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Review Article

A REVIEW ON DIABETES MELLITUS AND ASSOCIATED CO-MORBIDITY

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ABSTRACT

Diabetes mellitus is a metabolic disease prevalent globally. Many other disease also occurs in association with diabetes these are known as diabetic co-morbidities. Diabetics have both diabetes related Comorbidity i.e. cardiovascular disease, retinopathy, nephropathy and stroke, diabetic foot and non diabetes related Comorbidity such as depression, lung disease (COPD and Asthma) and musculoskeletal disease (low back pain, shoulder and neck pain, osteoarthritis of knee, hip or spine). These co-morbidities make diabetes treatment more challenging.

Key Words: Diabetes mellitus, co-morbidities, cardiovascular disease, diabetic retinopathy,

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by disturbance in carbohydrate, lipid and protein metabolism resulting high blood glucose level, high blood lipid level, nitrogen imbalance and sometime ketonaemia due to abnormality in insulin action and secretion. Hyperglycaemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal muscle with reduced glycogen synthesis. Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2 DM.(Tripathi KD 2008, Rang HP 2007)

Patients with type 1 DM are treated with Insulin replacement therapy while type 2 DM patients are treated and managed by diet and life style modification. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by balanced and healthy diet, decreasing weight, exercise and oral hypoglycemic medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include glibebclamide, meglitinide, acarbose , pioglitazone.

Co-morbidities

Co-morbidity is defined as the occurrence of one or more chronic conditions in the same person which has a known disease, occurs among patients with diabetes (Feinstein A 1967, Beckman JA et al 2002)

Causes of Co-morbidity

Some diseases can occurs together in one person by concurrence, and there is no pathological association between them. Diseases occur together because there are some associations between them. These associations can be summarised into two main groups: direct and indirect causal relationships between the diseases and shared risk factors. The direct and indirect causal relationships between heart disease, diabetes and chronic obstructive pulmonary disease have been demonstrated by substantial evidence from pathological and epidemiological studies.

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Diabetes mellitus vs co-morbidities

Diabetics have both diabetes related Comorbidity i.e. cardiovascular disease, retinopathy, nephropathy and stroke, diabetic foot and non diabetes related Comorbidity such as depression, lung disease (COPD and Asthma) and musculoskeletal disease (low back pain, shoulder and neck pain, osteoarthritis of knee, hip or spine) (Beckman JA et al 2002, Adler AI et al 2000, Anderson RJ et al 2001, Egede LE et al 2002) . Comorbidity among patients with diabetes is associated with considerable consequences for health care and related costs. The selection of drug therapy for reducing blood glucose is made more challenging when patients already have complications and comorbid conditions.

Micro vascular and macro vascular complication begins to develop within the pre diabetes state, than increase in prevalence with increasing duration of type II diabetes.

Micro vascular complications: (Retinopathy, Neuropathy and Nephropathy)

Macro vascular complications: (coronary artery disease, cerebro vascular disease and Peripheral vascular diseases)

Diabetes Mellitus and Cardiovascular co-morbidity

Patients with type 2 diabetes are at increased risk of cardiovascular co-morbidities. Most cardiovascular co-morbidities are heart disease (Cardiac attack, Atherosclerosis and HF) and High BP which shorten the average life expectancy.

High blood glucose in adults with diabetes increases the risk for cardiac attack, atherosclerosis, and CAD (Nathan DM et al 2005). People with type 2 diabetes also have higher rates of high BP, lipid disturbance and obesity, which contribute to their high rates of CVD. (National Institute of Diabetes and Digestive and Kidney Diseases 2005)

Heart failure (HF) is positively associated with mortality accompanied by co morbidities, such as diabetes mellitus (Curtis LH et al 2008, McMurray JJ et al 2005). HF is twice as common in men with diabetes and five times as common in women with diabetes as in age matched subjects without diabetes. Patients with diabetes have a nearly 2-fold risk for HF hospitalization or death

People with diabetes have a three to five times higher risk for CHD death than nondiabetic subjects (Stamler J 1993, Panzram G 1987)

Atherosclerotic plaque rupture and subsequent thrombocyte aggregation are the trigger for major cardiovascular events, and their prevention by lipid lowering and thrombocyte aggregation inhibition is a major therapeutic goal (Alin O et al 2008)

A first step in the screening for CHD is to detect people with incipient atherosclerosis e.g. with endothelial dysfunction (functional atherosclerosis). Endothelial dysfunction (the functional atherosclerosis) precedes by decades morphological atherosclerosis and cardiovascular complications (Stary HC 1995). People with diabetes have an early altered endothelial function. (Tooke JE 1999, Clarkson P 1996)

Scientific study suggest that advanced glycation end products (AGEs) might also play an important role in the development of endothelial dysfunction (Vlassara H et al 2002), leading to the long-term complications of diabetes (Vlassara H et al 2004)

It is a well known fact that a number of patients with diabetes and HF have associated cardiac risk factors such as hypercholesterolaemia, hypertension and obesity. Adequate control of these via dietary measures and exercise could prevent coronary artery disease, and subsequently reduce the incidence of subsequent HF. Trials have also shown that weight reduction and increased exercise reduces the risk of diabetes in HF patients (Diabetes Prevention Program Research Group 2002) ACE inhibitors should be considered in all patients with diabetes and LVSD, regardless of cause or symptom severity, in the absence of treatment contraindications. Data from the trial, comparing the beta-blocker carvedilol with

placebo in patients with LVSD and severe symptomatic HF, showed that the mortality benefit of therapy was significant in the subgroup of patients with diabetes and identical to that of patients without diabetes. (Packer M 2001)

Diabetic patient can work with their health care professional to develop and use an action plan to reach their ABC

A A1C (blood glucose) less than 7 percent
B BP less than 130/80 mmHg
C Cholesterol – LDL less than 100 mg/dl goals.

An action plan can help people to:

Reach and stay at a controlled weight. Being more weight is a risk factor for heart attack and stroke.

Eat foods that are low in saturated fats, trans fats, cholesterol, salt (sodium), and added sugars **–** choose lean meats, poultry, fish, nuts (in small amounts), fat free or low fat milk, and milk products.

Eat more fiber **–** whole grains, fruits, vegetables, and dry peas and beans.

Take medications as directed **–** and ask their doctor about taking daily aspirin.

Ask family and friends to help them manage their diabetes. This support can help people reach their goals (NATIONAL DIABETES EDUCATION PROGRAM 2007)

Depression associated with diabetes:-

Depression and Type 2 diabetes mellitus (DM) are among the most prevalent chronic diseases. Approximately 15% of adults will experience a major depressive episode at some point in their life **(**Kessler RC et. al. -2005). Depressive episodes often begin early in adult life and are associated with a higher risk of subsequent development of Type 2 diabetes. Co morbid depression in patients with DM is strongly associated with burden of DM symptoms (Ludman EJ, et al – 2004) Several studies have reported a cognitive decline in T2DM (Richardson JTE 1990, Biessels GJ 1994) It is possible that metabolic disturbance and other factors could interact, result in an altered central nervous system function and impaired cognition (Strachan MW et al 1997). Long duration of DM being an atherogenic factor, it may increase the risk of CNS functional imbalance through well recognized associations with stroke, causing cerebral infarctions [Vermeer SE et al 2003]. Chronic hyperglycemia is one of the determinants of cognitive decline in type 2 diabetic patient. The harmful effects of hyperglycemia are mediated through an increased influx of glucose through the polyol pathway forming sorbitol resulting in advanced glycation end products (AGE) (Brands AMA et al 2004). Other likely mechanisms of cognitive dysfunction in T2DM are extensive leukoaraiosis (White matter hyperintense lesions – WMHLs) (Biessels GJ et al 1999), atrophy in the region of hippocampus and amygdala (den Heijer T et al 2003) and imbalance insulin action. Insulin action disturbance contributes through the indirect mechanism of up-regulating hypothalamic–pituitary–adrenal axis, thereby causing hypercortisolemia related cognitive dysfunction (Lee ZSK et al 1999) Hypertension usually exists as a co-morbid condition with DM and may be a part of a larger metabolic syndrome, including high blood glucose and lipid disturbance. High blood pressure and diabetes, along together, increase the risk of CNS functioning impairment (Hassing LB et al 2004, Elias PK et al 1997) .

The link between depression and diabetes may be bi-directional meaning that diabetes may lead to the development of depression or vice versa (S.H. Golden et al - 2008, A. Pan et al – 2010). Diabetes has been shown to be one of the most psychologically and behaviorally demanding medical illnesses (Ciechanowski, et. al – 2000). Although early diabetes may be largely asymptomatic, the fear of development of chronic complications, and complex treatment regimens necessary to maintain glucose, lipid and blood pressure control in order to

prevent these chronic complications, are perceived as a mental load by the patient and may resulting depression.(Gazmararian at. al – 2009). Mainly selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed in patients with co-morbid depression (55% of the cohort with depression and diabetes) (Gill et. al- 2008).However, there have been only a handful of randomized controlled trials assessing the role of anti-depressant drug treatment in people with diabetes and depression (Lustman et al – 2006, Anderson et al – 2010, Gulseren et al – 2005, Paile-Hyvarinen et al – 2003). For those patients requiring intervention, the available treatment for depression can be broadly classified into cognitive-behavioral (CBT) and pharmacological. Cognitive - behavioral is proven to be an effective treatment for diabetic patients and co-morbid depression (Lustman et al 1998).

Diabetic retinopathy

Diabetic retinopathy (DR) is an important cause of visual impairment and blindness among adults aged 20–74 years in the USA and the UK (Bunce C 2010, National diabetes fact sheet 2005). The microvascular complications like diabetic retinopathy (DR) usually play a critical role in the life of diabetics. (Fioretto P 2010) reported that for the prevention of progression of vasculopathy early detection is needed. Diabetic retinopathy can be classified into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

Non-proliferative diabetic retinopathy characterized by swelling in blood vessel of retina and leakage from it. Microaneurysms are outpouchings of capillaries and are among the first clinically detectable signs of retinopathy. They arise due to balloon of weakened capillary walls or endothelial buds attempting to revascularize ischemic retina. They appear as minute red dots, commonly temporal to the macula.

Proliferative diabetic retinopathy (PDR) is the most advanced stage of diabetic retinopathy. It is associated with new blood vessel formation which are more fragile and are more susceptible to breaking and bleeding.It commonly arising on the optic disk (New vessels on the disk NVD) or arise on other parts of the retina (new vessel elsewhere or NVE) induced by ischemic changes in the retina and an imbalance between angiogenic and antiangiogenic factors (Abdulrahman A et al 2011)

Intravitreal triamcinolone acetonide (IVTA) is reported to generate favorable results in the treatment of diffuse DME (diabetic macular edema)

Ranibizumab is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF-A. Scientific studies of intravitreal ranibizumab demonstrated reduced foveal thickness and maintained or improved visual acuity in patients with DME (Chun et al., 2006).

Diabetes and nephropathy

Kidney is an excreatory organ of our body that is responsible for blood purification and act as a filter in our system. Sometimes this filtering system breaks down. Diabetes can harm the kidneys and cause them to stop working. Failing kidneys lose their capacity to filter out waste products, resulting in kidney disease. Diabetes can damage this renal system. In Diabetes, High levels of blood sugar make the kidneys filter too much blood and this extra work is hard for renal system. After many years, they start to leak and useful protein is lost in the urine. Having little amounts of protein in the urine is called microalbuminuria. In time, the stress of overwork causes the kidneys to lose their filtering ability. Waste products then begin to build up in the blood. Finally, the kidneys fail. Diabetic nephropathy is a major underlying cause of morbidity and mortality in both type 1 and type 2 diabetes mellitus (Thomas s et al 2014).

Diabetic nephropathy is defined as the appearance of persistent 'clinical' albuminuria in an individual with diabetes mellitus for more than 5 years and associated retinopathy, in the absence of urinary tract infection (UTI), other renal diseases or heart failure. (Thomas s et al 2014) Long-term studies in type 1 diabetes have demonstrated that microalbuminuria is associated with a 20-fold risk of progression to overt renal disease compared with normoalbuminuria. (Karalliedde J et al 2011, Viberti GC et al 1982 and Karalliedde J et al 2010)
Good glycaemic control can prevent diabetic nephropathy in both type 1 and type 2 diabetes and there is facts that, once microalbuminuria has occured, excellent glycaemic control slows the development of the kidney lesion. (Thomas s et al 2014)

Diabetes and cancer
Type 2 diabetes is associated with increased risks for several cancers, including colon, (Jiang Y et al 2011) postmenopausal breast, (Larsson SC et al 2007) pancreatic, (Ben Q et al 2011) ,liver (Wang C et al 2012),endometrial, (Friberg E et al 2007) and bladder cancers and non-Hodgkins lymphoma.

Normal cells develop into malignant cancer cells through a complex process, including initiation (DNA damage from a carcinogen or reactive molecule), promotion (stimulation of initiated cells' growth), and progression (more aggressive growth with angiogenesis and metastasis). Most cancers extend over at least 10–20 years. Numerous factors, some related to metabolic states in overweight, obesity, and type 2 diabetes, as well as dietary intake and physical activity, appear to promote or inhibit cancer development. (Shikata K et al 2013, Giovannucci et al 2010 and World Cancer Research Fund 2007).

Diabetes and liver disease
The liver plays a central role in the regulation of sugar metabolism. Its usual performance is important for the maintenance of blood glucose levels and of a continued supply of glucose to organs that require a glucose as energy source. This central role for the liver in glucose homeostasis offers a clue to the pathogenesis of glucose intolerance in liver diseases. Nonalcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver function tests among adults associated with obesity, diabetes, lipid imbalance and insulin resistance strongly supporting that NAFLD is the hepatic manifestation of the syndrome. People with diabetes appear to have an increased risk of developing NAFLD and certainly have a higher risk of developing fibrosis and cirrhosis in comparison to non diabetic persons.(Angulo P et al 2002, Day CP et al 2006 and McCullough AJ 2006) It has been estimated that 70–75% of type 2 diabetic patients may have some form of NAFLD Recent data suggest that the presence of NAFLD in type 2 diabetes may also be linked to increased cardiovascular disease (CVD) risk independently of components of the metabolic syndrome (Targher G et al 2005 and Targher G etal 2006)

CONCLUSION: The result of the study find out that diabetes is a disorder associated with co morbidities which worsen the disease and produce long term complication. Proper glycemic control is a preventable measure that control diabetes and its associated co morbidities

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