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Diabetes Mellitus - Types and Complications – A review

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Abstract

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia due to defects in either insulin secretion or resistance or both.The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. The incidence of diabetes increases with age. Although it is seen in all age groups mostly in age greater than 50years, Asians are more prone to diabetes due lack of healthy life style changes. The pathological changes in diabetes is due beta cell dysfunction resulting in absolute lack of insulin leading chronic hyperglycemia. Monitoring of blood glucose levels by fasting, post lunch can help in providing right intervention. It is important to maintain tight glycemic control to prevent disease process and minimize the complications associated with diabetes. However diabetes not only decreases quality of life but also leading to psychological distress.

Key words: Diabetes Mellitus, Insulin resistance, Advance Glycation End products, Diabetic Retinopathy.

Introduction:

Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. The origin and etiology of DM can vary greatly that include defects in either insulin secretion or resistance or both at some point in the course of disease. Mostly patients with diabetes mellitus have either type I DM (which is immune-mediated or IDDM) or type II DM (NIDDM). Type II DM is the most common form characterized by hyperglycemia, insulin resistance and relative insulin deficiency [1]. The global prevalence of diabetes is estimated at 415 million in 2019. Moreover, worldwide approximately 193 million diabetes remain undiagnosed predisposing them to the development of several long-term complications of untreated chronic hyperglycemia. The major pathologic hallmark of DM involves the vasculature leading to both microvascular and macrovascular complications. Abnormal glycemic index which is leading to hyperglycemia is associated with long-term damage and failure of various organ systems mainly affecting the eyes, nerves, kidneys, and heart [2]. The clinical diagnosis of diabetes is reliant on either one of the four plasma glucose (PG) criteria: elevated Fasting Plasma Glucose (FPG) (>126 mg/dL), 2 h Post Lunch Blood Sugar

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(PLBS) during a 75-g Oral Glucose Tolerance Test (OGTT) (>200 mg/dL), Random Blood Glucose (>200 mg/dL) with classic signs and symptoms of polyuria, polydipsia, polyphagia or hemoglobin A_1C level >6.5 %. It is important to obtain optimal glycemic control through dietary and lifestyle modifications and appropriate medications along with regular blood glucose level monitoring can prevent mortality and morbidity associated with DM and its complications and also improve the quality of life [3]

Epidemology:

Worldwide prevalence of diabetes has continued to increase dramatically. Globally, as of 2019, an estimated 415 million people had DM, with type II making up about 90% of the cases. The incidence increases with age, with peak incidence at puberty. After the pubertal years, the incidence rate significantly drops in young women, but remains relatively high in young adult males up to the age 29-35 years [1]

Etiology Classification:

I. Type I diabetes (cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated

B. Idiopathic

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

III. Other specific types

A. Genetic defects of Beta-cell function: Genetic defects of some genes includeChromosome 12, HNF-1

(MODY3), Chromosome 7, Glucokinase (MODY2),Chromosome 20, HNF-4_ (MODY1), Chromosome

13, insulin promoter factor-1 (IPF-1;MODY4), Chromosome 17, HNF-1_ (MODY5), Chromosome 2,

Neuro*D1* (MODY6),Mitochondrial DNA

B. Genetic defects in insulin action: Genetic defects such as,Type A insulin resistance, Leprechaunism,

Rabson-Mendenhall syndrome, Lipoatrophic diabetes

C. Diseases of the exocrine pancreas: Diseases that include Pancreatitis,Trauma/pancreatectomy, Neoplasia,

Cystic fibrosis, HemochromatosisFibrocalculousPancreatopathy

D. Endocrinopathies: Some of these include, Acromegaly, Cushing's syndrome, Glucagonoma,

Pheochromocytoma, Hyperthyroidism**,** Somatostatinoma, Aldosteronoma.

E. Drug or chemical induced: Some common that induce are, Vacor, Pentamidine, Nicotinic acid,

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Glucocorticoids, Thyroid hormone, Diazoxide, Beta adrenergic agonists, Thiazides, Dilant, Interferons.

F. Infections:some common infections that include, Congenital rubella, Cytomegalovirus

G. Uncommon forms of immune-mediated diabetes: Some common forms of immune system include, "Stiff

man" syndrome, Anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes: Certain genetic syndromes like Down

syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington

chorea, Laurence-Moon-Biedl syndrome, Myotonic dystrophy, Porphyria, Prader-Willi syndrome.

IV. Gestational diabetes mellitus [4]

Medications associated with development of diabetes and their mechanisms:Some the below mentioned medications have tendencies of developing diabetes.

Pathogenesis:

Depending upon etiology of DM, hyperglycemia may result from the following:
1. Reduced insulin secretion
2. Decreased glucose use by the body
3. Increased glucose production [6]

Type I Diabetes Mellitus: Type I diabetes is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous beta cell antigens. Type I diabetes most commonly develops in childhood,becomes manifest at puberty, and progresses with age.Most patients with type 1 diabetes depend on exogenousinsulin for survival, without insulin they develop serious metaboliccomplications such as ketoacidosis and coma. Although the clinical onset of type 1 diabetes is abrupt, this disease in fact results from a chronic autoimmune attack on beta cells that usually starts many years before the disease becomes evident. The classic manifestations of the disease (hyperglycemia and ketosis) occur late in its course, after more than 90 % of the beta cells have been destroyed. The fundamental immune abnormality intype I diabetes is a failure of self-tolerance in T cells. This failure of tolerance may be a result of some combination of defective clonal deletion of self-reactive T cells in the thymus, as well as defects in the functions of regulatory T cells or resistance of effector T cells to suppression by regulatory cells [7]

Several features characterize type I diabetes mellitus as an autoimmune disease:
1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets
2. Immunocompetent with class II MHC molecule
3. Presence of islet cell specific autoantibodies

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4. Alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment
5. The involvement of monokines and TH1 cells producing interleukins in the disease process
6. Response to immunotherapy
7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their family members [1].

Type 2 Diabetes mellitus: Type 2 DM is characterized by impaired insulin secretion and resistance to insulin action. In the presence of insulin resistance, glucose utilization by tissues is impaired, hepatic glucose production is increased and excess glucose accumulates in the circulation. This hyperglycemia stimulates the pancreas to produce more insulin in an attempt to overcome insulin resistance. The simultaneous elevation of both glucose and insulin levels is strongly suggestive of insulin resistance [8]

The following metabolic defects are crucial to the development of type II diabetes:
1. Inability of islet β -cells to compensate for the fuel surfeit
2. Increased glucagon secretion
3. Reduced incretin response
4. Impaired expansion of Subcutaneous Adipose Tissue (SAT), Hypoadiponectinaemia
5. Inflammation of adipose tissue
6. Increased endogenous glucose production
7. Development of peripheral insulin resistance [9]

Obesity and Insulin Resistance: The association of obesity with type II diabetes has been recognized for decades, with visceral obesity being common in a majority of affected patients. In fact, the term metabolic syndrome has been applied to a constellation of findings dominated by visceral obesity, which is accompanied by insulin resistance, glucose intolerance, and cardiovascular risk factors such as hypertension and abnormal lipid profiles. In the absence of weight loss and lifestyle modifications, persons with metabolic syndrome are at significant risk for the development of type II diabetes, underscoring the importance of obesity to the pathogenesis of this disease. The risk of diabetes increases as the body mass index (a measure of body fat content) increases, suggesting a dose-response relationship between body fat and insulin resistance.

Some possible mechanisms include:

1. Role of excess free fatty acids (FFAs): Cross-sectional studies have demonstrated an inverse correlation between fasting plasma FFAs and insulin sensitivity. The level of intracellular triglycerides often is markedly increased in muscle and liver tissues in obese persons, presumably because excess circulating FFAs are deposited in these organs. Intracellular triglycerides and products of fatty acid metabolism are potent inhibitors of insulin signaling and result in an acquired insulin resistance state. These lipotoxiceffects of FFAs are mediated through a decrease in activity of key insulin-signaling proteins.

2. Role of inflammation**:** Over the past several years, inflammation has emerged as a major player in the pathogenesis of type 2 diabetes. It is now known that a permissive inflammatory milieu (mediated not by an autoimmune process as in type I diabetes but rather by proinflammatory cytokines that are secreted in response to excess nutrients such as FFAs) results in both peripheral insulin resistance

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and beta cell dysfunction. Excess FFAs within macrophages and beta cells can engage the inflammasome, a multiprotein cytoplasmic complex that leads to secretion of the cytokine interleukin IL-1β. IL-1β, in turn, mediates thesecretion of additional pro-inflammatory cytokines from macrophages, islets, and other cells that are released into the circulation and act on the major sites of insulin action to promote insulin resistance. Thus, excess FFAs can impede insulin signaling directly within peripheral tissues, as well as indirectly through the release of proinflammatory cytokines. Not surprisingly, there are now several ongoing trials of cytokine antagonists (particularly of IL-1β) in patients with type 2 diabetes.

3. Role of adipokines:Adipose tissue is not merely a passive storage depot for fat; it can operate as a functional endocrine organ, releasing so-called adipokinesin response to extracellular stimuli or changes in metabolic status. Thus, adipocytes also release IL-1β and other proinflammatory cytokines into the circulation in response to excess FFAs, which promote peripheral insulin resistance. By contrast, adiponectinis an adipokine with insulin sensitizing activity, which probably acts by dampening the inflammatory response.

4. Peroxisome proliferator-activated receptor-γ **(PPARγ):**PPARγis a nuclear receptor and transcription factor expressed in adipose tissue and plays a seminal role in adipocyte differentiation. Activation of PPARγpromotes secretion of antihyperglycemicadipokines such as adiponectin, and shifts the deposition of FFAs toward adipose tissue and away from liver and skeletal muscle. [7]

Complications: [1]

Acute complications

1. Hypoglycemia

2. Hyperglycemic crisis **(**Diabetes Ketoacidosis (DKA)**,** Hyperglycemic hyperosmolar state(HHS))

Chronic complications:

1. Micro vascular complications
    a) Diabetic retinopathy
    b) Diabetic nephropathy
    c) Diabetic neuropathy
2. Macrovascular disease
    a) Atherosclerosis
    b) Stroke
    c) Ischemic heart disease
    d) Peripheral vascular disease (PVD)
3. Other complications and associated conditions
    a) Impaired growth and development
    b) Associated autoimmune conditions
    c) Hypothyroidism
    d) Hyperthyroidism
    e) Celiac disease
    f) Vitiligo
    g) Primary adrenal insufficiency (Addison's disease)
    h) Lipodystrophy (lipoatrophy and lipohypertrophy)

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i) Necrobiosis lipoidicadiabeticorum
j) Non-alcoholic fatty liver disease
k) Infections seen in patients with diabetes
l) Limited joint mobility
m) Edema

Diabetes can be a devastating disease because the abnormal glucose metabolism and other metabolic derangements have serious pathologic effects on virtually all the systems of the body. The pathogenesis of the long-term complications of diabetes is multifactorial, although persistent hyperglycemia (glucotoxicity) seems to be a key mediator.

At least three distinct metabolic pathways seem to be involved in the pathogenesis of long term complications; it is likely that all of them play a role in a tissue-specific manner.

1. Formation of Advanced Glycation End products (AGEs):

AGEs are formed as a result of nonenzymatic reactions between intracellular glucose-derived precursors (glyoxal, methylglyoxal, and 3-deoxyglucosone) with the amino groups of both intracellular and extracellular proteins. The natural rate of AGE formation is greatly accelerated in the presence of hyperglycemia. AGEs bind to a specific receptor (RAGE), which is expressed on inflammatory cells (macrophages and T cells) and in endothelium and vascular smooth muscle.

The detrimental effects of the AGE-RAGE signaling axis within the vascular compartment include

1. Release of pro-inflammatory cytokines and growth factors from intimal macrophages
2. Generation of reactive oxygen species in endothelial cells
3. Increased procoagulant activity on endothelial cells and macrophages
4. Enhanced proliferation of vascular smooth muscle cells and synthesis of extracellular matrix

In addition to receptor-mediated effects, AGEs can directly cross-link extracellular matrix proteins, whichdecreases protein removal while enhancing proteindeposition. AGEs cross-linked proteins can trap otherplasma or interstitial proteins; for example, low-densitylipoprotein (LDL) gets trapped within AGE-modifiedlarge vessel walls, accelerating atherosclerosis, while albumin can get trapped withincapillaries, accounting in part for the basement membranethickening that is characteristic of diabetic microangiopathy [7]

2. Activation of protein kinase C: Activation of intracellular Protein Kinase C (PKC) by calcium ions and the second messenger DiAcylGlycerol (DAG) is an important signal transduction pathway in many cellular systems. Intracellular hyperglycemia can stimulate the de novo synthesis of DAG from glycolytic intermediates and hence cause activation of PKC. The downstream effects of PKC activation are numerous and include production of proangiogenicmolecules such as Vascular Endothelial Growth Factor (VEGF), implicated in the neovascularization seen in diabetic retinopathy, and profibrogenic molecules such as transforming growth factor-β, leading to increased deposition of extracellular matrix and basement membrane material [7]

3. Disturbances in polyol pathways: In some tissues that do not require insulin for glucose transport (e.g., nerves, lens, kidneys, blood vessels), hyperglycemia leads to an increase in intracellular

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glucose that is then metabolized by the enzyme aldose reductase to sorbitol, a polyol, and eventually to fructose, in a reaction that uses NADPH (the reduced form of nicotinamide dinucleotide phosphate) as a cofactor. NADPH is also required by the enzyme glutathione reductase in a reaction that regenerates reduced glutathione (GSH), GSH is one of the important antioxidant mechanisms in the cell, and any reduction in GSH increases cellular susceptibility to oxidative stress. In neurons, persistent hyperglycemia appears to be the major underlying cause of diabetic neuropathy (glucoseneurotoxicity) [7]

Microvascular complications:

The underlying driver of microvascular disease is tissue exposure to chronic hyperglycemia. Microvascular disease tends to occur predominantly in tissues where glucose uptake is independent of insulin activity (eg, kidney, retina and vascular endothelium) because these tissues are exposed to glucose levels that correlate very closely with blood glucose levels [14]

Mainly there are three different microvascular complications in chronic hyperglycemia.

1. Diabetic retinopathy
2. Diabetic nephropathy
3. Diabetic neuropathy

1. Diabetic retinopathy (DR):

The ocular involvement may take the form of retinopathy, cataract formation, or glaucoma [7]. It occurs due to hyperglycemia-mediated damage within the retinal microvasculature, lead to basement membrane thickening, increased capillary permeability formation of micro-aneurysms, and further lead to intravascular coagulation, resulting in retinal ischemia which drives the formation of new vessels within the retina (neovascularisation). These new vessels are fragile and may rupture causing retinal bleeds. Furthermore, the lack of lymphatic drainage within the retina causes fluid accumulation in the presence of hyperglycemia resulting in macular edema [14]

Classification of DR:

Diabetic retinopathy is broadly classified according to disease progression. The initial stage, non-proliferativeDR (NPDR; previously termed "background" retinopathy), can be further categorized as mild, moderate, or severe. Proliferative DR (PDR) represents the advanced stage of the disease.

Management of DR:

Goals of Therapy: The ultimate therapeutic objective in DR management is to prevent, slow, or reverse vision loss in order to maintain or improve vision-related quality of life (QOL).

A combination of surgical and pharmacologic therapies may be necessary to achieve treatment goals.

1. Surgical management
2. Pharmacologic management

1. Surgical management:

A. Focal Laser Photocoagulation (FLP)

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B.Panretinal (Scatter) Laser Photocoagulation (PLP)
C. Vitrectomy

2. Pharmacological management:

Although effective in arresting the progression of DR, surgical photocoagulation procedures destroy retinal tissue and do not improve vision. Therefore, the development of noninvasive treatment strategies is warranted.

Diabetic nephropathy: Renal failure is second only to myocardial infarction as a cause of death.Three lesions are encountered: (1) glomerular lesions; (2) renal vascular lesions, principally arteriolosclerosis; and (3) pyelonephritis, including necrotizing papillitis. The most important glomerular lesions are capillary basement membrane thickening, diffuse mesangial sclerosis, and nodular glomerulosclerosis [7]. In figure (9) representing the normal kidney along with glomerulus changes in diabetes.

Different pathways and networks involved in diabetic kidney disease:

Management of DKD: Management of CKD is done using the following therapeutic agents.

3. Diabetic neuropathy:

The most frequent pattern of involvement is that of a peripheral, symmetric neuropathy of the lower extremities affecting both motor and sensory function [7].

Neuropathies are the common long-term complication of diabetes, affecting up to 50% of the patients with diabetes.Diabetic sensorimotor polyneuropathy is one type of neuropathy described as a diffuse symmetrical and length-dependent injury to peripheral nerve fibers. This condition, most often referred to as diabetic peripheral neuropathy (DPN), is the most common diabetic neuropathy.

DPN is a common complication in patients with diabetes. It involves nerve damage, which can lead to numbness, loss of sensation, and pain in extremities, usually begin in feet and legs and eventually spread to hands, if left untreated [18]

Classification of Diabetic Neuropathy: [19]

A. Diffuse

1. Distal symmetric sensory-motor polyneuropathy
2. Autonomic neuropathy
A. Pseudo-motor B. Cardiovascular C. Gastrointestinal D. Genitourinary
3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

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B. Focal

1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy (amyotrophy)

Pathogenesis:

The pathogenesis of diabetic peripheral neuropathy is complex and is marked by both metabolic and vascular factors. Hyperglycemia is only one of the many key metabolic events known to cause axonal and microvascular injury. Major mechanisms involved in DPN is hyperglycemia, toxic adiposity, oxidative stress, mitochondrial dysfunction, activation of the polyol pathway, accumulation of advanced glycation end products (AGEs), and elevation of inflammatory markers [20]

Hyperglycemia and polyol pathway:

Long-standing hyperglycemia is a major factor responsible for the development of diabetic neuropathy. The glucose uptake into peripheral nerve is an insulin independent pathway therefore blood glucose enters directly into the cells.

The rate-limiting enzyme for polyol pathway is aldose reductase, which is expressed on Schwann cells. Excess glucose is shunted into the polyol pathway and is converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase respectively. The nerve cell membrane is relatively impermeable to sorbitol and fructose, which tend to accumulate within the nerve, formed Fructose and sorbitol both being osmotically active compounds lead to increase in the water content in the nerves. Further the oxidation/reduction status of the cell is altered with loss of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) and glutathione stores. It leads to a cascade of events like a reduced membrane Na- K ATPase activity, intra-axonal sodium accumulation which reduces nerve conduction velocity and brings about structural breakdown of the nerve. Myoinositol level is decreased because elevated levels of both glucose and sorbitol compete for the uptake of myoinositol in the tissues and cells. Moreover, reduced NADPH, a cofactor for the enzyme nitric oxide synthase, reduces nitric oxide formation leading to impaired vascular supply to the nerve [19]

Clinical features:

These may include: pain, tingling, "pins and needles," burning, numbness, sensitivity to light touch, muscle weakness, sharp pains, and issues with balance and reflexes, particularly affecting the feet and legs. These symptoms are often worse during moments of rest, such as at bedtime, and may improve with activity and exercise

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Treatment:

Treatment of DPN generally focuses on slowing or preventing its progression by optimizing blood glucose control, actively caring for your feet, managing any complications, and alleviating pain [18]. Refer table 3

Conclusion: Diabetes is most prevalent among all the age groups. Diabetes Mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. Treatment regimens may improve glycemic control but dietary factors may also play an important role in adjuvant with treatment in minimizing disease condition as well as complications associated with diabetes. It is important to maintain healthy life style for better glycemic control in improving disease condition as well as comorbidities.Clinical pharmacist can play an important role in educating the patients about the proper use of medication, screening for drug interactions, explain monitoring devices and proper management of complications associated with diabetes.It is important to create the awareness among health care professionals as well as every individual in early recognition of symptoms will be effective in prevention of disease process.

Acronyms

ACE: Angiotensin Converting Enzyme
CD4: Cluster of Differentiation
CTGF: Connective tissue growth factor
CrCl: Creatinine Clearance
DME: Diabetic macular edema
GI: Gastrointestinal
IDDM: Insulin Dependent Diabetes Mellitus
IR: Immediate Release
JAK/STAT: Janus Kinases/Signal Transducer and Activator of Transcription Protien
MHC: Major Histocompatibility complex
NIDDM: Non-insulin Dependent Diabetes Mellitus
NFkB: Nuclear Factor Kappa Beta
NADPH: Nicotinamide adenine dinucleotide phosphate
RAAS: Renin angiotensin aldosterone system
ROS: Reactive oxygen species
SAA: Serum amyloid A
TGF-B: Transforming growth factor beta
VEGF: Vascular Endothelial Growth Factor

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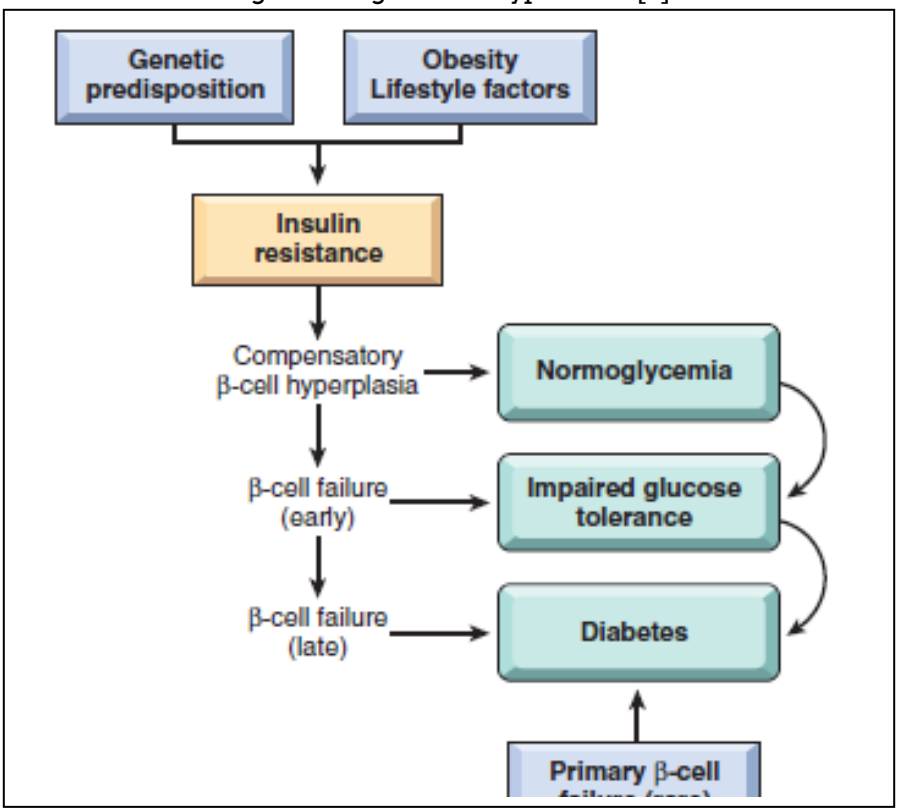
Table: 1 Drug induced hyperglycemia[5]

Insulin resistance and deficiency	Insulin deficiency	Insulin resistance
Atypical anti-psychotics	β blockers	β adrenergic agonists
Gluco corticoids	Calcineurin inhibitors	Growth hormone
Nicotinic acid	Diazoxide	Megestrol
Protease Inhibitors	Didanosine	
Statins	Diphenyl hydantoin, Gatifloxacin, L-asparaginase, Pentamidine, Thiazide diuretics.	

Source: *David R. Repaske MD, PhD, Medication-induced diabetes mellitus, Pediatric Diabetes September (2016); 17: 392–397.*

Fig: 1 Pathogenesis of type II DM [7]



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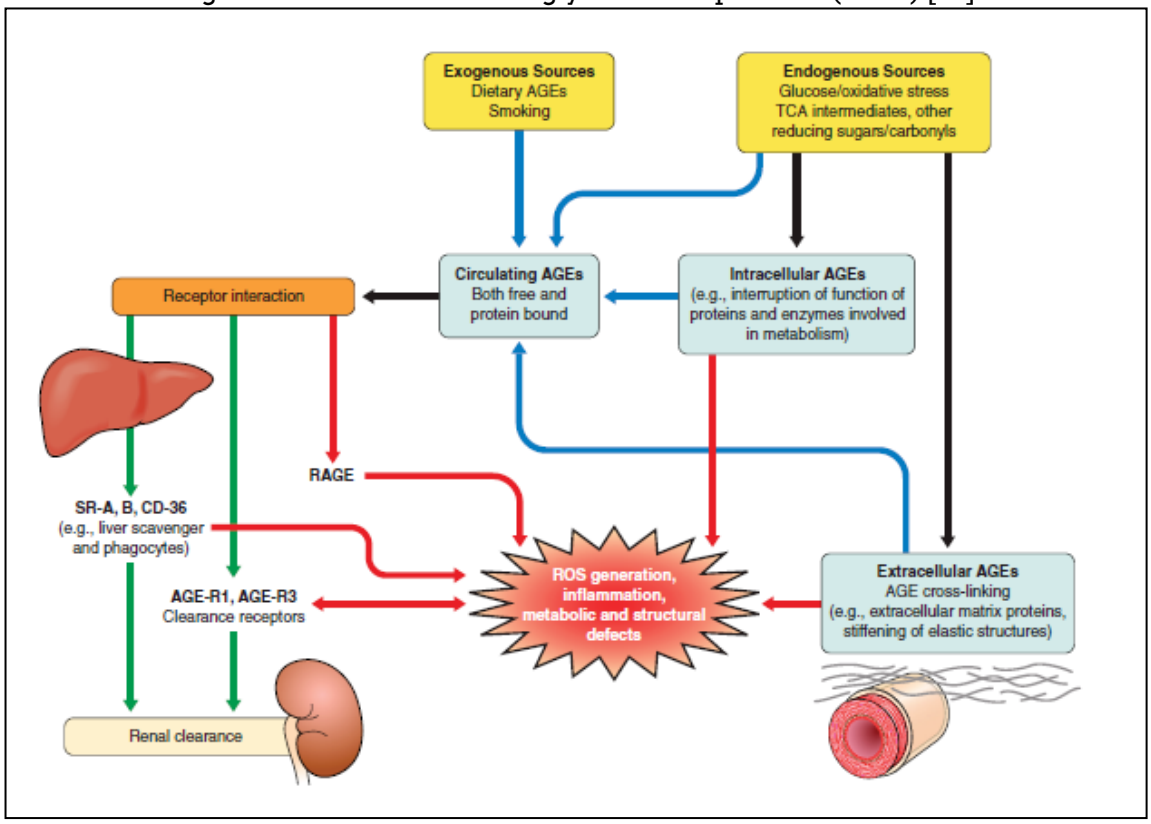
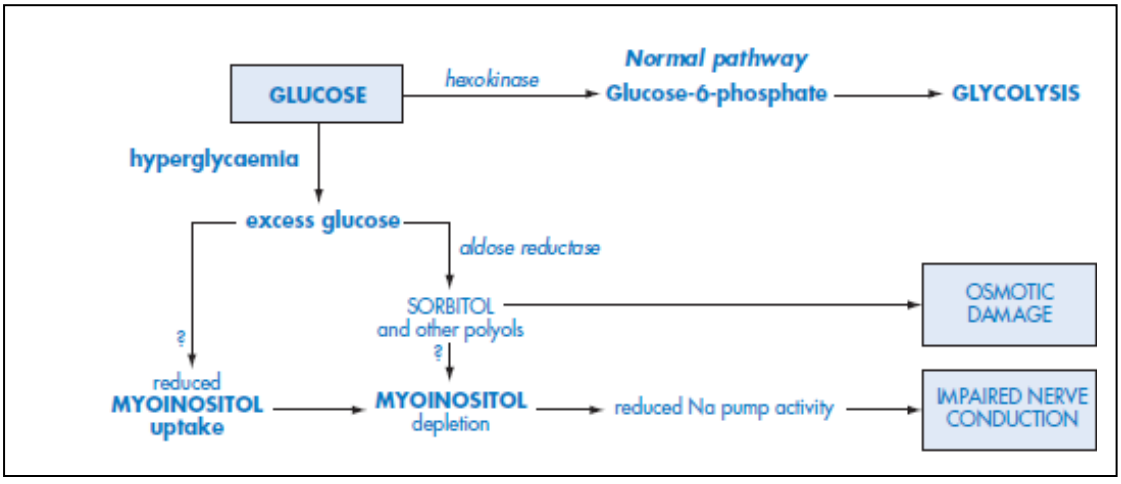
Source:*Robbins basic pathology / [edited by] Vinay Kumar, Abul K. Abbas, Jon C. Aster. – 9th ed. P. ; cm. Basic pathology.*

Fig: 2 Formation of advanced glycation end products (AGEs) [10]



Source:*Josephine M. Forbes and Mark E. Cooper, MECHANISMS OF DIABETIC COMPLICATIONS,Physiol Rev 93: 137–188, 2013.*

Fig: 3 Flow chart of polyol pathway [13]



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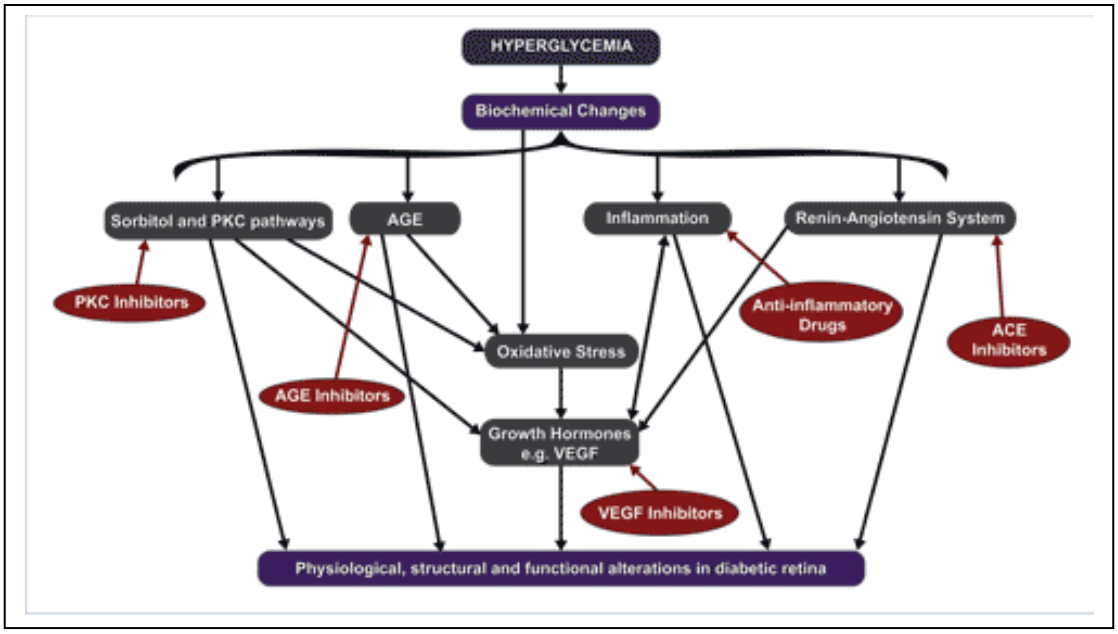
Source: *Russell J Greene, Pathology and Therapeutics for Pharmacists, Third edition*

Fig: 4Hyperglycemia induced Biochemical pathways contributing to DR pathophysiology and potential targets for management of DR [15]



Source:*Catherine A. Opere, PhD, Understanding Diabetic Retinopathy, US Pharm.(2011);36(4):46-52.*

Table: 2 pharmacological agents for management of DR [15]

Drug	Brand	Formulation	Dosage
Corticosteroids			
Triamcinolone acetonide	Triesence	40 mg/ml suspension	4 mg multiple or 20 mg single; Intravitreal
Dexamethasone implant	Ozurdex	0.7 mg implant	Implant into the vitreous
VEGF Inhibitors			
Bevacizumab	Avastin	100 mg/ 4 ml 400 mg/16 ml	single 1.25 mg(0.05 ml); Intravitreal

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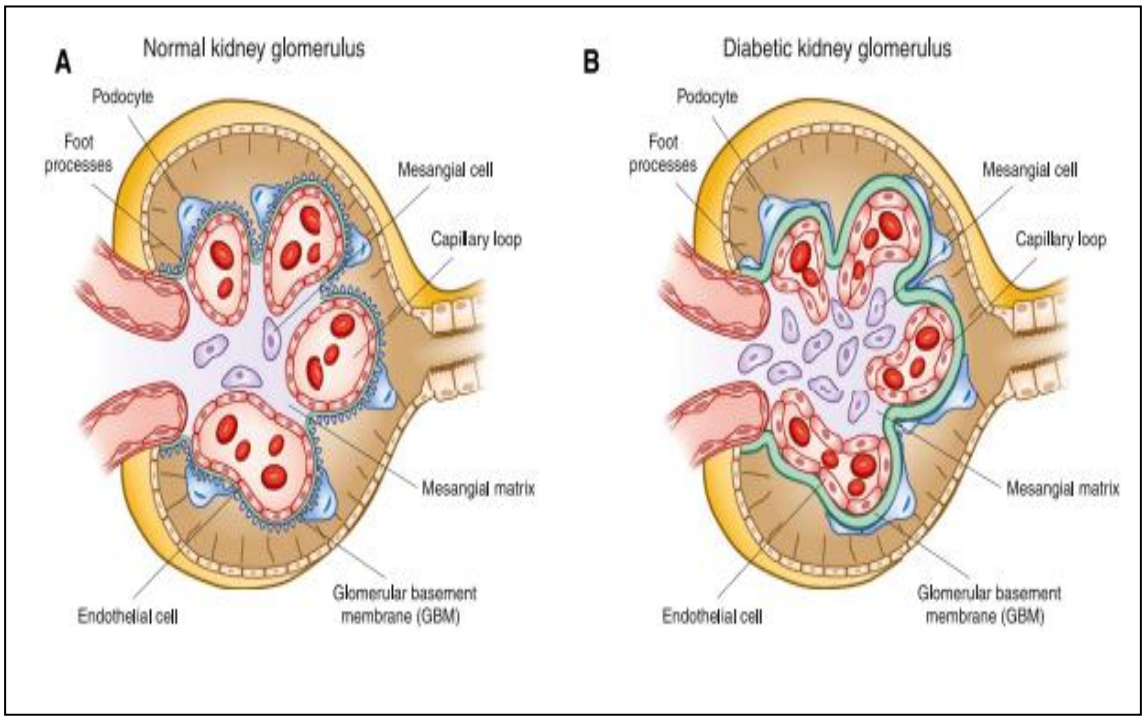
Pregaptanib	Macugen	0.3 mg/0.09 ml solution	0.3 mg once every 6 wk; max of 6 injections
Ranibizumab	Lucentis	0.5 mg/0.05 ml solution	DME: 0.3- 0.5 mg; Intravitreal DME secondary to occlusion; 0.5 mg monthly for 6 months intravitreal
ACE Inhibitors			
Lisinopril	Prinivil; Zestril	2.2,5,10,20, 30, 40 mg tablets	10-20 mg/day; oral
Antiplatelet Drugs			
Ticlopidine	Ticlid	250 mg tablet	BID; oral

Source:*Catherine A. Opere, PhD, Understanding Diabetic Retinopathy, US Pharm.(2011);36(4):46-52.*

Fig: 5 Normal kidney morphology and structural changes in diabetes mellitus [16]



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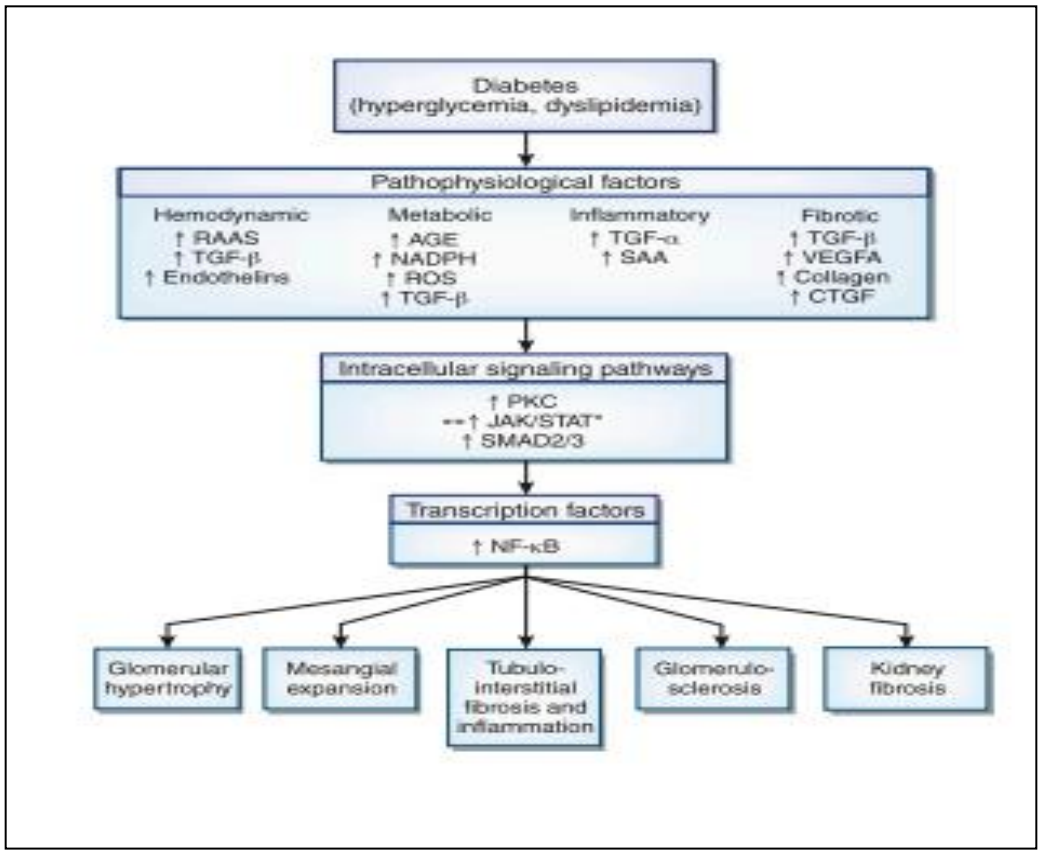
Source:*Radica Z. Alicic,*† Michele T. Rooney,* and Katherine R. Tuttle*Diabetic Kidney DiseaseChallenges, Progress, and Possibilities, Clin J Am SocNephrol 12: 2032–2045, (2017).*

Fig: 6 Pathways involved in initiation and progression of Diabetic kidney disease (DKD) [16]



Source:*Radica Z. Alicic,*† Michele T. Rooney,* and Katherine R. Tuttle*Diabetic Kidney DiseaseChallenges, Progress, and Possibilities, Clin J Am SocNephrol 12: 2032–2045, (2017).*

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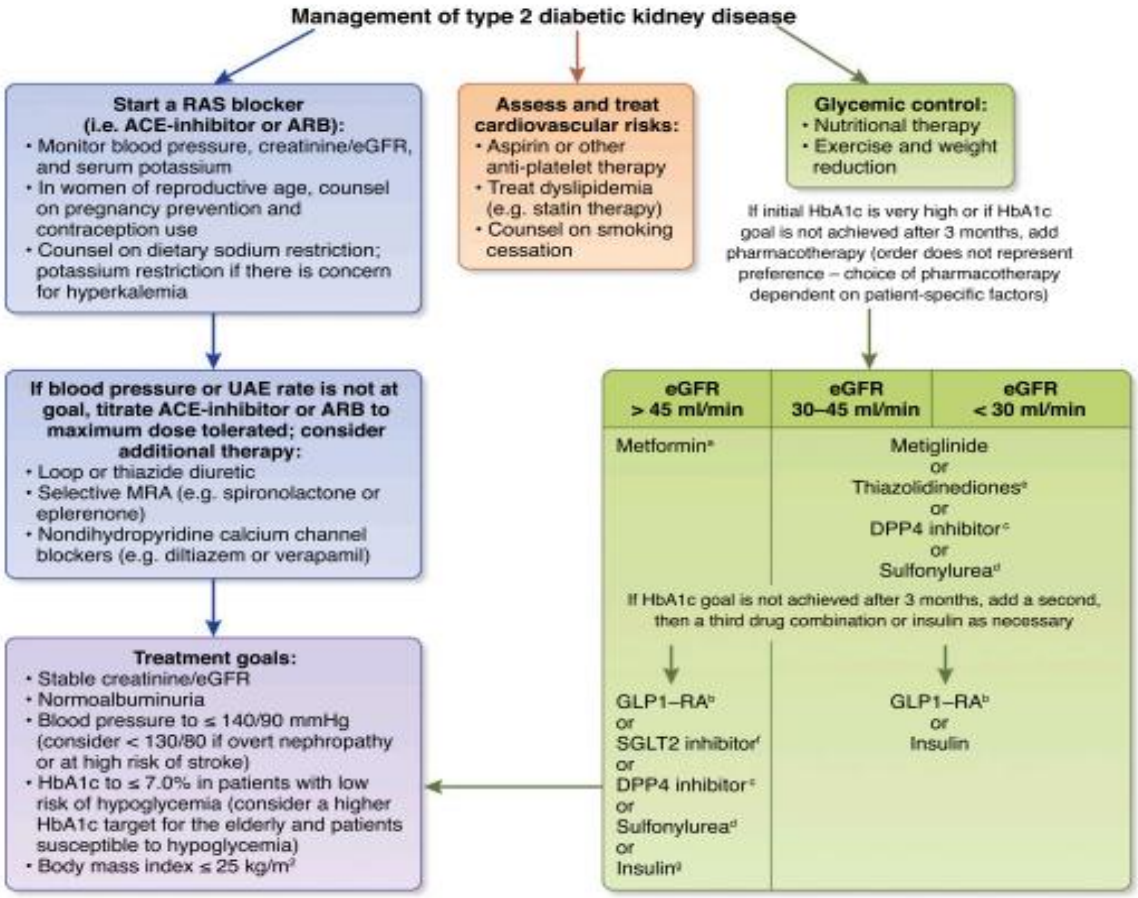
Fig: 7 Management of type II diabetic kidney disease **[17]**



Source: *Lili Tong and Sharon G. Adler, Diabetic Kidney Disease, Clin J Am SocNephrol 13: 335–338, (2018).*

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Table: 3 Treatment for Diabetic neuropathy [21]

Drug Name	Dosing Range	Adverse Effects	Special Considerations
Gabapentin	300-3600 mg daily in 3 divided doses	Dizziness, somnolence, GI upset, Peripheral edema	Dosage adjustment in renal impairment
Pregabalin	50-300 mg daily in 2 or 3 divided doses	Dizziness, somnolence, weight gain, Peripheral edema	Dosage adjustment in renal impairment
Tricyclic antidepressants (amitriptyline, desipramine, nortriptyline)	10-150 mg daily; usually dosed at bedtime due to drowsiness	Dry mouth, blurred vision, constipation	First choice in patients with underlying insomnia or depression; avoid in patients with cardiac conduction abnormalities and in those in risk of suicide; anticholinergic effects are worse with amitriptyline use; avoid in elderly due to risk of falls
Duloxetine	60-120 mg daily	Constipation, Nausea, somnolence, dizziness, decreased appetite	Avoid in hepatic impairment; avoid in CrCl< 30ml/min
Oxycodone	IR: 10-30 mg every 4 h controlled release: 10-30 mg every 12 h	Constipation, somnolence, dizziness, nausea, vomiting, itchiness	Risk of addiction, physical dependence, and tolerance
Tramadol	50-100 mg every 4-6 h (max dose 400 mg daily)	Constipation, somnolence, dizziness, nausea, vomiting, itchiness	Risk of addiction, physical dependence, and tolerance; avoid use in those with seizures
Morphine	IR: 10-30 mg every 4-6 h CR: 15-30 mg every 12-24h	Constipation, somnolence, dizziness, nausea, vomiting, itchiness	Risk of addiction, physical dependence, and tolerance
Lidocaine	Apply patch to affected area: patch may remain in place up to 12 h;	Skin irritation	Used as adjunct therapy to oral medications

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	remove patch for 12 h		
Capsaicin	Apply topically to affected area 3-4 times daily	Stinging and burning sensation	Used as adjunct therapy to oral medications

Source:*Elizabeth G. Montfort, PharmD, Neuropathic Pain: A Review of Diabetic Neuropathy, US Pharm. (2010);35(5):HS8-HS15.*

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