diabetes. In the present review, detailed mechanism and management of the diabetes have been emphasized.

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INTRODUCTION

Diabetes mellitus is not a single disorder, it represents a series of metabolic conditions associated with hyperglycaemia and caused by defects in insulin secretion and/or insulin action. Exposure to chronic

hyperglycaemia may result in microvascular complications in the retina, kidney or periphera.

Mechanism

Diabetes mellitus (DM) is a set of related diseases in which the body cannot regulate the amount of sugar (specifically, glucose) in the blood.

The blood delivers glucose to provide the body with energy to perform all of a person's daily activities. The liver converts the food a person eats into glucose. The glucose is then released into the bloodstream. In a healthy person, the blood glucose level is regulated by several hormones, primarily insulin. Insulin is produced by the pancreas, a small organ between the stomach and liver. The pancreas also makes other important enzymes released directly into the gut that helps digest food. Insulin allows glucose to move out of the blood into cells throughout the body where it is used for fuel. People suffered diabetes either do not produce enough insulin (type 1 diabetes) or cannot use insulin properly (type 2 diabetes), or both (which occurs with several forms of diabetes). In diabetes, glucose in the blood cannot move efficiently into cells, so blood glucose levels remain high. This not only starves all the cells that need the glucose for fuel, but also harms certain organs and tissues exposed to the high glucose levels.

TYPES OF DIABETES

There are two main types of diabetes type 1 and type 2 with their clinical relevance shown in Table 1 and another type of diabetes is gestational diabetes mellitus.

Table 1: Types of diabetes with clinical relevance

	Type I	Type II
Clinical	Onset <20 years Normal weight Decreased blood insulin Anti-Islet cell antibodies Ketoacidosis common	Onset >30 years Obesity Normal or increased blood insulin No anti-Islet cell antibodies Ketoacidosis rare
pathogenesis	Auto immunity, immunopathologic mechanism Severe insulin deficiency	Insulin resistance Relative insulin deficiency
Genetics	50% concordance in twins HLA-D linked	60-80% concordance in twins No HLA-D association
Islet cells	Insulitis early Marked atrophy and fibrosis Severe β-cell depletion	No insulitis early Focal atrophy and amyloid deposits Mild β-cell depletion

Type 1 diabetes

Type 1 diabetes is an autoimmune disease in which the β-cells of the pancreas do not produce sufficient insulin, a hormone which helps use blood sugar (glucose) for energy. The cells become starved of energy and there will be excess of glucose in the blood. This is then followed by life threatening conditions of hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar. When hypoglycemia develops, cells do not get enough glucose and patients suffer of confusion, loss of consciousness, and coma. Even death can results when the brain is deprived of glucose for too long. Hyperglycemia and prolonged absence of insulin may lead to ketoacidosis, which is accumulation of ketones in the blood when the body uses fat for energy instead of glucose. This is because fatty acids cannot be converted into glucose at steady state. Ketones make the blood acidic and slow down all body functions. This also leads to a coma and eventually death [1-6].

Type 2 diabetes

Type 2 diabetes mellitus is a complex endocrine and metabolic disorder. The interaction between several genetic and environmental factors results in a heterogeneous and progressive disorder with variable

degrees of insulin resistance and pancreatic β-cell dysfunction. Overweight and obesity are major contributors to the development of insulin resistance and impaired glucose tolerance. When β cells have not longer able to secrete sufficient insulin to overcome insulin resistance, impaired glucose tolerance progresses to type-2 diabetes. Abnormalities in other hormones such as reduced secretion of the incretin glucagon-like peptide 1 (GLP-1), hyperglucagonaemia, and raised concentrations of other counter-regulatory hormones also contribute to insulin resistance, reduced insulin secretion, and hyper glycaemia in type 2 diabetes[7-13]. Overweight and obesity contribute to insulin resistance through several pathways, including an imbalance in the concentrations of hormones (eg, increased leptin, reduced adiponectin, and increased glucagon), increased concentrations of cytokines (eg, tumour necrosis factor α, interleukin 6), suppressors of cytokine signalling (eg, suppressor of cytokine signalling), other inflammatory signals, and possibly retinol-binding protein 4.1[14-17], Concurrent alterations in β-cell function often include a period of compensatory hyperinsulinaemia with abnormal secretory dynamics. When insulin secretion is no longer sufficient to overcome insulin resistance, glucose intolerance progresses to type 2 diabetes. The decline in β-cell function seems to involve chronic hyperglycaemia (glucotoxicity), chronic exposure to non-esterifies fatty acids (lipotoxicity), oxidative stress, inflammation, and amyloid formation[18–20] Patients with type 2 diabetes usually have pancreatic α-cell dysfunction that results in increased (or non-suppressed) glucagon secretion in the presence of hyperglycaemia and probably reduced prandial GLP-1 secretion[21]

Gestational diabetes

Gestational diabetes mellitus (GDM) is defined as any abnormal carbohydrate intolerance that begins or is first recognized during pregnancy[22]. It does not exclude the possibility that unidentified glucose intolerance have preceded the pregnant state. GDM complicates approximately 7% of pregnancy, which accounts for more than 2,00,000 cases per year[23]. A recent study from India by Seshiah et al. reported the incidence of GDM as 18.9%[24]. The clinical importance of GDM lies in the fact that it is associated with significant maternal and fetal morbidity. In the present review we discuss about the pathophysiology, screening, diagnosis, complications and various management issues pertaining to GDM.

Pathophysiology

Type 1 diabetes

T1DM is the result of a combination of genetic and environmental influences. It most commonly results from autoimmune destruction of insulin-producing β-cells in the pancreas. Eisenbarth proposed that one or more environmental factors, such as enteroviruses, dietary factors or toxins, might trigger the development of T-cell dependent autoimmunity in genetically susceptible individuals[25] Autoimmunity is manifested by detectable antibodies to ICA512/IA-2, insulin autoantibody (IAA) and glutamic acid decarboxylase (GAD). Insulitis with gradual β-cell destruction leads to pre-diabetes and finally to overt DM. These patients are susceptible to other autoimmune diseases, such as Hashimoto's thyroiditis, celiac disease, Addison's disease, and myasthenia gravis. Forty genetic loci have been associated with T1DM by a genome-wide association study and meta-analysis[26]. A number of genetic loci in the major histocompatibility (HLA) region are associated with increased susceptibility to developing T1DM, including the alleles DR3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302. The risk of T1DM is approximately 5% if there is an affected first-degree relative and slightly higher if the affected parent is the father rather than the mother. To date, interventional trials have failed to delay the onset or prevent T1DM in those genetically at risk. Ongoing research by international networks is exploring ways to prevent, delay or reverse the progression of T1DM (e.g. TrialNet, TRIGR) [27].

Type 2 diabetes

Chronic fuel surfeit is the primary pathogenic event that drives the development of type 2 diabetes in genetically and epigenetically susceptible people[28,29]. Many chronic ally overnourished and overweight or obese individuals, however, do not develop diabetes at all or develop it very late in life. They remain resistant to type 2 diabetes and safely partition excess calories to subcutaneous adipose tissue (SAT) rather than to the heart, skeletal muscle, liver, and islet β cells, owing to the following mechanisms: successful islet β-cell compensation; maintenance of near-normal blood nutrient concentrations; development of minimal insulin resistance; increased expansion of SAT relative to visceral adipose tissue (VAT); and limited increase in liver fat.[30,31] In this way, key organs of the body avoid nutrient-induced damage. Susceptible over nourished individuals develop type 2 diabetes owing to the failure of these adaptive responses to safely dispose of the fuel surfeit. The following metabolic defects are crucial to the development of type 2 diabetes: inability of islet β -cells to compensate for the fuel surfeit; increased glucagon secretion and reduced incretin response; impaired expansion of SAT, hypoadiponectinaemia, and inflammation of adipose tissue; increased endogenous glucose production; and development of peripheral insulin resistance. Importantly, the fuel surfeit is not safely deposited into SAT, such that it has to be disposed of elsewhere. The “elsewhere” is less healthy VAT and “ectopic” storage in organs, such as the liver, heart, skeletal muscle, and pancreas, which causes widespread tissue damage. Worsening islet β-cell function can lead to the need for insulin therapy [30-38].

Gestational diabetes

Insulin resistance and impaired beta cell function, both contribute to GDM. Pregnancy is a diabetogenic state characterized by impaired insulin sensitivity. This is particularly noted as the pregnancy enters the 2nd trimester. The major contributors are the placental hormones namely, human placental lactogen, progesterone, cortisol, growth hormone and prolactin. These hormones cause decreased phosphorylation of insulin receptor substrate and thus profound insulin resistance. Cytokines like tissue necrosis factor have also been implicated in pathogenesis of insulin resistance. Logically, the pancreas should compensate for this demand by increasing insulin secretion. However, in GDM there is deterioration of β cell function, particularly the first phase insulin secretion. In a study on Latino women with GDM, 67% reduction of β cell function was noted as compared to the normal pregnant control. The second phase insulin release is comparable to that in individual with normal glucose tolerance. The defects in β cell have been attributed either to autoimmune process or enzymatic defect like glucokinase. Autoimmunity should be suspected in women who do not have typical characteristics of increased risk of GDM, i.e. who are lean and Caucasians. Thus, the combination of insulin resistance and secretory defect during pregnancy results in GDM [39-45].

Diabetic ketoacidosis (DKA)

DKA results from absolute insulin insufficiency, leading to metabolic acidosis (pH <7.3 or bicarbonate <15 m mol/L), hyperglycaemia (blood glucose >11 m mol/L), ketonaemia and ketonuria [46]. DKA is present at T1DM presentation in 15 to 67% of children, its frequency being inversely related to the incidence of T1DM in that area.[47] In those with established T1DM in the United States, the incidence of DKA has been reported to be 8 episodes per 100 patient-years. Risk factors that predict DKA include female sex, longer duration of diabetes, higher mean HbA1c, higher reported insulin dose, the presence of psychiatric disorders,[48]

insulin omission or insulin pump failure. DKA may also be present in up to 25% of young people presenting with T2DM. DKA should be treated as a medical emergency by an experienced medical team. Treatment of DKA in children differs in several

respects from that in adults: first, both fluids and insulin are calculated on per kilogram rather than an empirical basis. Fluid repletion should occur gradually with sodium chloride 0.9%. Boluses of fluid and insulin should be avoided. Bicarbonate should be given only in the setting of life-threatening hyperkalaemia, inotrope-resistant shock, or cardiac arrest. DKA is the major cause of hospitalization, morbidity and mortality in young people with T1DM. The most serious complication is cerebral oedema (CE), which occurs in 0.5 to 1.0%of DKA episodes, with 25%mortality. Demographic risk factors associated with increased risk for CE include younger age, new-onset diabetes, and longer duration of symptoms. Risk factors that are present at time of diagnosis or during treatment are increased serum urea, severe acidosis, greater hypocapnia after adjusting for the degree of acidosis, administration of sodium bicarbonate, and an attenuated rise in the measured serum sodium during treatment.[46]

Diabetic Nephropathy

The concept of the apparent renal benignity of type II diabetes is a paradox in view of the fact

that renal involvement in non-insulin-dependent diabetes had been known for a long time. The large body of medical literature documenting renal sequelae in type II diabetes has been forgotten or ignored, but according to Hegel,"What history teaches is this: that people have never learned anything from history or acted on principles deduced from it." In 1764, Cotugno noted that heat coagulated the urine of some diabetic patients.' In 1839, Rayer described renal hypertrophy in diabetic patients (by necessity of type II), and noted that the cortical substance was more fully developed, the vessels were enlarged, and "Malpighi's glands" were more prominent In 1859, Griesinger stated that "renal involvement complicates diabetes in a decisive fashion.

These reports support the fact that renal involvement in type II diabetes has been known for a long time. It is impossible to discuss all aspects of nephropathy in type II diabetes in the limited space of this review. Rather than attempting to be comprehensive, we shall discuss only those problems that appear to be at the cutting edge as we move into the second half of the 1990s. Therefore, we apologize to those authors whose work will not be recognized in this report[49-55]

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Beta Cell in Autoimmune Diabetes: Many Mechanisms and Pathways of Loss

T cells activated by antigens found in pancreatic β cells cause type-1 diabetes. T-cell activation results in the synthesis of cell-surface and secreted molecules normally used by the immune system to neutralize invading microorganisms. In type 1 diabetes, these immune effector mechanisms result in β-cell death. CD4 (T helper) and CD8 (cytotoxic) T cells and macrophages are found within the 'insulitis' lesion of affected humans and mice. Type-1 diabetes in humans has been transferred by bone marrow transplantation, but dependence on individual cell types is unlikely to be formally proven. Both CD4 and CD8 T-cell clones have been described that is capable of causing diabetes when injected into non-diabetic recipient mice. We have shown that CD8 T cells directly recognize b cells [via peptides bound to cell surface major histocompatibility complex (MHC) class I proteins], but CD4 T cells are unlikely to recognize β cells directly because they do not express MHC class II proteins, which are required for recognition by CD4 T cells. It is more likely that CD4 T cells recognize local antigen-presenting cells (APCs), including dendritic cells, macrophages or β cells. CD4 T-cell dependent β-cell death then precedes indirectly, without antigen-specific interaction between CD4 T cells and β cells. As well as being able to kill β cells in a CD8 T-cell independent manner, CD4 T cells participate in the activation of CD8 T cells by activating APCs (Ref. 3). APC activation by CD4 T cells involves CD4 ligand interactions, and probably takes place in draining lymph nodes. Activation of β-cell-specific T cells will not be considered in detail in this review. β-cell death

might also play a role in the initiation of β-cell autoimmunity. Although inconclusive, this is suggested by the requirement for CD8 T cells and evidence that the cell death receptor FAS might be necessary for initiation of insulitis[56-58].

Interleukin 1

IL-1 was found to be responsible for the toxic effects of supernatants of activated inflammatory cells. It decreases glucose-stimulated insulin release, which is initially temporary but can become permanent; an effect that is enhanced by other cytokines. Although there is some evidence for DNA strand breaks secondary to cytokine treatment

independent of NO production, β-cell toxicity caused by IL-1 is mediated mainly by induction of iNOS and production of NO beta cells are known to express high levels of IL-1 receptors. Recently, Okamoto and coworkers have shown that the synthesis of iNOS, under the control of the promoter of the gene encoding insulin results in β-cell destruction and the development of diabetes in the absence of insulitis. Administration of the NOS inhibitor aminoguanidine prevented the development of diabetes in these transgenic mice and in NOD mice. However, iNOS-deficient NOD mice develop diabetes normally. Cytokines (particularly TNF) and lipopolysaccharide (LPS) might exert their effects by inducing the production of IL-1 by intra-islet macrophages and, after cytokine treatment, most intra-islet iNOS is found in β cells. Intra-islet IL-1 has been found in the NOD mouse and the biobreeding (BB) rat, and both soluble IL-1 receptor and anti-IL-1 antibodies protect NOD mice from disease. Compared with IFN-g and TNF, the role of IL-1 in causing β-cell destruction in the NOD mouse has been much less directly tested. Essentially no studies have attempted to localize the effect of IL-1 to the β cell and there are no studies published on the effects of genetic manipulation of the gene encoding IL-1. The local concentration and effects of IL-1 in the NOD islet are also uncertain. The production of IL-1- responsive molecules, such as iNOS and FAS, is not easy to detect in b cells isolated from NOD mice in contrast to β cells treated with IL-1, whereas IFN-g responsive genes are easily detected[59-64].

Perforin and Non-perforindependent Mechanisms

Perforin is a key component of cytotoxic T-cell (CTL) granules and is a major effector molecule causing cytotoxicity of virus-infected cells, the classic targets of CTLs. NOD mice made deficient in perforin by gene targeting have insulitis but significantly decreased diabetes, which occurs later than in wild-type (wt) NOD mice. Although this clearly indicates a role for perforin, it is also good evidence for other mechanisms of β-cell destruction. There is a host of candidates to account for non-perforin-dependent β-cell destruction. These include cytokines such as the interferons, interleukin 1 (IL-1), TNF and TNF family members, including FAS ligand (FASL). The receptors for these are expressed on β cells, whereas receptors for other proinflammatory cytokines such as those that signal via GP130, including IL-6, might be missing (H. Thomas and T.W.H. Kay, unpublished). Interferon g (IFN-g), IL-1 and TNF, especially in combination, activate pathways of gene regulation leading to production of nitric oxide (NO) and other free radicals within the β cell. TNF and FASL can also activate caspase cell death pathways in b cells. It is unclear whether this is the case for IFN-g, IL-1 and free radicals, although they can cause DNA damage[65-69].

Interferon *g*

Many direct effects of IFN-g on β cells have been demonstrated, including MHC class I and intercellular cell adhesion molecule 1 (ICAM-1) upregulation, as well as regulation of inducible NO synthase (iNOS) and FAS (Ref. 19) (both of which require a combination of IL-1 and IFN-g). MHC class I regulation has been studied in particular because of evidence that CD8 T-cell interactions with β cells are required for diabetes 2. It has been known for over a decade that combinations of cytokines that include

IFN-g are toxic to β cells as measured by microscopy, glucose-stimulated insulin release or, more recently, by DNA fragmentation. Nevertheless, drawing a parallel with β-cell destruction is not straightforward for many reasons, including the difficulty of accurately gauging the intra-islet concentration of cytokines within the insulitis lesion. Injection of anti-IFN-g monoclonal antibodies decreases diabetes in the NOD mouse, and targeting of the gene encoding IFN-g decreased diabetes in the lymphocytic choriomeningitis virus glycoprotein (LCMV-GP) transgenic mouse model, in which β cells were deliberately made the target of an antiviral immune response. The results of gene targeting of the IFN-g pathway in the NOD mouse are discrepant and still not fully understood. IFN-g deficient NOD mice have a normal incidence of diabetes, although diabetes is somewhat delayed. In contrast, IFN-g receptor-deficient NOD mice have reduced insulitis and do not develop diabetes. This discrepancy has not been explained – it might represent two views of the same 'half-full glass' or it might indicate undiscovered complexities in IFN-g biology. Given that a role for signals from the IFN-g receptor in diabetes pathogenesis is likely, is this related to the well-documented direct effects of IFN-g on β cells or, alternatively, to its action on dendritic cells, macrophages or other cells? To answer this question, we produced transgenic NOD mice that express dominant negative (DN) mutant IFN-g receptors on pancreatic β cells (RIP-DgR mice). β- Cells in these mice are unresponsive to IFN-g, whereas all other cells, including cells of the immune system and other cells within the complex local environment of the islet, respond normally MHC class I expression increased gradually with age in islet cells from wt NOD mice; however, no increase was observed in DgR β cells. The transgenic mice developed diabetes at a similar rate to that of wt mice. This result dissociates MHC class I upregulation from progression to diabetes, shows that the rise in MHC class I molecules is a result of local IFN-g and makes it unlikely that IFN-g promotes autoimmune diabetes by a direct effect on β cells. Lack of IFN-g responsiveness also rendered DgR cells unresponsive to other potentially noxious stimuli. This is because a combination of cytokines including IFN-g is required for many responses, such as FAS cell-surface expression and sensitivity, and iNOS production. Thus, b cells from RIP-DgR mice are protected from many possible mediators of β-cell toxicity and yet are destroyed *in vivo* in NOD mice. Even in the absence of perforin-producing CD8+ T cells, RIP-DgR β cells are destroyed by transfer of activated BDC2.5 β-cell-specific CD4+ T cells. These data lead us to believe that, in addition to perforin and the contents of the cytotoxic granules, other as yet uncharacterized immune effector

mechanisms contribute to β-cell destruction in NOD mice[70-76].

Tumor Necrosis Factor

TNF was regarded as either being protective against diabetes or as having effects too complex to interpret, has recently re-emerged as an important factor in the pathogenesis of diabetes in the NOD mouse. Transgenic NOD mice with β cells expressing the gene encoding TNF-a from birth under the control of the rat insulin promoter (RIP) had increased and accelerated diabetes. This result contrasts with RIP-TNF NOD mice, which express the transgene later in life and are protected from diabetes. Diabetes was not simply a result of TNF-induced β-cell cytotoxicity. TNF most likely increased the ability of APCs to activate beta cell specific T cells. Recently, NOD mice deficient in one form of the TNF receptor, TNFR1, were found to be protected from diabetes. These studies establish that TNF can promote diabetes, but do not provide insight into the mechanism, the source or the target cell of TNF. The importance of the direct β-cell effects of TNF was supported by experiments in which TNFR1-deficient islets were protected from diabetogenic clonal CD4 BDC2.5 T cells when both the islets and the T cells were transplanted into NOD/SCID (severe combined

immunodeficient) mice. These authors did not favor a direct β-cell cytotoxic role for TNF, because when wt and TNFR1-deficient b cells were mixed together they were both killed by

diabetogenic T cells. These data indicate that β cells must be exposed to TNF for β-cell specific CD4 T cells to be reactivated *in vivo* – possibly by TNF inducing antigen release from β cells although this has not been demonstrated. This study indicates that the effects of TNF on β cells themselves are important, and the results are somewhat at variance with the conclusion reached by Green *et al.* that the target of TNF is APCs (Ref. 24). The model of cotransplantationof T cells and genetically modified islets into SCID mice was complex but well validated. This is a useful model, which might not be exactly equivalent to following the evolution of spontaneous diabetes. Furthermore, TNF made by transgenic β cells might be mainly soluble and not equivalent to that made in BDC 2.5 cells, which might be membrane bound[77-80].

Management of T1DM in childhood

The diagnosis of T1DM is a pivotal moment for the child as well as for his/her family.T1DMis a life-long condition with serious short and long-term implications. It is essential that from the moment of diagnosis these families receive expert care from a team of health professionals experienced in childhood diabetes, including a physician, diabetes nurse, dietician and social worker. At onset, children presenting without DKA can be safely managed on an ambulatory basis provided that support services are available and that no other medical or social conditions exist that would place the child in danger. A meta-analysis of home based management at DM onset suggests that, in comparison to routine hospital admission, outpatient care is not associated with worse metabolic control, acute diabetic complications or psychosocial outcomes, or greater costs[81]. Early 'survival skills' to be mastered include insulin injections, blood glucose monitoring, basic nutrition planning, and detection and treatment of hypoglycaemia. In the subsequent weeks, more detailed information is provided about diabetes management (pathophysiology, insulin dose adjustment, effects of exercise, and sick days). Insulin initiation varies greatly among different centres but generally consists of two to four injections per day. The starting total daily dose is 0.4-0.6 units/kg body weight/day, usually lower in younger children, and is adjusted on a daily basis until target blood glucose is achieved. Families of children with T1DM should have a clear understanding of the rationale for blood glucose and HbA1c targets for their child. After initial stabilization and education, children and their families enter the long-term follow-up phase of their diabetes. This includes regular follow-up visits with their diabetes team with surveillance for psychosocial problems, associated conditions (hypothyroidism, coeliac disease), and microvascular and macrovascular complications. Special attention must be paid to those children and their families, most frequently the youngest children and adolescents, who have the greatest difficulty meeting the considerable demands of their diabetes regimen. Soon after initial presentation, most patients enter a transient remission or 'honeymoon' phase when exogenous insulin requirements decrease as a result of residual b-cell secretion. The duration of the honeymoon phase is proportional to the age of the child. Families need to be forewarned of the natural history of T1DM so that they do not develop false hope that their child's diabetes is 'going away'.

Glycaemic and HbA1c targets

The Diabetes Control and Complications Trial (DCCT) demonstrated conclusively that intensive glycaemic control delays and prevents the microvascular and macrovascular complications of T1DM[82,83]. Intensification of therapy is associated with an increased risk of hypoglycaemia that can be a limiting factor in achieving good metabolic control. Severe hypoglycaemia in young children has been associated with mild cognitive deficits later in life,

although the cause-and-effect relationship remains controversial. This demands that age-appropriate targets be set and that progressively tighter control be sought as the child grows older. Summarizes the glycaemic goals published in the 2008 Clinical Practice Guidelines of the Canadian Diabetes Association (CDA). Multiple studies attest to the difficulties in achieving these goals in all children with T1DM[84,85].

Insulin regimens

Approaches to insulin therapeutics vary from one centre to another. Most children and teenagers now start their treatment with a combination of intermediate-acting insulin (NPH) or basal insulin analogue (insulin glargine or insulin detemir), combined with rapid-acting insulin analogues (insulin lispro or insulin as part) given two or more times daily, with insulin doses calculated to match carbohydrate intake and ambient blood sugar. The choice of regimen should be tailored to the child's age, duration of diabetes, daily routines, targets of metabolic control, and individual and family preferences[86]. When rigorously applied, this basal-bolus approach can help to achieve and maintain near-normal glycaemia. for the onset, peak, and duration of action of commonly used insulin preparations. Increasingly, children and teenagers with T1DM are using continuous subcutaneous insulin infusion (CSII) pumps[87] CSII is a more sophisticated form of basal-bolus regimen whereby fast acting insulin analogue is administered by continuous infusion (basal rate) with intermittent boluses given before carbohydrate ingestion or to correct hyperglycaemia. A systematic review and meta-analysis of randomized controlled trials comparing CSII to MDI in children with T1DM found a modest improvement (0.24%) in HbA1c in the CSII group and found no differences in DKA or severe hypoglycaemia between groups. Quality of life and patient satisfaction have been reported to be at least equal or response leading to hyperglycaemia. For children and teenagers involved in exercise activities, more frequent monitoring with either insulin dose adjustment or appropriate food intake are needed to avoid the extreme hypoglycaemia that can occur with activity. Diabetes should not limit the ability of a child to participate in sport. Methods for adjusting insulin and carbohydrate intake to accommodate exercise have been proposed [86-88].

Hypoglycaemia

Hypoglycaemia (blood glucose <3.9 mmol/L or 70 mg/dL) is a common unwanted effect in people treated with insulin and occurs when there is an imbalance in insulin dose, food consumed and activity. Symptoms include autonomic (adrenergic) activation and/or neurological dysfunction (neuroglycopenia)[89] Recognition of symptoms of hypoglycaemia can be difficult in young children with T1DM and therefore increased monitoring of blood Glucose when hypoglycaemia might be expected (overnight, after insulin dose adjustment, strenuous exercise, or illness) is recommended. Families should have injectable glucagon at home to treat severe hypoglycaemia (coma, seizure, or severe confusion). Hypoglycaemia has been associated with reduced cognitive functioning and can, rarely, be a cause of death in young people with T1DM. Co-morbidities such as coeliac disease and Addison's disease can increase the risk of hypoglycaemia [90].

Blood glucose monitoring [81-83]

Children and adolescents with T1DM are encouraged to monitor blood glucose at least four times per day (before each meal and at bedtime). Maintenance of a blood glucose logbook is essential to follow patterns and to make appropriate dose adjustments. Continuous glucose monitoring technologies have been developed and are increasingly being used in clinical care as an adjunct to intermittent monitoring[81]. HbA1c is a measure of glycaemic control over the previous 4e12 weeks, weighted more heavily toward the most recent 4 weeks. Lower HbA1c values have been associated with fewer and delayed microvascular and macrovascular complications[82,83]. The goal of diabetes

management should be to maintain the lowest possibleHbA1c without severe or prolonged hypoglycaemia or hyperglycaemia.

Management of type 2 diabetes mellitus in the elderly

Type 2 diabetes mellitus (DM) is an epidemic that continues to increase rapidly, affecting millions of people worldwide [91-93]. More than 10% of Americans ≥20 years old and 23% of Americans ≥60 years old have DM. Among adults 60–74 years of age, 11% have undiagnosed DM. Age is an important contributor to DM, as well as obesity and sedentary lifestyle. Nearly half of people with DM are ≥65 years old[94-95]. DM related morbidity and mortality, and comorbidities such as chronic kidney disease (CKD), congestive heart failure (CHF), cognitive impairments, depression, physical disability and frailty [96-98]

Treatment options for elderly diabetics

(a) Lifestyle interventions
(b) Oral hypoglycemic agents
(c) Incretins
(d) New oral agents
(e) Insulin

Lifestyle interventions:

Obesity is a common and growing problem in the elderly and is strongly associated with metabolic syndrome, DM, hypertension, hyperlipidemia and cognitive dysfunction[99-103]. Decreased physical activity and energy expenditure with aging predispose to fat accumulation, fat redistribution, and muscle loss which cause insulin resistance. In the elderly BMI may not increase with adiposity which makes this data more difficult to interpret[103]. Meta-analyses of exercise and diet studies have concluded that HbA1c can be lowered by aerobic and resistance exercise and by dietary intervention, by 0.6–0.8% and 0.5%, respectively [104]. Current guidelines recommend that patients with DM should perform at least 150 min per week of moderate-intensity aerobic exercise and should perform resistance exercise 3 times per week [105]. Therefore, the focus of treatment of DM should be on reduction of intra-abdominal fat with modest and balanced diet restriction and preservation of muscle mass and strength through physical activity prescribed according to elderly patient's health status and abilities [106].

Oral hypoglycemic agents

Metformin (biguanide): Metformin is the only biguanide available. It is currently the recommended first line treatment and the most widely used insulin sensitizer in the elderly because of effectiveness in lowering blood glucose, a low risk of hypoglycemia and relatively low adverse effect profile. It can be used as monotherapy or in combination with other oral hypoglycemic agents such as sulfonylurea, GLP-1 receptor agonists, DPP-4 inhibitors or with insulin. Together with diet, metformin can reduce fasting glucose by 50–70 mg/dL and the HbA1c from 1.3 to 2.0%. It lowers blood glucose levels by sensitizing the liver to the effects of insulin[107].

Sulfonylureas: Sulfonylureas stimulate insulin release by binding to a specific site on the sulfonylurea receptor on _ cells (KATP channel complex) and inhibiting its activity which causes cell membrane depolarization and the cascade of events leading to insulin secretion. It remains an effective mean of achieving blood glucose control after failure of diet alone in older patients. Hypoglycemia is the major concern with sulfonylureas especially with long acting ones in elderly patients with reduced renal function and liver dysfunction and in patients with poor nutritional status and alcohol abuse. Weight gain (up to 1–3 kg) and overeating to counteract or prevent hypoglycemia are major limitations to achieving optimal glycemic control [108].

Meglitinides – (repaglinide and nateglinide): Meglitinides are insulin secretagogues with rapid onset and relatively short duration of action that control postprandial hyperglycemia.

Hypoglycemia risk is less than with sulfonylureas, which makes this class of medication a more suitable alternative in elderly patients with CKD or those that

are intolerant to metformin or sulfonylureas. Nateglinide is mainly metabolized by the liver and excreted by the kidneys unchanged. Therefore, it does not require dose adjustment in renal failure. Repaglinide is metabolized primarily (90%) by the liver and the remaining 10% is metabolized by the kidneys, requiring dosage adjustment in renal failure. Repaglinide should be used cautiously in patients with hepatic insufficiency and CKD. However, several studies reported the safety and efficacy of repaglinide with a lower risk of hypoglycemia in elderly patients with DM .The need for multiple daily doses may reduce compliance with this medication class [109-110].

Thiazolidinediones (rosiglitazone and pioglitazone): Thiazolidinediones (TZDs) are insulin sensitizers that reduce insulin resistance in peripheral tissue especially in muscle and also decrease hepatic gluconeogenesis by activating the peroxisome proliferator-activated receptor gamma[111].

α-Glucosidase inhibitors: Acarbose, miglitol, voglibose (only in Europe) are the available glucosidase inhibitors. They are extensively studied and widely used in Europe and Japan. They slow the rate of carbohydrate absorption by inhibiting the upper gastrointestinal enzymes (α-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides in a dose-dependent fashion. In addition, they stimulate secretion of glucagon like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[112,113]. They are much more effective in lowering blood sugar in patients on high starch diets. They show modest HbA1c reduction (0.5–0.8%) and can be used in combination therapy. They can be quite useful in the elderly because of absent hypoglycemia risk and their effect on postprandial hyperglycemia. In addition, α-glucosidase inhibitors can increase insulin sensitivity in elderly diabetics [114].

Incretins

Incretins, GLP-1 and GIP, are short-lived gut hormones. They enhance the synthesis and release of insulin from pancreatic β- cells and decrease glucagon release from pancreatic-β -cells. These incretin hormones are released in response to oral glucose and other nutrients and increase insulin secretion, attenuate postprandial glucagon secretion and hepatic gluconeogenesis with resulting improvement in postprandial glycemia. Both GIP and GLP-1 are rapidly metabolized by the enzyme dipeptidyl peptidase-4 (DDP-4) resulting in short plasma half-lives[115,116]. Incretin based therapy is a good choice for elderly diabetics because of its low risk of hypoglycemia, a fairly benign side effect profile, and its glucose dependent mechanism of action which limits hypoglycaemia[117].

New oral agents:

Bile acid sequestrates: Colesevelam is a bile acid binding resin approved for treatment of hypercholesterolemia. It can also lower blood glucose and can be used in DM treatment. It lowers HbA1c 0.5% when added to metformin, sulfonylurea or insulin. The major side effect of colesevelam is constipation; thus, it should be avoided in patients with gastroparesis or other gastrointestinal motility disorders, in patients after major gastrointestinal surgical procedures, and in others at risk for bowel obstruction. Other adverse effects include: elevated serum triglycerides and possible malabsorption of fat-soluble vitamins. There are no data in the elderly[118].

Bromocriptine: Bromocriptine (Cycloset), a sympatholytic dopamine D2 receptor-agonist, was FDA-approved for DM treatment. The dose range is 1.6–4.8 mg, taken with food in the morning within two hours of awakening. It is used as mono therapy or in combination therapy with insulin and oral agents and has a favourable safety profile and tolerability. Its effect on blood glucose may be due to action in the central nervous system. The mechanism of action of bromocriptine in diabetes has not been clearly elucidated. Side effects include nausea, fatigue, dizziness, orthostatic hypotension,

vomiting, and headache. Its efficacy in glycemic control is modest (HbA1c reduction of 0.1–0.4%). There are no data in the elderly[119].

Insulin

Insulin is the most effective antidiabetic medication when dosed appropriately. The progressive decline of β-cell function with advancing age means that the majority of elderly diabetics will require insulin eventually[120]. However, insulin has been underutilized in elderly diabetics due to concern about hypoglycemia and complexity of administration. Nevertheless, insulin should not be perceived as the last resort in the elderly. At the same time, laboratory values e.g. blood glucose and HbA1c, should not be the only guides to starting insulin. Before initiating insulin, assessment of psychosocial condition, functional, and cognitive status of patients is essential for the safe and effective use of insulin[121]. Major limitations include inability to self-administer due to poor vision, impaired manual dexterity, poor functioning or impaired cognition and potential for hypoglycaemia [122].

Management of Gestational diabetes mellitus:

Management of Gestational Diabetes mellitus is done by the following:

(a) Glucose monitoring

(b) Medical nutrition therapy (MNT) and exercise

(c) Insulin therapy

(d) Oral medication

(e) Obstetrical management

Glucose monitoring:

Self-monitoring of blood glucose is the cornerstone for achieving the set targets of plasma glucose in order to reduce perinatal mortality. Recommendations from Fourth International Workshop Conference on GDM suggest lowering the capillary whole blood glucose concentration to: preprandial < or = 95 mg/dl and either 1 h postprandial < or = 140 mg/dl or 2 h values < or = 120 mg/dl. Comparable plasma reference capillary blood glucose threshold as suggested by ADA position statement on GDM are preprandial < or = 105 mg/dl and either 1 h < or = 155 mg/dl or 2 h value < or = 130 mg/dl. There is however increased risk of IUGR if the overzealous lowering of blood glucose is achieved. A mean glucose level of <87 mg/dl has been shown to be associated with higher incidence of IUGR[123,124].

Medical nutrition therapy (MNT) and exercise:

Diet is the cornerstone of the management of hyperglycemia in GDM irrespective of the pharmacological therapy. The targets to be achieved by MNT are to provide sufficient nutrition to the mother and foetus, provide adequate calories for maternal weight gain, to achieve normoglycemic state and lastly to prevent ketosis. Addition of 300 kcal/day is usually required in 2nd and 3rd trimester in normal weight women[125]. MNT for GDM centers on a carbohydrate-controlled meal plan. The amount and distribution of carbohydrate should be individualized according to the clinical setting like hunger, glycemic control, weight gain and ketosis. A minimum of 175 g carbohydrate per day should be provided, which should be distributed into 3 small to moderate meal and 2 - 4 snacks. The calculated daily calorie intake is based on prepregnant body weight. For body mass index (kg/m2) 20—25, >25—34 and >34, the respective calorie intake are 30, 25 and 20 kcal/kg[126,127].

Insulin therapy:

Insulin therapy is the most validated treatment option when MNT fails to achieve the target glycemic control. How long a trail of MNT is to be given before resorting to insulin is not known. When diagnosed late in pregnancy, with shortage of time period available for achieving targeted glycemic values, insulin therapy needs immediate introduction. Lacking a general consensus for the initiation of insulin, some discrepancies are encountered at the threshold of fasting plasma glucose. Either > 95 or > 105 mg/dl have been proposed by different authors [123,126-128]. Most authorities consider 1 h postprandial

>140 mg/dl and/or 2 h >120 mg/ dl to initiate insulin therapy. The prepregnant BMI and present pregnant weight determines the total dose of insulin required at initiation. For non-obese patient 0.8 µ /kg and for overweight and obese 0.9 µ /kg is the starting dose. 2/3rd of the total in ratio of 2:1 (basal:regular) is administered in morning and 1/3rd in the ratio of 1:1 (regular:basal) given at dinner and bedtime, respectively. The total dose needs to be increased by 10—20% every 3—7 days. Intensively treated (multiple insulin injection and/ or 7 times SHBG) women has better pregnancy outcome as compared to those with conventional therapy [129].Human insulin is currently recommended by ADA[130].

Oral medication

Oral medications for glycemic control during GDM appears a novel step because they are easy to administer, are non-invasive, cheaper and have better patient acceptability. Before a new drug is given clearance for its use in pregnancy, its fetal and maternal safety is to be made sure. For it being safe for fetus, the drug should not cross placenta and even if it does so, it must not have any teratogenic effect on fetus in utero. Two drugs, which are currently center of attraction, are glyburide (2nd generation sulfonylurea) and metformin. It was way back in 2000 when the original study on glyburide opened a new chapter in the management of diabetes in pregnancy [131]. Many experts and organization (5th International Workshop On Gestational Diabetes And North America Diabetes In Pregnancy Study Group) have shown faith in the use of glyburide as an alternative to insulin during pregnancy [132-137]. Glyburide does not cross placenta even when concentration have reached 3—4 times the therapeutic levels [138-140].

Obstetrical management:

Fetal monitoring: Fetal surveillance has dual purpose to play. Firstly, it can be marker of adequate maternal glycemic control. USG performed in late 2nd or early period of 3rd trimester and repeating every 2—4 weeks, to measure abdominal circumference may serve as additional guide to SHBG for maternal glycemic status. Treatment plan can be intensified if evidence of abdominal circumference exceeding the accepted values for that gestational age. Secondly, fetal congenital malformation can be detected with sonography in women with fasting plasma glucose >120 mg/dl or Aic% >7%.

Timing and mode of delivery: Pregnancy should continue till 40 weeks as in nondiabetic pregnant women in setting of adequate glycemic control and no other known complication. Contrary to the general thinking, GDM by itself is not an indication for cesarean section. Even then increased incidence of cesarean section in pregnancy complicated by GDM is observed compared to women without diabetes. This is solely due to overestimation of obstetrical complication. ACOG suggests consideration of caesarean section without labour when the fetal weight exceeds 4.5 kg. With weight between 4 and 4.5 kg, associated adverse parameters should be taken into account [141].

EFFECTS OF DIABETES

Gastrointestinal symptoms in diabetes mellitus, and their relation to anxiety and depression

Gastrointestinal complaints are commonly reported by diabetic patients. Previous studies indicate that about 70–75% of diabetic patients have a least one gastrointestinal symptom [142-144]. The gastrointestinal disturbances in diabetes may result from various factors such as autonomic neuropathy, microand macroangiopathy, altered visceral motor or sensory function but also from psychiatric comorbidity [143,145]. Glucose control and gastrointestinal symptoms are closely linked. On the one hand hyperglycemia is known to impair gastric and small intestinal motility, possibly through vagal-cholinergic neural inhibition or by altering serum osmolality and gastrointestinal peptide secretion [146].

On the other hand, gastrointestinal motility disorders such as diabetic gastroparesis may give rise to postprandial glycemic dysregulation. Thus, gastrointestinal disorders resulting from diabetes may negatively influence diabetic control, diabetic complications, and eventually also survival [147]. Gastrointestinal symptoms also negatively affect health related quality of life in diabetes, especially in type 2 diabetes [148].

EFFECT OF DIABETES ON LOWER URINARY TRACT

Long-standing diabetes can cause bladder dysfunction, which involves autonomic neuropathy leading to functional parasympathetic and possibly sympathetic denervation of the detrusor[151,152]. Impaired detrusor function results in a lower maximum flow rate for any given level of bladder outlet resistance and can increase post-void residual. Benign prostatic hyperplasia (BPH) can also cause lower urinary tract symptoms, including a reduced maximum flow rate and increased post-void residual. However, the underlying pathophysiology is different since BPH does not primarily impair detrusor function but rather enhances bladder outlet resistance via static and dynamic components.[153] If diabetes and BPH are associated it cannot be assumed that α1 adrenoceptor antagonists are similarly efficacious in diabetic and in nondiabetic patients with BPH since the 2 disease states affect lower urinary tract function by different mechanisms. However, the efficacy in diabetic patients with BPH has not been investigated for any α1-adrenoceptor antagonist to the best of our knowledge. Therefore, we also determine whether the α1-adrenoceptor antagonist tamsulosin is similarly effective in reducing lower urinary tract symptoms of patients with BPH with or without diabetes.

Oral dryness and peripheral neuropathy

Human saliva is the principal defense factor of the mouth and is important for maintaining good oral health. It provides lubrication during mastication and swallowing of food and facilitates clear speech as well as normal perception of taste. Saliva also plays a significant preventive role for the oral mucous membranes and for neutralizing acids to protect the oral hard tissue. Both immune and non-immune mechanisms are involved in these processes and many factors can influence salivary flow rate. Reduced salivary flow and altered composition of saliva may increase the susceptibility of such oral manifestations as caries, periodontal disease, and oral mucous lesions. Furthermore, oral dryness is often a painful condition and has also shown to have a negative effect on individual's emotional well-being and quality of life .More than 90% of the saliva is produced by three pairs of major salivary glands: parotid (serous glands that secrete a very watery fluid), submandibular, and sublingual (mixed serous and mucin-secreting glands producing mostly mucous, protein-rich saliva). The secretion of saliva is under the control of the autonomic nervous system. Depending on which division of the autonomic nervous system is activated, the amount and composition of saliva can vary. The sympathetic system is coupled to protein secretion and produces a slight quantity of low-viscous saliva, and the parasympathetic system coupled to fluid secretion produces large volumes of watery, protein-poor saliva. Diabetes mellitus has been reported to directly affect the structure and function of saliva glands.

Psychosocial problems

An important part of treatment is self-care, which is the patient's own responsibility. The management of diabetes self-care is regarded as highly affected by a person's psychological and social situation. Psychosocial stress, anxiety, and depression have a negative impact on the disease itself [154-156], its outcome[157,158] and its management[159] . Coping is a behavior often discussed in connection with the management of diabetes self-care. There are several different coping strategies, all with the purpose of

managing a stressful situation and avoiding the anxiety it causes[160] Problem oriented coping strategies are found to be positively related to successful management of diabetes self-care[161] Coping is also regarded as associated with metabolic control. Researchers have found a connection between negative coping strategies such as resignation, protest, and intrusion (of the disease into life) and higher HbA1c-values[162]. Studies show that psychological and psychosocial interventions and enhanced support have positive effects on diabetes self management and psychological well-being in patients with type 1 and 2 diabetes[163-165] . However, it may be even more important to identify patients with psychosocial problems that may affect their management of self-care early in the course of the disease. This early identification would enable the provision of psychosocial interventions and support that could help prevent unnecessary negative physical and social consequences of the disease.

Fatigue in patients with diabetes

Among people with diabetes, fatigue is a pervasive and distressing complaint. Although fatigue also occurs in other medical disorders, the importance of fatigue may be greater in individuals with diabetes. Clinicians who work with patients affected by diabetes have noted anecdotally the considerable toll that fatigue takes on their patients, yet there is little empirical research describing the severity of the problem. Fatigue in diabetes may be associated with physiological phenomena, such as hypo- or hyperglycemia or wide swings between the two. Fatigue may also be related to psychological factors such as depression or emotional distress related to the diagnosis or to the intensity of diabetes self-management regimens. Fatigue may also be related to such lifestyle issues as lack of physical activity or being overweight—especially common in people with type 2 diabetes. Research is needed to clarify these relationships in order to help people with diabetes manage this symptom[166]. The variables related to fatigue depicts in figure 1.

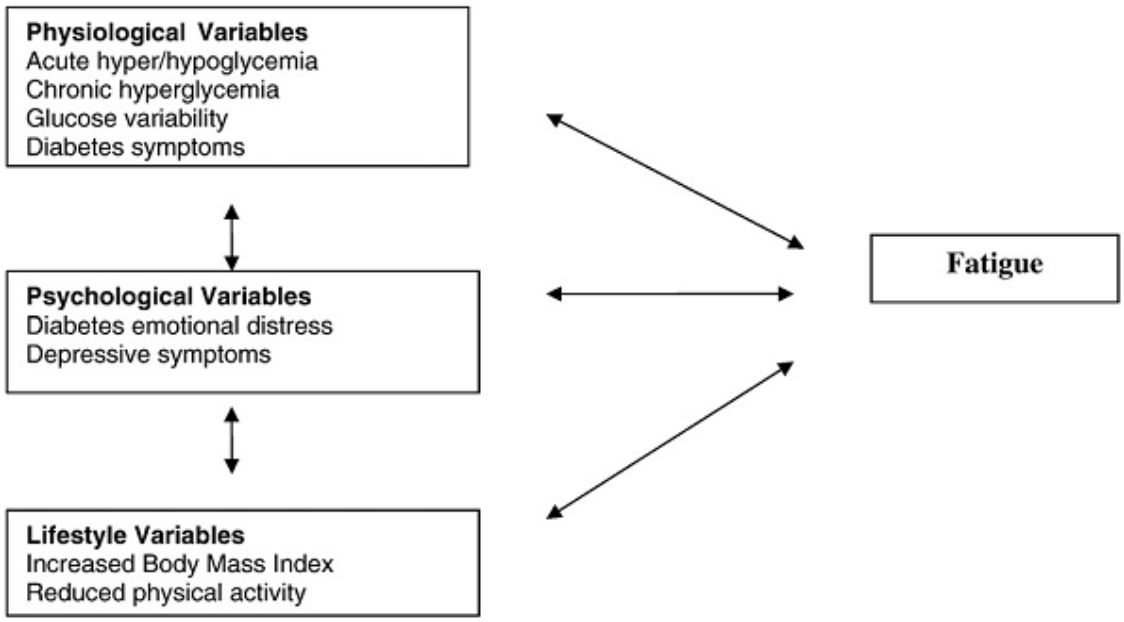

Figure 1: Variables in diabetes

Sexual Function/Infertility

Sexual dysfunction consists of many domains which can be affected by diabetes through a variety of pathways. Its domains include sexual drive, erectile function, ejaculatory function, sexual problem assessment and sexual satisfaction. Risk factors for sexual dysfunction are similar to those of cardiovascular disease and diabetes including

hypertension, dyslipidemia, depression and lower urinary tract symptoms.[167] While the etiology of diabetic sexual dysfunction remains under investigation, neurological, vascular, hormonal, muscular and psychogenic mechanisms have been suggested as likely mechanisms.[168,169] Atrophy or apoptosis of cavernous smooth muscle can occur due to loss of Bcl-2 expression in cavernous smooth muscle.[170] Neuropathic damage to the somatic and autonomic nerves has been seen in patients with diabetes. Recent studies have demonstrated a vascular etiology for sexual dysfunction.[171] Diabetes related hypogonadism also has been associated with erectile dysfunction.[172] Diabetic patients are subject to reduction in sexual desire and various degrees of erectile dysfunction, both of which may be attributed to the lethargy, fatigue and malaise associated with hyperglycemia.[173]

CONCLUSION: It has been concluded through this review that diabetes is increasing day by day. It is a slow killer which has no known curable treatment till now. Its complications can only be reduced through proper awareness and proper medications. The main complications related to the diabetes are; blindness, kidney problems and heart attack. It is important to control blood glucose level of the patient by continuous monitoring to avoid the complications. The main aim of this review is to spread the detail knowledge of mechanism, pathophysiology and management of diabetes to control this killer disease. Further studies are needed to save world population from this epidemic disease.

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