East African Scholars Journal of Medical Sciences
Abbreviated Key Title: East African Scholars J Med Sci
ISSN 2617-4421 (Print) | ISSN 2617-7188 (Online) |
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-2 | Issue-9| Sept -2019 | DOI: 10.36349/EASMS.2019.v02i09.001

Review Article

Diabetes Mellitus and Systemic Diseases – A Reveiw

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Abstract: diabetes mellitus is a serious metabolic disorder affecting all the age groups, according to WHO over 180 million people suffers from diabetes malleus & over 95% population suffers from type 2 diabetes. Diabetes is associated with both micro vascular and macro vascular complications, the current review focus on co-relation of diabetes with various major body systems & pathologies associated with them.

Keywords: Diabetes mellitus, Risk factors, Systemic complications.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by persistent increased concentration of blood glucose above normal level leading to hyperglycemia (Watkins, P.J., & Thomas, P.K. 1998). It is characterised by autoimmune destruction of β cells of pancreas with its adverse consequences on metabolism of lipids, carbohyradates, water and minerals (Vojetkova, J. *et al.*, 2012). According to WHO, approximately 180 million people worldwide currently have type 2 DM (formerly called adult-onset diabetes); over 95% of people with diabetes have this form. The number of people with type 2 DM is estimated to double by 2030 (World Health Organization. 2007). More than 382 million people are currently affected worldwide, and this number is expected to rise to 592 million by 2035 (International Diabetes Federation. 2013).

Recent findings have strongly suggested that diabetes affects the systemic overall health of an individual, commonly referred to diabetic complication. They include cardiovascular disease, respiratory system, hepatic, gastrointestinal problems, musculoskeletal and microvascular complications Diabetes mellitus is a global health issue affecting children, adolescent and adults.

DIABETES MELLITUS AND NERVOUS SYSTEM

Neuropathies of Diabetes

Diabetic neuropathies are common in type-1 and type-2 diabetes. Patient suffering from diabetes neuropathy (hyperglycaemic) complains of pain in the feet and lower legs, which rapidly resolve on establishment of euglycaemia. Diabetic patient shows poor nerve conduction velocity and recovers with correction of hyperglycemia (Gregersen G. 1968; Ward, J. D. *et al.*, 1971).

Foot Ulceration

Diabetic sensory polyneuropathy is a major risk factor for the development of plantar ulceration because of the loss of protective sensation (Boulton, A. J. M. *et al.*, 1986; Young, M.J. *et al.*, 1992). Autonomic neuropathy which gives rise to anhydrosis and dry fissured skin also contributes, as does foot deformity, which leads to abnormal pressure distribution in the foot when standing or walking (Boulton, A. J. *et al.*, 1983). Its main etiological factor is loss of venevasomotor reflex because of sympathetic failure.

Neuropathic Osteoarthropathy (Charcot Joint)

Neuropathic joint degeneration affects about 10% of patients with neuropathy and more than 16% of

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http://www.easpublisher.com/easjms/

Article History
Received: 14.07.2019
Accepted: 29.08.2019
Published: 02.09.2019

those with a history of plantar ulceration. It is related to loss of protective joint sensation and osteopenia (Stevens, M. J. *et al.,* 1992; Cundy, T.F. *et al.,* 1985). It most commonly involve tarsometatarsal, followed by the metatarsophalangeal and then the subtalar and ankle joints. Diabetic neuropathy affects the blood vessel and blood flow by sympathetic denervation causing structural and functional changes in arterial smooth muscles. Degenerative changes lead to calcification and even ossification and thus to stiffening of the arteries (Edmonds, M. E. *et al.,* 1982).

DIABETES LINKED WITH CARDIOVASCULAR SYSTEM

Type 2 diabetes mellitus (T2DM) is commonly associated with cardiovascular disease (CVD) and risk factors, such as hypertension, obesity, and dyslipidemia. CVD is the most common cause of death in people with diabetes. It has been found that presence of diabetes significantly increases the risk (two- to fourfold) for developing CVD (Barrett-Connor, E.L. *et al.,* 1991). According to the study done by SR Preis *et al.,* . It has been found that T2DM is associated with clustered risk factors for CVD. Adults with diabetes have a 77%–87% prevalence of hypertension, a 74%–81% prevalence of elevated low-density lipoprotein cholesterol (LDL-C), and a 62%–67% prevalence of obesity (Preis, S. R. *et al.,* 2009).

Blood Pressure Control:

Intensive lifestyle intervention may be sufficient to lower blood pressure in patients with mild hypertension (American Diabetes Association. 2014). Evidence suggests that insulin resistance plays a significant role in the interplay between diabetes, hypertension, and CVD. Various studies indicate that the presence of hypertension is a very strong driver of CV outcomes in individuals with diabetes (Chen, G. *et al.,* 2011). It has been suggested that CVD risks starts to increase above a blood pressure of 115/75, and is then doubled for every 20 mmHg increase in systolic blood pressure, or for every 10 mmHg increase in diastolic blood pressure (Lewington, S. *et al.,* 2002). Maintaining the blood pressure to a normal value in patients with hypertension and diabetes reduces the risk of cerebrovascular accidents and congestive heart failure (Curb, J. D. *et al.,* 1996).

Dyslipidemia:

Altered lipid profile associated with T2DM has been most common cause of increase insulin resistance (Krentz, A.J. 2003). And is characterised by increased concentration of small dense LDL-C particles. Management of LDL-C concentrations remains a major goal of diabetes treatment, with current guidelines emphasizing lowering LDL-C to a target goal of 100 mg/dL for T2DM patients without overt CVD. Preventory measures include regular physical activity and maintaining a healthy eating pattern. Recommended guidelines include atleast 150 minutes per week of moderate aerobic physical activity remains a cornerstone of T2DM management and prevention of CVD in T2DM (American Diabetes Association. 2014).

Antiplatelet Therapy:

Diabetic patients have altered fibrinolytic and prothrombotic mechanisms leading to increased bleeding tendencies and there is an increased thrombotic tendency, due to platelet hyper-reactivity, decreased fibrinolysis, and increased activation of prothrombotic coagulation factor (Ferreiro, J.L. *et al.,* 2010). A number of antiplatelet agents have been shown to be of benefit for the prevention of CV events in certain groups, with aspirin being the most commonly used. Other antiplatelet drugs include clopidogrel, prasugrel, ticagrelor.

DIABETES AND RESPIRATORY SYSTEM

Diabetic patients most commonly suffer from various respiratory complications including .Decreased vital lung capacity and pulmonary volumes , decreased diffuse lung capacity for carbon monoxide , lower basal bronchial tone, lower cough reflex sensitivity , increased incidence of obstructive sleep apnea, increased respiratory infections. Disorders of respiratory muscles or phrenic nerve

Respiratory System Infections:

Compared to healthy subjects, patients with T1D and T2D are at increased risk for respiratory tract infections and the risk increases with recurrences of common infections (Muller, L. M. A. J. *et al.,* 2005). Multistage damage of immunity functions belongs to factors contributing to respiratory infections (Jesenak, M. *et al.,* 2008). Patients with diabetes are more prone to tuberculosis infection and the course may be more serious (Webb, E. A. *et al.,* 2009). *Staphylococcus aureus*, *Legionella pneumoniae*, *mycosis* (*mucormycosis*, *aspergillosis*) and also resistant nosocomial infections represent other eventual pathogens causing infections in diabetic patients (Durdik, P. *et al.,* 2010).

Pulmonary Volumes:

Poor metabolic control has been found to be associated with reduced vital capacity in children and adolescents with T1DM (Pieniawska, A. *et al.,* 2012). Studies done by V Suresh *et al.,* (2011) had shown that pulmonary function abnormalities were found in 51.2% of children with mean T1D duration 3 years, thereof 45.6% had restrictive pattern of spirometry and 7.7% had an obstructive pattern. And similarly low FVC (forced vital capacity) and low FEV (forced expiratory volume) is found in patients with T2DM (Suresh, V. *et al.,* 2011).

Cough Reflex Sensitivity:

Behera *et al.,* reported that diabetic patients with neuropathy had significantly higher cough reflex

threshold to citric acid compared to diabetic subjects without neuropathy (Behera, D. *et al.*, 1995). The suggestion of vagal denervation has been expressed. Cough reflex sensitivity (CRS) was examined by inhalation of increasing concentration of tussigen (0.61-1250 μmol/l) with computer-guided nebulisation. Patients with cardiovascular autonomic neuropathy, examined by heart rate variability, required significantly higher concentration of capsaicin needed for two coughs and also for five coughs compared to patients without diabetic autonomic neuropathy (Havlicekova, Z. *et al.*, 2009).

DIABETES AND GASTROINTESTINAL TRACT

BOTH TYPE 1 and Type 2 DM affect a patient's entire git from esophagus to the anus. It is believed that hyperglycemia leads to autonomic neuropathy which leads to git abnormalities. Most common problems encountered in patients with DM are constipation diarrhoea, abdominal pain, nausea and vomiting.

Symptoms and Complications*:*

Acc. To study done by J.H SELLIN and E.B CHANG (2008) patients with DM complains of upper git involving nausea, vomiting and heartburn (Sellin, J.H., & Chang, E.B. 2008). The pacemaker cells of the intestinal tract—the interstitial cells of Cajal (ICCs)—seem to be disrupted or altered in some way in diabetes. Other potential causes of intestinal dysfunction include ischemia, hypoxia, and mitochondrial dysfunction (Leinninger, G.M. *et al.*, 2006).

Esophagial Disorders:

Esophageal complaints among patients with diabetes include heartburn, dysphagia and odynophagia (ie, painful swallowing). Autonomic and motor neuropathy is the main causes for these complaints (Sellin, J.H., & Chang, E.B. 2008).

Gastric Abnormalities*:*

Patient usually involve gastroparesis or upper GI bleeding .symptoms include nausea vomiting , early satiety, bloating ,epigastric pain swere conditions may cause weight loss (Feldman, M. *et al.*, 2006). Coordination takes place among smooth muscle, enteric and autonomic nerves, and the ICCs hyperglycemia lead to delayed gastric emptying secondary to vagus autonomic nerve impairment, as well as damage to enteric nerves and the ICCs (Huizinga, J.D. 1998).

Diabetic Diarrhea:

Diarrhea is most common in patients with type 1 DM in men. Autonomic neuropathy certainly plays a role in this condition by altering sympathetic function in the gut and by reducing input from alpha-2 adrenergic receptors. These changes lead to decreased fluid and electrolyte absorption (Talal, A.H. *et al.*, 1997).

Colonic Disease*:*

Constipation, typically requiring laxative use, is the most common gastrointestinal complaint reported by patients with diabetes. Smooth muscle myopathy and loss of ICC function are the most likely causes of constipation among these patients. Autonomic neuropathy and neuroendocrine imbalances could also contribute to the problem (Maleki, D. *et al.*, 2000).

DIABETIC EFFECT ON HEPATIC SYSTEM

Type 2diabetes is most commonly associated in patients who have liver diseases, such as nonalcoholic fatty liver disease, chronic viral hepatitis, hemochromatosis, alcoholic liver disease, and cirrhosis.

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***Non Alcoholic Fatty Liver Disease*:**

It occurs when there is lipid accumulation within the hepatocytes. This can be associated with hepatocyte injury and inflammation that results in hepatic fibrosis and ultimately in cirrhosis. Diabetes is present in 21% to 45% of patients with non-alcoholic fatty liver disease (Harrison, S.A. 2006).

Viral Hepatitis:

The National Health and Nutrition Examination Survey identified a 3-fold increased risk of type 2 diabetes in subjects who were aged more than 40 years and had chronic HCV, compared with HCV-negative participants. The reason for the link between HCV infection and type 2 diabetes may relate to viral effects because specific HCV genotypes (particularly genotype 1) have been linked to insulin resistance (Hui, J. M. *et al.*, 2006).

Hemochromatosis*:*

Conte *et al.*,. found increased prevelance of hemochromatosis in patients with Type 2 DM. Its pathogenesis involve accumulation of iron in exocrine cells, accumulation occur particularly in insulin secreting beta cells. It leads to increase insulin resistance .leading to hyperglycemia (Rahier, J. *et al.*, 1987).

Alcoholic Liver Disease*:*

In a prospective follow-up study of 8663 men, heavy drinking (_270 g/wk) was associated with a 2-fold increased risk of developing type 2 diabetes compared with moderate drinking (60-120g/wk). Excessive alcohol intake may have a direct effect on the development of type 2 diabetes by decreasing insulin-mediated glucose uptake in the acute situation and by damaging pancreatic islet cells with chronic use (Wei, M. *et al.*, 2000).

OSTEOPOROSIS AND DIABETES

Type 1 diabetes has been associated with low bone density. Duration of diabetes seems to play a key role given the lower BMD (bone mineral density) found

among patients who have had diabetes for >5 years. In the Iowa Women's Health Study, women with type 1 diabetes were 12.25 times more likely to report having had a fracture compared to women without diabetes (Nicodemus, K.K., & Folsom, A.R. 2001).

Pathogenesis:

Both type 1 and type 2 are associated with a decrease in bone quality that leads to increase in low stess fractures called as Diabetic Osteopathy. One of the main pathological mechanisms behind this is excessive accumulation of Advanced Glycation End products (AGEs) on collagen of bone extracellular matrix. In patients with diabetes mellitus, concentrations of bone resorption biomarkers , such as aminoterminal and carboxyterminal crosslinking telopeptide of type 1 collagen (NTX and CTX) or deoxypyridinoline, can be increased, decreased or not altered , depending on the study, and difference exist between patients with T1DM and those with T2DM (Hofbauer, L. C. *et al.*, 2007).

DIABETES RELATED MICROVASCULAR AND MACROVASCULAR DISEASES

Pathogenesis:

Chronic hyperglycemia plays a major role in the initiation of diabetic vascular complications through many metabolic and structural derangements, including the production of advanced glycation end products (AGE), abnormal activation of signaling cascades (such as protein kinase C [PKC]), elevated production of reactive oxygen species (ROS, oxygen-containing molecules that can interact with other biomolecules and result in damage), and abnormal stimulation of hemodynamic regulation systems (such as the renin-angiotensin system [RAS]).

MICROVASCULAR COMLICATIONS

Diabetic Retinopathy:

Diabetic retinopathy (DR) is a microvascular complication that can affect the peripheral retina, the macula, or both and is a leading cause of visual disability and blindness in people with diabetes (World Health Organization. 2007). In studies including people with both type 1 diabetes and type 2 diabetes, after 30 years of diabetes, most patients had some form of DR, and over half had proliferative DR; people with type 1 diabetes and taking insulin had the highest prevalence of DR, and people with type 2 diabetes diagnosed after age 30 had the lowest prevalence of DR (Klein, R. *et al.*, 1984).

Diabetic Neuropathy*:*

Approximately one half of people with diabetes have some form of peripheral neuropathy (PN), either polydiabetic or monodiabetic neuropathy. People with diabetes also frequently have autonomic neuropathy, including cardiovascular autonomic dysfunction, which is manifested as abnormal heart rate (HR) and vascular control (Vinik, A.I. *et al.*, 2003). People with diabetic neuropathy most commonly encounter loss of lower-extremity sensation coupled with impaired peripheral vascular function can contribute to lower-extremity (commonly foot) ulceration (Boulton, A.J. 1997).

Diabetic Nephropathy

It is more common in both type 1 and type 2 DM. Its 1st complication is microalbuminurea which progress to overt albumin urea, indicating severe renal failure leading to end stage renal disease (ESRD) . Other characteristic features of DN include thickening of glomerularn basement membranes and glomerular hyperfiltration, leading to mesangial (central part of the renal glomerulus) extracellular matrix expansion and further increases in urinary albumin excretion (Friedman, E. 1990).

MACROVASCULAR COMLICATION OF DIABETES

Cerebrovascular disease: stroke is the main risk in people with diabetes is up to 2 to 4 fold greater greater, more so in white people and women. Diabetes adversely affects the cerebrovascular circulation by increasing the risk. As in other diabetes-related complications, hyperglycemia appears to be a significant factor in stroke. Hyperglycemia is a significant predictor of fatal and nonfatal stroke and death from stroke. Hyperinsulinemia (ie, elevated blood insulin levels) also appears to be a risk factor for stroke (Shinozaki, K. *et al.*, 1996).

Peripheral Artery Disease:

It is characterised by occlusion of lower extremity arteries which causes intermittent claudication and pain especially upon exercise and activity. Diabetes related PAD is more common leading to foot ulcerations and lower extremity amputation.

MUSCULOSKELETAL COMPLICATIONS OF DIABETES

Conditions Affecting Hands

a).Diabetic cheiroarthropathy(stiff hand syndrome):This syndrome is characterized by thick, tight, waxy skin reminiscent of scleroderma. Limited joint range of motion (inability to fully flex or extend the fingers) and sclerosis of tendon sheaths are also seen.

b)Flexor tenosynovitis (trigger finger): Patients complain of a catching sensation or locking phenomenon that may be associated with pain in the affected fingers.

C*) Carpel tunnel syndrome*: Carpal tunnel syndrome (CTS) is seen in up to 20% of diabetic patients. Its specific relationship to diabetes is thought to be median nerve entrapment caused by the diabetes. Classically, patients complain of burning, paresthesias, or sensory loss in the median nerve distribution.

Conditions Affecting Shoulders

a*). Adhesive capsulitis*: This term refers to a stiffened glenohumeral joint usually caused by a reversible contraction of the joint capsule.

b*).Calcific periarthritis*: It is roughly three times more common than in people without diabetes. Shoulder radiographs show calcium deposits outside of the joints, often in the area of the rotator cuff tendons.

Conditions Affecting the Feet

***Diabetic Osteoarthropathy*:**

It is a severe, destructive form of degenerative arthritis resulting from a loss of sensation (brought on by underlying diabetic neuropathy) in the involved joints. It most commonly affects the pedal bones. Loss of sensation leads to inadvertent (and unnoticed) repeated microtrauma to the joints, which leads to degenerative changes (Kim, R. P. *et al.,* 2001).

CONCLUSION

Being a serious metabolic disorder diabetes mellitus is associated with various general body systems and having more risk factors associated with it, leading to serious health complication effecting normal life style of healthy individuals if it is not controlled, however it doesn't means that whole population being diabetic couldn't enjoy healthy life style, the above mentioned complications are clinical situations in case of uncontrolled diabetes mellitus occasionally.

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