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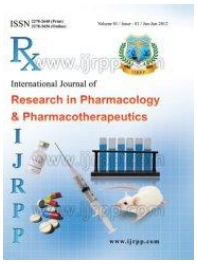

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Review article ***Open Access***

A review on causes of diabetes and foot ulcer

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ABSTRACT
Current review was regarding Diabetes mellitus along with its causes for foot ulcer. Many studies were conducted regarding etiology of diabetes mellitus. This review highlights the prevalence of diabetes and its neuropathic complications leading to ulceration stage. Current review details the underlying mechanism foot ulcer and its reason. Diabetes mellitus is increasingly common conditions in low income countries that expose patients to increased risk of mortality and morbidity. There is a long preclinical period (up to 9 to 13 years) marked by the presence of immune markers when β-cell destruction is thought to occur. Hyperglycemia occurs when 80% to 90% of β- cells are destroyed. There is a transient remission followed by established disease with associated risks for complications and death. Type 2 diabetes is usually characterized by the presence of both insulin resistance and relative insulin deficiency. Insulin resistance is manifested by increased lipolysis and free fatty acid production, increased hepatic glucose production, and decreased skeletal muscle uptake of glucose. β-Cell dysfunction is progressive and contributes to worsening blood glucose control over time. Identifying participants in the pre-clinical stages by screening offers participants and providers an opportunity to modify long-term risk before serious complications occur. Early detection of diabetes can be facilitated by periodic screening of the people regularly. Counselling of the community may help in lifestyle modification and its role in controlling hypertension and diabetes along with its complications and which should also be emphasized.
Keywords: Diabetes mellitus, Foot ulcer, Prediabetes, Peripheral neuropathy.

INTRODUCTION
Diabetes is a predominant global risk for mortality and are seen with a drastic rise in developing nations in accordance with rise in age [1, 2]. Data on type 2 diabetes showed that 150 million were affected in 1980 to almost double to nearly 350 million in 2014 [3]. In developing countries, about 50% of population with type 2 diabetes remains undiagnosed [4]. Substantial burden of diabetes is on the rise in India. Patient awareness and timely diagnosis and intervention hold the key to limiting this twin epidemic [5]. The report of World Health Organization (WHO) shows that India tops the world with the largest number of diabetic subjects. This increase is attributed to the rapid epidemiological transition accompanied by urbanization, which is occurring in India. In 2011, the Indian Council of Medical Research – India Diabetes study estimated that 62.4 million populations were affected with diabetes and 77.2 million with pre-diabetes, respectively [6]. The International Diabetes Federation estimated that 40.9 million populations were affected with type 2

diabetes and may further rise to 69.9 million by 2025 [7]. Diabetes prevalence was highest in urban areas (12.4%), followed by midland (8.1%), highland (5.8%) and coastal areas (2.5%) [8]. Similar studies conducted in south Indian city Chennai, showed that the overall rise in prevalence of diabetes was 6% from 2000 to 2014 (13.5 to14.3%) [9]. In Indian scenario, 3.8% of diabetic subjects in rural and 11.8% in urban area showed the largest prevalence of diabetes in the world and the prevalence of hypertension ranges from 12%-17% in rural and 20-40% in urban population respectively [10]. Overweight and obesity showed impact on hypertension and diabetes on various studies [11]. In many countries, up to 50% of people with diabetes remain undiagnosed [12-14]. Failure to improve these levels of detection will mean that the opportunity to improve health outcomes with early intervention will be lost. Early treatment with successful glucose control significantly reduces the morbidity and mortality associated with diabetes. Earlier detection of diabetes also allows for the implementation of other treatments that reduce the vascular complications of diabetes [15,16] The biggest increase in diabetes cases is expected in India. India currently, have around 40 million cases of diabetes and these numbers are projected to increase countries where adoption of western lifestyles and the stress of urbanization both of which are expected to increase the morbidity associated with unhealthy lifestyles unfortunately are not on the decline [17].

ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

Table No.1 Classification of diabetes mellitus as per American Diabetes Association, 2007

TYPES	CAUSES
Type 1 DM (10%)	
a. Type 1A DM	Immune mediated (auto immune destruction of beta cells leads to insulin deficiency)
b. Type 1B DM	Idiopathic (insulin deficiency with tendency to develop ketosis)
Type 2 DM (80%)	
1. Other specific type of Diabetes (10%)	a. Genetic defect of beta cell function due to mutation in various enzyme (eg. Hepatocyte nuclear transcription factor-HNF, glucokinase) b. Genetic defect in insulin action (type A insulin resistance) c. Disease of exocrine pancreas (eg. Chronic pancreatitis, pancreatic tumours, post-pancreatetomy) d. Endocrinopathies (eg. Acromegaly, cushing syndrome, pheochromocytoma) e. Drugs or chemical induced (eg. Steroids, thyroid hormone, thiazides, beta-blockers) f. Infections (eg. Congenital rubella, cytomegalovirus) g. Uncommon forms of immune-mediated DM (anti-insulin receptors antibodies) h. Other genetic syndrome (eg. Down's syndrome, turner,s syndrome)
2. Gestational Diabetes	About 4% Women develop metabolic changes during pregnancy

PREDIABETES

Prediabetes is a condition that can lead to type 2 diabetes and heart disease. When you have pre-diabetes, your blood glucose (sugar) levels are higher than normal but are not high enough to be called diabetes [18]. People with pre-diabetes have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Some people have both IFG and IGT. It is important to assess patients for pre-diabetes or diabetes so they can be treated effectively and monitored for disease progression [19]. IFG is associated mainly with hepatic insulin resistance, resulting in fasting hyperglycemia,

whereas IGT is associated predominantly with muscle insulin resistance. Individuals with IFG and IGT manifest both muscle and hepatic insulin resistance. Among subjects with IGR, those with combined IFG and IGT most closely resemble subjects with Type 2 diabetes [20]. It has also been shown that there is progressive impairment of insulin secretion (or β-cell dysfunction) as well as worsening insulin resistance, in people with IGR, resulting in gradual increases in fasting and post-prandial plasma glucose concentrations. Progression to overt diabetes from IGR probably occurs gradually over a period of many years [21].

PATHOPHYSIOLOGY OF DIABETES

Type 1 DM accounts for 5-10% of all diabetes cases. It generally develops in childhood or early adulthood and results from immune mediated destruction of β-cells, resulting in an absolute deficiency of insulin. There is a long preclinical period (up to 9 to 13 years) marked by the presence of immune markers when β-cell destruction is thought to occur. Hyperglycemia occurs when 80% to 90% of β- cells are destroyed. There is a transient remission ("honeymoon" phase) followed by established disease with associated risks for complications and death. The factors that initiate the autoimmune process are unknown, but the process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various β-cell antigens (e.g., islet cell antibody, insulin antibodies) [22]. The signs and symptoms of type 1 diabetes are usually acute and have a rapid onset. The classic signs and symptoms of diabetes are the three "polyps":

- Polyuria (excessive urination)
- Polydipsia (excessive thirst)
- Polyphagia (excessive hunger)

Type 2 DM accounts for as many as 90% of DM cases and is usually characterized by the presence of both insulin resistance and relative insulin deficiency. Insulin resistance is manifested by increased lipolysis and free fatty acid production, increased hepatic glucose production, and decreased skeletal muscle uptake of glucose. β-Cell dysfunction is progressive and contributes to worsening blood glucose control over time. Type 2 DM occurs when a diabetogenic lifestyle (excessive calories, inadequate exercise, and obesity) is superimposed upon a susceptible genotype. The signs and symptoms of type 2 diabetes are Frequent urination (Frequent bed-wetting in children who have been toilet trained), excessive thirst, excessive hunger,weakness and fatigue, drowsiness, irritability, blurred vision or any change in sight, fruity breath, nausea and vomiting, sudden unexplained weight loss [22-24]. Uncommon causes of diabetes (1% to 2% of cases) include endocrine disorders (e.g., acromegaly, Cushing's syndrome), gestational diabetes mellitus (GDM), diseases of the exocrine pancreas (e.g., pancreatitis), and medications (e.g., glucocorticoids, pentamidine, niacin, and α-interferon). Impaired fasting glucose and impaired glucose tolerance are terms used to describe patients whose plasma glucose levels are higher than normal but not diagnostic of DM (see Diagnosis). These disorders are risk factors for developing DM and cardiovascular disease and are associated with the insulin-resistance syndrome. Micro vascular complications include retinopathy, neuropathy, and nephropathy. Macro vascular complications include coronary heart disease, stroke, and peripheral vascular disease [22-25].

PATHOPHYSIOLOGY OF DIABETIC FOOT ULCER

Etiological factors

The etiological pathways leading to diabetic foot ulcer include peripheral neuropathy [26]. This is present in more than 50% of diabetic persons above 60 years of age [27]. Peripheral neuropathy must usually be profound before leading to loss of protective sensation; the consequent vulnerability to physical and thermal trauma increases the risk of foot ulceration 7 fold [28,29]. Another factor in ulceration is excessive plantar pressure [30]. This is related to both limited joint mobility (at the ankle, subtalar, and first metatarsophalangeal joints) and to foot deformities [31,32]. Other causes include trauma (when repetitive), rubbing from footwear, injuries (mostly falls), cellulitis complicating tinea pedis, and selfinflicted trauma (eg, cutting toenails) [33]. Persons who had a previous foot ulceration could withstand fewer cycles of stress to their feet before an ulcer recurred [34].

Contributory factors

Once a foot ulcer develops, several factors may contribute to adverse outcomes. The main cause is atherosclerotic peripheral vascular disease, which is

twice as common in persons with diabetes as in persons without diabetes and particularly affects the femoropopliteal and smaller vessels below the knee, while frequently sparing the pedal vessels [35]. Diabetes is also associated with several intrinsic wound healing disturbances, including impaired collagen crosslinking and matrix metalloproteinase function, and immunologic perturbations, especially in polymorphonuclear leukocyte function [36-40]. Furthermore, persons with diabetes have a higher rate of onychomycosis and toeweb tinea infections that can lead to skin disruption [41-44]. Having a foot ulcer dramatically worsens physical, psychological, and social quality of life. The obesity and poor vision that are associated with diabetes may also impair selfcare. Optimal prevention (and treatment) outcomes require both a motivated patient and an effective medical care system [45,46].

CONCLUSION

Diabetes mellitus is increasingly common conditions in low income countries that expose patients to increased risk of mortality and morbidity. Identifying participants in the pre-clinical stages by screening offers participants and providers an opportunity to modify long-term risk before serious complications occur. Early detection of diabetes which can be facilitated by periodic screening of the people regularly. Counselling of the community may help in lifestyle modification and its role in controlling hypertension and diabetes along with its complications and which should also be emphasized. Risk factor management can decrease progression of prediabetes to diabetes so that diabetes can be prevented or delayed. Education about risk factors, complications, diet control, physical activity, regular checkups and screening will go a long way in achieving better control of diabetes and thus reduce the burden due to diabetes complications. Pharmacists are in the ideal position to reach this population and provide screening. Pharmacist-led educational interventions and discussions can provide simple, significant contributions in imparting knowledge on diabetes and hypertension along with its risk factors and complication by providing free screening benefits to the people living in the community.

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