ECRONICON OPEN ACCESS

EC ENDOCRINOLOGY AND METABOLIC RESEARCH

Review Article

Epidemiological Review of Chronic Diabetes Complications (Cardiovascular Disease, Nephropathy and Retinopathy)

Amin Muhammad Ibrahim*

Medical Officer, Ayodele Medical Centre, Iju Lagos, Nigeria

***Corresponding Author:** Amin Muhammad Ibrahim, Medical Officer, Ayodele Medical Centre, Iju Lagos, Nigeria.

Received: June 28, 2018; **Published:** July 31, 2018

Abstract

The world is currently in the midst of a diabetes epidemic which has not shown any sign of waning. As more people have diabetes and suffer complications, the disease burden will undoubtedly increase. Macrovascular complications e.g. coronary artery disease, cerebrovascular disease and peripheral arterial disease are common among people with diabetes. Cardiovascular diseases are a significant cause of mortality in people with diabetes. Among the microvascular complications nephropathy is a leading cause of end stage renal disease while retinopathy is among the most common causes of visual impairment or blindness. The pathogenetic pathways of diabetic complications are the polyol pathway, formation of advanced glycation end products, protein kinase C activation and recently the hexosamine biosynthetic pathway. These hyperglycemia induced pathways act both individually and in concert to generate intermediaries e.g. growth factors, adhesion molecules, cytokines etc. which are involved in tissue damage. The occurrence of these complications has extensive geographical variation as is the collective effort to prevent or manage them which often depends on the socioeconomic standard and the commitment of the region involved. Appreciating the reality of the threat posed by diabetes complications would enable concerned bodies make well informed decisions on the appropriation of healthcare resources and also make healthcare providers and patients intensify efforts in working together towards preventing these complications.

Keywords: *Cardiovascular Disease; Nephropathy; Retinopathy*

Introduction

The World Health Organization (WHO) estimated that 422 million people were living with diabetes mellitus (DM) in 2014. The prevalence almost doubled from 1980 (4.7%) to 2014 (8.5%) [1]. This rapid rise is occasioned by the observable change in lifestyle which seems to favour physical inactivity and obesity [2]. The complications of diabetes are numerous and could potentially affect every system of the human body. Such complications are associated with significant disability and mortality which may predate the diagnosis of the disease. In 2015, five million adults died as a direct consequence of diabetes, constituting 13.1% of all non-communicable diseases deaths. More than 50% of these occurred in those less than 60 years old [1] with the overwhelming majority unequivocally associated with chronic complications e.g. cardiovascular diseases.

Classification of diabetes complications

The extensive reach of diabetes within the body systems makes the unanimity of a single method of classifying diabetes complications quite challenging. A reasonable, albeit imperfect attempt is only made here to put the most common complications in corresponding categories.

1. Acute complications; diabetic ketoacidosis, hyperglycemic hyperosmolar state, hypoglycemia, lactic acidosis.
2. Macrovascular complications; cerebrovascular disease, coronary artery disease and peripheral vascular disease.
3. Microvascular complications; retinopathy, nephropathy, neuropathy and erectile dysfunction.

4. Immune related complications; infections common in diabetes e.g. Oral, skin and respiratory tract.
5. Combined; diabetic foot.
6. Iatrogenic; weight gain with Thiazolidinediones and lactic acidosis with biguanides.

Mechanisms of diabetes complications

Polyol pathway: Glucose is metabolized by glycolysis to produce cellular energy. It is phosphorylated by hexokinase to glucose-6-phosphate, isomerized by glucose-6-phosphate isomerase to fructose-6-phosphate and further metabolized along the pathway to yield end products i.e. ATP, NADH, pyruvate and H_2O [3]. In normoglycemic state the activity of this pathway is adequately equilibrated with blood glucose levels. Conversely, hyperglycemia elicits a saturation of this pathway which necessitates the diversion of the excess glucose through the polyol pathway. The excess glucose is converted to sorbitol by aldose reductase and sorbitol is oxidized to fructose by sorbitol dehydrogenase [4]. NADPH and NADH are co-factors in the first and second reactions and their utilization in these reactions lead to decreased cellular levels of reduced glutathione [5] which is required to combat the generation of reactive oxygen species [6]. Also, fructose and sorbitol accumulate within the cells creating osmotic stress [7]. Cells that do not require insulin for glucose transport e.g. retina, kidney cells and nervous tissues are particularly vulnerable to this insult [6].

Advanced Glycation End-products (AGEs): These are products of non-enzymatic reactions between sugars and proteins, lipids or nucleic acids [8]. This process occurs extensively within the cells and it is considered an integral part of ageing [10]. It also occurs in several chronic diseases but its role in diabetes has generated enormous attention. Hyperglycemia promotes the formation of AGEs and enhances their pathological consequences in several ways:

(i) **Cross linking of molecules:** The cross linking of molecules in the extracellular matrix of the basement membrane alters their structure and function [8]. The involvement of molecules like collagen, laminin, elastin etc. in this phenomenon is the culprit behind vascular thickness/stiffness that characterizes diabetic vasculopathy [9].

(ii) **Activation of Receptor for AGEs (RAGE):** RAGE is found in several cells including endothelial and smooth muscle cells [8,11,12]. Binding of AGEs to RAGE and its subsequent activation leads to upregulation of nuclear factor kappa beta (NF-kB). NF-kB increases the production of pro-inflammatory cytokines e.g. IL-1α, IL-6 and TNF-α [8]. RAGE stimulation also increases the transcription of genes for adhesion molecules e.g. vascular endothelial growth factor (VEGF), endothelin-1 and intracellular adhesion molecules-1 (ICAM-1) [11].

(iii) **Others:** AGEs inhibit the action of endothelial derived nitrous oxide (NO) [13] which is an important vasodilator. They also promote oxidative stress and the oxidation of low density lipoprotein (LDL) [14] which is implicated in the pathogenesis of atherosclerosis.

Protein kinase C (PKC) activation: The increased activity of protein kinase C enzyme in diabetes is well documented. This hyperglycemia induced process is directly related to the persistent elaboration of diacylglycerol (DAG) [15] which activates PKC. Activation of PKC increases the expression of VEGF [17], thromboxanes, endothelin and other substances which have a wide variety of effects including increased vascular permeability, angiogenesis, fibrosis and cytokine activation [15,16].

Hexosamine biosynthetic pathway: In this pathway, fructose-6-phosphate is converted to glucosamine-6-phosphate by glutamine: fructose-6-phosphate transferase (GFAT) and finally to UDP N-acetyl glucosamine. The theory that this pathway contributes to diabetes complications has only recently been advanced. It is thought that its role in perpetuation of insulin resistance [18] and vascular alteration are possible patterns of contribution [5].

Macrovascular complications

(a) **Cerebrovascular diseases:** Cerebral arterial disease, intracerebral hemorrhage and cerebral infarction

(b) **Coronary artery disease (CAD):** Ischaemic heart disease (IHD), atherosclerotic heart disease, angina pectoris, myocardial infarction (MI) and sudden death.

(c) **Peripheral artery disease:** Lower extremity arterial disease, limb threatening ischaemia, intermittent claudication and critical limb ischaemia.

Cardiovascular diseases (CVDs) are the commonest cause of mortality in diabetic patients [19]. The relative risk for cardiovascular events is 1 - 3 in men and 2 - 5 in women when compared to those without diabetes [20]. Although the prevalence of CVDs in people with diabetes vary significantly among various populations, socioeconomic and sociocultural factors which influence individuals lifestyle appear to determine their preponderance in a population. In developed countries adverse cardiovascular events are common in lower socioeconomic class. Also, emerging trends have demonstrated an increased incidence of these diseases in developing countries due to the phenomenon of "epidemiologic transition" [21]. The variation of CVDs prevalence is also due to age, gender and the type of diabetes i.e. type 1 diabetes (T1DM) or type 2 diabetes (T2DM). The relative risk of CAD mortality is 2.58 for women and 1.85 for men when compared to those without diabetes. Although, the absolute risk is higher in men [22]. A Finnish study found that women with T2DM are 9.5 times more likely to have CAD [22].

Available data suggests that The Netherlands (40.52%), France (30.88%), Australia (32.2%) and the United Arab Emirates (29.4%) have a high prevalence of CVDs in adult patients with diabetes. The United States has a prevalence of 26% and Canada has 8.59%. The global incidence ranges from 14.3 per 1000 CVD events in DM patients per year in Honk Kong to 46.9 per 1000 per year in Brazil [22]. The CVD prevalence generally increases with age. Hence, epidemiological studies conducted in higher age groups are likely to indicate a higher prevalence. CVDs were reported in 6% of T1DM patients between ages of 15 - 25 and 25% between 45 - 59 years old [23]. In Europe, 8% of people with T1DM between 15 to 60 years old have had at least one form of CVD while in the US the prevalence is 8.29% for those between 15 - 54 years. The prevalence of CAD was about 31% in both Switzerland and Qatar; Portugal and China had around 12% and Cameroun had 23.57% [22].

Among patients with CVDs, 8.40% of those above 60 years had a history of stroke in Mexico. The result was almost the same for Saudi Arabia (8.36%) in the age bracket of 15 - 100 years. However, Canada has a lower prevalence of stroke (2.45%) in those 20 years and above [22].

Modifiable risk factors

(a) **Physical inactivity:** One of the most important risk factor for diabetes and its macrovascular complications particularly coronary artery disease. Several studies have established that tremendous cardiometabolic benefits can be achieved by modest improvement in physical activity [24-26].

(b) **Obesity:** An independent risk factor for CVDs [27,28]. As much as 86% of T2DM patients are either overweight or obese [29]. Sustained weight loss is necessary for both adequate blood glucose control and improvement of macrovascular complications.

(c) **Smoking:** About 1 in 5 deaths in the United States as well as 6 million deaths per year globally are attributed to smoking [30]. The role of smoking as a core risk factor cannot be overemphasized and it poses a great threat to life when associated with diabetes.

(d) **Dyslipidemia:** The major abnormalities in diabetes are elevated triglycerides, LDL and reduced HDL. A cross sectional studies of patients in Pakistan found that 97% of males and 87% of females had at least one dyslipidemia [31]. Another multicenter Chinese study by Yan., *et al.* (2016) recorded a prevalence of 67% among people with T2DM [32].

(e) **Hypertension:** Data from various researches have indicated that hypertension could be present in 20 - 70% of people with DM [33-35]. This increases with the sample age and lower cut off for the diagnosis of hypertension.

(f) **Diet:** Diet high in saturated fats, salt and refined sugar content have been linked with CVDs. Whole grains, fruits and vegetables are suggested to be protective. Consumption of AGEs in diet [10] also promotes diabetes complications.

Mechanisms of Cardiovascular complications in DM

Macrovascular complications occur as a result of the interaction between vascular and hemodynamic factors which culminate in atherosclerosis and vascular narrowing. The role of AGEs, PKC, oxidative stress and chronic inflammation are well known. However, the designation of diabetes as a typical prothrombotic vascular disease deserves more attention. Hyperglycemia is associated with elevated Von Willebrand factor/factor VIII, tendency towards platelets adhesion and aggregation which promotes hypercoagulation [36]. Also, the elevation of fibrinogen and plasminogen activator inhibitor (PAI) impairs fibrinolysis [36]. These alterations in conjunction with intrinsic endothelial dysfunction primes diabetes as a menacing vascular disease.

Microvascular Complications

These include retinopathy, nephropathy and neuropathy. However, only nephropathy and retinopathy will be discussed in this issue.

Diabetic Nephropathy (Diabetic kidney disease (DKD))

Diabetic Nephropathy is a complex clinical entity that is characterized by a variable alteration in glomerular filtration rate (GFR) and persistent proteinuria which occur as a result of diabetes. It is associated with hypertension which may initially co-exist with diabetes or develop as the kidney disease progresses [37]. The albuminuria is either microalbuminuria (urinary albumin excretion of 30 - 300 mg/day or 20 - 200 ug/min) or macroalbuminuria (UAE of more than 300 mg/day or more than 200 ug/min) [37]. The pathological changes in DKD start early in the disease process but takes several years before the onset of end stage renal disease (ESRD) [38]. The disease process could be halted or reversed with appropriate intervention [38]. Initially, hyperfiltration occurs which is observed as elevated GFR. This is followed by gradual decline in GFR and albuminuria before the onset of ESRD [39]. The structural abnormalities include mesangial cell proliferation, extracellular matrix expansion, thickening of the glomerular basement membrane [40] and loss of podocytes. Both diffuse and nodular glomerulosclerosis occur in DKD [41]. These abnormalities are considered a consequence of hyperglycemia induced AGEs formation, protein kinase C activation and generation of reactive oxygen species.

The haemodynamic disruption leads to reduced vascular resistance in both afferent and efferent arterioles which leads to increased intra-renal hydrostatic pressure and precipitates a dysfunctional autoregulation [42]. Central to this dysfunction is the role of angiotensin II, a potent vasoactive peptide. However, it also has a variety of effects which include promoting hypertrophy of mesangial and tubular epithelial cells, augmenting the production of ROS and enhancing the activities of growth factors [40,42]. Endothelin-1 and Urotensin are vasoactive substances that have also been implicated. Emerging evidences from research involving human and animal subjects have identified a growing list of growth factors that are suggested to play a critical role in the pathogenesis of DKD. These include transforming growth factor-beta (TGF-β), platelet derived growth factor (PDGF), VEGF and connective tissue growth factor (CTGF). TGF-β is a fibrogenic growth factor involved in increased collagen synthesis and mesangial expansion. Angiotensin II particularly enhances the activities of TGF-β [41].

Risk factors: Traditional risk factors include hyperglycemia, hyperlipidemia, obesity, hypertension and smoking. Blacks and Asians are more predisposed as well as Pima Indians. Family history of DKD is also a very important risk factor.

Global epidemiology of Diabetic nephropathy

Diabetic nephropathy is the leading cause of ESRD in the developed world [37] where it accounts for almost half of cases and an important cause in developing countries. Data from the National Health and Nutrition Examination Survey (NHANES) in the US indicated

that the prevalence of DKD was 2.2% in 1988-1994, 2.8% in 1999 - 2004 and 3.3% in 2005 -2008 in the general population. The number of people with DKD in the corresponding period was 3.9 million, 5.5 million and 6.9 million respectively [43]. The prevalence among people with diabetes was 34% in 2008. However, a more recent analysis of several cross sectional studies involved in NHANES revealed that the prevalence of DKD; defined as persistent albuminuria, persistent reduction in GFR or both was 28.4% (95% confidence interval of 23.8% - 32.9%) between 1988 - 1994 and 26.2% (95% CI of 22.6% - 29.9%) from 2009 to 2014 [44]. At the end of 2014 the number of adults with DKD was 8.2 million [44]. They equally noted that the prevalence of albuminuria decreased from 20.8% (1988 - 1994) to 15.9% (2009 - 2014) while reduced GFR increased from 9.2% to 14.1% in the same period. It is essential to highlight that the burden of DKD extends well into the subgroup of undiagnosed diabetes and prediabetes. In one of such studies the results showed that 41.7% and 17.7% of participants with CKD had undiagnosed diabetes and prediabetes respectively. After adjusting for age, gender and race; undiagnosed diabetes and prediabetes still accounted for 39.1% of CKD [45].

Europe: In Spain 21% of patients with diabetes start renal replacement therapy each year. In some regions e.g. Canarias, this could be as high as 35%. The estimate for DKD among T1DM and T2DM patients in 2005 was 33000 and 405000 in respectively [46]. A prospective Spanish study of 1225 adults with diabetes revealed that 14.2% had microalbuminuria, 5.1% had macroalbuminuria and 3.4% had renal failure at baseline. After a follow up for an average of 4.3 years the annual incidence of microalbuminuria was 2.7% [47]. An outpatient screening of people with diabetes in Germany (Bavaria) detected microalbuminuria in 19.6% of T1DM and 17.2% of T2DM individuals. 11.7% of T1DM and 7.8% of T2DM patients had macroalbuminuria [48]. In 2004, 61000 patients were undergoing dialysis based on data from the German QUASI-Niere Registry. Also, the proportion of people living with diabetes on renal replacement therapy increased from 21.6% in 1996 to 27.1% in 2004 [49]. Although more recent findings have suggested a relatively stable rate of ESRD due to DM in some developed countries [50].

Africa: A cross sectional study by Jan Mohammed., *et al.* (2013) involving outpatients in Tanzania revealed that 83.7% of participants had CKD. 80% had significant albuminuria and 24.7% had a GFR of less than 60 ml/min [51]. However, Mpondo., *et al.* (2016) stated that the high prevalence of schistosomiasis in the region where the study was conducted was a possible cofounding factor for albuminuria [52]. They also cited another study from Darussalam, Tanzania that observed a prevalence of 10.7% and 4.9% for microalbuminuria and macroalbuminuria respectively [53]. A systematic review by Noubiap., *et al.* 2015 evaluated 32 studies from 16 African countries. The result indicated that when proteinuria is used as a criterion for DKD the prevalence ranged from 5.3% in South Africa to 53.1% in Cameroun while the prevalence ranged from 4.6% in Tanzania to 43.1% in Nigeria on the basis of GFR [54] alone.

Duration of DM before onset of DKD

The progression of DKD is variable even though the pathogenetic process starts early in the disease. In T1DM it could take up to 15 - 20 years before the onset of proteinuria [55]. On the contrary, the diagnosis of nephropathy may predate that of diabetes in T2DM. Also, the advancement from one stage of the disease to the other differs among patients. While some have a progressive disease others have a stable or retrogressive outcome [38]. Findings from the EURODIAB study indicated that the incidence of microalbuminuria in T1DM was 12.6% at 7.3 years [56] while the UK prospective diabetes study (UKPDS) reported a proteinuria prevalence of 25% in T2DM after 10 years of diagnosis [57].

DKD and Cardiovascular diseases

Patients with DKD do not only have a higher frequency of CVDs but also have a less favourable outcome [58]. Shared risk factors are often an explanation for such co-existence although other factors may be involved. Several studies have adequately demonstrated that reduced eGFR and albuminuria are strong predictors of mortality in CVDs [59,60]. The finnDianne study illustrated that patients with DKD had 3.6 fold higher mortality compared with demographically matched population without DM. The excess mortality was observed only in the subgroup of patients with CKD [61]. Sudden cardiac death and heart failure are leading causes of mortality in diabetic patients ESRD [58].

DKD and Diabetic Retinopathy

Endothelial dysfunction, capillary hyperpermeability, reactive oxygen species, thickened basement membrane and growth factors e.g. VEGF are common to both DKD and retinopathy. A meta-analysis by He., *et al.* showed that the positive and negative predictive value of diabetic retinopathy to predict DKD were 0.72 and 0.69 respectively [62]. Retinopathy is present in about 95% of T1DM patients with DKD [63].

Diabetic Retinopathy (DR)

DR is among the leading causes of blindness globally [64]. Although, other eye diseases e.g. cataract and glaucoma are present in people living with diabetes, DR is still the most important eye condition in diabetes. The underlying abnormality is hyperglycemia induced damage to the retina blood vessels which leads to varying degrees of visual impairment or loss. The spectrum includes non-proliferative DR, proliferative DR and diabetic macular edema.

(a) **Non-proliferative Diabetic Retinopathy (NPDR):** This is characterized by microaneurysms, dot and blot hemorrhages, hard exudates and cotton wool spots [65]. Venous beading and intraretinal macrovascular abnormalities also occur [65]. Dot and blot hemorrhages are due to rupture of microaneurysms, hard exudates are made of lipids from capillary leakages while cotton wool spots are secondary to nerve infarction. Intraretinal microvascular abnormalities (IRMA) are areas of remodeled capillary beds. The presence of venous beading is a significant predictor of progression to PDR.

(b) **Proliferative Diabetic Retinopathy (PDR):** Neovascularization is the most important feature and these new vessels are fragile and bleed very easily. Other features are vitreous hemorrhage, fibrovascular proliferation and traction retinal detachment.

(c) **Diabetic Macular edema (DME):** Leakage of protein and lipid rich fluid into the macular consequent upon the disruption of the blood retina barrier. DME is the most common cause of sudden visual impairment in T2DM [65].

Risk Factors: Hyperglycemia, hyperlipidemia, smoking, hypertension and longer duration of diabetes are known risk factors. Addition risk factors are genetics, anemia and nephropathy. Pregnancy is associated with both increased incidence and progression to PDR.

Disease burden

Several large scale epidemiological studies have suggested that DR is assuming an epidemic proportion. Yau., *et al.* (META-EYE study group) published a meta- analysis of 35 population based studies from around the world to determine the global prevalence of DR. The overall prevalence was 34.6% for all DR with 6.96% for PDR, 6.81% for DME and 10.2% for vision threatening DR (VTDR). They concluded that approximately 93 million people had DR, 17 million had PDR, 21 million had DME and 28 million had VTDR in 2010 [66]. In the Wisconsin Epidemiological study of diabetes retinopathy, 13% of those who have had diabetes for more than 5 years and 90% of individuals with diabetes for more than 10 - 15 years had DR provided they were diagnosed less than 30 years of age [67]. 60% of those with T1DM and diabetes duration of more than 20 years had proliferative retinopathy. The overall incidence of DR over ten years period was 74% and 64% of those who DR at baseline had worsened DR. The WESDR XXII revealed that the 25 year cumulative progression of DR in T1DM was 83%. Progression to PDR was 42% and improvement was observed in 18% of the study population [68]. In addition, the WESDR XXIII illustrated that the 25 year cumulative incidence of DME was 29% and clinically significant DME was 17% in T1DM [69]. The estimate for DR in newly diagnosed T2DM in the UKPDS was 39% and 35% for men and women respectively [70] while the prevalence in T1DM was 54.2% in DCCT [71].

A systematic review by Burgess., *et al.* (2013) of 62 studies covering 21 African Countries reported a DR prevalence range of 30.2 - 31.6% and 7.0 - 62.4% from population based and clinic based studies respectively. PDR ranged from 0 - 6.9% and maculopathy from 1.2 - 31.1% in clinic based surveys. Hospital based surveys reported a DR rate from 20.5% in Egypt to 47.1% in Nigeria while PDR rate was 1.0 - 12.6%. In eastern African the rate was from 15.7% in Seychelles to 41.1% in Ethiopia with a PDR rate from 1.2% in Tanzania to 9.9% in Ethiopia [72].

Blindness associated with DR: The WHO estimated that DR accounted for 5% of global blindness in 2002 [73]. They equally recommended that eye care for people living with diabetes become part of strategic vision 2020 plans [73]. DR is considered the most common cause of new onset blindness in adults aged 20 - 74 years old [64]. In 2010, 32.4 million people were reported blind and 191 million visually impaired globally. 0.8 million blind and 3.7 million visually impaired cases were due to DR. South Asia accounted for 35% of blindness and 40% of visual impairment. The prevalence of blindness appeared higher in developed countries with higher proportion of elderly people e.g. 15 - 17% in the Americas and Europe. In those above 50 years, blindness from DR increased from 574000 in 1990 to 731000 in 2010 while visual impairment increased from 1.86 million to 3 million [74].

Conclusion

The complications of diabetes currently affect a lot of people. The devastating consequences and widespread reach of diabetes necessitates a holistic appraisal of our current commitment towards the prevention and management of these complications. Well thought out programs should be established in the global, regional and local levels that are tailored towards reducing the burden of individual complications. Screening for chronic complications on a regular basis should be carried out by health workers particularly primary care physicians to detect these complications early enough and institute management accordingly. Where such programs already exist, adequate networking and adherence should be encouraged to channel the benefits to the patients. Also, lifestyle intervention remains the indisputable panacea to risk factor modification. It is required for the prevention of both microvascular and microvascular complications by achieving optimal glycemic control. It also helps in the improvement of diabetes co-morbidities e.g. Obesity, dyslipidemia and hypertension.

Conflict of Interest

There is no conflict of interest or sources of funding for this work.

Bibliography

1. "Global Report on Diabetes". World Health Organization Geneva (2016).
2. Ibrahim Amin M. "Epidemiology of the Diabetes Epidemic A growing public health concern". *South African Journal of Diabetes* 10.3 (2017): 7-11.
3. Berg JM., *et al*. "Biochemistry, 5th Edition". New York: WH Freeman (2002).
4. Stephen SM Chung., *et al*. "Contribution of the Polyol pathway to Diabetes Induced Oxidative stress". *Journal of American Society of Nephrologists* 14.3 (2003): s233-s236.
5. Michael Brownlee. "The Pathobiology of Diabetic Complications: A unifying mechanism". *Diabetes* 54.6 (2005): 1615-1625.
6. Ferndinando Giacco and Michael Brownlee. "Oxidative Stress and Diabetes Complications". *Circulation Research* 107.9 (2010): 1058-1070.
7. David Tomlinson. "Neurobiology of Diabetic Neuropathy". *International Review of Neurobiology* 50 (2002).
8. Varun Parkash Singh., *et al*. "Advanced Glycation End-product and Diabetes Complications". *Korean Journal of Physiology and Pharmacology* 18.1 (2014): 1-14.
9. Cooper ME., *et al*. "Mechanism of Diabetic Vasculopathy: An overview". *American Journal of Hypertension* 14.5 (2001): 475-486.
10. Richard D Semba., *et al*. "Does Accumulation of Advanced Glycation End-product contribute to the ageing phenotype?" *The Journal of Gerontology Series A: Biological and Medical Sciences* 65A.9 (2010): 963-975.

11. Guiseppina Basta., *et al*. "Advanced Glycation End-product Activate Endothelium Signal-Transduction Receptor RAGE: A Mechanism for Amplification of Inflammatory Responses". *Circulation* 105.7 (2002): 816-822.

12. Fangqi Gong., *et al*. "Expression of receptor for Advanced Glycation End-products on the Surface of Circulating Endothelial cells is upregulated in Kawasaki Disease". *Pediatric Research* 71.6 (2012): 720-724.

13. Xu B., *et al*. "Inhibition of Human Endothelial Cells Nitric Oxide Synthesis by Advanced Glycation End-products but not Glucose: relevance to diabetes". *Clinical Sciences* 109.5 (2005): 439-446.

14. Richard Bucala., *et al*. "Modification of Low density Lipoprotein by Advanced Glycation End-products Contribute to the Dyslipidemia of Diabetes and Renal Insufficiency". *Proceedings of the National Academy of Sciences of the United States of America* 91.20 (1994): 9441-9445.

15. Noh H and King GL. "The Role of Protein Kinase C Activation in Diabetic Nephropathy". *Kidney International* 106 (2007): s49-s53.

16. Park JY., *et al*. "The Role of Protein Kinase C Activation on the Pathogenesis of Diabetic Vascular Complications". *Peritoneal Dialysis International* 19.2 (1999): s222-s227.

17. Pedro Geraldes and George L King. "Activation of Protein Kinase C Isoforms and its Impact on Diabetic Complications". *Circulation Research* 106.8 (2010): 1319-1331.

18. Maria G Buse. "Hexosamines, Insulin Resistance and the Complications of diabetes: current status". *American Journal of Physiology, Endocrinology and Metabolism* 290.1 (2006): E1-E8.

19. Benjamin M Leon and Thomas M Maddox. "Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research". *World Journal of Diabetes* 6.13 (2015): 1246-1258.

20. Rivellese AA., *et al*. "Cardiovascular Risk in Women with Diabetes". *Nutrition, Metabolism and Cardiovascular Diseases* 20.6 (2010): 474-480.

21. Robert C Block., *et al*. "An Epidemiologic Transition of Cardiovascular Disease Risk in Carriacou and Petite Martinique Grenada: The Grenada Heart Project 2005-2007". *Preventing Chronic Diseases* 9 (2012): E90.

22. International Diabetes Federation. "Diabetes and Cardiovascular Diseases Brussels Belgium: International diabetes Federation" (2016): 72-92.

23. Koivisto VA., *et al*. "Cardiovascular Disease and its Risk Factors in IDDM in Europe. EuroDiab IDDM Complications Study Group". *Diabetes Care* 19.7 (1996): 689-697.

24. Mercedes R Carnethon. "Physical activity and Cardiovascular Disease: How much is enough?" *American Journal of Lifestyle Medicine* 3.1 (2009): 44S-49S.

25. Jonathan Myers. "Exercise and Cardiovascular Health". *Circulation* 107.1 (2003): e2-e5.

26. Reddigan JI., *et al*. "Relation of Physical activity to Cardiovascular Disease Mortality and the Influence of Cardiometabolic Risk Factors". *American Journal of Cardiology* 108.10 (2011): 1426-1431.

27. Robert H Eckel. "Obesity and Heart Disease". *Circulation* 96.9 (1997): 3248-3250.

28. Manson JE., *et al*. "Body weight and Mortality among Women". *New England Journal of Medicine* 333.11 (1995): 677-685.

29. C Daousi., *et al*. "Prevalence of obesity in type 2 diabetes in Secondary Care: association with cardiovascular risk factors". *Postgraduate Medical Journal* 82.966 (2006): 280-284.

30. Facts sheet. "Smoking and tobacco use. Centers for Disease Control and Prevention" (2018).

31. Maliha Sarfaaz., *et al*. "Prevalence and Pattern of Dyslipidemia in Hyperglycemic Patients and its associated Factors among Pakistani Population". *Saudi Journal of biological Sciences* 23.6 (2016): 761-766.

32. Yan L., *et al*. "Prevalence of Dyslipidemia and its Control in Type 2 Diabetes. A multicenter study in endocrinology clinics in China". *Journal of Clinical Lipidology* 10.1 (2016): 150-160.

33. Unadike BC., *et al*. "Prevalence of hypertension amongst persons with diabetes mellitus in Benin City, Nigeria". *Nigeria Journal of Clinical Practice* 14.3 (2011): 300-302.

34. K Venugopal and MZ Mohammed. "Prevalence of hypertension in type 2 diabetes". *Chrismed Journal of Health and Research* 1.4 (2014): 223-227.

35. Mohammed Berraho., *et al*. "Hypertension and Type 2 Diabetes: A cross sectional study in Morocco (EPIDIAM study)". *Pan African Medical Journal* 11 (2012): 52.

36. Carr ME. "Diabetes Mellitus: a hypercoagulable state". *Journal of Diabetes Complications* 15.1 (2001): 44-54.

37. Katie Bennett and Bhandari Sumer Aditya. "An Overview Diabetic Nephropathy: Epidemiology, Pathophysiology and treatment". *Journal of Diabetes Nursing* 19.2 (2015): 61-67.

38. Jorge L Gross., *et al*. "Diabetic Nephropathy Diagnosis, Prevention and treatment". *Diabetes Care* 28.1 (2005): 164-167.

39. Andy KH Lim. "Diabetic Nephropathy: Complications and treatment". *International Journal of Nephrology and Renovascular Disease* 7 (2014): 361-381.

40. Mohanad Naji Sahib., *et al*. "Pathogenesis of diabetic kidney Disease: Review of cellular aspect of renal lesions". *African Journal of Pharmacy and Pharmacology* 3.11 (2009): 507-514.

41. Hemanth Kumar N., *et al*. "Diabetic Nephropathy: Pathogenesis and Newer Targets in Treatment". *International Journal of Pharmaceutical Science Review and Research* 6.2 (2011): 91-105.

42. Atul Arya., *et al*. "Pathogenesis of Diabetic Nephropathy". *International Journal of Pharmacy and Pharmaceutical sciences* 2.4 (2010): 24-29.

43. Ian H de Boer., *et al*. "Temporal Trends in the Prevalence of Diabetic Nephropathy in the United States". *Journal of the American Medical Association* 305.24 (2011): 2532-2539.

44. Maryam Afkarian., *et al*. "Clinical manifestations of Kidney disease among US adults with Diabetes 1988-2014". *Journal of the American Medical Association* 316.6 (2016): 602-610.

45. Laura C Plantiga., *et al*. "Prevalence of Chronic Kidney Disease in US Adults with undiagnosed diabetes or prediabetes". *Clinical Journal of the American Society of Nephrology* 5.4 (2010): 673-682.

46. Martinez-Castelao A., *et al*. "Epidemiology of diabetic Nephropathy in Spain". *Kidney International Supplements* 99 (2005): s20-s24.

47. Esmaties E., *et al*. "Incidence of Diabetic Nephropathy in type 1 diabetic patients in Spain: Estudio Diamante". *Diabetic Research and Clinical Practice* 57.1 (2002): 355-343.

48. Piehlmeier W., *et al*. "Experimental and clinical endocrinology and diabetes" 107.4 (1999): 244-251.

49. Wolfang Pommer. "Prevalence of Nephropathy in the German diabetes population: Is early referral to Nephrological care a realistic demand today?" *NDT Plus* 1.4 (2008): iv2-iv5.

50. Alberto Martinez-Castelao., *et al*. "The Concept and Epidemiology of Diabetic Nephropathy have changed in recent years". *Journal of Clinical Medicine* 4.6 (2015): 1207-1216.

51. Jan Mohammed MN., *et al*. "Prevalence of chronic kidney disease in diabetic adult out-patients in Tanzania". *BMC Nephrology* 14 (2013): 183.

52. Bonaventura CT Mpodo., *et al*. "Prevalence of Chronic Kidney Disease in Diabetic Adult Outpatients in Tanzania". *BMC Nephrology* 17.1 (2016): 71.

53. Lutale JJ., *et al*. "Microalbuminuria among type 1 and type 2 Diabetic patients of African Origin in Dare Salam, Tanzania". *BMC Nephrology* 8 (2007): 2.

54. Jean Jacques N Noubiap., *et al*. "Diabetic Nephropathy in Africa: A systematic review". *World Journal of Diabetes* 6.5 (2015): 759-773.

55. Andersen AR., *et al*. "Diabetic Nephropathy in type 1 diabetes: An Epidemiological study". *Diabetologia* 25.6 (1983): 496-501.

56. Chaturvedi N., *et al*. "Microalbuminuria in type 1 diabetes: Rates, Risk Factors and Glycemic Threshold". *Kidney International* 60.1 (2001): 219-227.

57. Adler AI., *et al*. "Development and Progression of Nephropathy in Type 2 Diabetes: the United Kingdom Prospective Diabetes Study UKPDS 64". *Kidney International* 63.1 (2003): 225-232.

58. Ragnar Palsson and Uptal D Patel. "Cardiovascular Complications of Diabetic Kidney Disease". *Advances in Chronic Kidney Disease* 21.3 (2014): 273-280.

59. Astor BC., *et al*. "Glomerular. Filtration Rate, Albuminuria, Risk of Cardiovascular Disease and all Cause Mortality in the US Population". *American Journal of Epidemiology* 167.10 (2008): 1226-1234.

60. Hemmelgam BR., *et al*. "Relation between Kidney Function, Proteinuria and Adverse Outcome". *Journal of the American Medical Association* 303.5 (2010): 423-429.

61. Groop PH., *et al*. "The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes". *Diabetes* 58.7 (2009): 1651-1658.

62. F He., *et al*. "Diabetic Retinopathy in Predicting Diabetic Nephropathy in Patients with type 2 diabetes and Renal Disease: A meta analysis". *Diabetologia* 56.3 (2013): 457-466.

63. Chia-Hsuin Chang and Lee-Ming Chuang. "Microalbuminuria and Diabetic Retinopathy in Type 2 Diabetic Patients: From Risk association to Risk Prediction". *Journal of Diabetes Investigation* 4.1 (2003): 42-44.

64. Donald S Fong., *et al*. "Diabetic Retinopathy". Diabetes Care 26.1 (2003): s99-s102.

65. Raman Deep Singh., *et al*. "Diabetic Retinopathy: an update". *Indian Journal of Ophthalmology* 56.3 (2008): 179-188.

66. Joanne WY Yau., *et al*. "Global Prevalence and Major Risk Factors of Diabetic Retinopathy". *Diabetes Care* 35.3 (2012): 556-564.

67. Prevention of Blindness from Diabetes Mellitus: report of a WHO consultation in Geneva Switzerland. ©world health organization (2005).

68. Ronald Klein., *et al*. "The Wisconsin Epidemiological Study of Diabetic Retinopathy XXII. The twenty-five year Progression of Retinopathy in Persons with type 1 diabetes". *Ophthalmology* 115.11 (2008): 1859-1868.

69. Ronald Klein., *et al*. "The Wisconsin Epidemiologic study of Diabetic Retinopathy XXIII. The twenty Five Incidence of Macular Edema in Persons with Type 1 Diabetes". *Ophthalmology* 116.3 (2009): 497-503.

70. Kohner EM., *et al*. "United Kingdom Prospective Diabetes Study 30: Diabetic retinopathy at time of diagnosis of non insulin dependent diabetes mellitus and associated risk factors". *Archives of Ophthalmology* 116.3 (1998): 297-303.

71. Malone JI., *et al*. "Prevalence and Significance of Retinopathy in Subjects with type 1 diabetes of less than 5 years duration screened for diabetes control and complications trial". *Diabetes Care* 24.3 (2001): 522-526.

72. PI Burgess., *et al*. "Epidemiology of Diabetic Retinopathy and Maculopathy in Africa: a systematic review". *Diabetic Medicine* 30.4 (2013): 399-412.

73. World Health Organization. Diabetic Retinopathy, Priority eye diseases (2018).

74. Janet L Leasher., *et al*. "Global Estimate for the Number of People Blind or Visually Impaired by Diabetic Retinopahty: a meta analysis from 1990-2010". *Diabetes Care* 39.9 (2016): 1643-1649.

Volume 3 Issue 3 August 2018