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CONTINUING PHARMACYEDUCATION SERIES-RISK FACTORS AND COMPLICATIONS OF DIABETES

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ABSTRACT

Diabetic is a complex metabolic condition that requires meticulous management and a global approach. Poor management and control of diabetes often lead to poor disease outcomes. The management of diabetes and its complications presents an increasing challenge to health care systems throughout the world. New findings regarding complications of diabetes, their prevalence and incidence, and risk factors involved were discussed in this paper. Various risk factors associated with diabetes include-diabetic neuropathy, diabetic retinopathy, hypoglycemia, metabolic syndrome, T.B musculoskeletal disease, hypoglycemia, Chronic liver disease and coronary heart disease, Foot ulcers and amputations, mental function and dementia, infections, depression and changes in bone quality[1]. So, prevention of diabetes will need deeper understanding by the patients and their surroundings before medical advancements throw up a magical cure to it. Pharmacist can play an important role by screening patients at higher risk for diabetes, assessing patient health status and adherence to standards of care, patient education referring patients to other health care professionals as appropriate for other complications monitoring the outcomes[2]. A buildup of awareness and high motivation levels among society as a whole will ensure active co-operation of every individual for a healthy living.

KEYWORDS:

Diabetic complications, pathogenesis, symptoms, hypoglycemia, SMBG, management

INTRODUCTION

Diabetes is a chronic disease associated with significant morbidityand mortality. According to the diabetes atlas published by international diabetes federation (IDF) estimated that there were 49.5 million persons with diabetes in India in 2009, and this number is predicted to rise to almost 70 million people by 2025 by which time every fifth diabetic subject in the world would be an Indian[3]. Diabetes is not a disorder giving rise to risk of micro vascular damage ie, retinopathy, nephropathy and neuropathy and significant morbidity due to specific diabetes related macro vascular complications like ischemic heart disease,stroke,peripheral vascular disease and diminish quality of life[1]. The American Diabetes Association(ADA) estimated the national

cost of diabetes in U.S.A for 2009 to be 49.5 billion dollars increasing to U.S 192 billion dollars in 2020[3].New findings regarding complications of diabetes, their prevalence& incidence, and risk factors involved were discussed in this paper. Complications of diabetes can be divided into acute and chronic. Acute complications are usually metabolic-corresponding to glycemic status or may be due to the sequels of treatment. The division between acute and chronic complications is rather arbitrary and is based upon the duration of onset of complications [5]

Acute Complications:

- Diabetic ketoacidosis
- Hyperosmolar hyperglycemic state
- Hypoglycemia
- Diabetic gastroporesis
- Acute renal failure

Chronic Complications:

- Diabetic microangiopathy-Retinopathy, nephropathy and neuropathy.
- Dermopathy
- Coronary heart disease
- Cerebrovascular disease
- Peripheral vascular disease
- Cardiopathy
- Erectile dysfunction
- Connective tissue disorder including diabetic cheiroarthopathy

PATHOGENESIS OF DIABETIC COMPLICATIONS

Current research into the pathophysiology of diabetic complications indicates that hyperglycemia is possibly the most important and is definitely central to the development of diabetic complications. The changes that take place in the target organs like the eyes, kidneys, nerves and the heart are medicated through several factors like vascular or endothelial factor, tissue factors, genetic factors and others.The vascular endothelium is not just a passive conduct for passage of blood but a very active and dynamic organ and reacts to several physical and chemical stimuli. The normal endothelial function depends upon adequate supply of nitric oxide necessary vasodilatory signaling and detoxification of reactive oxygen species (ROS) .Chronic hyperglycemia causes a high concentration of glucose within the cells, as the vascular endothelium does not need insulin for the passage of glucose across the cell membrane. Endothelial dysfunction causes ischemia of the target organ and tissue damage.Chronic hyperglycemia also causes glycation of different types of cellular proteins. Glucose gel attached to a terminal aminoacid residue to produce a schiff's base that undergoes an Amadori rearrangement and ultimately an irreversible reaction occurs that cross links the proteins. This is called Advanced Glycation End Product (AGE) formation, a very important factor for several diabetic complications including diabetic retinopathy and nephropathy. Several cross-link breakers are undergoing trials at the present moment with hopes of reversing the process[3].

The Protein kinase (PKC) is a group of enzymes involved in the down regulation of pathways leading to diabetic complications. Chronic hyperglycemia causes a high accumulation of di- acyl glycerol (DAG) in the endothelial cells and activates PKCs. PKC activation leads to increased vascular permeability, extracellular matrix synthesis, contractility, cell growth and angiogenesis. Recent researches have shown that diabetic complications are associated with a preferential activation of beta isoform of PKC. Ruboxistaurin a specific inhibitor of PKCβ-2 isoform has been shown to prevent rise of albumin excretion rate as well as changes in kidney of the db/dbmouse.The transforming growth factor-β (TGF-β) is a very important profibrotic growth factor implicated in the development of diabetic neuropathy and over pressed in response of PKC activation. Several other growth factors are similarly over expressed and cause diabetic microvascular complications- platelet derived

growth factor (PDGF), insulin like growth factor (IGF-I) and vascular endothelial growth factor (VEGF). Last one is particularly responsible in the angiogenesis diabetic retionopathy.Thealdosereductase/ Polyol pathway has also been implicated in the pathogenesis of AGE formation, PKC activation, stimulation of growth factors and diabetic complications. Also reductase is responsible for conversion of glucose into sorbitol that has some osmotic effects.Genetic factors have an important role in the pathogenesis of diabetic complications, particularly diabetic nephropathy. Several genes are under investigation of which angiotensin- converting enzyme (ACE) gene and DD gene have been found to have some modulating effect[5].

DIABETIC NEPHROPATHY (KIDNEY DAMAGE):

Nephropathy is a very serious complication of diabetes

- Glomeruli in the kidney become damaged and leak protein in the Urine. Overtime this may lead to kidney failure
- Urine tests showing macroalbuminuria are important markers for kidney damage.
- Diabetics Nephropathy leading cause of end stage renal disease (ESRD) in about 20-40% of patients with diabetes. If kidneys fail, dialysis is required.(refer fig.1)

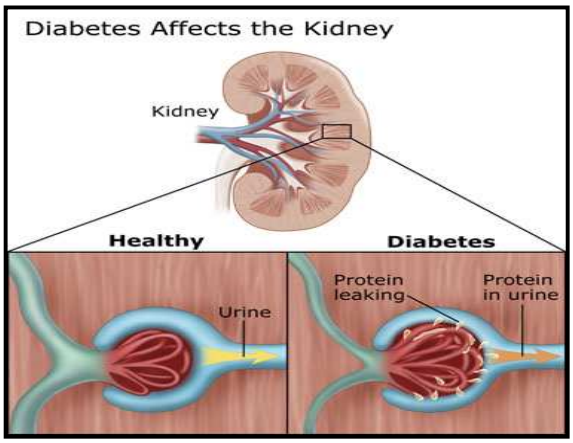

Fig 1: Diabetic nephropathy

SYMPTOMS:

Swelling in Feet and Ankles, Itching, Fatigue, Pale Skin Colour.

CLASSIFICATION:

Mogensen's classification is widely accepted as a simple but still comprehensive grading system of diabetic neuropathy[5].

Stage-1:Stage of acute renal hypertrophy and hyper function

Stage-2: Stage of Normoalbuminuria

Stage-3: Stage of microalbuminuria/ stage of incipient diabetic nephropathy.

Stage-4: Stage of clinical/ overt nephropathy/ proteinuria/ macroalbuminuria.

Stage-5: End stage renal disease/ failure.

DIAGNOSIS:

Test for microalbuminuria is very important for all type-2 diabetic patients and type-1 patients.Measurement of GFR, creatinine clearance and ultra-sonogram of the kidneys are necessary in clinical practice.

MEASUREMENT OF URINARY MICROALBUMIN:

Special reagents are necessary to measure very small quantity(micro) of albumin(hence called micro albumin) accurately. Several methods are available unfortunately most laboratory results are not standardized.

a) Timed sample: patient voids bladder. Time is noted. Time is noted again when urine is collected. Normal range is less than 20 micro gram/min. microalbiminuria:20 -200 micro grams/min
b) 24 hours sample: first morning void is discarded thereafter; urine is collected till next morning void. Normal range of urine albumin excretion (UAE) is less than 30 mg/24 hrs. Microalbuminuria: 30-300mg/24 hrs.
c) Spot/ Random sample for micro albumin/ creatinineratio (or,albumin/ creatinineratio,ACR). Perhaps the method of choice and obviates the necessity of urine collection over a long period of time. Normal value is less than 30micro gm/mg of creatinine. Microalbuminuria:30-300 micro gm/mg of creatinine.
d) Micro albumin urine test strip (Micral-2) gives a color reaction that is matched against the standard printed on the container. The test strips contain anti –human albumin antibody that reacts with human albumin. This is a very good screening test for microalbuminuria and can be performed in clinic or, office setting[5].

ASSESSMENT OF RENAL FUNCTION:

Measurement of blood urea, creatinine, GFR,creatinine clearance, USG of thekidneys, serum electrolytes, calcium and phosphate are necessary in advanced renal disease.In patients of advanced diabetic nephropathy, erythropoietin secretion is also reduced from the kidneys and most patients suffer from variable degrees of anemia. Many patients suffer from frequent episodes of hypoglycemia as degradation of insulin by the kidneys is reduced[5].

Some important formula'sfor calculating creatinine clearance.

a. Creatinine clearance(UXV)/P
(U= urinary concentration of creatinine; V= 24 hrs of volume of urine in ml; P= plasma concentration of creatinine)
b. Cockcroft and Gault formula

Creatinine clearance

$$= \frac{(140 - \text{Age}) \times (\text{Weight in kg})^*}{(\text{Plasma creatinine}) \times 72}$$

*multiplied by 0.85 for females.

RENAL BIOPSY:

Most patients of diabetic nephropathy do not require a renal biopsy; however, it is to be remembered that many patients of diabetes may develop nephropathy due to other causes and where in doubt, a renal biopsy is definitely helpful.

MANAGEMENT:

- Glycemic control is the paramount importance for prevention of diabetic nephropathy.
- Protein restriction is recommended at 0.8/kg body weight in microalbuminuria.
- Control of hypertension is extremely important in all stages of diabetic nephropathy.
- Thiazide diuretics can be used in diabetics.
- Once clinical nephropathy sets in, the patient should be sent to nephrologist[5,7].

CARDIO-VASCULAR DISEASE:

- Heart attacks accounts for 60% and strokes for 25%of death in patient with diabetes.
- Heart disease mainly occurs in diabetic patients with concurrent hypertension&hyperlipidemia.
- Risk of stroke doubles within 5yrs of type-III diabetes
- Some experts estimated that the mortality diagnosis neuropathy-related heart conditions range between 15-23%
- Women with diabetes are at particularly high risk of heart problems
- Intensive blood sugar control is even more important in reducing these risks than blood pressure and cholesterol-lowering drugs[2,5].

DIABETIC NEUROPATHY (NERVE DISORDERS):

Diabetes reduces or distorts nerve function, causing a condition called neuropathy

Two types of neuropathy:

a) Peripheral –effect nerves in toes, feet, legs, hands, arms and particularly Sensation.

b) Autonomic: Effects nerves that help regulate digestive, bowel, heart&sexual function. (refer fig.2)

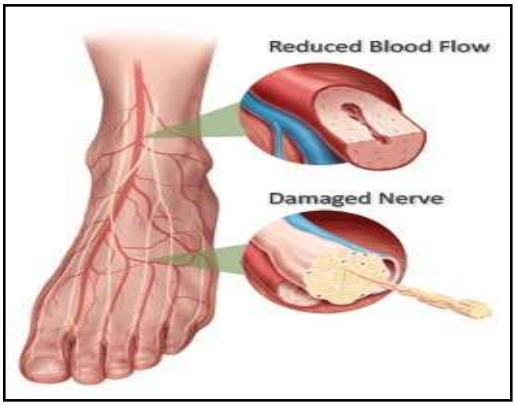

Fig 2: Diabetic Neuropathy

SYMPTOMS:

Tingling, Weakness, Burning, Sensations, Loss Of the Sense Of Warm Or Cold, Numbness, Deep Pain.

CLASSIFICATION OF DIABETIC NEUROPATHY:

The simplest and most practical classification in vogue is to divide the diabetic neuropathies into two groups:

a) Symmetricalpolynephropathies include sensory, motor and autonomic neuropathies.

b) Focal neuropathies include mononeuropathy (lesion of one single nerve), mononeuropathymultiplex (lesions of several individual nerves), plexopathy (involvement of a nerve plexus), radiculopathy (lesions of nerve root) and cranial neuropathy (lesions of cranial nerves)[1,5.]

MANAGEMENT OF DIABETIC NEUROPATHY:

- Glycemic control is directly co-related with the evolution and progression of diabetic neuropathy in type-1 and type-2 diabetes.
- Relief of symptoms is very important. The painful neuropathies respond well to tricyclic anti-depressants (amitriptyline or, nor-triptyline) and anti-convulsions (carbamazepine or, gabapentin).
- Physiotherapy for gait management and orthotic support (special foot wear) for foot deformities are necessary for some patients.
- Postural hypotension needs to be managed by training the patient to get from bed gently. Patients may be advised to dangle the legs for sometime sitting at the edge of the bed before standing. Fludrocortisones may be helpful in some patients (0.5-2 mg/day)[4,5,11].

DIABETIC RETINOPATHY:

- Diabetes accounts for 12000-24000 of neuro cases of blindness annually and is the leading cause of new cases of blindness in adults age between 20-74 yrs
- People with diabetes are also at higher risk for developing cataracts & certain types of glaucoma
- The(PDAG) primary open angle glaucoma is especially high for women with type-III diabetes. (refer fig.3)

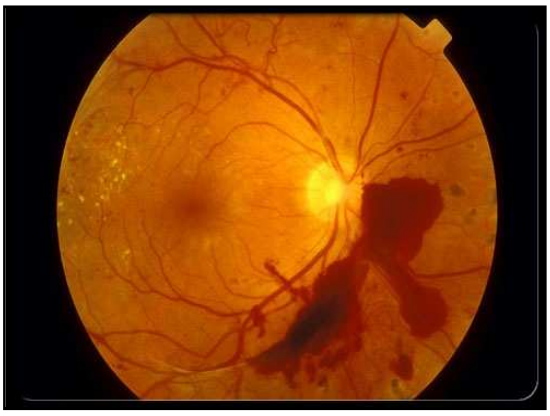

Fig 3: Diabetic Retinopathy

CLASSIFICATION OF DIABETIC RETINOPATHY:

a) Non-proliferative diabetic retinopathy(NPDR) or, background diabetic retinopathy(BDR) is the first change of the disease. The earliest change is the thickening of the vascular basement membrane and loss of vascular pericytes.

b) Severe NPDR(Pre-proliferative retinopathy): This stage is more advanced with further ischemia of the retina.

c) Proliferative diabetic retinopathy(PDR): The hallmark of this stage is formation of new blood vessel in retina and into vitreous(neovascularization).

DIAGNOSIS:

- Direct ophthalmoscopy with dilated pupils (approximately ½ hour after 1% tropicamide given to each eye) is a useful examination for an experienced physician.

- Indirect ophthalmoscopy is very useful for evaluation of changes in the retina.
- Indirect bio microscopy with a slit-lamp provides 3-D viewing of the optic disk and the macula with excellent evaluation of macular edema and neovascularization.
- Fundus fluorescein angiography(FFA) is a photographic picture of retina, after IV injection of sodium-fluorescein, taken with a fundus camera[12].

MANAGEMENT:

- Glycemic control is effective in prevention of (primary& secondary) diabetic retinopathy in both type-I and type-II diabetic patients.
- Control of hypertension
- Cessation of smoking
- Laser treatment has revolutionized the outcome of Diabetic Retinopathy in terms of loss of vision. The mechanism by which laser prevents further visual loss is rather hypothetical.

HYPOGLYCEMIA:

- Tight blood sugar control increases the risk of low blood sugar (insulin shock),occurs in blood glucose levels falls below normal (blood sugar level below 70mg/dl)
- Caused by insufficient intake of food or excess exercise or alcohol
- Mild hypoglycemia is common, but severe episodes are rare, even among these taking insulin

RISK FACTORS FOR SEVERE HYPOGLYCEMIA:

- Patients attempting tight control of blood glucose & HbA1c Levels
- Patients who donot comply with treatment
- Infections such as gastroenteritis or respiratory illness

SYMPTOMS:

- Sweating, Trembling, Hunger, Rapid Heartbeat, Confusion, Weakness,Disorientation,Combativeness.
- In rare and worst cases ,Coma, Seizure, Death[2,5, 8].

DIABETIC KETO-ACIDOSIS (DKA):

- Life Threatening Complications caused by insulin depletion
- It is nearly always due to non-compliance with insulin treatment

SYMPTOMS:

- Nausea and Vomiting, Rapid heartbeat, smell of acetone, dehydration, other serious complication-aspiration pneumonia and adult respiratory distress syndrome. If Condition persists, coma, and eventually death, may occur.

FOOT ULCERS & AMPUTATIONS:

- 15% of patients with diabetes have serious foot problems
- About 85% of amputations start with foot ulcers, which develop in about 12% of people with diabetes. Those most at risk are people with long history of diabetes and people with diabetes who are overweight or who smoke.
- In general foot ulcers develop from infections, such as those resulting from blood vessel injury. Even more infections can develop into severe complications.
- The American diabetes association recommends all diabetic patients should have at least one detailed foot examination every year by a qualified physician.(refer fig.4)[5,17,19].

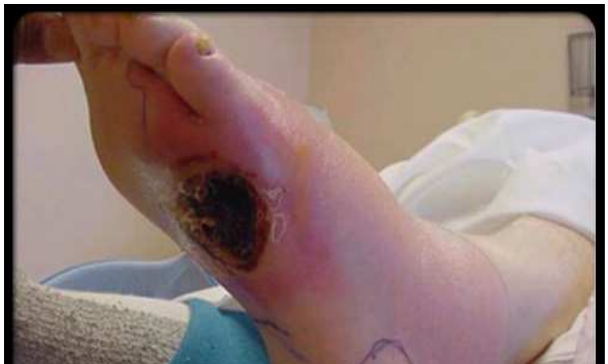

Fig 4: Foot Ulcer

MANAGEMENT OF DIABETIC FOOT:

- Wash your feet daily with lukewarm water.
- Dry the feet especially between the toes.
- Moisturize feet and ankles.
- Check daily for blister cuts and redness or swelling if any of these are observed then report to the doctor immediately.
- Use footwear as recommended by the doctor[5,8].

MENTAL FUNCTION&DEMENTIA:

- Some studies indicate that patients with type-II diabetes face a higher than average risk of developing dementia caused either by Alzheimer's disease or problems in blood vessels in the brain[11].

INFECTIONS:

RESPIRATORY INFECTION:

People with diabetes face a higher risk of influenza & its complications, including pneumonia, possibly because the disorder neutralize the effects of protective proteins on the surface of the lungs.

URINARY TRACT INFECTION:

Women with diabetes face a significantly higher risk for urinary tract infections, which are likely to be more complicated and difficult to treat than in general population[2,8].

DEPRESSION:

Diabetes doubles the risk of depression; depression in turn increases the risk for hyperglycemia & complications of diabetes.

Restoring mental health and illness, both through medication and Psychotherapy, not only improve quality of life but may help patients control their blood glucose levels[14].

CHANGES IN BONE QUALITY:

Diabetes changes bone quality and density, but the effects, depending on the type of diabetes.

Type-I Diabetes:

Associated with a slightly reduced bone density, putting patients at risk for osteoporosis& possibly fractures medications –bi phosphates alendronate and risedronate.

Type-II Diabetes:

Associated with increased bone density but is also associated with fractures. In such cases the bone quality itself may be impaired[14].

PREVENTION OF COMPLICATIONS:

- Have a health check up regularly once in a year.
- Have a good glycemic control.
- Visit Ophthalmologist for eye check up once in a year.
- Screening for micro albuminuria is important.
- Identification of patient together with B.P 125/75mm of HG
- Initiation of A.C.E Inhibitors and all antagonists.
- Inspect feet regularly for any cuts or bruises.
- Use Creams and Lotions to prevent dry foot.
- Avoid walking bare foot
- Seek help early if any ulcer detected
- Kidney profile, liver function test and a lipid profile check should be done at least once in a year
- Get a cardiac risk assessment done every year by doing on ECG and stress test or ECHO.
- Visit a dietician regularly and get your B.M.I check every month [17,19].

PATIENT EDUCATION:

SMBG are recommended to allow to patients to understand current levels of glycemia and ongoing patterns of glycemia and to modify their diet. Consistent communication between the health care and health care professional is essential to an effective implementation of self monitoring and maintenance of patient motivation.(refer fig.5 & fig.6)[3,10,19].

Fig 5: Self-Monitoring Of Blood Glucose

Fig 6: Patient education bi-cycle wheel

CONCLUSION:

Diabetes is a disorder that slowly degrades vital functions of the body and creates disabilities affecting sense of well being among diabetics. Management of glycemia and diabetes is crucially important for the prevention of both acute and chronic complications[23]. Pharmacist can play an important role in diabetes care by screening patients at high risk for diabetes, assessing patient health status and adherence to standards of care, educating patient to empower them to care for themselves, referring patients to other health care professionals and monitoring the outcomes. Self monitoring of blood glucose should form an integral part of overall diabetes care management program. A buildup of awareness and high motivation levels among society as a whole will ensure active co-operation of every individual for a healthy living[24].

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