A Review of the Relationship between Type 1 Diabetes and Renal Injury

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Abstract
In the past it was believed that diabetes was a kidney injury due to the frequency of urination. Diabetes is now known to be one of the most common causes of nephropathies such as chronic kidney disease and end stage renal disease. Renal injury that incites frequent urination and diabetic nephropathies is a hallmark of diabetes caused by prolonged hyperglycemia and oxidative stress. In this review we discuss the history, pathophysiology, genetics, symptoms, treatments, and environmental factors associated with the renal effects of Type 1 Diabetes.The writing of the paper involved reviewing relevant literature on history and epidemiology, pathophysiology, underlying genetic differences, symptomatic links between T1D and kidney disease, diagnosis, and treatment of diabetic renal injuries. Renal damage that increases the risk of development of diabetic nephropathy (DN) occurs five years after initial diagnosis. Approximately, one-third of the individuals afflicted with T1D develop diabetic nephropathy throughout their lifetime.The literature seems to suggest that the increase in the incidence of type 1 diabetes is leading to a rise in diabetic kidney injury. Although genetic factors or familial history may make individuals or entire racial/ethnic groups more susceptible to developing renal injuries, proper care of glucose levels, regulation of blood pressure, and healthy lifestyle choices can prevent or delay the onset of diabetic nephropathy.
Key Words: *Diabetes, Hyperglycemia, Type 1 Diabetes, Renal Injury, Diabetic Nephropathy.*

I. Background

Type 1 diabetes (T1D) is an autoimmune disease in which insulin producing beta cells are destroyed. For this reason, insulin supplementation is required to regulate the subsequent elevated blood glucose levels. However, insulin supplements are not enough to combat the unpreventable damage T1D and hyperglycemia inflict upon the kidneys. Individuals with diabetes are more susceptible to kidney failure because of the impact of increased glucose concentrations in the kidneys [1]. The pathogenesis of diabetic kidney disease is characterized by conditions such as chronic kidney disease (CKD) or end stage renal disease (ESRD).Though, diabetic renal complications are unpreventable, critical renal problems typically occur 15-25 years after diabetes onset [2]. Although, environmental factors such as smoking, hypertension, and diet as well as genetic compositions have been shown to predispose individuals to critical renal complications earlier than 15-25 years after T1D onset [3]. Treatments such as regulation of blood sugar, blood pressure, and reduced exposure to toxins such as tobacco smoke can delay clinical nephropathy [2]. In addition, procedures such as dialysis and transplants help to alleviate the burden of clinical nephropathy.

As part of this mini-review, we performed a literature search through PubMed, Google scholar, Web of Science to assess the link between link between type 1 diabetes and renal injury. The paper is organized into history, epidemiology, pathogenesis, risk factors, signs and symptoms and concluded with treatment options.

II. History

Diabetes is regarded as one of the world's oldest maladies that plague the human race. For instance, there is a report of Ancient Egyptian text describing the symptoms of insatiable thirst and frequent urination [4]. During the early days of understanding diabetes, people thought that the frequent urination characteristic of diabetes along with urinary protein excretion was a kidney injury. It was not until 1889 that experiments by Joseph Von Mering and Oskar Minkowski demonstrated that a substance that regulates the body's sugar

concentration is secreted by the pancreas and without the pancreas, symptoms characteristic of diabetes would arise [5]. This finding dismissed the notion that diabetes is a kidney disease and revealed that diabetes is a systemic disease.

The new discovery regarding diabetes and its treatment resulted in a research frenzy. At this stage of history, scientists were inspired to analyze the effects of insulin deficiencies on the kidneys leading to several papers including a 1917 review paper that analyzed the differential kidney function in diabetes induced dogs [6]. Despite the insight the review provided about diabetes mellitus, this study and others were unable to translatetheir animal discoveries to specific cases in humans because individuals who expressed similar diabetic symptoms, reacted differently to specific treatments such as diet regimens [4]. In 1921, a group of scientists successfully harvested and isolated insulin from the pancreas and used it to treat individuals suffering from diabetes[5]. Subsequent experiments utilizing isolated insulin to treat individuals with diabetes led to the distinction between T1D and T2D in 1936 [7].

III.   Epidemiology

 The emergence of distinctions between different types of diabetes allowed for analysis of the incidence of both types of diabetes and the timeframes associated with the occurrence of renal damage. The overall prevalence of diabetes is rising rapidly. In 2017, 425 million adults across the globe were living with diabetes, one fifth of whom were projected to develop CKD [8]. The incidence of type 2 diabetes cases outnumber the prevalence of type 1 diabetes by 90% [9]. Although prevalence of T1D is lower than that of T2D, individuals diagnosed with T1D experience renal injury that develops into nephropathies such as chronic kidney disease and ESRD at a higher incidence. The increased likelihood of developing nephropathies is mostly likely due to the increased development of proteinuria in individuals with T1D in comparison to T2D [2, 10]. In these individuals, developing diabetic kidney disease (DKD) ranges from 25-40% for T1D patients as compared to 5-40% for T2D subjects [11].

Type 1 diabetes has previously been described as juvenile diabetes because of the large global onset of T1D among young people between the ages of 0 to 14 [12]. Numerous studies have been conducted worldwide measuring the incidence rates of T1D in young people across the globe including the DIAMOND project, EURODIAB, and SEARCH [9]. According to these studies, the incidence of T1D is highest in children of European descent and low in Asian and Pacific Island populations globally. In America, incidence is highest in non-Hispanic white children and lowest in Native American populations [13,14].

The incidence of T1D in adults is quite low, with only 25% of T1D diagnosis occurring in adults [9]. The misidentification of T1D as T2D or other forms of diabetes as well as the general lack of attention given to the incidence of T1D in adult populations has led to scant statistical data concerning its incidence. One review aimed at discussing the incidence of T1D in adults,suggests that diagnosis of T1D in later years is associated with higher mortality rates. The authors retrieved the majority of their statistics about adults with T1D from death certificates from the years of 1982 – 2014 [15].On the contrary, another study, states that individuals diagnosed with T1D later in life have better preserved beta cell function and an overall decrease in the severity of the effects of T1D including renal injury[16]. These studies point to complications depending on time of onset and diagnosis. For instance,diabetes onset and diagnosis later in life seemed to be associated with better prognosis than early onset and diagnosis. This is because of the possible extended period of β-cell dysfunction that allows renal damage to accrue.

Despite the severity of T1D based on age of onset, the renal damage that increases risk of development of diabetic nephropathy (DN) typically occurs five years after initial diagnosis [17]. Roughly one-third of the individuals afflicted with T1D develop diabetic nephropathy throughout their lifetime [18]. Nonetheless, there are more data available about the prevalence of diabetic nephropathy caused by T2D amongst different populations. However, in general African Americans, Native Americans, and individuals of Hispanic descent seem to be more susceptible to early development of renal complications and failure. Hence, DKD occurs more frequently in African American, Asian-American and Native American individuals [10].Incidence of these renal complications have been reported to be lowest in non-Hispanic white individuals [17].

On a global level, the doubling of albuminuria (too much albumin in urine) was noted in diabetes patients from Zimbabwe. Albuminuria is often regarded as a hallmark of kidney disease. Despite the low incidence of T1D among Asian populations compared to other ethnic groups, a meta-analysis of T1D and DN of Arabic populations revealed high incidence of DN, affecting approximately 18.2 % individuals with T1D [20]. Other studies involving Swedish and Finnish populations found that the occurrence of DN has reduced since 1990 [21]. The link between T1D and DN pathogenesis as it relates to various populations is driven by underlying elements of genetic, health care disparities, and environmental factors.

IV.   Pathogenesis

The development of T1D is preceded by the expression of anti-islet autoantibodies [22]. The autoantibodies including macrophages, beta cell autoantigens, T cells, and B cells accumulate and attack the

pancreatic islets. Nevertheless, in some cases, these anti-islet autoantibodies diminish overtime and the onset of T1D is prevented[4,23]. Destruction of the insulin producing beta cells leads to elevated blood glucose levels. The unregulated production of glucose is one of the primary factors that causes T1D renal damage, which later progresses to diabetic nephropathy.

Hyperglycemia plays a primary role in type 1 diabetes driven byrenal complications.However, it is not the only factor that contributes to damage that results in the development of diabetic nephropathy. Hyperglycemia increases the occurrence of oxidative stress,which together,play a critical role in inflicting damage that then causes kidney injuries characteristic of diabetic nephropathy [24]. The early stages of kidney damage produced by hyperglycemia are characterized by filtration problems, which are denoted by frequent urination and albuminuria. Filtration problems are a direct result of excessive amounts of glucose in the blood. Combination of blood glucose with proteins leads to the production of advanced glycosylated end product (AGE). AGE binds to the glomerulus and causes glomerular basement membrane (GBM) thickening, glomerular lesions, and by that initial renal filtration complications[2,25].

Oxidative stress is created as a byproduct of the formation of AGE. AGE interacts with and proliferates production of specific macromolecules such as protein kinase C which in turn produces reactive oxygen species (ROS) [26]. The generation of ROS induces oxidative stress. Oxidative stress causes kidney injury by interfering with the renin-angiotensin system (RAS) and signaling pathways oftransforming growth factor-beta (TGF-β), which causes expansion of the extracellular matrix, podocyte separation, and induces tubular and vascular damage [27,28].

The damage inflicted by hyperglycemia and oxidative stress overtime worsens and leads to mesangial matrix expansion, glomerulosclerosis, artery obstruction, increased blood pressure, increased glomerular pressure, and clinical albuminuria [29]. Uncontrolled hyperglycemia wreaks havoc on the kidneys by interfering with filtration and forming products that further deteriorate the internal kidney structure (Figure 1). However, even with glucose control, specific genetic alleles predispose individuals to renal damage.
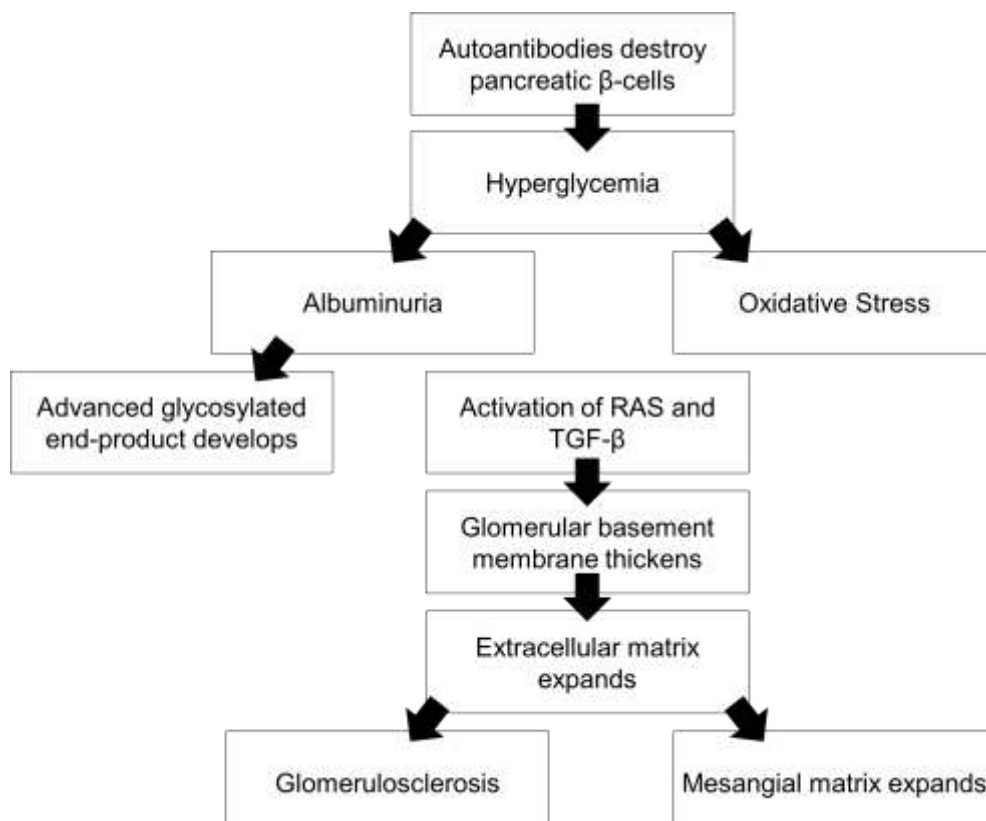

Figure 1. Diabetic nephropathy pathogenesis.

The Role of Genetics

The demographic of individuals most commonly diagnosed with T1D differs greatly from the demographic of individuals most commonly diagnosed with DN. For thisreason, studies investigating genes that predispose individuals to the type 1 diabetes renal complication has proven to be inconsistent among large populations. However, it is known that there is a genetic mechanism underlying severe T1D renal

complications. For instance, previous studies have shown that familial history increases an individual's susceptibility of developing renal injuries that progress to DN, CKD, or ESRD [30,31]. In fact, individuals with a family history of high blood pressure and heart issues are posed with a greater risk of diabetic kidney ailments [2].

Angiotensin-converting enzyme (ACE) is an enzyme that regulates blood pressure as an essential part of the angiotensin-renin system [32]. Specific alleles of the ACE gene and polymorphisms have been found to increase susceptibility and protect against development of severe diabetic renal issues. The insertion or deletion polymorphisms of the ACE gene dictate the concentrations of ACE within the serum. Individuals with the insertion allele, II, have been shown to have a lesser serum ACE concentration than individuals with deletion alleles, ID or DD. Expression of the deletion alleles, DD, is also associated with an increased risk of developing ESRD [29]. Other experiments have revealed that the ACE gene genotype II acts as a protective factor. However, this protection has been shown to be true for select groups such as individuals with Asian backgrounds. The D allele of the ACE gene has been shown to increase susceptibility to diabetic nephropathy when compared to individuals with the genotype II [33].

Several genetic studies have been conducted to identify genes associated with the development of diabetic nephropathy. Amongst the studies, several gene classes have been identified including the renin-angiotensin system, glucose metabolism pathway, lipid metabolism, growth factors, angiogenesis, oxidative stress, inflammation, glomerular membrane maintenance, along with others [34,35]. All the identified classes are based on pivotal renal processes ranging from the development of hyperglycemia to the strength of the glomerulus against the effects of elevated glucose levels.

Epigenetic investigations have identified methylation patterns, microRNA, and histone modifications that govern an individual's susceptibility to diabetic nephropathy. In particular,single nucleotide polymorphisms (SNPs) of Cytochrome C Oxidase 6A1 (COX6A1) has been reported to be significantly associated with the development of DKD or ESRD T1D patients. The mitochondrial protein, COX6A1 is involved in electron transport. Recently, research involving individuals of European backgrounds with either T1D or T2D and DKD or ESRD was performed. In this study, a SNP for and methylation of the CpG islands of the COX6A1 gene were found to contribute to the development of oxidative stress in the kidney, thereby inducing renal damage [36]. Further, microRNAs (miRNA) involved in the different steps of diabetic renal injury such as hyperglycemia, glomerular lesions, oxidative stress, and extracellular matrix expansion were studied to identify both contributing factors and therapies of diabetic kidney damage [37]. miRNAs associated with TGF-β were frequently investigated for their involvement in expansion of the extracellular matrix in diabetic renal injury and have been shown to regulate the acceleration of T1D kidney damage in the tubules, glomerular, and mesangial cells [37].

Risk Factors

Aside from genetic background that predisposes individuals to developing diabetic kidney disease, there are other factors that increase the likelihood of experiencing diabetic renal injury. Just as T1D mostly affects males, men are more likely to experience DKD than women, which has been attributed to hormone imbalances [21]. The decline in glomerular filtration associated with aging makes age a risk factor of DKD as well [17]. Hypertension is another risk factor with increases in systolic blood pressure correlating to an increase in the development of albuminuria and a higher risk of developing ESRD [38]. Alongside hypertension, dyslipidemia is a risk factor that is known to increase the likelihood of individuals with diabetes developing DKD [39]. Maintenance of health is important in preventing the development of DKD, consequently obesity and smoking are risk factors [10,21].

Signs & Symptoms

Early stages of diabetic nephropathy are typically not characterized by any signs or symptoms. The onset of symptoms typically does not occur until close to complete kidney failure [40]. The first symptom typically seen is frequent urination with the appearance of proteins like albumin in the urine, which occurs as a result of impaired glomerular filtration [41]. Following the onset of proteinuria, individuals begin to experience an increase in blood pressure as a result of the expansion of the extracellular matrix [42]. Another symptom that follows the onset of diabetic nephropathy is edema or swelling [41]. Edema is caused by the buildup of AGE along the glomerular, which interferes with filtration and decreases serum albumin,disrupting the maintenance of fluids in the blood vessels [43,44]. Impairment of filtration also results in the elevated presence of waste proteins in the blood such as creatinine [45]. Aside from these symptoms, individuals with diabetic nephropathy may experience nausea, trouble sleeping, and weakness [1,40].

Diagnosis

The detection of diabetic renal injuries that progress to diabetic nephropathy is a difficult process for individuals with T1D because pathogenesis varies based upon age of diabetes onset, genetic makeup, and

familial history. The onset of T1D is accompanied by early renal injuries such as hyperfiltration and hypertrophy, however, diagnosis of renal injuries typically occurs 5-20 years following diabetes onset[2]. Proteinuria is most commonly, the initial indicator of development of diabetic nephropathy and is evaluated through assessments of urinary and serum albumin and creatinine levels [46,47]. Albumin is one of the most common proteins in blood that plays a role in retaining fluid in blood vessels [48]. A change in albumin concentration is indicative of kidney damage because it denotes defects in blood filtration. Increases in urinary albumin excretion or an albumin excretion rate of 30 mg/dL or greater is indicative of renal damage [46]. However, decreases in serum albumin levels or hypoalbuminemia is also associated with renal injury and represented by serum albumin levels less than 3.4 g/dL [49]. Creatinine is a waste protein found in the blood that is a byproduct of muscle function [50]. Creatinine is normally filtered out of the blood by the kidneys; therefore, an accumulation of serum creatinine corresponds to renal injury. Serum creatinine levels greater than 1.4 mg/dL are associated with renal damage [51]. Serum creatinine levels are also utilized to estimate glomerular filtration rates, which can assess kidney function [52].

Following the assessment of proteinuria development, the onset of diabetic renal injuries are confirmed utilizing further filtration assessments. Serum concentration of urea, a waste product similar to creatinine, is often times evaluated to gauge kidney function [50]. Blood pressure is another measure of kidney filtration that reveals the impact of elevated glucose levels [49]. Glomerular filtration assessments are the main methods of diagnosing diabetic renal injury, however, in the event of atypical instances of diabetic renal injuries, kidney biopsies are conducted. Kidney biopsies with light and electron microscopy are used to identify extracellular matrix accumulation of thickening of the glomerular basement membrane. There are different classes used for kidney tissue analysis, which act as an indication of the severity of renal injuries [53].

Treatment

Treatment of T1D renal injuries consists of methods to delay pathogenesis or prevent further injury induced by kidney failure. The first target in treatment of diabetic renal injuries is prevention of hyperglycemia through daily insulin usage throughout the duration of diabetes [2]. Other forms of glycemic control include usage of medications such as metformin and close monitoring of glycosylated hemoglobin (HbA1c) levels. Metformin is a drug that works to decrease glucose levels by interfering with glucoseproduction in the liver. Metformin usage has been shown to decrease insulin dependence as well as decrease glycosylated hemoglobin levels [54]. HbA1c, similar to AGE, is the combination of glucose and hemoglobin which is utilized to assess blood glucose levels over periods of time and prevent microvascular complications [55]. Maintenance of a HbA1c level less than 7% reduces glomerular glucose accumulation thereby ensuring a decrease in glucose levels and preventing elevated blood and glomerular pressure [56].

Strict regulation of blood pressure is another recommended diabetic renal injury treatment method. Control of blood pressure is an essential treatment necessary for the prevention of extracellular matrix expansion and further renal damage. Hypertension associated with diabetes is most often treated utilizing inhibitors of the renin angiotensin aldosterone system (RAAS) [57]. RAAS inhibitors work to inhibit the formation of angiotensin II, which is responsible for blood vessel contractions [58]. ACE and RAAS inhibitors are also utilized to reduce the occurrence of glomerular injuries, the resulting proteinuria, and hypertension [59,60].

Adjusting lifestyle choices is another a treatment method enlisted in deterring T1D renal injuries. Dietary regulations are often utilized to prevent the development of hyperglycemia or hypertension that could increase an individual's susceptibility to AGE formation [61]. Several studies have been conducted that evaluate the impact of protein consumption on progression of renal injuries. Some studies have demonstrated that low protein diets decrease proteinuria, however, studies conducted on a large scale have been unable to attain consistent findings [62-63]. A study by the Mobbs group demonstrated that a ketogenic diet can reduce glucose metabolism [66]. Aside from particular diets, medical nutrition treatment (MNT) can also be helpful. MNT enables patients to work with a dietitian to establish plans to regulate their diabetes through appropriate dietary strategies. Some of these methods have been shown to significantly reduce fasting blood glucose levels and HbA1c, and consequently decrease the risk of developing diabetic renal injury [64, 65]. Physical activity and exercise have also been shown to decrease the onset of diabetic nephropathy by decreasing blood pressure and glucose levels [66]. Reducing and refraining from use of tobacco products is another way to decrease development of albuminuria [2].

In the incidence of severe kidney failure, kidney rehabilitation or replacement methods are utilized to restore kidney function. Dialysis treatments take the role of the kidney and filter the blood, which reduces urinary albumin excretion (UAE) and serum creatinine levels [67]. However, there are negative side effects associated with dialysis such as the onset of cardiovascular issues. As a result of the downsides of dialysis, transplants are preferred and demonstrate decreased mortality rates in individuals suffering from diabetic renal issues when compared to dialysis [68]. Kidney and pancreas transplants are the ultimate renal replacement therapy in that both kidney function and insulin production may be restored. Cases involving the combined

kidney and pancreas transplants are rare. Even in cases of either solely undergoing kidney or pancreatic transplant, the benefits regarding blood sugar and blood pressure levels can be attained[69–71].

V. Conclusion

The increase inincidence of type 1 diabetes seems to be leading to a rise in diabetic kidney injury. Although genetic factors or familial history may make individuals or entire racial/ethnic groups more susceptible to developing renal injuries, proper care of glucose levels, regulation of blood pressure, and healthy lifestyle choices can prevent or delay the onset of diabetic nephropathy.

Acknowledgements

References

[1]. Zimmerman RS. Diabetes Mellitus: Management of Microvascular and Macrovascular Complications [Internet]. Cleveland Clinic. 2016 [cited 2018 Nov 16]. Available from: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diabetes-mellitus/#top
[2]. Shahbazian H, Rezaii I. Diabetic kidney disease; review of the current knowledge. J Renal Inj Prev. 2013;2:73–80.
[3]. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl. 2013;3:368–71.
[4]. Patlak M. New Weapons to Combat an Ancient Disease: Treating Diabetes. The FASEB Journal. 2002;16:1853e–1853e.
[5]. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23:373–8.
[6]. Fitz R. OBSERVATIONS ON KIDNEY FUNCTION IN DIABETES MELLITUS. Arch Intern Med (Chic). 1917;XX:809–27.
[7]. Poretsky L, editor. Principles of Diabetes Mellitus [Internet]. 2nd ed. Springer US; 2010 [cited 2018 Nov 16]. Available from: //www.springer.com/us/book/9780387098418
[8]. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. Brussels, Belgium; 2017.
[9]. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of Type 1 Diabetes. Endocrinology and Metabolism Clinics of North America. 2010;39:481–97.
[10]. Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: world wide difference of prevalence and risk factors. J Nephropharmacol. 2015;5:49–56.
[11]. Papadopoulou- Marketou N, Chrousos GP, Kanaka- Gantenbein C. Diabetic nephropathy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. Diabetes/Metabolism Research and Reviews. 2017;33:e2841.
[12]. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. The Lancet. 2001;358:221–9.
[13]. Tuomilehto J. The Emerging Global Epidemic of Type 1 Diabetes. Curr Diab Rep. 2013;13:795–804.
[14]. Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, et al. Prevalence of Diabetes in U.S. Youth in 2009: The SEARCH for Diabetes in Youth Study. Diabetes Care. 2014;37:402–8.
[15]. Diaz-Valencia PA, Bougnères P, Valleron A-J. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. BMC Public Health. 2015;15:255.
[16]. Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How Does Age at Onset Influence the Outcome of Autoimmune Diseases? [Internet]. Autoimmune Diseases. 2012 [cited 2018 Nov 16]. Available from: https://www.hindawi.com/journals/ad/2012/251730/
[17]. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. JAMA. 2016;316:602–10.
[18]. Sharaf El Din UAA, Salem MM, Abdulazim DO. Diabetic nephropathy: Time to withhold development and progression - A review. Journal of Advanced Research. 2017;8:363–73.
[19]. Machingura PI, Chikwasha V, Okwanga PN, Gomo E. Prevalence of and Factors Associated with Nephropathy in Diabetic Patients Attending an Outpatient Clinic in Harare, Zimbabwe. Am J Trop Med Hyg. 2017;96:477–82.
[20]. Abdel- Motal UM, G A, Abdelalim EM, Ponnuraja C, Iken K, Jahromi M, et al. Prevalence of nephropathy in type 1 diabetes in the Arab world: A systematic review and meta-analysis. Diabetes/Metabolism Research and Reviews. 2018;34:e3026.
[21]. Harjutsalo V, Groop P-H. Epidemiology and risk factors for diabetic kidney disease. Adv Chronic Kidney Dis. 2014;21:260–6.
[22]. Baynest HW. Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. Journal of Diabetes & Metabolism [Internet]. 2015 [cited 2018 Nov 16];06. Available from: https://www.omicsonline.org/open-access/classification-pathophysiology-diagnosis-and-management-of-diabetesmellitus-2155-6156-1000541.php?aid=53137
[23]. Drummond K, Mauer M. The Early Natural History of Nephropathy in Type 1 Diabetes: II. Early Renal Structural Changes in Type 1 Diabetes. Diabetes. 2002;51:1580–7.
[24]. Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nat Clin Pract Endocrinol Metab. 2008;4:444–52.
[25]. Makita Z, Radoff S, Rayfield EJ, Yang Z, Skolnik E, Delaney V, et al. Advanced Glycosylation End Products in Patients with Diabetic Nephropathy. New England Journal of Medicine. 1991;325:836–42.
[26]. Giacco Ferdinando, Brownlee Michael, Schmidt Ann Marie. Oxidative Stress and Diabetic Complications. Circulation Research. 2010;107:1058–70.
[27]. Kashihara N, Haruna Y, Kanwar VKK and YS. Oxidative Stress in Diabetic Nephropathy [Internet]. Current Medicinal Chemistry. 2010 [cited 2018 Nov 16]. Available from: http://www.eurekaselect.com/72755/article
[28]. Singh DK, Winocour P, Farrington K. Mechanisms of Disease: the hypoxic tubular hypothesis of diabetic nephropathy. Nature Reviews Nephrology. 2008;4:216–26.
[29]. Miranda-Díaz AG, Pazarín-Villaseñor L, Yanowsky-Escatell FG, Andrade-Sierra J. Oxidative Stress in Diabetic Nephropathy with Early Chronic Kidney Disease [Internet]. Journal of Diabetes Research. 2016 [cited 2018 Nov 16]. Available from: https://www.hindawi.com/journals/jdr/2016/7047238/
[30]. Conway BR, Maxwell AP. Genetics of Diabetic Nephropathy: Are There Clues to the Understanding of Common Kidney Diseases? NEC. 2009;112:c213–21.
[31]. Sego S. Pathophysiology of diabetic nephropathy. Nephrol Nurs J. 2007;34:631–3.

[32]. Permutt MA, Wasson J, Cox N. Genetic epidemiology of diabetes. J Clin Invest. 2005;115:1431–9.
[33]. U.S. National Library of Medicine. ACE gene [Internet]. Genetics Home Reference. [cited 2018 Nov 16]. Available from: https://ghr.nlm.nih.gov/gene/ACE
[34]. Ng DPK, Tai BC, Koh D, Tan KW, Chia KS. Angiotensin-I converting enzyme insertion/deletion polymorphism and its association with diabetic nephropathy: a meta-analysis of studies reported between 1994 and 2004 and comprising 14,727 subjects. Diabetologia. 2005;48:1008–16.
[35]. Brennan E, McEvoy C, Sadlier D, Godson C, Martin F. The Genetics of Diabetic Nephropathy. Genes. 2013;4:596–619.
[36]. Liu R, Lee K, He JC. Genetics and Epigenetics of Diabetic Nephropathy. KDD. 2015;1:42–51.
[37]. Swan EJ, Maxwell AP, McKnight AJ. Distinct methylation patterns in genes that affect mitochondrial function are associated with kidney disease in blood-derived DNA from individuals with Type 1 diabetes. Diabetic Medicine. 2015;32:1110–5.
[38]. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease. Clin J Am Soc Nephrol. 2017;12:2032–45.
[39]. Radcliffe NJ, Seah J, Clarke M, MacIsaac RJ, Jerums G, Ekinci EI. Clinical predictive factors in diabetic kidney disease progression. J Diabetes Investig. 2017;8:6–18.
[40]. Wu H, Kong L, Zhou S, Cui W, Xu F, Luo M, et al. The Role of MicroRNAs in Diabetic Nephropathy [Internet]. Journal of Diabetes Research. 2014 [cited 2018 Nov 16]. Available from: https://www.hindawi.com/journals/jdr/2014/920134/
[41]. American Diabetes Association 2451 Crystal (last). Kidney Disease (Nephropathy) [Internet]. American Diabetes Association. [cited 2018 Nov 16]. Available from: http://www.diabetes.org/living-with-diabetes/complications/kidney-disease-nephropathy.html
[42]. Stoycheff N, Stevens LA, Schmid CH, Tighiouart H, Lewis J, Atkins RC, et al. Nephrotic Syndrome in Diabetic Kidney Disease: An Evaluation and Update of the Definition. American Journal of Kidney Diseases. 2009;54:840–9.
[43]. Lloyd IJ. The extra-cellular-matrix in hypertension: The link between renal function, autoregulation and sodium metabolism, a review and hypothesis. Medical Hypotheses. 1985;18:169–86.
[44]. Chaudhry S, Wong E. Chronic kidney disease (CKD) | McMaster Pathophysiology Review [Internet]. [cited 2018 Nov 16]. Available from: http://www.pathophys.org/ckd/
[45]. Hommel E, Mathiesen ER, Aukland K, Parving H-H. Pathophysiological aspects of edema formation in diabetic nephropathy. Kidney International. 1990;38:1187–92.
[46]. Piccoli GB, Grassi G, Cabiddu G, Nazha M, Roggero S, Capizzi I, et al. Diabetic Kidney Disease: A Syndrome Rather Than a Single Disease. Rev Diabet Stud. 2015;12:87–109.
[47]. Levey AS, Becker C, Inker LA. Glomerular Filtration Rate and Albuminuria for Detection and Staging of Acute and Chronic Kidney Disease in Adults: A Systematic Review. JAMA. 2015;313:837–46.
[48]. Gross JL, Azevedo MJ de, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. Diabetes Care. 2005;28:164–76.
[49]. University of Rochester Medical Center. Albumin (Blood) [Internet]. Health Encyclopedia. [cited 2018 Nov 16]. Available from: https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=albumin_blood
[50]. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, Boer IH de, Goldstein-Fuchs J, et al. Diabetic Kidney Disease: A Report From an ADA Consensus Conference. Diabetes Care. 2014;37:2864–83.
[51]. Salazar JH. Overview of Urea and Creatinine. Lab Med. 2014;45:e19–20.
[52]. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol. 2002;13:2140–4.
[53]. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137–47.
[54]. Qi C, Mao X, Zhang Z, Wu H. Classification and Differential Diagnosis of Diabetic Nephropathy [Internet]. Journal of Diabetes Research. 2017 [cited 2018 Nov 16]. Available from: https://www.hindawi.com/journals/jdr/2017/8637138/
[55]. Petrie JR, Chaturvedi N, Ford I, Hramiak I, Hughes AD, Jenkins AJ, et al. Metformin in adults with type 1 diabetes: Design and methods of REducing with MetfOrmin Vascular Adverse Lesions (REMOVAL): An international multicentre trial. Diabetes, Obesity and Metabolism. 2017;19:509–16.
[56]. Kojić Damjanov S, Đerić M, Eremić Kojić N. Glycated hemoglobin A1c as a modern biochemical marker of glucose regulation. Med Pregl. 2014;67:339–44.
[57]. Ahmad J. Management of diabetic nephropathy: Recent progress and future perspective. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2015;9:343–58.
[58]. te Riet Luuk, van Esch Joep H.M., Roks Anton J.M., van den Meiracker Anton H., Danser A.H. Jan. Hypertension. Circulation Research. 2015;116:960–75.
[59]. Taubman Mark B. Angiotensin II. Circulation Research. 2003;92:9–11.
[60]. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. New England Journal of Medicine. 1993;329:1456–62.
[61]. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139:244–52.
[62]. Molitch ME, Adler AI, Flyvbjerg A, Nelson RG, So W-Y, Wanner C, et al. Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney International. 2015;87:20–30.
[63]. Piccoli GB, Ventrella F, Capizzi I, Vigotti FN, Mongilardi E, Grassi G, et al. Low-Protein Diets in Diabetic Chronic Kidney Disease (CKD) Patients: Are They Feasible and Worth the Effort? Nutrients. 2016;8:649.
[64]. Morris SF, Wylie-Rosett J. Medical Nutrition Therapy: A Key to Diabetes Management and Prevention. Clinical Diabetes. 2010;28:12–8.
[65]. Razaz JM, Rahmani J, Varkaneh HK, Thompson J, Clark C, Abdulazeem HM. The health effects of medical nutrition therapy by dietitians in patients with diabetes: A systematic review and meta-analysis: Nutrition therapy and diabetes. Primary Care Diabetes [Internet]. 2019 [cited 2019 Aug 26];0. Available from: https://www.primary-care-diabetes.com/article/S1751-9918(19)30144-5/abstract
[66]. Poplawski MM, Mastaitis JW, Isoda F, Grosjean F, Zheng F, Mobbs CV. Reversal of Diabetic Nephropathy by a Ketogenic Diet. PLOS ONE. 2011;6:e18604.
[67]. Jerums G, MacIsaac RJ. Diabetic nephropathy: How does exercise affect kidney disease in T1DM? Nature Reviews Endocrinology. 2015;11:324–5.
[68]. Mailloux LU. Dialysis in Diabetic Nephropathy [Internet]. Available from: https://www.uptodate.com/contents/dialysis-in-diabetic-nephropathy#topicContent
[69]. Chan G, Tang SC-W. Current practices in the management of diabetic nephropathy. Journal of the Royal College of Physicians of Edinburgh. 2013;43:330–3.

[70]. Pérez-Sáez MJ, Pascual J. Kidney Transplantation in the Diabetic Patient. Journal of Clinical Medicine. 2015;4:1269–80.
[71]. Tobin GS, Klein CL, Brennan DC. Kidney Transplantation in Diabetic Nephropathy [Internet]. Available from: https://www.uptodate.com/contents/kidney-transplantation-in-diabetic-nephropathy#topicContent