Review Article

DIABETIC PANDEMONIUM: A REVIEW

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Accepted on: 21-10-2012; **Finalized on:** 30-11-2012.

ABSTRACT

Chronic hyperglycemia that persists even in fasting states is the defining characteristic of the diabetes. Diabetes mellitus is the only non-infectious disease designated as an epidemic by the world health organization. India with 50.8 million diabetics in 2010 and 87.0 million by 2030 is regarded as diabetic capital of the world. The complications of diabetes mellitus include retinopathy, nephropathy, angiopathy, neuropathy, diabietic myonecrosis, periodontal complications, erectile dysfunction and several others. Early detection of these diabetic aftermaths permits early intervention in the progression of the disease and restricts further life threatening complications. The present review is an effort to summarize several complications associated with diabetes and the available treatment options.

Keywords: Diabetes mellitus, gastroparesis, neuropathy, nephropathy, retinopathy.

INTRODUCTION

Diabetes mellitus is ranked seventh among the leading causes of death and is considered third when its fatal complications are taken into account[1]. India has become the diabetic capital of the world with 50.8 million diabetics by 2010, the number is projected to 57 million by 2025 and unfortunately this number is expected to cross 87.0 million by 2030[2,3].

Prevalence estimates of diabetes and impaired glucose tolerance (IGT) are high for all Asian countries and are expected to increase further in the next two decades[4]. Unlike in the West, where older populations are most affected, the burden of diabetes in Asian countries is disproportionately high in young to middle-aged adults[5,6].

Diabetes mellitus (DM) is characterized by hyperglycemia, lipoprotein abnormalities, raised basal metabolic rate, defect in reactive oxygen species scavenging enzymes and high oxidative stress induced damage to pancreatic β cells. DM is a metabolic disorder of multiple aetiology characterized by disturbance of carbohydrate, fat and protein metabolism which result from defects in insulin secretion or insulin action.

The effects of diabetes mellitus include long term damage, dysfunction and failure of various organs. Diabetes mellitus present characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non–ketotichyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment, death. Diabetic complications include hypertension, atherosclerosis etc. Microcirculatory and long-term complications include retinopathy, nephropathy, neuropathy and angiopathy and several others.

Estimated global healthcare expenditures to treat and prevent diabetes and its complications was at least 376 billion U.S. Dollars (USD) in 2010 and by 2030, this number is projected to exceed some USD490 billion[7].

Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. Present review presents a brief yet comprehensive description of various diabetes associated ailments including their treatment options available.

VARIOUS COMPLICATIONS OF DIABETES INCLUDE

1. DIABETIC NEUROPATHY

Among the three microvascular complications of diabetes, neuropathy remains the most difficult to diagnose, control, or reverse. It is a complex heterogeneous disorder that encompasses a wide range of abnormalities affecting both peripheral and autonomic nervous systems[8].

Diabetic neuropathy is categorized as:

1. Diffuse (multiple nerve involvement)

   A. Distal symmetric sensorimotor polyneuropathy (affecting sensory and motor function)

   B. Autonomic neuropathy (affecting involuntary function).

2. Focal neuropathy (single nerve involvement)

1. Diffuse (multiple nerve involvement)

A. Distal symmetric sensorimotor neuropathy **-** often referred to as peripheral neuropathy, affects 72% of Patients who are diagnosed with neuropathies[9]. Initially small and large fibres may be affected in varying degrees, but later both types may be involved. This is a length-dependent process, with the longest nerves affected earliest[10]. Acute sensory neuropathy is characterized primarily by pain while chronic sensorimotor neuropathy

proceeds in a gradual; subtle way with harmful effects. It is unrecognized because patients are asymptomatic until a specific situation arises such as a foot ulcer[11].

Symptoms

Symptoms include numbness, tingling and pain. Different terms can be used by the patient to describe the abnormal sensation: deep, aching, stabbing tingling, burning, "like water running over skin, discomfort heightened if bed sheet touch feet or by walking around barefoot, electric shock. Feeling like "dead skin", "wearing gloves or socks" (numbness despite pain) and gait ataxia may be reported.[10] Paraesthesia (in feet), is most marked in the evening. The paresthesias may be variously described as coldness, burning, tingling and ache, cramp-like or crushing. Often a patient relates a sensation of walking on air or pillows, or feeling that their feet are swollen[12].

***B. Autonomic neuropathy* -** This is the least recognized and understood complications of diabetes[13].It involve the entire autonomic nervous system (ANS), i.e. both parasympathetic and sympathetic divisions of the ANS[14, 15].

Signs and symptoms

Resting tachycardia, orthostatic hypotension, silent myocardial ischemia, oesophageal dysmotility, gastroparesis, diabeticorum, fecal incontinence, gallbladder atony and enlargement, neurogenic bladder (diabetic cystopathy), retrograde ejaculation, heat intolerance, gustatory sweating, hypoglycemia unawareness, hypoglycemia-associated autonomic failure, pupillomotor function impairment(e.g., decreased diameter of dark adapted pupil), are common complications associated [16].

2. Focal neuropathy

The focal and multifocal neuropathies are confined to single or multiple peripheral nerves and their involvements are referred to as mononeuropathy or mononeuritis multiplex. Mononeuropathies are due to vasculitis and subsequent ischemia or infarction. It involves cranial nerves III, IV, VI, and VII, thoracic and peripheral nerves, including peroneal, sural, sciatic, femoral, ulnar, and median[17]. Focal neuropathy differs from multifocal neuropathy in the face that FDN may relapse but their course remains self-limited while multifocal neuropathy can lead to very disabling neurological deficit[18].

Symptoms

Ophthalmoplegia, diplopia,[19] aching pain behind or above the eye (more prominent if 3rd cranial nerve is affected). Ptosis is marked, the eye is deviated outward (internal rectus muscle affected) [20].

Treatment

Hyperglycemic control delays appearance of neuropathy and slows progression intensive IDDM therapy[21] and pancreatic transplantation appears to halt the progression and frequency of neuropathy[22]. Aldose reductase inhibitors (ARIs) are also found to improve poltneuropathy but still they are found to produce mixed results on human trials[23].

2. RETINOPATHY

Diabetic retinopathy (DR) is defined as the presence of typical retinal microvascular lesions in an individual with diabetes[24]. In the western population, DR has been shown to be the cause of visual impairment in 86 percent of type 1 diabetic patients and in 33 per cent of type 2 diabetic patients[25].

Symptoms

Microaneurysms, haemorrhages, hard exudates (HEx), cotton wool spots (CWS), intraretinal microvascular abnormalities (IRMA), venous beading (VB), new vessels and fibrous tissue comprise the clinical features of DR[26].

Diabetic retinopathy is primarily classified into-

a. Non proliferative DR (NPDR) or simple, or background retinopathy-

It includes red-dots in the fundus, and exudates. Presence of red dots is initial indirect signs of vascular hypermeability and capillary closure, [27] decreased numbers of retinal pericytes and the appearance of acellular capillaries. Pericytes play a critical role in the maintenance of endothelial tight junctions and microvascular blood flow. DR leads to breakdown of small-vessel and capillary endothelium integrity. Retinal haemorrhage is an indication of disruption of endothelium and basal lamina, enabling blood components to diffuse into the neuroretina[28]. Retinal ischemia is attributed to changes in vascular autoregulation and microthrombosis formation[29].

b. Proliferative DR (PDR)

As the disease progresses, a proliferative stage develops when new retinal vessels proliferate from existing vasculature (angiogenesis)[30]. Pre-retinal or vitreous haemorrhage in combination with neovascularisation of the disc covering > 25% of the surface area of the disc, is considered a high risk for progressive loss of vision[31]. Blood vessels usually arise in the interface between perfused and non-perfused areas of the retina and doptic disk[32]. These new vessels are extremely immature, fragile, permeable and bleed very easily. On proliferation of retinal blood vessels they may grow outside of the retinal plane onto the vitreous body[33].

Treatment

The National Institute for Clinical Excellence guidelines recommend that DR screening tests have a sensitivity of at least 80%, specificity of at least 95%, and a technical failure rate of no greater than 5%[34]. The retina may be examined by ophthalmoscopy and slit lamp biomicroscopy using 78 D lens, or by using retinal photography[35].

Optical coherence tomography (OCT), [36] laser photocoagulation and vitrectomy have also improved the quality of life in the patients and prevented debilitating visual loss [37].

3. NEPHROPATHY

Diabetic nephropathy has become the leading cause of end-stage renal disease (ESRD) in Europe and the US managed by renal replacement therapy (kidney dialysis and/or renal transplantation)[38]. Diabetic nephropathy is characterized by the presence of proteins in urine at the concentration of 0.5 g/24 h and the condition has been referred to as overt nephropathy, clinical nephropathy, proteinuria, or macro albuminuria[39].

It has been estimated that about 20 to 30% of individuals with type 1 or type 2 diabetes develop evidence of nephropathy[40]. Diabetic nephropathy is more prevalent among African Americans, Asians, and Native Americans than Caucasians[41].

Symptoms

Microalbuminuria (incipient nephropathy), which may progress to overt proteinuria (dipstick urinalysis positive for proteinuria) followed by the emergence of hypertension, a declining GFR and later development of ESRD, renal hypertrophy, glomerular basement membrane thickening, mesangial expansion and diffuse intercapillary glomerulosclerosis (degenerative process resulting in scarring of the renal glomeruli)[42]. Swollen feet and ankles, leg cramps, especially at night Weakness, paleness, anaemia, dry itchy skin, A need to urinate more often, especially at night are some important indications.

Intensive blood glucose control, Intensive blood pressure control, Renin-angiotensin system blockade, Dyslipidemia, Diet intervention are the strategies for the treatment of DN.

4. UTI'S ASSOCIATED WITH DIABETES

Human urine support bacterial growth due to its favourable chemical composition[43]. Diabetics are more prone and 80% involve upper urinary tract infections,[44] with micro-organisms Escherichia coli, Staphylococcus saprophyticus, Proteus, Klebsiella and enterococci[45]. Defects in the function of lymphocytes, neutrophils, and monocytes contribute to the impact of infectious diseases. Polymorphonuclear neutrophils (PMNs) in these patients show alterations in chemotaxis, adherence, phagocytosis, intracellular killing, and bactericidal activity accompanied by decreased levels of leukotriene B4, prostaglandin E, and thromboxane B2[46].

Bacteria colonising the perineum and vagina can enter the bladder and extend towards the kidneys. The most important defence mechanisms of the host, are the urine flow from the kidneys to the bladder and the intermittent voiding, that results in complete emptying of the bladder. Patients with urinary obstruction, stasis and reflux have more difficulty in clearing bacteria and these conditions seem to influence the development of a UTI [47].

Few factors such as age, metabolic control, and duration of DM, diabetic cystopathy, more frequent hospitalisation, instrumentation of the urinary tract, recurrent vaginitis and vascular complications are also proposed to contribute to increased risk of UTI'S [48].

Symptoms and treatment

Dysuria, frequency, urgency, haematuria, and/or abdominal discomfort,[49] are common and rare infections include malignant otitis externa, mucormycosis, emphysematous cystitis, and emphysematous pyelonephritis, soft-tissue infections. Treatment of UTI'S include sufficient fluid intake, complete emptying of the bladder during voiding, less use of spermicides and restrictive catheter use[50]. Oral or vaginal administration of lactobacilli is also found to be effective as it competitively cause exclusion of uropathogens[51].

5. DIABETIC FOOT

Diabetic foot ulcers are estimated to affect 15% of all diabetics during their lifetime and precede almost 85% of all foot amputations[52]. Diabetes by virtues of its other complications like neuropathy and vasculopathy and other factors alter the musculoskeletal and soft tissue mechanics in a manner that elevates planter pressure and makes tissue damage more likely, causing non resolving neuro-ischemic ulcers at the weight bearing sites. This is why most of the skin injuries in diabetics are seen on the planter surface, frequently at the site of highest pressure under the foot [53].

It is estimated that more than 5% of diabetic patients are found to have a history of foot complications (foot ulceration, charcot osteoarthropathy and amputation-removal of a limb or other appendages or outgrowth of the body is done) which may rise to as high as 25%[54].

Diabetic foot infections (DFIs) usually arise in skin ulceration that occurs due to peripheral (sensory and motor) neuropathy complicated by deformity, callus, and trauma.

Secondary medical complications, such as osteomyelitis and amputation are linked to vascular insufficiency, infection and failure to implement effective treatment of DFUs (diabetic foot ulcers)[55]. Infection proceeds when micro-organisms (1 or more species) colonize the wound and proliferate leading to tissue damage, penetrating to deeper tissues, often reaching bone[56].

Signs and symptoms

Presence of foot deformity, particularly claw toes and prominent metatarsal heads, other microvascular complications increases in plantar foot pressures, peripheral oedema and a past history of foot ulcers are prominent risk for ulcers. Diabetics are immune-compromised and fail to mount any physiologic response to the infection, therefore secondary signs are to be detected including exudates, delayed healing, friable granulation tissue, discoloured granulation tissue, foul odour, pocketing at the wound base, and wound

breakdown[57]. Indications for amputations are usually vascular diseases, diabetes (85%), trauma (10%) and tumors (3%)[58].

Treatment

Diagnostic tests with greater sensitivity have been developed that identify infections or pathogens within hours instead of days e.g. polymerase chain reaction assay[59]. Moulded insole, Extra depth shoes, Rocket sole shoe, Polymer insole material shoes, Custom-made foot wear, Cobra pad are different types of foot wears that has shown improvement in 86% of neuropathic ulcers[60].

6. CARDIOVASCULAR COMPLICATIONS AND DIABETES

Cardiovascular disease (CVD) is a leading cause of disability and the leading cause of death in the world. There are a number of risk factors for CVD, including age, obesity, sedentary lifestyle, tobacco use, but one of the most notable risk factors is diabetes. People with diabetes have a two- to four-fold higher risk of developing cardiovascular disease than their counterparts without diabetes. Cardiovascular complications account for at least two-thirds of health care costs for people with type 2 diabetes[61].

The so-called "Asian Indian Phenotype" refers to an amalgamation of clinical (larger waist-to-hip and waist-to-height ratios signalling excess visceral adiposity), biochemical (insulin resistance, lower adiponectin, and higher C-reactive protein levels) and metabolic abnormalities [raised triglycerides, low high-density lipoprotein (HDL) cholesterol] are more prevalent in individuals of South Asian origin and predispose this group to developing diabetes and premature CHD [62].

Signs and symptoms

Include shortness of breath (usually associated with chest pain, physical activity, or emotional stress), dizziness, diaphoresis, nausea and jaw pain, fatigue, swollen ankles (fluid retention), low cardiac output, and palpitations[63].

Treatment

Antihypertensive therapy leads to 35% to 40% reduction in stroke incidence and a 20% to 25% reduction in MIs. Due to Reno-protective effects, ACE inhibitors and ARBs (angiotensin receptor blocker) are often used as initial therapy in patients with diabetes. In addition, low-dose aspirin therapy, smoking cessation, and other lifestyle changes have proved beneficial.

7. SEXUAL DISORDERS

Erectile dysfunction (ED) is a common condition among men with diabetes[64] and it is associated with reduced quality of life among those affected[65]. Indiabetic men, the prevalence of impotence have been estimated to be between 35-50%[66]. The cause of ED in diabetic men is multi-factorial with neuropathy, atherosclerosis of penile blood vessels and psychological factors being the main underlying contributors[67].

The Autonomic nervous system imperfections due to diabetes, accounts for a vast range of sexual and reproductive disorders [68]. Sexual problems in women with diabetes mostly include decreased sexual desire, sexual dissatisfaction, orgasmic disorder, arousal disorder and lubrication[69]. Intruitos vagina, labium minora and clitoris are the most deteriorated genital sites affected by diabetes in women [70]. In men with diabetes, erectile dysfunction is more frequent orgasmic disorder, premature ejaculation, hypoactive sexual desire disorder and retrograde ejaculation[71].

The pathogenic factors of sexual dysfunction among diabetic women include hyperglycaemia, infections, as well as vascular, neural, neurovascular and psychosocial derangements. Hyperglycaemia reduces hydration of vaginal mucosa and results in poor vaginal lubrication and dyspareunia[72].

Depression seems to be the most established risk factor for sexual dysfunction in women with diabetes[73]. Thyroid disorders, hypothalamic-pituitary disorders, and polycystic ovary syndrome can also contribute to sexual problems in these women[74].

Treatment

Hormonal replacement therapy improves sexual function in menopausal women eg. Use of estrogens for the treatment of FSD Estrogens may improve sexual function by inducing the proliferation of the superficial cell layer of the vaginal mucosa, improving the vaginal pH and elasticity, and increasing vaginal blood flow to enhance lubrication[75].

8. GASTROPARESIS

Complications involving the gastrointestinal tract are common in patients with diabetes mellitus [76]. Diabetic gastroparesis (DGP) is a clinical condition characterized by delayed gastric emptying and associated upper gastrointestinal (GI) symptoms in the absence of mechanical obstruction[77].

NO regulates the muscle tone of the lower esophageal sphincter and pylorus. Dysfunction of NO neurons in the myenteric plexus may be responsible for many GI diseases, including DGP[78].

Normal gastric myoelectrical activity is initiated by the ICC (interstial cells of cajal), located in the muscular wall of the gastric antrum and corpus, at a rate of 3 cycles/min disturbance in this cycle also contribute to DGP[79]. Electrolyte abnormalities (eg, hypokalemia, hypomagnesemia) and GI hormones (eg, motilin, gastrin) may also have roles in the pathogenesis of DGP [80].

Gastric emptying is controlled by fundus and is dependent upon the volume of the gastric content. As a result of impaired vagal function proximal stomach relaxes less and the emptying of fluids in diabetic patients prolongs[81].

Symptoms

Symptoms include, early feeling of satiety, nausea, vomiting, regurgitation, abdominal fullness, epigastric pain belching, abdominal pains, bloating, weight loss, and anorexia[82]. Patients with gastroparesis may vomit foods which they had eaten many hours even many days ago. Episodes of nausea and vomiting may continue for days, months or may appear time to time[82].

Treatment Goals and Management Options

Glucose control- Insulin therapy, upper gastrointestinal symptom control-Prokinetic drugs, Antiemetic agents Analgesic agents, Botulinum injection, Gastric electrical stimulation

Adequate nutrition-Small frequent meals, Liquid supplements, Enteral feeding Percutaneous endoscopic jejunostomy, total parenteral nutrition Improve gastric emptying-Glucose control, Prokinetic drugs, Gastric surgery[83].

9. PERIODONTAL DISEASES

Diabetes is most common from age 40 years, when vascular disease is starting to affect the fine vessels supplying the tooth and diabetes greatly accelerates vascular disease in the teeth as well as in the rest of the body. Saliva washes the teeth clear of debris and bacteria but age and diabetes affect the autonomic nervous system and hyperglycaemia glycosuria causes dehydration. Both reduce salivary flow. The resulting dry mouth and teeth are uncomfortable (particularly for people with dentures), but also predispose patients to caries and periodontal disease. Further, hyperglycaemia affects immune function and the inflammatory response, setting the scene for caries, periodontal disease and the problems associated with progressive dental and periodontal destruction and infection[84].

Neutrophil adherence, chemotaxis, and phagocytosis are often impaired, which may inhibit bacterial killing in the periodontal pocket and significantly increase periodontal destruction[85]. Periodontal pocket are the site of persistent bacterial wounding, thus intact wound-healing response is critical to maintain tissue health. High glucose levels in the gingival crevicular fluid may directly hinder the wound-healing capacity of fibroblasts in the periodontium by inhibiting attachment and spreading of these cells that are critical to wound healing and normal tissue turnover[86].

Treatment

A periodontal treatment plan for the diabetic patient should encompass the following goals

• Complete periodontal assessment, even in children and identify level and consistency of diabetic control and consultation with primary care provider and complete medical history of diabetic state (updated at each visit)

• Continued appropriate diabetic control throughout treatment

• Consider systemic antibiotics if diabetes is poorly controlled

• Provide patient education and motivation

• Prepare the office for diabetic medical emergencies [87].

10. ENCEPHALOPTHY

The relationship between diabetes and cognitive dysfunction was already proposed in 1922[88]. Brain was found to be another site for diabetic end-organ damage where cerebrovascular accidents were found to possess significant effects on cognitive deficits [89] and the condition is referred to as diabetic encephalopathy.

The cognitive domains predominantly affected are attention, processing speed (or complex information processing), verbal memory,[90] metabolic syndrome with hypertension, dyslipidemia and obesity show worse cognitive performances [91].

Recent studies reported an association between type 2 diabetes and the development of both vascular dementia and Alzheimer's disease[92]. Children diagnosed with T1DM before the age of 6[93], at a time when the brain is still developing[94] are particularly vulnerable showing impaired results on cognitive tests, affecting memory and learning abilities.

Structural abnormalities have been accompanied by increased sorbitol and decreased taurine levels, suggesting activation of the polyol-pathway and impaired neurotrophic support[95].

11. DIABIETIC MYONECROSIS

Diabetic myonecrosis (DM) or diabetic muscle infarction (DMI) was first described in 1965 by Angarwall and Stener[96]. It is a rare complication of diabetes and is associated with non-traumatic swelling of the affected extremity and sudden onset of muscle pain. Disease can be bilateral in more than one third of cases [97].

According to a proposed mechanism it begins with a thromboembolic event, leading to compartment syndrome and resultant ischemic muscle injury. This process is followed by inflammation, hyperemia, and reperfusion associated with reactive oxygen species that cause further damage both directly and through worsening of the compartment syndrome from oedema[98].

Symptoms and treatment

Clinical features include proximal muscle involvement; symmetric pattern; acute muscle pain and swelling; and chronic squeal of atrophy, induration, and contractures. Bilateral extremity involvement is common[99]. Most important, MRI reveals multifocal areas of involvement in a patchwork pattern (characteristic of DMI),[100] infarction, inflammatory tissue reaction, hemorrhage, fibrosis, and muscle regeneration. Acute cases reveal necrotic muscle, nerve, and blood vessels infiltrated by polymorphonuclear cells at the margins of the zone. The

walls of small vessels become hyalinized and thickened and the lumens narrow.[99]

Diabetes myonecrosis is a self-limiting disease, full recovery is expected overtime in most of the cases. Tight glycemic control and cessation of smoking is prudent. Excisional biopsy, early debridement and mobility have lead to complications and delayed recovery[101].

12. DIABETES AND SKIN DISEASES

Type-2 patients develop more frequent skin lesions due to infections, while type 1 patients are associated with more auto immune type cutaneous lesions[102.]

The Skin diseases associated with diabetes include-

a) **Necrobiosis lipoidica -** Necrobiosis lipoidica (NL) appears in 0.3% to 1.6% of diabetics[102]. It begins as an erythematous, slowly enlarging irregular plaque with an elevated border. NL becomes more brownish yellow, telangiectatic, porcelain-like, and depressed[103]. Although not painful to pinprick and fine touch, may ulcerate or from trauma, resulting in pain [104]. Proposed causative factors include obliterative endarteritis, immune mediated vasculitis, immune factors, delayed hypersensitivity, non-enzymatic glycosylation platelet aggregation, defective mobility of neutrophils, and vascular insufficiency[103].

b) **Diabetic dermopathy -** Affects 7% to 70% of diabetics (predominantly men> 50 yrs). Also known as shin spots and pigmented pretibial papules, is considered the most common cutaneous manifestation of DM[104].

c) **Acanthosis nigricans -** Seen in situations of insulin resistance, including type II DM, obesity, and total lipodystrophy[105]. Clinically it is represented as hyper pigmented velvety plaques in body folds, mostly the axillae and neck[106.] Other locations include the groin, umbilicus, areolae, submammary regions, and hands (tripe hands) [103].

d) **Acquired perforating dermatosis** - Characterized by the transepidermal elimination of some component of the dermis. Consists of pruritic, 2- to 10-mm, hyperkeratotic, dome-shaped, often umbilicated papules and nodules on the extensor limbs, trunk, dorsal hands, and less so the face[107].

e). **Diabetic thick skin-** Consists of abnormal collagen, which may be caused by hyperglycemic accelerated non-enzymatic glycosylation. These glycosylation end products lead to increased cross-linking rendering the collagen fibers resistant to degradation by collagenase, which in turn leads to excessive accumulation of abnormal collagen [Brik R *et al* (1991)]. Quantitative estimations of skin thickness are done by microscopic measurement, caliper measurement, ultrasonography, and radiologic investigation[107].

CONCLUSION

Diabetes with a long list of associated complications is the latest challenge for the physicians/clinicians and especially for researchers. Indians are the vulnerable target for this disorder because of genetics, sedentary life style and other reasons. It is easier to understand and control hyperglycemia than diabetes than its complications thus timely diagnoses and intervention may be sort and continuous research efforts must be carried on to minimise human sufferings.

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