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EC MICROBIOLOGY
Review Article

Long Term Complication of Poor Glycemic Control in Diabetic Patients

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Abstract

Introduction: Diabetes mellitus is a metabolic disease characterized by hyperglycemia. The hyperglycemia is mostly due to a defect in insulin secretion and action or both. Though advancement in pharmaceutical intervention and improved lifestyle habits have aimed at preventing diabetes by controlling prolong hyperglycemic state. But despite all the efforts, diabetes at the chronic stage presents various life-threatening complications due to poor glycemic control. There is a various microvascular and macrovascular complication of chronic diabetes. Complication varies from Hyperglycemia plays an important role in microvasculopathy but also appears to be a causative factor in macrovasculopathy. The treatment of diabetes attempts to decrease tissue harm due to hyperglycemia and ensure adequate glucose delivery to various tissues of the body.

Aim of the Study: The study aims to understand the various complication of diabetes mellitus in chronic stages due to poor glycemic control.

Methodology: The review is a comprehensive research of PUBMED since the year 1998 to 2017.

Conclusion: The importance of controlling the hyperglycemic state cannot be overstated. There is a major effect of hyperglycemia on human vasculature, and it is one of the major reasons for significant morbidity and mortality in both type-1 and type-2 diabetes. The microvascular complication is diabetic neuropathy, nephropathy, and retinopathy, while the macrovascular complication is coronary artery disease, peripheral arterial disease, and stroke. Thus, it is imperative for physicians to understand the relation between diabetes and vascular diseases and resolve the poor hyperglycemic state.

Keywords: *Chronic Diabetes; Microvascular Complication; Macrovascular Complication*

Pathology of diabetes complication

The disruption in the vascular system of the body is due to impaired metabolism of carbohydrates, fats, proteins, and electrolytes associated with the hyperglycemic state. Under this state, many endothelial cells are damaged, including the retina, glomerulus, central, and peripheral nerves due to excessive glucose accumulation in these cells. Impaired lipid metabolism, increased production of reactive oxygen species (ROS), and reduced protective antioxidant system leas to insulin resistance and more damage to beta cells in the pancreas [1-3].

Methodology

A comprehensive and systematic search was conducted regarding long term complication in diabetic patients with poor glycemic control. PubMed search engine and Google Scholar search were the mainly used database for search process. All relevant available and accessible articles of all types were reviewed and included.

The terms used in search were: Chronic diabetes, Microvascular complication, Macrovascular complication.

Pathophysiology

The polyol pathway

Aldose reductase and sorbitol dehydrogenase are the essential enzymes involved in the polyol pathway. The increased blood glucose levels increase aldose reductase activity that converts glucose to sorbitol, which accumulated intracellularly and increased cellular osmotic injury and thus increasing oxidative stress [4].

Increased hexosamine pathway activity

The normal glycolysis pathway shifts to hexosamine pathway when blood glucose level increases which in turn worsen diabetic complication and increases oxidative stress by production of diphosphate-N-acetyl glucosamine [2].

Activation of protein kinase-C (PKC) pathway

Hyperglycemia induces the formation of diacylglycerol, which activates the PKC pathway, which worsens diabetic complications by more production of angiogenic proteins such as vascular endothelial factors (VEGF) and, methylglyoxal (atherogenesis proteins) [5].

Increased production of advanced glycation end products

The elevated intracellular glucose level leads to increase the formation of reactive dicarbonyl species such as methylglyoxal (MGO) which binds to protein molecules and form advanced glycation end products (AGEs), accumulation of which disrupts the metabolic activities and alter the gene expression of DNA [5].

Following are some delayed complication of diabetes [6]:

Central and peripheral nervous systems

- Brain stroke
- Autonomic neuropathy
- Peripheral neuropathy

Eyes

- Retinopathy
- Cataracts
- Blindness

Cardiovascular system

- Cardiomyopathy
- Myocardial infarction

- Atherosclerosis
- Hypertension
- Endothelial cell dysfunction

Oral cavity

- Caries, Gingivitis, periodontitis

Gastrointestinal system

- Delayed gastric emptying
- Diarrhea
- Constipation
- Dyspepsia
- Exocrine gland insufficiency

Genital system

- Impotence
- Sexual disfunction
- Urogenital dysfunction

Skin and soft tissues

- Impaired wound healing
- Skin infection

Bone

- Osteopenia, fractures

Foot

- Foot ulceration
- Foot amputation

The microvascular complication of diabetes

Diabetic nephropathy

Diabetic nephropathy is genetically susceptible in many patients and as well as triggered by certain environmental factors such as the reaction of cytokines with reactive oxygen species/ advanced glycation end products.55 The earliest indicator of diabetic nephropathy is the excretion of albumin in the urine. Nearly one-third of diabetic patients with uncontrolled blood sugar suffer from diabetic nephropathy. It is associated with morphological impairment of the glomerular endothelial cell barrier and the basement membrane. This enhances protein filtration in urine, which is reflected as impaired protein degradation in patients with diabetes. The further progression in oxidative stress leads to gene expression of angiotensinogen and further impairment in renal function [7,8].

Diabetic retinopathy

In many cases, diabetes mellitus is indirectly diagnosed during an eye test for having an impaired vision, which if left untreated, can lead to loss of sight. The risk of blindness in diabetes is associated with having diabetes for decades. The diabetic retinopathy is induced by hyperglycemic state by stimulation of PKC, which in turn elevated many other metabolic pathways, stimulation of cell growth, apoptosis, and increase in permeability of the cell. Such changed are known to be associated with the progression of other diabetes-related vascular complications such as cardiomyopathy, neuropathy, nephropathy and, atherosclerosis. The cataract formation in diabetes is associated

with hyperglycemia and apoptotic growth factors stimulated by states of oxidative stress in diabetic retinopathy. In addition to this, the increased level of glucose in retinal cells may increase the risk of retinopathy and accompanying blindness. An important feature of diabetic retinopathy is diabetic macular edema (DME) which arises from the breakdown of blood-retinal barrier and further vascular leakage and extravasation of fluid into neural retina leading to thickening of the retina [9,10].

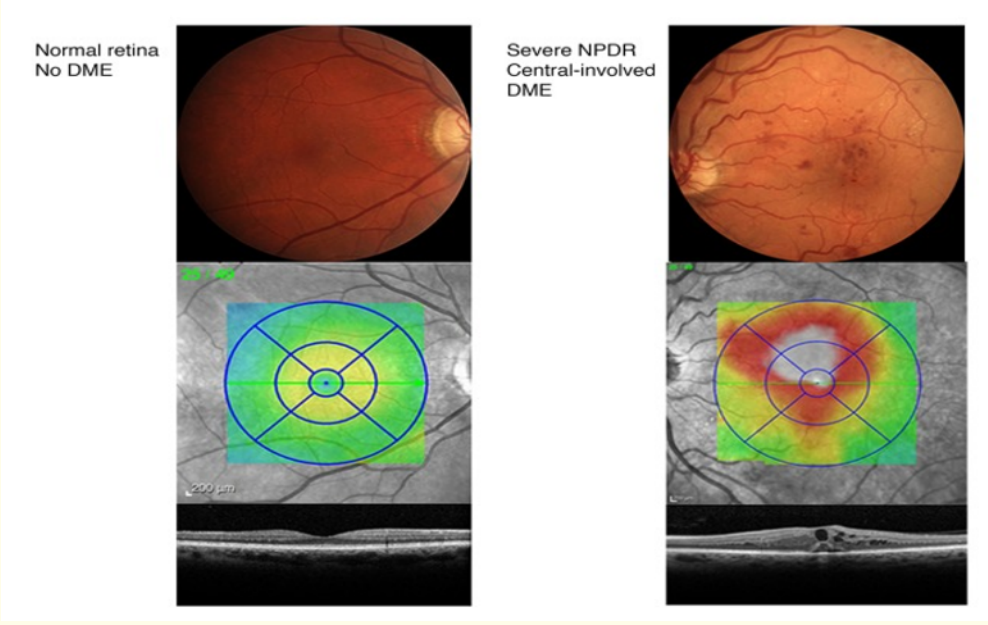


Figure 1: *Showing color fundus and OCT images of normal retina and retina with NPDR showing DME [10].*

Diabetic retinopathy is broadly divided into 2 categories [10]:

- Non-proliferative retinopathy (NPDR)- characterized by microaneurysms, retinal hemorrhage, intraretinal microvascular abnormalities.
- Proliferative retinopathy (PDR)- characterized by hallmark feature of pathological retinal neovascularization.

Diabetic neuropathy

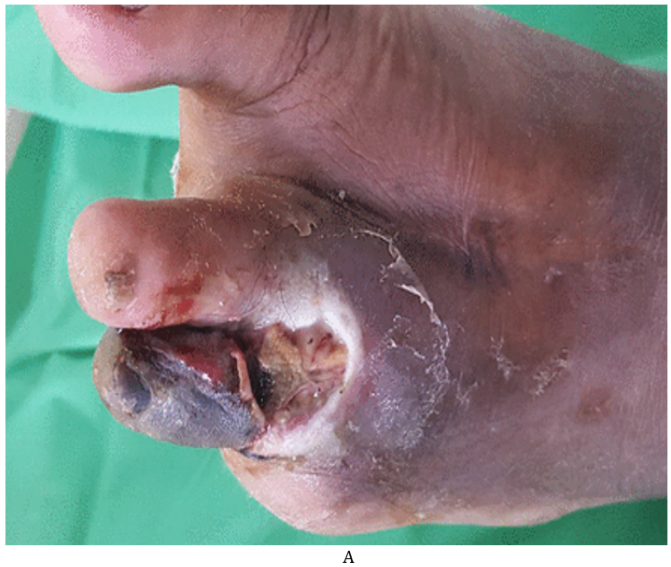
Diabetic neuropathy is a complication of the prolonged hyperglycemic state over the years. The chronic hyperglycemic state withers lead to sensory or motor neuropathic problems or autonomic nervous system dysfunction such as arrhythmias, gastroparesis, sexual dysfunction [6].

Peripheral neuropathy is one of the major complications of chronic diabetes, which can lead to sensory or sensorimotor neuropathies that increase the risk of ulceration of foot or amputation. The increased activation of the polyol pathway reduces NADPH, which is required for activation of glutathione reductase, aldolase reductase; this further leads to worsening of oxidative stress and accelerate neuro-degradation [11].

Autonomic neuropathy may include GIT dysfunction; the patient may present with symptoms such as bloating, vomiting, early satiety, abdominal pain, and heartburn. Slow emptying of the stomach is usually seen in diabetic enteropathy; it also leads to acid reflux disease, delayed bowel movement, constipation, diarrhea and infection. Erectile dysfunction is another common complication which his due to disturbed communication between vascular and neuronal system due to weak blood circulation in penile tissues. The other factor, such as hormonal change, malnutrition, and penile tissue infection, may also lead to the same [12,13].

Diabetic foot

Diabetic foot ulceration is due to combined neuropathy and ischemia. It is due to loss of sensation, impaired wound healing in the injured area, leading to wound infection, ulceration, and further foot amputation. The ulceration is frequently associated with foot trauma, which is due to decreased proprioception. The symptoms vary from numbness and tingling sensation to sharp pain and sensitivity to touch. Since all the staged of wound healing cascade is impaired in diabetes, it is difficult to prevent the progression of ulcer to gangrene. In addition to this many other systems are impaired such as inflammation, proliferation, angiogenesis, apoptosis, reduced chemotaxis and matrix formation, decreased bacterial resistance and deterioration of the antioxidant protective system. All the together lead to failure of appropriate wound healing along with the other complication of diabetes such as peripheral vascular disease; wound healing becomes impaired leading to amputation of the foot [14,15].



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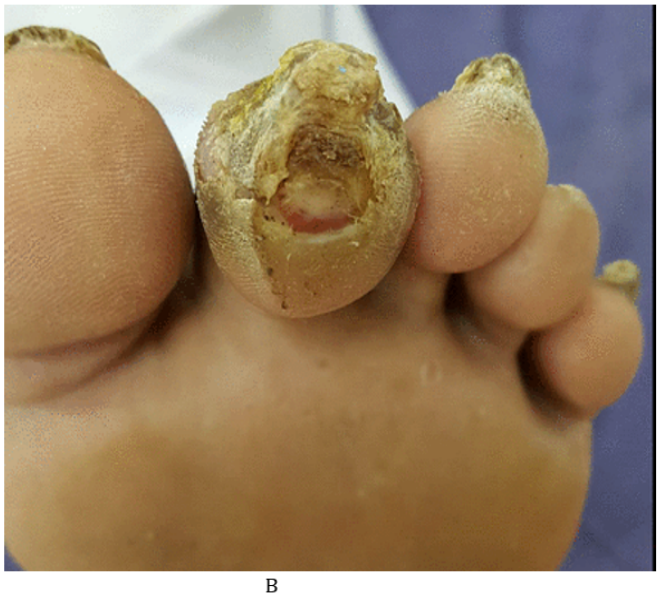

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Figure 2: *Showing A. gangrene and ulcer in the foot with a high risk of amputation, B. Hammer toe deformity with callus and ulcer [16].*

Macrovascular complication impaired

Atherosclerosis

The impairment in endothelial cells in macrovascular complications has many factors, such as increased blood glucose level, lips, MGO, and inflammatory factors. The excessive production of ROS can induce vasoconstriction with increased lipid peroxidation and inflammatory reaction leading to atherosclerosis [17].

Atherosclerosis is the process of deposition of lipid (low-density lipoprotein) in a sub-endothelial layer of large blood vessels, and it often occurs in patients suffering from diabetes mellitus than the other without diabetes. Atherosclerosis increases the endothelial permeability of blood vessels. The high-density lipoprotein provides antioxidant and anti-inflammatory protective actions that are suppressed due to the presence of increased inflammation and excessive liberation of ROS; this, in turn, causes oxidation of phospholipids and sterols. The other complication, such as plaque formation and calcification, can lead to the development of a more severe vascular complication [18].

Coronary artery disease

Stroke, peripheral arterial disease, and coronary artery disease are a common complication in diabetes mellitus and are the leading cause of high mortality among these patients. The increased blood pressure and dyslipidemia cause diabetes-induced cardiomyopathy. Cardiomyopathy may further lead to cardiac fibrosis and is enhanced by excessive production of oxidative free radicals disrupting myocardial cells and causing dysregulation of cellular homeostasis, contractile dysfunction, myocardium remodeling, and subsequent death of cardiomyocytes. The oxidative stress is responsible for the inhibition of anti-oxidant protective system in diabetic patients [19].

Peripheral arterial disease (PAD)

PAD is defined as an atherosclerotic occlusive disease of lower limbs and is associated with increased risk of foot amputation and also a marker of atherothrombosis in cardiovascular, cerebrovascular, and renovascular beds. In this way, patients suffering from PAD are at greater risk of developing MI, stroke, and greater risk of death. The hyperglycemic state of diabetes fosters the development of PAD in a similar way that of coronary artery disease, which includes derangement in vessel walls due to vascular inflammation, endothelial cell dysfunction, blood cell abnormalities including smooth muscle cells and platelets and other factors affecting hemostasis [20].

Conclusion

Diabetes mellitus is one of the major metabolic disorders affecting millions of people worldwide. The disorder is prevalent in both developed and developing countries and is a significant cause of morbidity and mortality of the major population. It is associated with modern lifestyle, diet, reduced physical activity and increased obesity as well as genetic factors. Chronic diabetes develops when left untreated, which can lead to various long-term complications due to poor blood glucose control, subsequently leading to death. The complication is mostly due to hyperglycemia-induced cellular and molecular impairment of neural and vascular tissues of the body. Apart from this, oxidative stress plays a major role in the development of a long-term complication, neuropathy and angiopathy may lead to cells, tissues and organ system dysfunction. Hence it is important to control the blood glucose state of individuals with early intervention of complications to avoid further long-term complications.

Bibliography

1. Kolluru GK., *et al*. "Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing". *International Journal of Vascular Medicine* (2012): 918267.
2. Brownlee M. "The pathobiology of diabetic complications: a unifying mechanism". *Diabetes* 54.6 (2005): 1615-1625.
3. Forbes JM and Cooper ME. "Mechanisms of diabetic complications". *Physiological Reviews* 93.1 (2013): 137-188.
4. Semba RD., *et al*. "The role of O-GlcNAc signaling in the pathogenesis of diabetic retinopathy". *Proteomics-Clinical Applications* 8.3-4 (2014): 218-231.

5. Koya D and King GL. "Protein kinase C activation and the development of diabetic complications". *Diabetes* 47.6 (1998): 859-866.

6. Lotfy M., *et al*. "Chronic complications of diabetes mellitus: a mini review". *Current Diabetes Reviews* 13.1 (2017): 3-10.

7. Wolf G., *et al*. "From the periphery of the glomerular capillary wall toward the center of disease: podocyte injury comes of age in diabetic nephropathy". *Diabetes* 54.6 (2005): 1626-1634.

8. Durvasula RV., *et al*. "Activation of a local tissue angiotensin system in podocytes by a mechanical strain". *Kidney International* 65.1 (2004): 30-39.

9. Madsen-Bouterse SA and Kowluru RA. "Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives". *Reviews in Endocrine and Metabolic Disorders* 9.4 (2008): 315-327.

10. Duh EJ., *et al*. "Diabetic retinopathy: current understanding, mechanisms, and treatment strategies". *JCI Insight* 2.14 (2017).

11. Hotta N., *et al*. "Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on the progression of diabetic neuropathy and other microvascular complications: a multivariate epidemiological analysis based on patient background factors and severity of diabetic neuropathy". *Diabetic Medicine* 29.12 (2012): 1529-1533.

12. Rodrigues ML and Motta ME. "Mechanisms and factors associated with gastrointestinal symptoms in patients with diabetes mellitus". *Jornal de Pediatria* 88.1 (2012): 17-24.

13. Jesmin S., *et al*. "Diminished penile expression of vascular endothelial growth factor and its receptors at the insulin-resistant stage of a type II diabetic rat model: a possible cause for erectile dysfunction in diabetes". *Journal of Molecular Endocrinology* 31.3 (2003): 401-418.

14. Margolis DJ., *et al*. "Diabetic neuropathic foot ulcers and amputation". *Wound Repair and Regeneration* 13.3 (2005): 230-236.

15. Edmonds M. "Diabetic foot ulcers". *Drugs* 66.7 (2006): 913-929.

16. Mishra SC., *et al*. "Clinical updates: Diabetic foot". *The BMJ* 359 (2017).

17. Di Marzio D., *et al*. "Macroangiopathy in adults and children with diabetes: from molecular mechanisms to vascular damage (part 1)". *Hormone and Metabolic Research* 38.11 (2006): 691-705.

18. Lanzer P., *et al*. "Medial vascular calcification revisited: review and perspectives". *European Heart Journal* 35.23 (2014): 1515-1525.

19. Nancy MD., *et al*. "A detailed review of the mechanisms involved in chronic stages of type II diabetic complications". *International Journal of Phytopharmacology* 4 (2013): 60-73.

20. Thiruvoipati T., *et al*. "Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes". *World Journal of Diabetes* 6.7 (2015): 961.

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