



Diabetes and Complications at a Glance for Pharmacy Researchers

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ABSTRACT

Defective insulin secretion & resistance to insulin action along with alterations of lipid and protein metabolism may leads to hyperglycaemia, which is characteristic of a chronic metabolic disorder i.e. Diabetes mellitus (DM). Diabetic morbidity is due to microvascular complications (Diabetic retinopathy, Diabetic nephropathy, Diabetic peripheral neuropathy, and Diabetic autonomic neuropathy) whereas diabetic mortality is result of macrovascular complications (Coronary heart disease, Peripheral vascular disease, cerebrovascular disease). Persistent hyperglycaemia causes microvascular complications but macrovascular complications are due to persistent hyperglycaemia associated with hypertension, dyslipidaemia, smoking. Principle aim of this review is to provide concise insights of diabetes & complications for pharmacy researchers as there is more research warranted on oral hypoglycaemic agents. This review also provides important pathophysiological characteristics of diabetic musculoskeletal & rheumatological complications.

Keywords: Complications, Diabetes mellitus, Dyslipidaemia, Hyperglycaemia, Macrovascular, Microvascular.

INTRODUCTION

Defective insulin secretion & resistance to insulin action along with alterations of lipid and protein metabolism may leads to hyperglycaemia, which is characteristic of a chronic metabolic disorder i.e. Diabetes mellitus (DM). Patients with type 1 diabetes mellitus (T1DM) show presence of diabetes which is immune-mediated or idiopathic. A complex pathophysiology that combines progressive insulin resistance and β -cell failure and has a heritable basis is characteristic of type 2 diabetes mellitus (T2DM). Comparative summary of diabetes is referred in table 1. Diabetes also can be related to the gestational hormonal environment, genetic defects, other infections, and certain drugs.¹ Insulin secretion, Tissue glucose uptake (Peripheral i.e. primarily muscle & Splanchnic i.e. liver plus gut), decreased free fatty acid (FFA) & decreased glucagon are the factors responsible for the maintenance of normal glucose tolerance in healthy subjects.²

Age above 45 years, overweight or obesity (BMI greater than 25 kg/m²), family history of diabetes, sedentary way of life, hypertension, prolonged use of medications such as corticosteroids, tacrolimus, cyclosporine and niacin and smoking are general risk factors for diabetes. Table 2, provides information about glucose testing, interpretation, symptoms and complications of diabetes.³

PATHOPHYSIOLOGY OF DIABETES

Types of Diabetes

Two major classes of diabetes mellitus are, insulin dependent diabetes mellitus (IDDM) or Type 1, and non-insulin dependent diabetes mellitus (NIDDM) or Type 2.⁴

Type 1 Diabetes Mellitus (T1DM)

Beta-cell (β) destruction caused by an autoimmune process resulting in absolute insulin deficiency is sign of Type 1 diabetes mellitus (formerly called type I, IDDM or juvenile diabetes).⁵ Presence of anti-glutamic acid decarboxylase (GAD), islet cell (ICAs) or insulin (IAAs) antibodies are the evidences of beta-cell destruction by autoimmune processes. Insulin therapy is must in all type 1 diabetic patients to maintain normglycemia. Overwhelming fatigue, increase appetite, smell of acetone, muscular atrophy in thigh, sudden appearance of weight loss accompanied by polyuria, nocturia and polydipsia are clinical features of Type 1 Diabetes (T1DM).⁶

Table 1: Difference between Diabetes Insipidus & Diabetes Mellitus

| Character | Diabetes Insipidus | Diabetes Mellitus |
|---------------------|---|---|
| Symptoms | Polydipsia, polyurination (excess diluted urine) | ↑ blood glucose, polyuria, polyphagia, polydipsia |
| Prevalence | 0.003% population | 0.77 % population |
| Etiology | ↓ ADH, Brain Cancer, head injury, lithium toxicity, genetics | Autoimmune Disease (Type1DM) Genetics, lifestyle, infection (Type2DM) |
| Suggested treatment | Hypertonic saline solution (3% or 5%) IM, IV Thiazide diuretics | Insulin, Oral hypoglycemic agents, Lifestyle management |



Table 2: Glucose testing, interpretation, symptoms and complications of diabetes³

| Test | Result | Diagnosis | Symptoms | Complications |
|---|------------|---|--|--|
| Fasting plasma glucose, mg/dl | ≤ 99 | Normal | Excess urine Hunger Thinning Thirst Blurred vision | Myocardial infarction Diabetic neuropathy Renal failure Diabetic retinopathy Arterial insufficiency and limb amputations Involvement of peripheral nerves Ulcers of the skin Carpal tunnel syndrome |
| | 100 to 125 | Impaired fasting glucose | | |
| | ≥ 126 | Diabetes, confirmed by repeating the same test on a different day | | |
| Glucose, mg/dl (oral glucose tolerance test, 2 hours after ingestion of 75g glucose load) | ≤ 139 | Normal | | |
| | 140 to 199 | Impaired fasting glucose | | |
| | ≥ 200 | Diabetes, confirmed by repeating the same test on a different day | | |

Type 1 diabetes mellitus (T1DM) & autoimmunity

The disease recognizes two major subtypes: 1A (autoimmune) and 1B (idiopathic). Selective loss of pancreatic insulin-secreting beta-cells is due to genetically determined chronic immune-mediated disorder (1A subtype) which is associated with several immunologic abnormalities due to a long subclinical prodromal phase that lasts for years. Such characteristics can be predictors of developing T1DM.⁷

Table 3: Characteristics of T1DM

| | |
|---|--|
| Genetic and environmental triggers^{8,9} | The genetics of T1DM are quite well understood. It is clear at this point that multiple genes can have predisposing effects, resulting in a complex interaction. Environmental factors are like dietary factors, cow's milk in young infants, viral infections and psychological stress. |
| Autoantibodies^{10,11} | Auto antibodies to islet antigens can be detected in serum samples from pre-diabetic individuals and newly diagnosed cases |
| T lymphocytes^{12,13} | Current evidence from animal models indicates that auto reactive lymphocytes can have destructive or regulatory effector functions, depending on which cytokines they produce |
| Antigen presenting cells (APC) | Activated APC are detectable early in human pancreas. Once destruction of some islet cells has occurred, it is supposed that local APC will increasingly present β-cell antigens. |

Type1 diabetes mellitus (T1DM) & vitamin D^{14,15}

There is strong epidemiologic data showing that the population in countries with a high prevalence of type 1 diabetes mellitus is commonly vitamin D deficient. Improvement of C-peptide levels and arrest of the deterioration of pancreatic function can be seen after replacement of vitamin D in patients with new onset of type 1 diabetes. The risk of the development of type 1 diabetes mellitus for offspring is decreased by vitamin D supplementation during pregnancy.

Type 2 Diabetes Mellitus (T2DM)

The plasma insulin concentration is insufficient to control normal glucose homeostasis due to insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell, which characterises type 2 diabetes mellitus (formerly called NIDDM, type II or adult-onset).¹⁶ Insulin resistance related to intra-abdominal (visceral) obesity seen in T2DM along with hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia). T2DM is common form of diabetes mellitus, highly associated with a family history of diabetes, older age, obesity and lack of exercise (figure 1). It is more common in women, especially women with a history of gestational diabetes, and in Blacks, Hispanics and Native Americans. Impaired glucose tolerance is result of insulin resistance and hyperinsulinemia. Adult Onset Diabetes (Multifactorial), Maturity Onset Diabetes of the Young (MODY) & Obese Type 2 Diabetes with DKA (Minority Group) are three forms of T2DM.

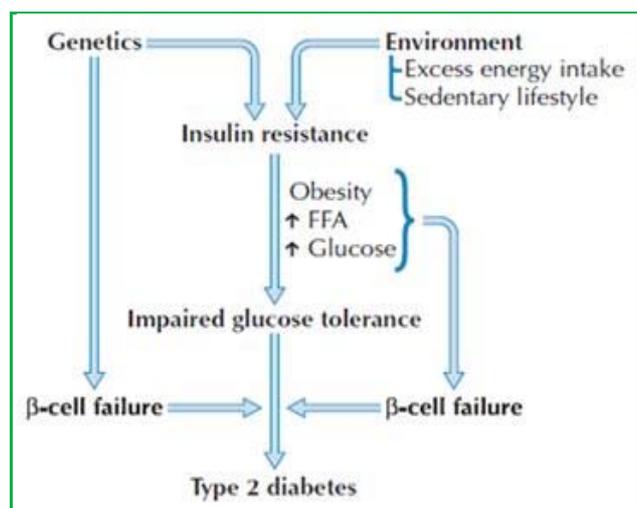


Figure 1: T2DM pathophysiology

Factors causing increase in visceral fat are enlisted like stress-related factors (overeating, smoking, increase in alcohol intake, disorders of nervous and endocrine systems: increase in cortisol, abnormality in sex, hormone secretion), lowered energy consumption due to a lack of exercise, genetic factors & aging.¹⁷

Table 4: Characteristics of T2DM

| | |
|--|---|
| Impaired insulin secretion 18,19 | Impaired glucose tolerance (IGT) is induced by a decrease in glucose-responsive early-phase insulin secretion. Decrease in additional insulin secretion after meals causes postprandial hyperglycaemia. It progressively involves glucose toxicity and lipo-toxicity. |
| Insulin resistance 18,20 | Insulin resistance (mainly in liver & muscles) develops and expands prior to disease onset. Glucolipotoxicity and inflammatory mediators are also important as the mechanisms for impaired insulin secretion and insulin signaling impairment. |

Table 5: Summary of Diabetes Mellitus Types

| Features | T1DM | T2DM |
|--------------------------------|--|---|
| Age at onset | Usually < 40 | Usually > 40 |
| Proportion of all diabetes | About 10% | About 90% |
| Seasonal Trend | Fall and Winter | None |
| Appearance of symptoms | Acute or subacute | Slow or subacute |
| Metabolic Ketoacidoais | Frequent | Rare |
| Obesity at onset | Uncommon | Common |
| β -Cells | Decreased | Variable |
| Insulin | Decreased or absent | Variable |
| Inflammatory cells in islet | Present initially | Absent |
| Family history of diabetes | Uncommon | Common |
| Concordance in identical twins | 30-50% | 90-95% |
| Antibody to islet cell (ICA) | Yes | Uncommon |
| Insulin autoantibodies (IAA) | Yes (in younger age) | No |
| Treatment | Insulin, diet, Pancreas & Islet transplant | Diet, weight reduction, exercise, Insulin |

Insulin Resistance

Dysregulation in several neuroendocrine pathways can lead to insulin resistance and altered glucose and lipid metabolism in various tissues.²¹ In adipose dysfunction, inflammatory mediators such as cytokines and chemokines as well as inflammatory cells are implicated as important players contributing to metabolic dysregulation and insulin resistance. There are autonomic innervations (with both sympathetic and parasympathetic nerves) in metabolically active tissues such as adipose, muscle, liver and pancreas. Sympathetic activation releases catecholamines that are known to have an

insulin-antagonistic effect. An excess of FFA distribution to liver, skeletal muscle and pancreas promotes insulin resistance.

Complications of Diabetes

Diabetic morbidity is due to microvascular complications (Diabetic retinopathy, Diabetic nephropathy, Diabetic peripheral neuropathy, and Diabetic autonomic neuropathy) whereas diabetic mortality is result of macrovascular complications (Coronary heart disease, Peripheral vascular disease, cerebrovascular disease). Persistent hyperglycaemia causes microvascular complications but macrovascular complications are due to persistent hyperglycaemia associated with hypertension, dyslipidaemia, smoking.

Diabetic Retinopathy

Non proliferative DR (NPDR) (background retinopathy) & proliferative DR (PDR) are principle classes of diabetic retinopathy. Diabetic retinopathy may lead to blindness in diabetic patients. It is a significant health problem in diabetic population.²² Though the progression is well known, the underlying mechanism for diabetic retinopathy is unclear. During initial stages there, is capillary microaneurysm formation, dot and blot intraretinal haemorrhages without visual impairment. Capillary and arteriolar closure characterises the next stage of the disease process i.e. preproliferative retinopathy. Progressive visual impairment caused by scarring and bleeding are characteristics of proliferative retinopathy which results due to the growth of new blood vessels from the optic nerve head, or from elsewhere.^[23] Systemic factors (Gender, Duration of diabetes, Glycaemic control, Hypertension, Renal disease, Elevated serum lipids, Pregnancy, Alcohol, Anaemia, Obesity) & ocular factors (Posterior vitreous detachment, Old chorioretinopathy, Cataract surgery) are the risk factors for diabetic retinopathy.²⁴

Diabetic Nephropathy

Activation of vasoactive hormone pathways including the renin angiotensin system and endothelin along with increased systemic and intraglomerular pressure contribute to the development of diabetic nephropathy (DN).²⁵ Deposition of extracellular matrix (ECM) in the kidney is characteristic of diabetic nephropathy. Hyperglycaemia induces high reactive oxygen species (ROS) and extra cellular matrix protein (ECM) expression in the glomerular mesangial cells.²⁶ The hypertrophy of the kidney, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy and interstitial fibrosis represent the structural abnormalities associated with DN.²⁷ Increase in glomerular filtration rate (GFR), intraglomerular hypertension, subsequent proteinuria, systemic hypertension and eventual loss of renal function are the functional modifications allied to DN.²⁸ In pathogenesis of diabetic nephropathy microinflammation is one of the key factors. Activation of inflammatory pathways in the

diabetic kidney is triggered by abnormalities of blood glucose, blood pressure or dyslipidemia followed by functional and structural renal injury.²⁹ Though there are hemodynamic changes of glomerular hyperperfusion and hyperfiltration as the earliest measurable clinical signs of nephropathy but fails to guess the demise of kidney function. Reduction in podocyte number along with podocyte foot process effacement, thickening of the glomerular basement membrane these are some structural changes seen during diabetic nephropathy.³⁰

Diabetic Peripheral Neuropathy

In diabetic peripheral neuropathy there is degenerative changes of axons and affects all nerve fibers. First it affects the non-myelinated autonomic nerve fibers then causes medial artery calcification followed by microvascular thermoregulatory dysfunction, and arteriovenous shunting.³¹ Peripheral neuropathy can be the result of genetics, chronic disease, environmental toxins, alcoholism, nutritional deficiencies, or side effects of certain medications. Hyperglycemic environment not only destroy nerve cells but also affects nerve repair mechanisms. The pathophysiology of diabetic neuropathy includes increased oxidative stress yielding advanced glycosylated end products (AGEs), polyol accumulation, decreased nitric oxide/impaired endothelial function,¹⁶ impaired (Na⁺/K⁺)-ATPase activity and homocysteinemia.³² Involvement of damaged nerve type with respective symptoms includes as; 1) Sensory nerves (numbness, tingling, increased sensitivity to touch, and burning in the feet, legs, hands, and arms), 2) Autonomic nerves (problems with digestion, breathing, vision, heartbeat, sexual function, and bladder control) & 3) Motor nerves (muscle weakness, cramping, or twitching). Diabetic foot ulcer is a time dependant outcome of DM, results from a complex interaction of a number of risk factors. Neuropathy (with alterations in motor, sensation, and autonomic functions) plays the central role and causes ulcerations due to trauma or excessive pressure in a deformed foot without protective sensibility. Once the protective layer of skin is broken, deep tissues are exposed to bacterial colonization. Infection is facilitated by DM-related immunological deficits, especially in terms of neutrophils, and rapidly progresses to the deep tissues.³³

Diabetic Autonomic Neuropathy

Diabetic patients are under high risk of cardiac arrhythmias and silent myocardial ischemia leading to sudden death. Cardiac autonomic neuropathy (CAN) have important clinical and prognostic relevance with morbidity and mortality in diabetic patients.^[34] Heart rate variability (HRV) and cardiac performance is primarily regulated by autonomic innervation. Early augmentation of sympathetic tone represents initial development of CAN in diabetes. Progressive autonomic neural dysfunction is associated with chronic hyperglycemia.^{35,36} Autonomic dysfunction may impair exercise tolerance and has been shown to reduce heart rate, blood pressure, and

cardiac output responses to exercise.³⁷ Diabetic autonomic neuropathy (DAN) induces vasoconstriction and reduces neuronal blood flow due to activation of protein kinase C. Vascular endothelium damage and reduces nitric oxide (NO) bioavailability as result of increased oxidative stress, with increased free radical production.³⁸⁻⁴⁰ DAN is a neuropathic disorder associated with diabetes that includes manifestations in the peripheral components of the ANS. DAN affects sensory, motor, and vasomotor fibers innervating a large number of organs. DAN may thus affect a number of different organ systems (e.g., cardiovascular, GI, and genitourinary).⁴¹ Hypoglycemia is the limiting factor in the glycemic management of diabetes. The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response to falling glucose levels in the setting of an absent glucagon response) and hypoglycemia unawareness (by reducing the autonomic and the resulting neurogenic symptom responses) and thus a vicious cycle of recurrent hypoglycaemia.⁴²

Diabetic Coronary Heart Disease

Diabetes also affects the heart muscle, causing both systolic and diastolic heart failure. Clinically, dyslipidemia is highly correlated with atherosclerosis, and up to 97% of patients with diabetes are dyslipidemic.⁴³ In addition to the characteristic pattern of increased triglycerides and decreased HDL cholesterol found in the plasma of patients with diabetes. In diabetes, the predominant form of LDL cholesterol is the small, dense form which is atherogenic. Diabetes decreases nitric oxide NO bioavailability because of either insulin deficiency or defective insulin signalling (insulin resistance) in endothelial cells.⁴⁴ Hyperglycemia also acutely inhibits the production of NO in arterial endothelial cells.⁴⁵ Diabetic cardiomyopathy a myocardial disease makes diabetic patients vulnerable to heart failure. Prevalence of asymptomatic diastolic dysfunction in patients with type 2 diabetes is 52-60%.^{46,47} Young patients with type 1 diabetes demonstrate left ventricular diastolic dysfunction, characterized by impaired early diastolic filling, prolonged isovolumetric relaxation, and increased atrial filling.⁴⁸ Hyperglycemia induces abnormal platelet function by impairing calcium homeostasis, producing plasminogen activator inhibitor-1, increasing fibrinolysis inhibitor. In addition, platelet function is abnormal, and there is increased production of several prothrombotic factors. These abnormalities contribute to the cellular events that cause atherosclerosis and subsequently increase the risk of the adverse cardiovascular events that occur in patients with diabetes.^{49,50}

Diabetic Peripheral Vascular Disease

In diabetic patients, there is increased risk of peripheral vascular disease (PVD) i.e. diabetic arteriopathy characterised by endothelial dysfunction, vascular



smooth muscle cell dysfunction, inflammation and hypercoagulability.⁵¹ Tibial artery's occlusion is susceptible in diabetic patients along with development of impaired wound healing and microangiopathy. Diabetes is a stronger risk factor for PAD in women than in men.^{52,53} Diabetes is a quantitative risk factor as each 1% increase in glycosylated hemoglobin is associated with a 25% increase in the risk for peripheral artery disease (PAD). The involvement of distal vessels in the extremities is typical and, together with microangiopathy and neuropathy, which imply a poor response to infection and a specific healing disorder, diabetes is associated with a risk of amputation 10 fold that of non-diabetic patients. Of importance is the fact that diabetic patients may have abnormally high pressure values in the ankle.⁵⁴ Being a key factor in the pathogenesis of diabetes, insulin resistance and its attendant metabolic abnormalities causes cardiovascular risk of diabetes. Diabetic patients with PAD are at higher risk of lower extremity amputation than those without diabetes due to critical limb ulceration of the foot.⁵⁵⁻⁵⁸

Diabetic Cerebrovascular Disease

The number of diabetic patients with stroke increased substantially from 6.2% to 11.3% in England.⁵⁹ T2DM predisposes patients to early and severe development of cerebrovascular disease, because of its metabolic and vascular changes: hyperglycemia, excess free fatty acids, insulin resistance, prothrombotic state and abnormal endothelial response.⁶⁰ Patients with diabetes mellitus significantly exhibit short- and long term mortalities after stroke.^{61,62} A study by He et al., concludes that patients with symptomatic type 2 DM shows the prevalence and morphology of carotid and cerebrovascular atherosclerotic plaques.⁶³ Relationship between diabetes, as a vascular risk factor, and the presence of silent lacunar lesions and cerebral atherosclerosis is reviewed by Nagata et al.⁶⁴ Development of sclerotic lesion in cerebral arteries results due to diabetes mellitus itself (even in relatively young subjects without hypertension and any other diabetic organ damage).⁶⁵

Diabetic Musculoskeletal & Rheumatological Complications

In diabetic patients connective tissue changes are observed in musculoskeletal system due to metabolic perturbations like microvascular abnormalities with damage to blood vessels and nerves, glycosylation of proteins and collagen accumulation in skin and periarticular structures. These musculoskeletal & rheumatological complications of diabetes mellitus are summarised as, 1) Conditions Affecting the Hands (Diabetic cheiroarthropathy, Flexor tenosynovitis, Dupuytren's contracture, Carpal tunnel syndrome), 2) Conditions Affecting the Shoulders (Adhesive capsulitis, Calcific periarthritis, Reflex sympathetic dystrophy), 3) Conditions Affecting the Feet (Diabetic osteoarthropathy i.e. Charcot or neuropathic arthropathy), 4) Conditions Affecting the Muscles (Diabetic muscle infarction), 5)

Conditions Affecting the Skeleton (Diffuse interstitial skeletal hyperostosis i.e. DISH).⁶⁶

Diabetic Cheiroarthropathy⁶⁷⁻⁷⁰

Diabetic cheiroarthropathy (DCA) is a syndrome of limited joint mobility, diabetic stiff hand characterized by painless limited extension of the proximal metacarpophalangeal joints. Patients with diabetes mellitus suffer from diabetic cheiroarthropathy due to hyperglycemia induced glycosylation and the crosslinking of collagen. Hence, the collagen proliferates extensively in the skin, subcutaneous tissues, tendons, muscles, and periarticular tissue. These collagen fibers become stiffer. Tight waxy skin over the digits developed due to low-grade ischemia induced fibrosis as a result of thickening of capillary basement membranes. Flexor tenosynovitis (trigger finger).⁷¹ Movement of the tendon is restricted by fibrous tissue proliferation in the tendon sheath causes flexor tenosynovitis (trigger finger or stenosing tenosynovitis). 11% diabetic patients are susceptible to flexor tenosynovitis. Dupuytren's contracture:⁷² Dupuytren's contracture in diabetic patients ranges from 20 to 63%. Palmar or digital thickening, tethering is seen in Dupuytren's contracture and its prevalence increases with age. The ring and middle finger of diabetic patients is mainly affected as compared with the fifth finger. Carpal tunnel syndrome:^{73,74} Compression of the median nerve within the carpal tunnel, diabetic neuropathy, or a combination of both leads to Carpal tunnel syndrome (CTS), demonstrated by paraesthesia over the median nerve cutaneous distribution of the thumb, index, middle, and lateral half of the ring fingers. Diabetic women are more susceptible to CTS than men. Adhesive capsulitis⁷⁵ characterised by progressive, painful restriction of shoulder movement, especially external rotation and abduction, also known as frozen shoulder. Calcific periarthritis:⁷⁶ As per the study conducted by Mavrikakis et al., adult onset diabetics demonstrated high prevalence to calcific shoulder periarthritis with existence of interrelation between diabetes mellitus and calcific tendinitis of the shoulders. Affecting one or more peripheral articulations, Charcot's osteoarthropathy shows presence of joint dislocation, subluxations and pathological fractures in patients with peripheral neuropathy accompanied by ulceration and amputation. It is chronic, devastating, progressive destruction of bone and joint integrity.⁷⁷ Being a rare complication of diabetes mellitus, Diabetic muscle infarction is not included in most standard orthopedic texts. Diabetic patient with lower extremity pain and swelling without systemic signs of infection should be considered in the differential diagnosis in susceptible cases of diabetic muscle infarction. Magnetic resonance imaging is sensitive and specific enough to make the diagnosis.⁷⁸ With unclear etiology Diffuse interstitial skeletal hyperostosis (DISH) is more common in type 2 diabetes. In addition to its association with diabetes, DISH syndrome may be associated with obesity, hyperlipidaemia and

hyperuricaemia. 50 % of DISH syndrome patients are diabetic with impaired glucose tolerance.^{79,80}

Diabetes & Chronic Obstructive Pulmonary Disorder (COPD)

There is a strong positive association between the occurrence of T1DM and symptoms of asthma due to the common factors influencing susceptibility to these disorders.⁸¹ As per Rana et al., a prospective cohort study involving almost 100,000 women demonstrated that subjects with COPD had a statistically significant, increased risk of developing type 2 diabetes.^[82] Development of insulin resistance or diabetes can be associated with reduced lung function.^[83,84,85] Patients with COPD suffers from oxidative stress which may result in insulin resistance by interfere with insulin signalling at various levels. Inflammation may be the common link between COPD & T2DM as there is observed upregulation of inflammatory markers in patients with COPD.^{86,87} T1DM youth with poor glycemic control are more susceptible for asthma.⁸⁸ Comparative studies between diabetics and nondiabetic controls revealed association between elevated glucose levels, as well as diabetes diagnoses and impaired lung function.^{89,90}

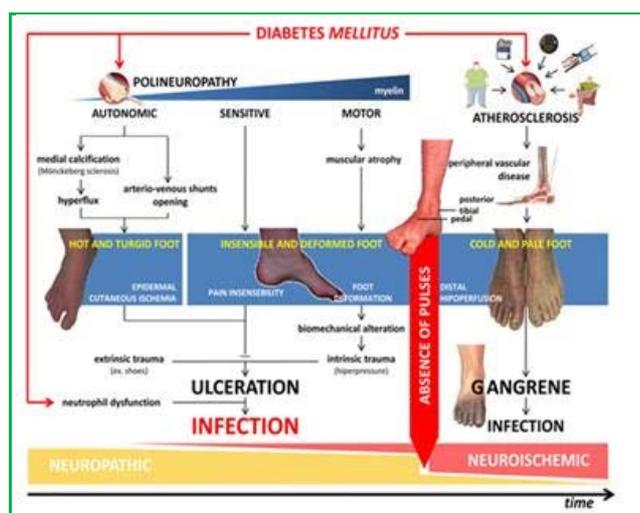


Figure 2: Diabetic peripheral neuropathy resulting in diabetic foot ulcer³³

Diabetes & Periodontal Disease

Prolonged exposure to hyperglycemia & poor glycaemic control may contribute to pathogenesis of periodontal disease in diabetic patient and making person more susceptible to microvascular and macrovascular complications.^{91,92} Bridges et al., in their cross sectional study demonstrated that periodontal parameters, including bleeding scores, probing depths, loss of attachment and missing teeth are significantly affected in diabetes.⁹³ Diabetic patients are 5 times more likely to be partially edentulous than nondiabetic subjects.⁹⁴ Relationship between diabetes and periodontal disease can be explained by mechanisms including changes in components of gingival crevicular fluid, an altered host response, microvascular disease, nonenzymatic glycation,

altered subgingival flora, genetic predisposition and changes in collagen metabolism.⁹⁵ Exacerbation of insulin resistance and worsening of glycemic control is seen in chronic periodontal diseases which can be reversed by periodontal treatment.⁹⁶

Diabetes & Pregnancy

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.⁹⁷ In diabetic women, there is physiological decrease in insulin sensitivity along with carbohydrate intolerance in early pregnancy.⁹⁸ Due to pregnancy-induced lipolysis, diabetic ketoacidosis is developed quickly and with relatively mild hyperglycemia in women with T1DM.⁹⁹ If left untreated, it may cause fetal death.¹⁰⁰ White's Classification of diabetes during pregnancy is summarised in table 6.

Table 6: White's Classification of diabetes during pregnancy¹⁰¹

| | |
|----------|--|
| Class A | Diet alone sufficient, any duration or age at onset |
| Class B | Age at onset \geq 20 years and duration < 10 years |
| Class C | Age at onset 10-19 years or duration 10-19 years |
| Class D | Age at onset < 10 years or duration \geq 20 years or background retinopathy or hypertension (not preeclampsia) |
| Class R | Proliferative retinopathy or vitreous hemorrhage |
| Class F | Nephropathy with proteinuria > 500 mg/day |
| Class RF | Criteria for both R and F classes coexist |
| Class H | Arteriosclerotic heart disease clinically evident |
| Class T | Prior renal transplantation |

Women with pre-existing diabetes are more susceptible to miscarriage, pre-eclampsia and preterm labour. Babies born to such women may suffer from macrosomia, birth injury, congenital malformations, perinatal mortality and stillbirth.

CONCLUSION

Persistent hyperglycaemia causes microvascular complications but macrovascular complications are due to persistent hyperglycaemia associated with hypertension, dyslipidaemia, smoking. Principle aim of this review is to provide concise insights of diabetes & complications for pharmacy researchers as there is more research warranted on oral hypoglycaemic agents. This review also provides important pathophysiological characteristics of diabetic musculoskeletal & rheumatological complications. Insulin resistance or diabetes can be associated with COPD opens gate for new area in pharmaceutical research to develop medicines improving glycaemic control along with positive outcomes in lung capacities. Gestational diabetes characterized by lipolysis, diabetic ketoacidosis is developed quickly and with relatively mild hyperglycemia in women with T1DM, which may lead to miscarriage, pre-eclampsia and preterm labour.

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