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REVIEW ARTICLE

A Short Review on "complications of diabetes mellitus"

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Abstract:
This review represents importance of the present is to perform a detail on complications of diabetes mellitus. Diabetes mellitus is group of syndrome characterized by hyperglycemia altered metabolism of lipids, carbohydrates and proteins with an increase risk complications from vascular disease And the include study of Short term complications including glaucoma, cataracts, Long term complications including diabetic cardiomyopathy, diabetic foot, Management of complications, Overviews of different diseases with diabetes mellitus including cardiac, Problem, vascular disease, Specific complications in diabetes mellitus including nephropathy, retinopathy, neuropathy, skin complications. It was reported that there is a higher incidence of retinopathy, neuropathy, nephropathy etc. together with diabetes. A wide spread pathological change is thickening of capillary membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complication like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and vascular insufficiency.

Keywords: Diabetes mellitus, nephropathy, retinopathy, neuropathy, skin complications.

Introduction

Diabetes mellitus is group of syndrome characterized by hyperglycemia altered metabolism of lipids, carbohydrates and proteins with an increase risk complications from vascular disease [1]. It was reported that there is a higher incidence of retinopathy, neuropathy, nephropathy etc. together with diabetes. A wide spread pathological change is thickening of capillary membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complication like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and vascular insufficiency. It may affect the disruption of carbohydrate and fat metabolism [2]. Diabetes is a metabolic disorder where in human body does not produce or properly uses insulin, a hormone that is required to convert sugar, starches, and other food into energy [3]. Human body has to maintain the blood glucose level at a very narrow range, which is done with insulin and glucagon. The function of glucagon is causing the liver to release glucose from its cells into the blood, for the production of energy. The condition may be multifactorial origin in which heredity, age, sex, pregnancy, obesity, autoimmune, infections and emotional disturbances may be important. It may precipitated by pancreatic disorders, hormonal disorders (e.g. acromegely and cushing syndrome), or by administration of drugs (corticosteroids or diuretic, especially thiazides) [4]

TYPE OF DIABETES MELLITUS

Two major types of diabetes mellitus are Type I and Type II.

Type I / Insulin dependent diabetes mellitus (IDDM) / juvenile onset diabetes mellitus

There is β cell destruction in pancreatic islets; majority of cases are autoimmune (Type IA) antibodies that destroy β cells are detectable in blood, but some are idiopathic (Type IB)-no β cell antibody is found. In all type I cases circulating insulin levels are low or very low, and patience is more prone to ketosis [2].

Type II / Non insulin dependent mellitus (NIDDM) / maturity onset diabetes mellitus

There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal pr even high, no anti β cell antibody is demonstrable; generally has a late onset (past middle age). Over 90% cases are type II diabetes mellitus. Causes may be (i) Defects in insulin secretion (ii) Resistance to insulin involving muscle, liver and the adipocytes.

Gestation diabetes mellitus (GDM)

This is glucose intolerance being recognized during pregnancy. It can complicate pregnancy leading to prenatal morbidity and mortality, so clinical detection important.

Other specific type of diabetes

Maturity onset diabetes youth (MODY) is due to impaired insulin secretion with minimal or no insulin resistance, so hyperglycemia is reported in early stage.

Pathological features of Diabetes Mellitus are due to the following factors:

1) Decrease in utilization of glucose by the body cells. This results in increase in blood glucose concentration to 300 to 1200 mg/dl.
2) Increase in mobilization of fats from the fat storage areas. This results in abnormal fat metabolism and deposition of cholesterol in arterial walls causing atherosclerosis.
3) Tissues get depleted from protein i.e. protein depletion in tissues.

PATHOPHYSIOLOGY:-

Insulin resistance means that body cells do not respond appropriately when insulin is present. Unlike type I diabetes mellitus the insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with production of insulin.

SYMPTOMS OF LONG TERM DIABETES

- Diabetes retinopathy shows symptoms of pain in the eyes and may even result in loss of vision.
- Renal (kidney) disease shows symptoms of swelling (edema) in the feet and legs. It then passes over total body and as the disease progresses, blood pressure also increases.
- Tingling, burning, numbness, tightness, shooting or stabbing pain in the hands, feet or other parts of your body, especially at night. Digestive problems also occur if, the nerve controlling internal organs get damaged (autonomic neuropathy).
- You may have scanty or profuse sweating, difficulty of sensing when your bladder is full, when there is a low blood sugar, increased sexual problems, weakness, dizziness, and fainting.
- Chest pain (angina) or shortness of breath dizziness or light headache, shoulder or stomach pain, fast heartbeat. When alarming symptoms given by the body are ignored sand the same status is maintained, it starts damaging body organs, such as heart, kidney, eye, feet, and skin [7].

COMPLICATION IN DIABETES MELLITUS

1. DIABETIC RETINOPATHY

Diabetic retinopathy (damage to the retina) caused by complications of diabetes mellitus which can eventually lead to blindness. Diabetes causes the damage of retinal blood vessels, leading to leakage of fluid and blood. There may be new development of blood vessels, which are fragile. This is known as neovascularisation. It is an ocular manifestation of systemic disease which affects up to 80% of all patients who have had diabetes for 10 years or more [8].

RISK FACTORS AND PREVALENCE

All people with diabetes mellitus are at risk – those with Type I diabetes (juvenile onset) and those with Type II diabetes (adult onset). The longer a person has diabetes, the higher the risk of developing some ocular problem. Between 40 to 45 percent of Americans diagnosed with diabetes have some stage of diabetic retinopathy. [9] After 20 years of diabetes, nearly all patients with type I diabetes and >60% of patients with type II diabetes have some degree of retinopathy. Prior studies had also assumed a clear glycemic threshold between people at high and low risk of diabetic retinopathy. However, it has been shown that the widely accepted WHO and American Diabetes Association diagnostic cut off for diabetes of a fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) does not accurately identify diabetic retinopathy among patients. [10],[11].

PATHOGENESIS

Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycemia-induced pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls.

These damages change the formation of the blood-retinal barrier and also make the retinal blood vessels more permeable. [15] Small blood vessels – such as those in the eye – are sespecially vulnerable to poor blood sugar (blood glucose) control. An over accumulation of glucose or fructose damages the tiny blood vessels in the retina. During the initial stage, called non proliferative diabetic retinopathy (NPDR), most people do not notice any change in their vision. Some people develop a condition called macular edema. It occurs when the damaged blood vessels leak fluid and lipids onto the macula, the part of the retina that lets us see detail. The fluid makes the macula swell, which blurs vision.

As the disease progresses, severe non proliferative diabetic retinopathy enters an advanced, or proliferative, stage. The lack of oxygen in the retina causes fragile, new, blood vessels to grow along the retina and in the clear, gel-like vitreous humour that fills the inside of the eye. Without timely treatment, these new blood vessels can bleed, cloud vision, and destroy the retina. Fibrovascular proliferation can also cause tractional retinal detachment. The new blood vessels can also grow into the angle of the anterior chamber of the eye and cause vascular glaucoma. Non proliferative diabetic retinopathy shows up as cotton wool spots or microvascular abnormalities or as superficial retinal hemorrhages. Even so, the advanced proliferative diabetic retinopathy (PDR) can remain asymptomatic for a very long time, and so should be monitored closely with regular checkups [12]

DEVELOPMENT OF DIABETIC RETINOPATHY

Diabetic retinopathy is basically a microangiopathy, the usual, initial presenting sign of which is the Address for reprints: appearance of retinal microaneurysms at the posterior pole. The pathology of diabetic retinopathy and other vascular retinopathies using injection methods, a variety of stains and the digestion technique. Light microscopic examination of retinal 'digests' is particularly appropriate to study alterations in the retinal vascular bed. From this study a clear pattern of disease was observed to occur in diabetic retinopathy. The results suggested that changes are confined to the small vessels in the form of endothelial proliferation, rare microaneurysms, and signs of impending cellular degeneration in a few vascular branches. These initial lesions are focal and located preferentially at the posterior pole of the retina.

Basement membrane thickness

This is believed to play an important role not only in diabetic retinopathy but in diabetic microangiopathy as a whole. Basement membrane thickening in several non-diabetic conditions, its inconstancy, and its presence in all types of diabetes. Electron microscopical studies of diabetic retinopathy show that basement membrane thickening is associated with a variety of haematogeneous elements, which could have arrived at this situation.

Distribution of retinal vascular lesion

It has been shown that there is no one lesion which is absolutely specific for diabetic retinopathy. The most characteristic features of diabetic retinopathy, microaneurysms, capillary closure, basement membrane thickening, and pericyte damage appear to differ from other vascular retinopathies only in their frequency and widespread distribution. Central retinal vein thrombosis, showing a marked degree of capillary closure.

Pericyte damage

There is abundant evidence that these cells are selectively involved in the diabetic process, the damage taking the form of a peculiar eosinophilic degeneration of the nucleus before the cell disintegrates altogether. Although similar changes can be observed in other retinopathies. [13]

COMPLICATIONS LINKED TO DIABETIC RETINOPATHY

A) Non-specific ocular disease associations

1) Cataract

Cataract is defined as opacification of the lens and is common in older age populations. Age-related cataract occurs earlier in patients with diabetes. A specific form of "snow-flake" cataract is recognized in younger diabetics. In addition, a rare form of "osmotic" reversible cataract occurs in young diabetic patients, including infants, due to rapid changes in fluid electrolyte balance in severe uncontrolled diabetes.

2) Glaucoma

Glaucoma is defined as loss of vision due to raised intraocular pressure and occurs in two forms: primary or secondary. Primary glaucoma may present as acute glaucoma or chronic glaucoma. Patients with diabetes may have a greater risk of developing primary chronic glaucoma with loss of visual field (side vision). Patients with PDR are at risk of developing secondary glaucoma, particularly rubeotic glaucoma [14].

3) Retinal Vein Occlusion / Optic disc swelling

Patients with diabetes are at higher risk of developing optic nerve disease due to vascular occlusion, which is distinct from diabetes-specific optic neuropathy and usually occurs in older patients with Type 2 diabetes and hypertension. This may be a form of ischemic optic neuropathy [15].

B) Specific complications

1) Retinal Detachment

Retinal detachment is caused by the accumulation of

fluid between the neural retina and the retinal pigment epithelium and in non-diabetic patients most commonly results from a tear in the retina. In patients with PDR, tractional retinal detachment may occur due to condensation and contraction of the vitreous gel in associatiosn with hemorrhages and fibrosis. Tractional retinal detachment may progress to combined tractional and rhegmatogenous retinal detachment. Central vision is lost when the macula is involved [16].

2) Rubeosis iridis and rubeotic glaucoma

Rubeosis iridis is the growth of new vessels on the iris in eyes with advanced retinal ischemia. Rubeosis may induce a severe form of intractable glaucoma due to closure by fibrovascular tissue of the aqueous fluid drainage route in the anterior chamber angle of the eye.

3) Optic neuropathy

Patients with diabetes may rarely experience optic neuropathy, which presents as swelling of the optic discs associated with gradual reduction in visual acuity.

4) Other ocular pathology in diabetes

Ocular muscle palsies are not uncommon in association particularly with Type 2 diabetes. In addition, corneal epitheliopathy is common and a cause of poor epithelial wound healing especially after ocular surgery.

SCREENING FOR DIABETIC RETINOPATHY

1. Opthalmoscopy

It is most commonly used technique to screen for doctors. When performed by an ophthalmologist, the specificity of direct and indirect opthalmoscopy was high, but sensitivity was low (34-50%), particularly for early retinopathy, in comparison to seven field stereo photographic assessment

2.Digital Imaging

It makes fundus photography easier and more widely accessible. It may be used to obtain fundus image through non dilated pupils. Mydriasis is usually necessary in older patients. Single- field fundus photography wit interpretation by trained readers could serve as a screening tool to identify patients with diabetic retinopathy.

3.Telemedical screening

A major advantage of digital technologies is the ability to transmit images to a centralized reading centre for grading. Implementing retinal images technology in a primary care setting result in a significant increase in the rate of diabetic retinopathy surveillance and in the rate of laser treatment for diabetic retinopathy [18].

TREATMENT

1. Focal laser treatment.

This laser treatment, also known as photocoagulation, can stop or slow the leakage of blood and fluid in the eye. It's done in your doctor's office or eye clinic. During the procedure, leaks from abnormal blood vessels are treated with laser burns. Focal laser treatment is usually done in a single session. Your vision will be blurry for about a day after the procedure. Sometimes you will be aware of small spots in your visual field that are related to the laser treatment. These usually disappear within weeks. If you had blurred vision from swelling of the central macula before surgery, however, you may not recover completely normal vision.

2. Scatter laser treatment.

This laser treatment, also known as pan retinal photocoagulation, can shrink the abnormal blood vessels. It's also done in your doctor's office or eye clinic. During the procedure, the areas of the retina away from the macula are treated with scattered laser burns. The burns cause the abnormal new blood vessels to shrink and scar. Scatter laser treatment is usually done in two or more sessions. Your vision will be blurry for about a day after the procedure. Some loss of peripheral vision or night vision after the procedure is possible.

3. Vitrectomy.

This procedure can be used to remove blood from the middle of the eye (vitreous) as well as any scar tissue that's tugging on the retina. It's done in a surgery center or hospital under local or general anesthesia. During the procedure, the doctor makes a tiny incision in your eye. Scar tissue and blood in the eye are removed with delicate instruments and replaced with a salt solution, which helps maintain your eye's normal shape. Sometimes a gas bubble must be placed in the cavity of the eye to help reattach the retina. If a gas bubble was placed in your eye, you may need to remain in a facedown position until the gas bubble dissipates — often several days. You'll need to wear an eye patch and use medicated eye drops for a few days or weeks. Vitrectomy may be followed or accompanied by laser treatment.

2. DIABETIC NEUROPATHY

Diabetic neuropathy is a common cause of morbidity and death among patients with diabetes, generating a huge economic burden. Apart from tight glycemic control, no other evidence-based treatments are known to ameliorate or prevent neuropathy. The duration and level of hyperglycemia are important determinants of microvascular complications of diabetes, including neuropathy.[22] The relative effect of cardiovascular risk factors specifically associated with diabetes (e.g., hypertension, dyslipidemia, and increased weight) or not associated with diabetes (smoking) on the development of neuropathy are incompletely elucidated. The Diabetes Control and Complications Trial reported a 60 percent

reduction in neuropathy in the intensively treated groups after five years, but the cumulative incidence of neuropathy (15 to 21 percent) and abnormal nerve conduction (40 to 52 percent) remained substantial. Such findings suggest that neuropathy can develop, despite intensive control of the glucose level. Thus, risk factors besides hyperglycemia are probably involved in the evolution of neuropathy. [23]

PATHOPHYSIOLOGY

The factors leading to the development of peripheral neuropathy in diabetes are not understood completely, and multiple hypotheses have been advanced. It is generally accepted to be a multifactor process. Important contributing biochemical mechanisms in the development of the more common symmetrical forms of diabetic polyneuropathy likely include the following,

Polyol pathway

Hyperglycemia causes increased levels of intracellular glucose in nerves, leading to saturation of the normal glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced nerve myoinositol, decreased membrane Na^+/K^+ -ATPase activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation. This is the rationale for the use of aldose reductase inhibitors to improve nerve conduction.

Advanced Glycation End Products (AGE)

The nonenzymatic reaction of excess glucose with proteins, nucleotides, and lipids results in advance glycation end products that may have a role in disrupting neuronal integrity and repair mechanisms through interference with nerve cell metabolism and axonal transport.

Oxidative Stress

The increased production of free radicals in diabetes may be detrimental via several mechanisms that are not fully understood. These include direct damage to blood vessels leading to nerve ischemia and facilitation of AGE reactions. Despite the incomplete understanding of these processes, use of the antioxidant alpha lipoic acid may hold promise for improving neuropathic symptoms.[24]

Related contributing factors

Problems that are a consequence of or co-contributors to these disturbed biochemical processes include altered gene expression with altered cellular phenotypes, changes in cell physiology relating to endoskeletal structure or cellular transport, reduction in neurotropins, and nerve ischemia. Clinical trials of the best studied neurotropin, human recombinant nerve growth factor were disappointing. However, with future refinements, one or more of these mechanisms may provide reasonable targets for pharmacological intervention. In the case of focal or asymmetrical diabetic neuropathy syndromes, vascular injury or autoimmunity may play more important roles [25].

CLASSIFICATION OF DIABETIC NEUROPATHY

It is originally proposed a purely clinical and descriptive classification. Subsequently, research gave a simple classification based on anatomical characteristics, which is now widely accepted [34].

Classification of diabetic neuropathy.

1. Diffuse

A .Distal symmetric sensory-motor polyneuropathy
B. Autonomic neuropathy
C. Symmetric proximal motor neuropathy (amyotrophy)

2. Focal

A. Cranial neuropathy
B. Radiculopathy/plexopathy
C. Entrapment neuropathy

1. Diffuse

A Distal symmetrical sensory-motor polyneuropathy

It is the most common type of diabetic neuropathy. It involves both small and large fibers and has insidious onset. Typically, the most distal parts of the extremities are affected first, resulting in a stocking pattern of sensory loss. As the sensory symptoms advance above the knees, the distal upper limbs and later the anterior aspect of trunk and subsequently the vertex of the head gets involved. It is predominantly sensory neuropathy, with autonomic involvement which is usually subclinical. Clinically apparent motor deficit develops only in rare cases.

Its symptoms are extremely variable, ranging from severely painful symptoms at one extreme to the completely painless variety, which may present with an insensitive foot ulcer at the other end. The neuropathic symptoms may be positive or negative. Motor involvement results in foot deformity. This abnormality redistributes weight bearing and leads to callus and ulcer formation. The proprioceptive loss makes the gait more unsteady and there is a sense of walking on cotton wool. Acute painful neuropathy is a distinct variant of distal

sensory neuropathy, presenting acutely with severe sensory symptoms with few sensory or motor signs and often it follows a period of flux in glycaemic control [26].

B Autonomic neuropathy

Autonomic neuropathy is a serious and often overlooked component of diabetic neuropathy. Any organ of body which is supplied by autonomic nerves can be affected. Studies have confirmed the presence of parasympathetic dysfuction in 65% of the type 2 diabetic patients 10 years after diagnosis and of combined parasympathetic and sympathetic neuropathy in 15.2%. Autonomic neuropathy is not simply an "all or none" phenomenon and its symptoms range from minor to severe. The severe form may affect survival and can cause sudden death.

Symptoms and signs of autonomic neuropathy

1. Cardiovascular: Postural hypotension, Resting tachycardia,Painless myocardial infarction, Sudden death (with or without association with general anaesthesia), Prolonged QT interval
2. Gastrointestinal: Oesophageal motor incoordination, Gastric dysrhythmia, hypomotility (gastroparesis diabeticorum), Pylorospasm. Uncoordinated intestinal motility (diabetic diarrhoea, spasm), Intestinal hypomotility (constipation), Gallbladder hypocontraction (diabetic cholecystopathy), Anorectal dysfunction (faecal incontinence)
3. Genitourinary: Diabetic cystopathy (impaired bladder sensation, atonic bladder, post micturition dribbling, detrusor hyporeflexia or hyperreflexia), Male impotence, Ejaculatory disorders, Reduced vaginal lubrication, dyspareunia
4. Respiratory: Impaired breathing control, Sleep apnoea
5. Thermoregulatory: Sudomotor, Vasomotor
6. Pupillary: Miosis, Disturbances of dilatation

C Proximal motor neuropathy

It typically affects the elderly males (> 50 year) suffering from type 2 diabetes mellitus but it can also occur in females and type 1 diabetes mellitus. It may be symmetrical or asymmetrical, and with or without sensory loss. Patient usually presents with difficulty in getting up from squatting position, pain in climbing stairs and marked weight loss (sometimes upto 40% of original weight). It predominantly affects anterior (quadriceps) and adductor compartments of thigh. Wasting and weakness of quadriceps is so severe that the knee often gives way, and patient may fall. This has been labeled as diabetic amyotrophy also. The cause of diabetic amyotrophy is unknown but neurological deficit and anatomical distributions suggest nerve root involvement presumably due to occlusion of the vasa nervosum and infarction. Examination shows wasting and weakness of the anterior and adductor compartments of thigh. The knee jerk is absent, while the ankle jerk may be intact. Sometimes, other muscles, especially the anterior tibial and peroneal muscles may also be involved. [27]

2.Focal neuropathies or mono-neuropathies

The diabetic patients are also susceptible to a variety of asymmetric and focal neuropathies.

A Cranial Neuropathy

The third, fourth, and sixth cranial nerves are commonly involved. Elderly patients are the most affected. The third cranial nerve palsy presents with eye pain, diplopia, and ptosis but pupillary response to light is usually spared. The pupillary sparing favours vascular aetiology of IIIrd nerve palsy. Exclusion of other causes of IIIrd nerve palsy is necessary before labelling diabetes as a cause. Spontaneous recovery generally occurs within 6-12 weeks, although recurrent or bilateral lesion may also occur.

B Truncal Neuropathy

Symptomatic truncal polyneuropathy though less common, tends to occur in the setting of long standing diabetes with other microvascular complications especially peripheral neuropathy. Most of the affected individuals are in the 5th or 6th decade of life, with a variable duration of diabetes. [13] It usually presents with gradual onset of pain and dysaesthesia in the lower anterior chest or upper abdomen with nocturnal intensification. On examination, hypoaesthesia or hyperaesthesia may be present in the appropriate thoracic segment and abdominal muscle weakness leading to abdominal swelling.

C Entrapment neuropathy

Also known as pressure palsy, this is relatively uncommon. Median nerve is mostly affected and is secondary to soft tissue changes associated with limited joint mobility. The precise pathogenesis of diabetic peripheral neuropathy despite recent advances remains obscure; however, consensus is that neuropathy in diabetes mellitus is a multifactor disease. The possible etiologic factors suggested include, hyperglycaemia, polyol pathway, non-enzymatic glycation, free radical and oxidative stress. Many of these hypotheses are based on studies of different animal models of diabetes, but none of these truly reproduce the changes as seen in diabetic neuropathies in humans.[28]

SCREENING OF DIABETIC NEUROPATHY

1. Chronic sensorimotor

All patients with diabetes should be screened for diabetic peripheral neuropathy at diagnosis of type 2 diabetes and 5 years after the diagnosis of type I diabetes and at least annually by examining sensory function in the feet and checking ankle reflexes. One or more of the following can be used to assess sensory function: pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), or pressure sensation (using a 10-g monofilament pressure sensation at the distal halluces). Any history of neuropathic symptoms should be elicited, and a careful clinical examination of the feet and lower limbs should be performed. The feet should be examined for ulcers, calluses, and deformities, and footwear should be inspected at each diabetes care visit. All patients with diabetic peripheral neuropathy, whether symptomatic or not, require foot care education and consideration for podiatric referral.

2.Monofilament testing

The monofilaments produce a characteristic force perpendicular to the contacting surface. The force of downward contact increases linearly until the monofilament buckles. Furthermore, repeated use of the devices throughout the day led to a far lower buckling force, thus leading the clinician to over diagnose the loss of protective sensation. Monofilaments can fail for several reasons: they can become damaged, old and uncalibrated. This contributes to lower loading forces and an over diagnosis of peripheral sensory neuropathy. Monofilament units should be replaced frequently and only calibrated instruments should be used. Throwaway or give-away devices are of questionable quality and durability.

3.Vibration Perception Threshold (VPT):

This testing is the most widely used quantitative sensory testing approach. VPT is associated with large normative and neuropathy databases. VPT evaluation fulfills the key criteria that make it desirable for longitudinal cohort evaluation: The instrument is sensitive, specific and reliable. [29]

TREATMENT

1. Tricyclic antidepressants

TCAs include imipramine, amitriptyline, desipramine and nortriptyline.These drugs are effective at decreasing painful symptoms but suffer from multiple side effects that are dosage dependent. One notable side effect is cardiac toxicity, which can lead to fatal arrhythmias. Among the TCAs, amitriptyline is most widely used for this condition, but desipramine and nortriptyline have fewer side effects.

2. Serotonin-norepinephrine reuptake inhibitors

The SSNRI duloxetine (Cymbalta) is approved for diabetic neuropathy, while venlafaxine is also commonly used. By targeting both serotonin and norepinephrine, these drugs target the painful symptoms of diabetic neuropathy, and also treat depression if it exists. On the other hand, selective serotonin reuptake inhibitors are not useful.

3. Selective Serotonin reuptake inhibitor

SSRIs include fluoxetine, paroxetine, sertraline and citalopram and are not recommended to treat painful neuropathy because they have been found to be no more efficacious than placebo in several controlled trials. Side effects are rarely serious, and do not cause any permanent disabilities. They cause sedation and weight gain, which can worsen a diabetic's glycemic control. They can be used at dosages that also relieve the symptoms of depression, a common comorbidity of diabetic neuropathy.

4. Antiepileptic drugs

AEDs, especially gabapentin and the related pregabalin, are emerging as first line treatment for painful neuropathy. Gabapentin compares favorably with amitriptyline in terms of efficacy, and is clearly safer. Its main side effect is sedation, which does not diminish over time and may in fact worsen. It needs to be taken three times a day, and it sometimes causes weight gain, which can worsen glycemic control in diabetics.

3. DIABETIC NEPHROPATHY

Diabetic nephropathy is an important cause of morbidity and mortality, and is now among the most common cause of end stage renal failure in developed country. About 30% of patients with type I diabetes has developed nephropathy after 20 years. The development of proteinuria indicative of nephropathy in a diabetic patient is a serious prognostic marker not only deciding a decline of renal function, but also indicating a huge increase in the tendency to cardiovascular disease .[30]

PATHOPHYSIOLOGY OF DIABETIC NEPHROPATHY

The pathophysiology of diabetic nephropathy manifests histologically as diabetic glomerulosclerosis, and is characterized by glomerular basement membrane thickening and mesangial expansion with increased extracellular matrix deposition. In Type I diabetics, there is a direct relationship between the extent of mesangial expansion and clinical severity of disease. It is demonstrated that direct correlation between the degree of mesangial expansion, and magnitude of proteinuria, severity of hypertension, and degree of renal impairment. Mesangial expansion in diabetic glomerulosclerosis may be considered the result of an imbalance between mesangial matrix protein production and degradation, favoring matrix protein accumulation. Overproduction of mesangial matrix proteins may be the result of glomerular hypertension and/or hyperglycemia-driven

synthesis of cytokines such as transforming growth factor-B, angiotensin II, and/or other growth factors. Alternatively, elevated glucose levels may inhibit matrix protein degradation through non-enzymatic glycosylation and/or through the inhibition of protein degradative pathways. Thus, the mediators of mesangial expansion constitute reasonable therapeutic targets when crafting a treatment strategy for diabetic nephropathy. Understanding the natural history of diabetic glomerulosclerosis is important to designing therapeutic interventions, as well as gauging responses to therapy. In this regard, the deleterious effect of hypertension on renal function in proteinuric diabetics [31]. Of equal or greater value in that report was the demonstration of the expected rate of loss of glomerular filtration rate over time, in patients with diabetic nephropathy.

STAGES OF DIABETIC NEPHROPATHY

- Diabetic nephropathy is a spectrum of progressive renal lesions secondary to diabetes mellitus ranging from renal hyperfiltration to end stage kidney disease.
- The earliest clinical evidence of nephropathy is the presence of microalbuminuria (Table 1). It occurs in 30% of type 1 diabetics, 5 to 15 years after diagnosis but may be present at diagnosis in type 2 diabetics as the time of onset of type 2 diabetes is often unknown. [8,9]
- Microalbuminuria progresses to overt proteinuria over the next 7 to 10 years.
- Once overt proteinuria develops, renal function progressively declines and end stage renal failure is reached after about 10 years. [32]

FACTORS AFFECTING DIABETIC NEPHROPATHY

1. Genetic factors:
Epidemiological studies have shown that the incidence of diabetic nephropathy peaks in the second decade of disease and after 25 years the risk rapidly declines, which is in contrast to other diabetic complications. The concept of a genetic predisposition for development of diabetic nephropathy has therefore been postulated. This is supported by studies that have shown familial clustering in different populations, but this could also be a result of shared environmental factors. Some studies have demonstrated that a predisposition to hypertension and a family history of cardiovascular disease and type 2 diabetes may be associated with increased risk of developing diabetic nephropathy. This also suggests a genetic association to the metabolic syndrome. Ethnic differences in the risk of developing diabetic renal disease have also been described supporting that genetic background has an impact.[33]

2. Metabolic factors
Hyperglycemia is necessary for the development of microvascular diabetic complications and it is associated with both onset of incipient and overt diabetic nephropathy.The level of hyperglycemia seems to be quantitatively linked to the risk of developing renal lesions. Hyperglycemia enhances the non-enzymatic glycosylation of proteins and advanced glycosylation end-products are formed. Increased serum levels of advanced glycosylation end-products seem to predict changes in kidney morphology such as expansion of mesangial cell matrix and glomerular basement membrane thickening [34]. Advanced glycosylation end-products may also affect the charge selectivity on the glomerular basement membrane, altering the filtering capacity. Advanced glycosylation end-products levels are well correlated to the degree of long-term glycemic control and, in addition, they are increased when renal function declines. Importantly, the level of these products do not return to normal when hyperglycemia is corrected since they may accumulate in the blood vessel-wall and remain there during the life-time of the proteins.

3.Hemodynamic factors
Early studies showed that systemic hypertension accelerates renal injury in diabetes and that the rate of progression of renal disease is slow in normal patients with type I diabetes. An increase in the intraglomerular pressure has been suggested to promote progressive renal injury early in diabetic nephropathy. [35]

A beneficial effect of angiotensin converting enzyme inhibition has been shown with respect to progression of both incipient and overt diabetic nephropathy and this includes reversal of structural changes.. This results in both systemic and intraglomerular hypertension, which accelerate the renal injury. [36]

The ability of the kidney to maintain a constant glomular filtrtion rate over a range of renal perfusion pressures is called autoregulation, and some data suggest that an impaired autoregulation is present in overt diabetic nephropathy.. Studies have shown that microalbuminuria and autonomic nephropathy coexist in patients with type 1 diabetes and among patients without nephropathy the prevalence of autonomic nephropathy is low [37]

4. Growth factors and puberty

The growth hormone and insulin-like growth factor-1 (IGF-1) influence the development of diabetic complications. Possibly, chronic hyperglycemia and/or lack of insulin in diabetes lead to impairment in the hepatic IGF-1 formation and a lower serum IGF-1 level,

inducing growth hormone hypersecretion by feed back. The increase in growth hormone concentration, in turn, might stimulate local IGF-1 production in the kidneys. Additionally, some studies have shown that puberty, partly due to the hormonal changes, e.g. high levels of growth and sex hormones together with a concomitant detoriation in glycemic control, may promote the development of microvascular complications .[38]

5. Environmental factors

Low birth weight has been associated with retardation of renal development, a reduced number of nephrons and an increased risk of systemic and intraglomerular hypertension. Low birth weight and intrauterine growth retardation have also been linked to cardiovascular risk factors and an increased risk of developing diabetic nephropathy. These findings support that prenatal factors may contribute to the development of diabetic nephropathy. Moreover, an impaired aerobic work capacity has been shown in patients with type 1 diabetes with incipient as well as overt nephropathy compared to those with normal renal function. Other potential environmental factors include diet and tobacco use and they are described in the section on clinical management. [39]

TREATMENT

1. ACE inhibitor drugs

which usually reduces proteinuria levels and slows the progression of diabetic nephropathy. Several effects of the ACEIs that may contribute to renal protection have been related to the association of rise in Kinins which is also responsible for some of the side effects associated with ACEIs therapy such as dry cough.

2. Angiotensin receptor blockers (ARBs)

However, combination therapy, according to the ONTARGET study,[4] is known to worsen major renal outcomes, such as increasing serum creatinine and causing a greater decline in estimated glomerular filtration rate (eGFR).

3. Oral hypoglycemic agents

Blood-glucose levels should be closely monitored and controlled. This may slow the progression of the disorder, especially in the very early stages. Medications to manage diabetes include oral hypoglycemic agents and insulin injections. As kidney failure progresses, less insulin is excreted, so lesser doses may be needed to control glucose levels

High blood pressure should be aggressively treated with antihypertensive medications, in order to reduce the risks of kidney, eye, and blood vessel damage in the body. It is also very important to control lipid levels, maintain a healthy weight, and engage in regular physical activity.

Patients with diabetic nephropathy should avoid taking the following drugs:

Contrast agents containing iodine

Commonly used non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen, or COX-2 inhibitors like celecoxib, because they may injure the weakened kidney.

4. SKIN MANIFESTATIONS

Among the many skin manifestations in diabetes mellitus, which vary from trivial to life-threatening lesions. Diabetes has been implicated the main reason for nontraumatic amputation, and an independent risk factor for cardiovascular disease. Nearly one-third of diabetic patients have some type of dermatologic manifestation. With time, the skin of all diabetic patients is affected in some form or another. Cutaneous signs of diabetes mellitus are extremely valuable to the clinician. For example, diabetic dermopathy, necrobiosis lipoidica diabeticorum, and the scleroderma-like syndrome of waxy skin with limited joint mobility can alert the physician to the diagnosis of diabetes. [41] Similar to other complications such as retinopathy and nephropathy, skin complication is largely the result of the combined effect of hyperglycaemia, neuropathy, and both microvascular and macrovascular angiopathies. Cutaneous manifestations can be classified as follows:

1. Infection
2. Dermal menifestations in Diabetes Mellitus e.g. Yellow nails
3. Vascular complications in Diabetes Mellitus e.g. Macroangiopathy, microangiopathy
4. Diabetic dermopathy e.g. Periungual telangiectasia
5. Treatment induced complications

INFECTIONS ASSOCIATED WITH DIABETES

1.Candida Infections

Yeast infections are common in diabetic patients. Involvement of the glans penis and of the vulva appears common in type II diabetes. Vaginal candidiasis is almost universal among women with long term diabetes, and yeast infections may even be the presenting manifestation of diabetes. Vulvo-vaginal candida infection is an especially common problem for the diabetic woman. It is a common cause of pruritus vulvae during glycosuria. Since these patients often have a reservoir of candida in the colon, oral nystatin may also be administered. Another option for vaginal candidiasis is oral administration of one dose 150 of mg of fluconazole.[42] It often begins at the lateral nail folds as erythema, swelling, and separation of the fold from the lateral margin of the nail. Further infection may result in involvement of the proximal nail fold and separation of the cuticle from the nail.

2. Phycomycetes Infections

Diabetic patients with leg ulcers, or non-healing surgical wounds, especially those of the lower extremities, may have a complicating phycomycetes infection. Such an infection should be suspected when lower extremity ulcers or post traumatic lesions are not responding to therapy. Diagnosis can be confirmed by culture and by histological demonstration of fungal elements invading vascular channels. Treatment consists of correction of acid-base imbalance, aggressive debridement of necrotic tissue, and intravenous amphotericin.

3. Pseudomonas Infections

Malignant external otitis, an uncommon, but serious, infection of the external ear canal by Pseudomonas, characteristically presents as and severe external ear canal pain and purulent discharge in an elderly diabetic patient. [43] The infection is thought to begin as a cellulitis of the ear canal, but natural cleavage planes allow progression through the osseous cartilaginous junction. With further extension the cranial nerves may be involved, especially the facial nerve. About half the affected individuals die of this infection. Treatment of choice consists of surgical debridement and administration of anti-pseudomonas antibiotics. Pseudomonas may cause web space infection on the feet similar to that due to dermatophytosis, but this assumption may be incorrect. The differential diagnosis includes candidiasis, infection due to pseudomonas, but a Wood's lamp examination often yields a green fluorescence. Soaks with dilute vinegar may eradicate superficial infection, with more advanced cellulitis; oral ciprofloxacin appears to be the treatment of choice.

DERMAL MANIFESTATIONS IN DIABETES MELLITUS

1. Yellow Skin

Diabetic skin often has a yellow hue. Traditionally considered to be carotenemia, recent evaluations indicate that serum carotene levels are not elevated as they had been years ago when the standard diabetic diet involved heavy consumption of vegetables.

One possible cause of yellow skin might be glycosylation end products. It is known that proteins which have a long turnover time, such as dermal collagen, undergo glycosylation and become yellow. Yellow skin is a common finding among patients with diabetes, probably best appreciated on the palms and soles because of sparse competition with melanocytic pigment in these areas. There is currently no significance associated with this finding other than that of a time proven observation. [44]

2.Dermatophytosis

Although dermatophyte infections are probably not more common in the diabetic population, they are of special concern. Toe web space infections may lead to inflammation and fissuring that can serve as a portal of entry for bacterial infection in a compromised diabetic foot. The oxygen demand of the subsequent inflammation may exceed the ability of the diabetic microcirculation, leading to gangrene. The infection itself is of little consequence, but the nail dystrophy which results may make proper nail care more difficult for the patient. Recently the FDA approved both itraconazole treatment,

VASCULAR COMPLICATIONS IN DIABETES MELLITUS

1.Macroangiopathy

Diabetics have a higher incidence and prevalence of large vessel disease. Development of myocardial infarction and stroke at a much younger age than their non-diabetic counterparts. Large vessel disease (atherosclerosis) may also be present in the lower extremities and result in skin atrophy, hair loss, coldness of the toes, nail dystrophy and mottling on dependence.

2.Microangiopathy

Microangiopathy is one of the major complications of diabetes mellitus. The small blood vessel changes affecting the retinal and renal vasculature are responsible for blindness and kidney failure Microvascular pathology has also been assumed to play a role in diabetic neuropathy, and in the so-called diabetic foot. Microangiopathy is clinically detected by an eye ground examination which demonstrates the presence of microaneurysms. More severe involvement may demonstrate hemorrhages, exudates, and even some devascularized areas as well.

DIABETIC DERMOPATHY

It appears as round to oval atrophic hyperpigmented lesions on the pretibial areas of the lower extremities. The lesions are usually bilateral and have an asymmetrical distribution. Histologically, lesions show edema of the papillary dermis, thickened superficial blood vessels, extravasation of erythrocytes, and a mild lymphocytic infiltrate. [45] The extravasated erythrocytes leave hemosiderin deposits, which provide the brownish hyperpigmentation.

The histology of affected diabetic tissue reveals a thickened capillary basement membrane. Electron microscopy of skeletal muscle capillaries reveals reduplication of the basal lamina. The skin has not been thought to be a good sample source in evaluation of

patients microangiopathy because small blood vessels of the dermis develop less basal lamina thickening than is found in skeletal muscle (which is also easily accessed using a needle biopsy).

The nail fold is an excellent site for viewing functional and structural changes in the microvascular of the skin. This patient illustrates microvascular engorgement and tortuosity involving the proximal nail fold. One may directly examine the skin to survey the superficial microcirculation. Any area of skin may be examined, but because nailfold capillary loops are in a horizontal axis relative to the skin surface, this area offers an excellent view of the entire microvascular loop. In order to see past the stratum corneum, it is helpful to first apply mineral oil to the skin surface and wait a few minutes until this layer becomes translucent. One may use a low power microscope or simply an ophthalmoscope. In general, the microcirculation of less pigmented individuals is often easier to visualize.

TREATMENT INDUCED SKIN LESIONS

Subcutaneous insulin injections in the insulin-dependent diabetes mellitus patients commonly gave rise to fat atrophy at the injection sites in children and young women in the past. It is now postulated that impurities contained in the older, less purified forms of insulin had a lipolytic or lipid-mobilizing effect causing this phenomenon. It should not be confused with the generalized diabetic lipodystrophies which occur very rarely. With the advance in insulin production, it is currently recommended that the daily injection of the purified insulin be made into the edge of the lipoatrophic areas. Improvement should usually be complete in 4 weeks. If not, injection of dexamethasone directly into the excavated areas is worth trying. Lipohypertrophy is much less frequent and treatment is unsatisfactory. Edema of the legs and abdomen occurring 1 to 2 weeks after the initiation of insulin treatment has been reported. This condition tends to resolve spontaneously and the pathogenesis is unknown. Sulphonylureas can cause various allergic reactions in a small proportion of patients. Urticaria, photosensitive dermatitis, Steven-Johnson syndrome and the antabuse-like flushing with alcohol are well documented. Treatment is by switching over to another preparation within the same family.[41]

DETECTION PARAMETER TO IDENTIFY SKIN COMPLICATIONS

1. Yellow Nails

For detection, the patient's thumbnail is photographed alongside the yellow nail of a person with diabetes. Another illustration of the nail of the hallux of a person with diabetes is also given. Clinically the yellow color is not usually the result of underlying dermatophytosis. Similar to the yellow color observed in diabetic skin, yellowing of the nails probably represents glycosylation end products. The protein glucose reaction presumably continues to evolve in the aging nail resulting in the most yellow pigment at the distal aspect of the slowest growing nail. The presence of the yellow glycosylation end products in the nail plate has not been confirmed to date, but one study of fingernails has demonstrated that diabetics have high levels of fructose-lysine, another marker of nonenzymatic glycosylation [46].

2. Sensory Neuropathy and Skin

Diabetics often develop sensory neuropathy on the feet, especially with long-standing disease. The clinical presentation usually involves tingling and numbness starting in the toes. The level of neuropathy may vary from mild numbness of the distal toes to profound anesthesia and neuropathic ulcers. Thermal sensitivity is also affected. Neuropathic patients who walk barefoot may sustain damage when during routine ambulation because they have inadequate sensation to withdraw the foot when it encounters noxious stimuli. Occasionally this unsensed trauma during ambulation results in fracturing the bones of the feet, eventuating into a Charcot foot. [47]

Patients with sensory neuropathy need to be instructed to make sure their shoes are devoid of foreign objects before the shoes are worn. In simple word, patients who do not follow necessary precaution may have severe damage by wearing shoes which, unknown to them, had objects (especially children's toys) included.

5. THE DIABETIC FOOT

Ten to fifteen per cent of diabetic patients develop foot ulcer at some stage in their lives. Diabetic foot problems are responsible for nearly 50% of all diabetes related hospital admission. Fifty per cent of all lower limb amputation is performed on people with diabetes. Many such amputations could be delayed by more effective patient education and medical supervision. Ischemia, infection and neuropathy combine to produce tissue necrosis. Although all these factors may coexist, the ischemic and the neuropathic foot can be distinguished.

PATHOPHYSIOLOGY OF DIABETIC FOOT:

There are mainly two forms of diabetes foot conditions,

1. The neuropathic foot

Peripheral neuropathy leads to somatic sensory and autonomic damage. Small fibre damage predominates initially, causing loss of pain and temperature sensation and later a numb or even anesthetic foot with loss of all sensory modalities. Sensory loss persists and abnormal forces which deform the foot occur unnoticed by the patient. Sympathtic damage causes loss of sweating and denervates peripheral blood vessel with profound effects.

Absence of sweating results in dry foot sometimes associated with cracking skin which acts as portal entry for sepsis. Vasomotor denevation causes a huge incresse in peripheral blood flow, opening of artevenous shunts, and arterial medial degeneration with calcification.

2. The ischemic limb

The blood supply to the foot is reduced by atherosclerosis of large vessels; the disease is common in people without diabetes, but the histopathology is the same and only the distribution may be different. It is age related; older patients and those who smoke are more likely to suffer foot problems from ischemia. [48]

TREATMENT

Foot ulcers in diabetes require multidisciplinary assessment, usually by diabetes specialists and surgeons. Treatment consists of appropriate bandages, antibiotics (against staphylococcus, streptococcus and anaerobe strains), debridement and arterial revascularisation. It is often 500 mg to 1000 mg of flucloxacillin, 1 g of amoxicillin and also metronidazole to tackle the putrid smelling bacteria. Specialists are investigating the role of nitric oxide in diabetic wound healing. Nitric oxide is a powerful vasodilator, which helps to bring nutrients to the oxygen deficient wound beds. Specialists are using forms of light therapy. [49,50]

6 DIABETIC CARDIOMYOPATHY

Of the causes leading to cardiac dysfunction, diabetes is the most prevalent. Indeed, it is the single most important risk factor for coronary artery disease and over 30% diabetics in the United-States are diagnosed with diabetic heart disease. [51] Furthermore, two-thirds of diabetics will eventually die of some sort of cardiovascular disease. [52]

SIGNS AND SYMPTOMS

One particularity of diabetic cardiomyopathy is the long latent phase, during which the disease progresses but is completely asymptomatic. In most cases, diabetic cardiomyopathy is detected with concomitant hypertension or coronary artery disease. One of the earliest signs is mild left ventricular diastolic dysfunction with little effect on ventricular filling. After the development of systolic dysfunction, left ventricular dilation and symptomatic heart failure, the jugular venous pressure may become elevated, the apical impulse would be displaced downward and to the left. Systolic mitral murmur is not uncommon in these cases. These changes are accompanied by a variety of electrocardiographic changes that may be associated with diabetic cardiomyopathy in 60% of patients without structural heart disease, although usually not in the early asymptomatic phase. [53]

POTENTIAL MECHANISMS LINKING DIABETES MELLITUS TO HEART FAILURE.

Diabetes mellitus is associated with multiple physiopathological changes in the cardiovascular system. Among these, endothelial dysfunction and hemostatic disorders may at least in part account for the higher risk of coronary artery disease (CAD) while microangiopathy, myocardial fibrosis, and abnormal myocardial metabolism have been implicated in the pathogenesis of a specific diabetic cardiomyopathy. [54] When it occurs in diabetic patients, heart failure (HF) along with coronary artery disease shows presence of other comorbidities frequently encountered in diabetic patients such as hypertension. The existence of a diabetic cardiomyopathy may increase the risk of heart failure in response to these insults; however, whether diabetic cardiomyopathy alone may be responsible for heart failure remains unknown.[55]

TREATMENT

1.Conventional therapies

At present there is not a single clinically effective treatment for diabetic cardiomyopathy clearly, the most logical treatment is intensive glycemic control through diet, sulfonylureas and metformin. There is a clear correlation between increased glycemia and risk of developing diabetic cardiomyopathy. Unfortunately, intensive therapy is associated with dangerous hypoglycemic episodes and weight gain, which can affect the quality of life of the patient. Novel drugs are tested for alternative oral hypoglycemic therapy. These include thiazolidinediones, which are PPARγ agonist and insulin sensitizers. Not only do they help control glucose concentration, but they also play a role in lowering circulating free fatty acids and triglycerides, which are major players in the development of the abnormalities seen in diabetic cardiomyopathy. [56]

2. Nutritional interventions

A) Transition metals

Given that many mechanisms involved in the pathogenesis of diabetic cardiomyopathy have a basis in free radical chemistry, and that many of the anti-oxidant defenses of the cells rely on trace metals. Indeed, in rats, selenium supplementation had a possible beneficial effect on the electrical activities of the diabetic heart, possibly due to the restoration of the diminished K+ currents and partially related to a restoration of the cell's glutathione redox cycle. Further, it is known that zinc deficiency is a risk factor for cardiomyopathies.[57] *It has shown tha*t oral magnesium supplementation may be effective in reducing plasma fasting glucose levels and raising high density lipoproteins in patients with Type II diabetes, although the long-term benefits and safety of magnesium treatment on glycemic control remain to be

Figure 1: Non Proliferative Diabetic retinopathy with Maculopathy

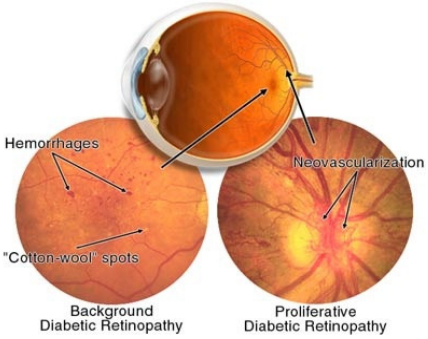

Figure 2: Proliferative Diabetic Retinopathy

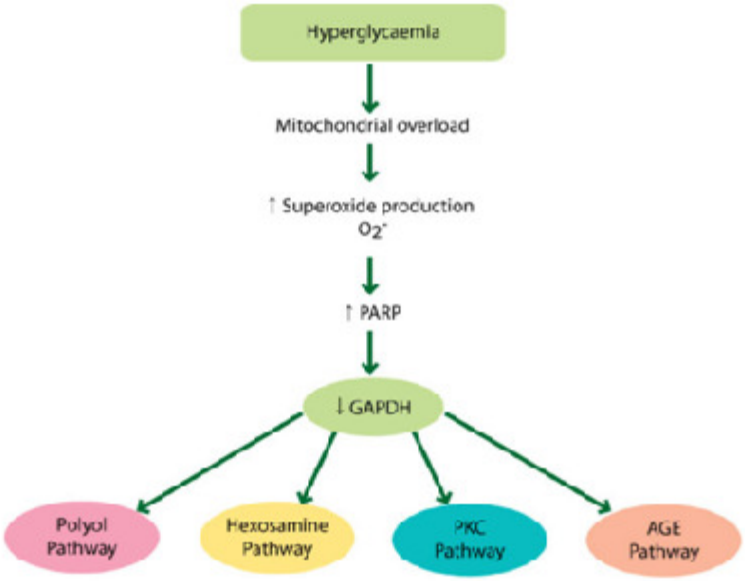

Figure 3: The pathogenetic mechanisms responsible for the development of microvascular complications in diabetes with diffuse neuropathy.

STAGES	SYMPTOMS
STAGE 1	• Glomerular hypertension and hyperfiltration • Normal albuminuria: urinary albumin excretion rate (AER) <20 µg/min • Raised GFR, normal serum creatinine
STAGE 2	"Silent phase" (structural changes on biopsy but no clinical manifestations) • Normoalbuminuria
STAGE 3	Microalbuminuria: AER 20 – 200 µg/min • Normal serum creatinine • There may be increased blood pressure
STAGE 4	Overt proteinuria (macroalbuminuria) AER > 200 µg/min • Hypertension • Serum creatinine may be normal • Increase in serum creatinine with progression of Nephropathy
STAGE 5	End stage renal failure • Requiring dialysis or transplant to maintain life

Table 1: Stages of diabetic renal disease

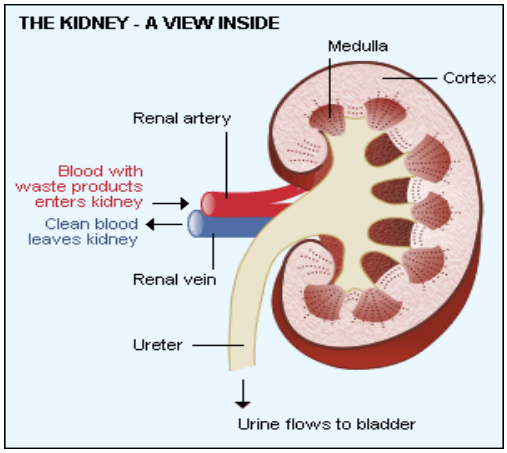

Figure 4 : A schematic view on the development of diabetic renal disease. [40]

Figure 5: Diabetic dermopathy

Figure 6: Periungual Telangiectasia

Figure 7: Yellow nails of diabetes

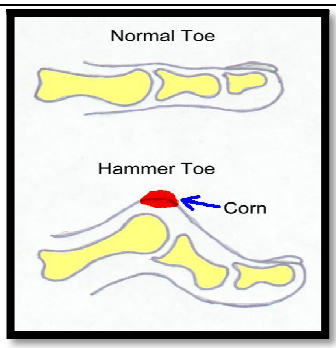

Figure 8: The erosion with callus on the tip of the toe.

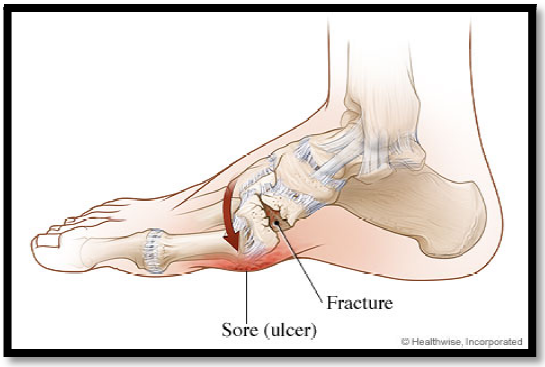

Figure 9: Charcot Foot.

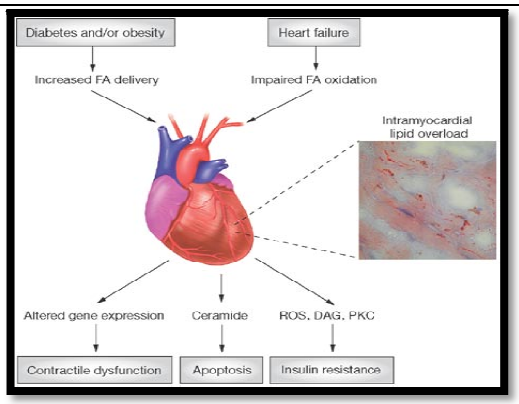

Figure10: Mechanism related to diabetes mellitus leading to heart failure.

CONDITIONS	ISCHAEMIA	NEUROPATHY
Symptoms	Cloudication Rest pain	Usually painless Sometimes painful neuropathy
Inspection	Dependent rubor Trophic changes	High arch Clawing of toes No tropic changes
Palpation	Cold Pulseless	Warm Bounding pulses
Ulceration	Painful Heels and toes	Painless Planter

Table 2: Distinguishing features between ischemia and neuropathy in diabetic foot

determined. [58]

B) Thiamine

Another nutritional intervention would be thiamine supplementation. As explained above, endothelial, as well as peripheral nerve dysfunctions are caused by the inability for these types of cells to regulate their glucose uptake. It was recently shown that high thiamine supplementation activates an enzyme, transketolase, which metabolizes the accumulating glyceraldehyde-3-phosphate. In vitro, thiamine was also shown to diminish advanced glycosylation end products, protein kinase C activity, inflammation and flux through the hexosamine pathway, the four causes of endothelial dysfunction. [59]

C) Taurine

Taurine is a semi-essential sulphur amino acid derived from methionine and cysteine metabolism. Recent studies have provided a role for taurine in fetal development and in diminishing the effects of diabetes in a diabetic mother and its offspring. Furthermore, experimental data suggest that taurine could have beneficial effects in diabetes. However, clinical studies have been too small and too short to have any real significance. [60]

CONCLUSION

Present project concludes that the need to know diabetic induced complications and regarding other manifestations is very important. As these complications may be fatal if not diagnosed earlier or the prognosis of complications is very bad. The diabetic patient if not treated properly, suffers through other health problems and eventually may lead to multiorgan system failure.

Diabetes is underdiagnosed in the elderly and is frequently undertreated. The greatest attention should be given to reduction of overall cardiovascular risk. This study aimed to explore the relationship between complications and risk factors in the type II diabetes population. Multi-disciplinary approaches to the control of risk factors and patient self management and education are critical to the progression and success of diabetes care. In addition, optimized control of glucose level which delays onset and progression of diabetic retinopathy as well as other complications like neuropathy and nephropathy. In simple word, patients who do not follow necessary precaution may have severe damage to various body systems leading to complications i.e. eye causing retinopathy, damaged nerves leading to neuropathy, damage to kidney leading nephropathy.

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