***Complications of Diabetes: Cardiovascular, Renal, and Neurological Implications***

**Abstract**

Diabetes mellitus poses significant health challenges primarily due to its severe complications affecting the cardiovascular, renal, and nervous systems. Chronic hyperglycemia drives these complications through mechanisms like oxidative stress, inflammation, and the formation of advanced glycation end products, manifesting as both microvascular and macrovascular damage. Cardiovascular complications, including stroke and coronary artery disease, represent the leading cause of mortality among diabetic patients. Renal involvement leads to diabetic nephropathy, characterized by kidney damage. Furthermore, metabolic and vascular disturbances cause neurological complications, notably diabetic neuropathy. Effective prevention and management of these complications rely on stringent blood glucose control, alongside lifestyle modifications and pharmacological interventions.

**Introduction**

Diabetes, insulin is continually secreted, or is not prescribed because insulin secretions malfunction. There are generally three forms of this medical condition; gestational type 2 diabetes and the most frequently occurring of them all is type 1 diabetes.It’s the immune system attacking the pancreas which produces insulin that causes type 1 diabetes. On the other hand, type 2 diabetes is when the body cannot use the insulin in it [1].

It is pivotal to understand diabetes-related issues as the main reasons for death and disease. Related problems occur after a long time of high sugar levels which causes damage to many biological systems via mechanisms such as Oxidative stress, inflammation and advanced glycation end-products accumulation (AGEs) in the body.There are two types of complications: microvascular and macrovascular complications. This study examines three major complications: cardiovascular, renal and neurological [2].

Cardiovascular complications are the most common cause of death in patients with diabetes. Diabetic nephropathy is one of the leading causes of end-stage renal disease, with coronary artery disease (CAD), stroke and peripheral artery disease (PAD) among those at greatest risk. Diabetic neuropathy especially impaired quality of life on the nerves because it affects both peripheral and autonomic nerves [3].

The aim of this review is to provide a comprehensive overview of these complications, discussing their pathophysiology, prevalence, and management strategies to underline the importance of their early detection and effective treatment in improving patient outcomes.

**Cardiovascular Complications**

* **Pathophysiology**

The development of cardiovascular complications in diabetes mellitus arises because of multi-factorial interactions involving metabolic disturbances, chronic hyperglycemia, and consequent vascular injury, the primary entry point for which is hyperglycemia-driven endothelial malfunction. According to [4], when there are high blood glucose levels, it triggers the manufacture of reactive oxygen species (ROS) and advanced glycation end-products (AGEs) that damage the performance of endothelial cells by lowering their availability of nitric oxide. Nitric oxide is necessary for vasodilatation.

Diabetes is characterized by persistent low-grade inflammation, in which inflammation plays a significant role. This leads to increased levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) – diabetes-related pro-inflammatory cytokines working together to recruit monocytes or induce endothelial injury causing atherosclerosis [5]. Consequently, increased levels of oxidants aggravate endothelial injury thereby stimulating and sustaining vascular dysfunction [6].

Diabetic patients have faster atherosclerosis development due to hyperglycemia, dyslipidemia and dyslipidemia that create lipids inside arterial walls manifesting as lipid-rich plaques therein [6].

* **Prevalence**

Diabetes mellitus is responsible for most deaths and disease in which the heart and blood vessels are involved. Diabetes patients have a much higher chance of having heart and blood vessel problems than people who do not have diabetes placing much importance on the interrelation between diabetes and heart condition.

***Coronary Artery Disease (CAD)***

Those diagnosed with diabetes have a clearly higher probability for having CAD. These are diseases such as angina, myocardial infarction or coronary artery bypass grafting for instance. In their milestone epidemiological research, The Framingham Heart Study showed that diabetic patients face a 2-4 times greater likelihood of developing CAD [7]. Diabetes is associated with a pro-inflammatory state, respectively, it results in such hazard enhancement through accelerated atherosclerosis and endothelial dysfunction.

***Stroke***

Ischemic stroke has a high risk of diabetes, taking a global focus on diabetes while treating diabetes. Cerebral artery atherosclerosis, altered coagulation factors with increased thrombotic tendencies, and microvascular brain disorders are important mechanisms [8]. The risk of stroke also increases dramatically in diabetic patients when hypertension, dyslipidemia or poor glycemic controls co-exist.

***Peripheral Artery Disease (PAD)***

Peripheral artery disease (PAD) is most common in diabetes mellitus as there are multiple developing atherosclerosis and faulty flow of blood in the body. In individuals with diabetes and PAD there is a significant risk of having complications like non-healing sores on the feet which may result in amputations if not treated well. The problem of PAD tends to be more common with older ages and longer duration of diabetes implying that we need to identify it early enough before it progresses too far and then manage it intensively.

* **Management**

In diabetes, caution must be taken to ensure one is able to carry out a number of activities that aim at lowering factors that cause risk, stopping the development of diseases as well as making sure that general cardiovascular results are positive.

***1. Glycemic Control***

It is essential to attain or keep optimal glycemic control levels because it helps in lowering chances of heart problems. DCCT is a trial known as Diabetes Control and Complications Trial which demonstrated that lowering sugar levels tightly goes a long way into minimizing occurrences of certain small vessel diseases but its efficacy is not the same as far as large vessel diseases are concerned [9][10]. Lifestyle changes, insulin treatment, or antidiabetic tablets lead to less than 7.0% reduction in HbA1c which helps in reducing vascular injury and improving heart disease prediction.

***2. Lifestyle Modifications***

Lifestyle interventions play a vital role in the management of an individual’s heart life risk factors especially those suffering from diabetes. This will help in better control of blood sugars and reduction in fats from saturated sources and salt consumed thereby supporting optimal glycaemia as well as lipid control [11]. Insulin sensitivity, blood pressure, and cardiovascular fitness all see significant improvement from regular physical activity and this includes aerobic exercises as well resistance training.

***3. Pharmacological Interventions***

In diabetic patients, effectiveness of pharmacotherapy is important in managing cardiovascular risk factors.

**Statins:** In the treatment of high cholesterol, particularly in lowering LDL cholesterol levels and preventing heart attacks, Statins are the preferred drugs. The Cholesterol Treatment Trialists (CTT) Collaboration has shown conclusive proof from meta-analyses and other large trials of Statins’ efficacy in primary as well as secondary prevention [12].

**Antihypertensive Agents:** Blood pressure control is very critical for individuals with diabetes since it helps in preventing heart diseases. Recommended measurement is <130 mm Hg systolic and <80 mm Hg diastolic whereby the most commonly used antihypertensive drug classes consist of ACEIs, ARBs, beta-blockers, and diuretics [13].

**Antiplatelet Therapy:** In order to prevent thrombotic events, diabetic patients with a high cardiovascular risk can take Low-dose aspirin. It is important, however, that the treatment for high cardiovascular risk is tailored according to eligible cases only [14].

***4. ADA Guidelines***

The management of cardiovascular risk for people who have diabetes is detailed by the ADA. These guidelines point to individualized care for patients, and the need to constantly have an eye on every single one of their cardiovascular risks in order to make decisions about them together with you– the patient is emphasized [15]. Examinations that are regularly conducted to check on HbA1c, lipid profiles, blood pressure, and renal function help in the determination of treatment adjustments while paving way for better cardiovascular health outcomes.

**Renal Complications**

* **Pathophysiology**

Diabetic nephropathy, which is a main diabetes complication, ranks first among causes of end-stage renal diseases globally. The pathogenesis of this condition is linked to a number of factors like glomerular hyperfiltration, advanced glycation end products (AGEs) accumulation and raised intraglomerular pressure.

Diabetic nephropathy begins with glomerular hyperfiltration. Hyperglycemia causes increased renal blood flow, GFR also increases in the beginning compensating for the increased metabolic demands [16]. However, prolonged hyperfiltration destroys the glomerular structure.This leads to mesangial expansion as well as basement membrane thickening with related podocyte injury causing glomerulosclerosis and consequent renal function reduction in the long run [13].

Advanced glycation end products (AGEs) are highly involved in the development of diabetic nephropathy which results from non-enzymatic glycation of proteins/lipids mainly due to high levels of blood sugar. AGEs have receptors on several cell types such as endothelial cells and podocytes where they bind causing a series of inflammatory mechanisms through oxidative stress. According to Forbes and Cooper [17], Through their interaction, pro-inflammatory cytokines and growth factors such as transforming growth factor-beta (TGF-β) are produced which in turn enhances collagen fiber synthesis thus leading to fibrogenesis in the kidney.

Further damage to the kidney is made worse by an increase in intra-glomerular pressure due to both the enhanced renal filtration as well as activation of RAAS. An increased angiotensin II levels through RAAS under hyperglycemic conditions leads to both efferent arteriole constriction and thus raised intra-glomerular tension. In addition to causing glomerular damage this tension also heightens proteinuria which is a major characteristic of diabetes related kidney disease [18].

* **Prevalence**

The increasing kidney ailment starting from diabetic mellitus, that is nephropathy is a notable alarm to the world at large because of its severity. This is because approximately 20-40% of all diabetics would eventually suffer from nephropathy; it happens in both type 1 and type 2 diabetics more often than others taken together with complications of diabetes [19].

**Type 1 Diabetes:** Nephropathy typically occurs after 10-15 years of disease in 30-40% of cases concerning type 1 diabetes. Factors influencing prevalence include genetic predisposition, glycemic control and blood pressure management [20].

**Type 2 Diabetes:** Nephropathy prevalence is lower in the beginning of type 2 diabetes than type 1 diabetes but increases by its duration and other risk factors such as high blood pressure, cholesterol. For example, research finds that within a decade from diagnosis approximately 30% of type II diabetic patients will get microalbuminuria which is an initial manifestation of nephropathy [21].Type 2 diabetes shows a higher prevalence worldwide than type 1 diabetes.

* **Management**

In order to effectively manage diabetic nephropathy, one would need to work on three goals concurrently; they include retaining renal function; stopping the disease from spreading too far, or at all and, lastly, lessening cardio-vascular risks.

***1. Glycemic Control***

Strict control over blood sugar is crucial to prevent and manage diabetes-related kidney disease. Research shows that keeping the amount of glucose in the blood within specific limits helps to significantly reduce the likelihood of such small blood vessel associated complications as nephropathy in type 1 and type 2 diabetes [22].To delay the growth of nephropathy and save kidney function, it is advisable to maintain HbA1c levels below 7.0%.

***2. Blood Pressure Management***

In diabetic nephropathy, hypertension is a frequent occurrence and it leads to the disease getting worse. To slow down how quickly the kidney deteriorates and to prevent cardiovascular problems from happening, you need to regulate your blood pressure. In general, the ideal pressure for patients who have both diabetes and kidney diseases is usually < 130/80 mmHg [24]. Antihypertensive agents, particularly those targeting the renin-angiotensin-aldosterone system (RAAS) such as ACE inhibitors and angiotensin II receptor blockers (ARBs) are favored due to their property to save kidneys. This can be illustrated by means of reducing intraglomerular pressure, diminishing proteinuria, and retarding nephropathy advancement [23]

***3. Use of RAAS Inhibitors***

RAAS inhibitors serve as essential components in addressing diabetic nephropathy. These medications work by limiting the synthesis or function of angiotensin II, which has a constriction effect on kidney efferent arterioles decreasing pressure within the glomerulus hence inhibiting protein absorption in urine.In humans, there have been trials like RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan Diabetic Nephropathy Trial) which showed that ACE inhibitors as well as ARBs can slow down kidney damage from diabetes before making it very severe [25][26]. ACE inhibitors together with ARBs are recommended for patients who have proteinuria because they help to keep their kidneys healthy and also avoid heart diseases."

***4. Importance of Early Detection and Regular Screening***

Timely implementation of interventions to slow down the progression of the disease necessitates early detection of diabetic nephropathy. Annual screening for microalbuminuria (defined as urinary albumin excretion of 30-300 mg/day) should start upon diagnosis in all diabetic patients with type 2 diabetes and after 5 years in type 1 diabetes [27]. The presence of chronic microalbuminuria serves as an indicator of need for more intense management approaches, for example, more optimal glycemic control, beginning use of RAAS inhibitors, addressing hypertension and dyslipidemia that can be managed.

It is also suggested to regularly track renal function through serum creatinine and estimated glomerular filtration rate (eGFR) so as to evaluate kidney activity and alter medical care appropriately [28]. On the basis of these assessments, timely intervention could ensure better results; further, it also significantly delays transition into dialysis or kidney transplant stage.

**Neurological Complications**

* **Pathophysiology**

Diabetic neuropathy is collectively known as neurological complications in diabetes and it arises from prolonged hyperglycemia. This condition’s pathophysiology is due to various factors including neurohormonal, metabolic as well as vascular disturbances.

Through the polyol pathway chronic hyperglycemia brings accumulation of sorbitol and fructose in the nerves causing osmotic stress and nerve damage. It also impairs Na+/K+ ATPase, key enzyme in maintaining the potential of nerve cell membrane, which results in malfunction of nerves [29]. Excess blood sugar ups ROS production so that ROS destroy components they are produced. Said hazardous substances are lipids, proteins and nucleic acids. This is what triggers inflammation due to glucose [30]. Nonetheless, high levels of proinflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) exacerbate neurodegeneration, derailing nerve conduction. Nerve blood flow impairment is observed alongside complications of the small vessels typically associated with diabetes. Ischemia and hypoxia occurring due to damage happening to the nerve providing small blood vessels lead to nerves being further injured with time. The endothelial dysfunction encountered in patients with diabetes is characterized by a decrease in nitric oxide levels thereby causing inadequate dilation that contributes to microcirculatory incompetence [31].

* **Prevalence**

Diabetic neuropathy emerges as a disturbance of high prevalence and importance in diabetes whereby up to 50% of diabetes patients can be affected by it. Neuropathy is incidence and types dependent, through advancing of the diabetic course and glycemic control, to different types of diabetes.

***Peripheral Neuropathy***

Diabetic neuropathy, a condition that affects peripheral nerves on the limbs in particular the hands and legs, is found in its most common form in about 50% of diabetics [32]. For example, patients who have been diagnosed for more than twenty five years have a neuropathy rate of greater than fifty percent i.e. [33]. The longer a person has been diabetic then more common neuropathy becomes, according to the progression of the illness.

***Autonomic Neuropathy***

Involving multiple organ systems and leading to diverse clinical manifestations, autonomic neuropathy affects the nervous system beyond conscious control. This kind of neuropathy is not as usual as peripheral one although it is found among many people who suffer from diabetes. According to some data, between 20-40% of patients with diabetes have autonomic dysfunction in some form [34]. Serious complications from autonomic neuropathy can result in resting tachycardia, orthostatic hypotension, gastroparesis, bladder dysfunction and other genitourinary manifestations.

***Focal Neuropathy***

Sudden and isolated nerve damage often affects distinct nerves (for example, cranial nerves or nerves supplying limbs) in mononeuropathy. In about 1-2% of diabetic patients, this kind is less frequent and may cause sharp and hard pain or even weak muscles in a certain region [35]. Yet, being spontaneous, it may be quite distressing for a patient during the acute stage (Journal article).

* **Management**

Caring for diabetic neuropathy is complex, and involves focusing on controlling blood sugar levels, managing symptoms, and preventing complications. By targeting a better quality of life for patients, it could ease neuropathic pain while also averting complications.

***1. Glycemic Control***

Maintaining blood sugar levels tightly in both type 1 and type 2 diabetes has been shown by several studies to decrease the occurrence and seriousness of neuropathy.It is recommended to lower HbA1c levels to target ranges (often below 7%) in order to reduce the likelihood of neuropathic complications. This may necessitate varying modifications in lifestyle as well as the use of oral hypoglycemic agents or insulin treatment based on the needs of each patient [36].

***2. Pain Relief and Symptomatic Treatment***

Symptom management, particularly pain relief, is a critical aspect of treating diabetic neuropathy. Various pharmacological options are available to manage neuropathic pain:

**Anticonvulsants:** Anticonvulsants, including gabapentin and pregabalin are frequently prescribed for neuropathic pain because they help nerves work correctly and reduce painful sensations. Consequently, their utilization is associated with improvement of the patient's perspective on life [37]..

**Antidepressants:** Another way in which neuropathic pain is managed is through tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors. They act by promoting pathways along which pain is restricted within the brain. Research results indicate that their efficiency can be clearly seen when tested on patients suffering from diabetic neuropathy [32].

**Topical Agents:** Capsaicin cream and lidocaine patches are examples of tropical treatment methods used for PAIN RELIEF IN only specific parts of the body through desensitization of the receptors transmitting pain or decoupling nerve impulses. According to [37], these substances can be especially beneficial for patients who cannot take medicines via their mouth.

***3. Non-Pharmacological Approaches***

Non-drug therapy is generally useful in controlling diabetic neuropathy and at the same time improving the outcomes of the patient.

**Lifestyle Modifications:** Maintain glycemic control and full-body health by doing exercises regularly, eating a balanced diet, and managing your weight. Patients with diabetic neuropathy have reported lower pain levels and increased quality of life from improved nerve functions through exercise [38].

**Physical Therapy:** Engaging in physical therapy and exercise programs allow people to maintain and improve mobility, strength and coordination which help reduce fall risk and increase functional outcomes. Previous research has also shown that structured exercise interventions involving aerobic and resistance training have been effective in reducing neuropathic symptoms as well as improving nerve function [38].

**Foot Care:** Good foot care is important in diabetic neuropathy for preventing problems such as ulcers and infections which occur regularly.As a result, it is recommended that patients should examine their feet frequently, wear appropriate shoes, remove calluses and heal sores [39]. Therefore, teaching about how to take care of ones feet becomes very important in looking after a patient.

***4. Emerging Therapies***

Research into novel treatments for diabetic neuropathy is ongoing, with several promising approaches under investigation:

**Gene Therapy:** Gene therapy focuses on correcting or modulating genetic factors causing neuropathy. Delivery of genes promoting nerve regeneration or blocking pathways causing nerve damage are being experimented in studies [40].

**Neurotrophic Factors:** Neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are subject to investigations concerning their capacity to stimulate the growth and repair of nerves. It is believed that these factors can contribute to nerve regeneration and function enhancement [41].

**Molecular Pathway Modulators:** An encouraging treatment approach is the envisaging of dealing with nerve injury via some particular molecular ways such as AGE (advanced glycation end-product) pathways, oxidative stress pathways among others. There are certain compounds which might prevent such processes and they are currently being tested in laboratories or on small groups of patients in hospitals under supervision of doctors [42].

**Conclusion**

In conclusion, the control of diabetes is impacted by its severe complications such as those related to the heart, kidney or braDetecting and managing these conditions earlier can help in protecting the kidney from failure as well as averting total renal failure which might come as a result. Diabetic neuropathy necessitates a comprehensive strategy which involves controlling sugar levels through drug management pain control as well as non medicine approaches used for enhancing an individual’s life quality like physical exercises.in. For instance, cardiovascular complications are the major cause of death in diabetic patients implying the fact that strict control of blood glucose levels, lifestyle changes as well as use of medication are necessary to reduce chances of getting heart disease and stroke. Research for better treatment in the future could increase due to continuing research in emerging therapies, which underlines the necessity for continuous improvement of health care for diabetes.

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**References**

1. Fonseca V: Journal of Diabetes and Its Complications. Journal of Diabetes and its Complications. 2012, 26:69. https://doi.org/10.1016/j.jdiacomp.2012.03.002
2. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M: Psychosocial Care for People With Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016, 39:2126–40. https://doi.org/10.2337/dc16-2053
3. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O: Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. New England Journal of Medicine. 2008, 358:580–91. https://doi.org/10.1056/nejmoa0706245
4. Kitada M, Zhang Z, Mima A, King GL: Molecular mechanisms of diabetic vascular complications. Journal of Diabetes Investigation. 2010, 1:77–89. https://doi.org/10.1111/j.2040-1124.2010.00018.x
5. Raggi P: Inflammation, depression and atherosclerosis or depression, inflammation and atherosclerosis? Atherosclerosis. 2016, 251:542–3. https://doi.org/10.1016/j.atherosclerosis.2016.07.902
6. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002, 287:2570–81. https://doi.org/10.1001/jama.287.19.2570
7. Kannel WB: Diabetes and cardiovascular disease. The Framingham study. JAMA: The Journal of the American Medical Association. 1979, 241:2035–8. https://doi.org/10.1001/jama.241.19.2035
8. Mozaffarian D, Benjamin EJ, Go AS, et al.: Heart Disease and Stroke Statistics—2016 Update. Circulation. 2016, 133: https://doi.org/10.1161/cir.0000000000000350
9. The Diabetes Control and Complications Trial Research Group: The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. New England Journal of Medicine. 1993, 329:977–86. https://doi.org/10.1056/nejm199309303291401
10. UK prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet. 1998, 352:837–53. https://doi.org/10.1016/s0140-6736(98)07019-6
11. ElSayed NA, Aleppo G, Aroda VR, et al.: 17. Diabetes Advocacy: *Standards of Care in Diabetes—2023*. Diabetes Care. 2022, 46:S279–80. https://doi.org/10.2337/dc23-s017
12. Obreli-Neto PR, Guidoni CM, de Oliveira Baldoni A, Pilger D, Cruciol-Souza JM, Gaeti-Franco WP, Cuman RKN: Effect of a 36-month pharmaceutical care program on pharmacotherapy adherence in elderly diabetic and hypertensive patients. International Journal of Clinical Pharmacy. 2011, 33:642–9. https://doi.org/10.1007/s11096-011-9518-x
13. Tervaert TWC, Mooyaart AL, Amann K, et al.: Pathologic Classification of Diabetic Nephropathy. Journal of the American Society of Nephrology. 2010, 21:556–63. https://doi.org/10.1681/asn.2010010010
14. Remuzzi G, Schieppati A, Ruggenenti P: Nephropathy in Patients with Type 2 Diabetes. New England Journal of Medicine. 2002, 346:1145–51. https://doi.org/10.1056/nejmcp011773
15. Tuttle KR, Bakris GL, Bilous RW, et al.: Diabetic Kidney Disease: A Report From an ADA Consensus Conference. Diabetes Care. 2014, 37:2864–83. https://doi.org/10.2337/dc14-1296
16. Kumar DS: Comparative study of Dyslipidemia in Diabetic patients with Diabetic Nephropathy and Diabetic patients without Nephropathy. Journal of Medical Science And clinical Research. 2020, 08: https://doi.org/10.18535/jmscr/v8i2.66
17. Forbes JM, Cooper ME: Mechanisms of diabetic complications. Physiological reviews. 2013, 93:137–88. https://doi.org/10.1152/physrev.00045.2011
18. Wong WT, Tian XY, Xu A, et al.: Angiotensin II type 1 receptor-dependent oxidative stress mediates endothelial dysfunction in type 2 diabetic mice. Antioxidants & Redox Signaling. 2010, 13:757–68. https://doi.org/10.1089/ars.2009.2831
19. Tuttle KR, Bakris GL, Bilous RW, et al.: Diabetic Kidney Disease: A Report From an ADA Consensus Conference. American Journal of Kidney Diseases. 2014, 64:510–33. https://doi.org/10.1053/j.ajkd.2014.08.001
20. Tian B, Liu N, Xu T, Liu X, Yao L: Simultaneous membranous nephropathy and diabetic nephropathy occurrence in a patient: A case report. Diabetic Nephropathy. 2021, 1:51–4. https://doi.org/10.2478/dine-2021-0009
21. Perkovic V, Jardine MJ, Neal B, et al.: Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2019, 380:2295–306. https://doi.org/10.1056/nejmoa1811744
22. The Diabetes Control and Complications Trial Research Group: The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. New England Journal of Medicine. 1993, 329:977–86. https://doi.org/10.1056/nejm199309303291401
23. Klemmer PJ, Harris AA: Carbon disulfide nephropathy. American Journal of Kidney Diseases. 2000, 36:626–9. https://doi.org/10.1053/ajkd.2000.16204
24. Cao Z, Cooper ME: Pathogenesis of diabetic nephropathy. Journal of Diabetes Investigation. 2011, 2:243–7. https://doi.org/10.1111/j.2040-1124.2011.00131.x
25. Brenner BM, Cooper ME, de Zeeuw D, et al.: Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2001, 345:861–9. https://doi.org/10.1056/nejmoa011161
26. Lewis EJ, Hunsicker LG, Clarke WR, et al.: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. The New England journal of medicine. 2001, 345:851–60. https://doi.org/10.1056/NEJMoa011303
27. Motawi TK, Shehata NI, ElNokeety MM, El-Emady YF: Potential serum biomarkers for early detection of diabetic nephropathy. Diabetes Research and Clinical Practice. 2018, 136:150–8. https://doi.org/10.1016/j.diabres.2017.12.007
28. Shoukry A, Bdeer SE-A, El-Sokkary RH: Urinary monocyte chemoattractant protein-1 and vitamin D-binding protein as biomarkers for early detection of diabetic nephropathy in type 2 diabetes mellitus. Molecular and Cellular Biochemistry. 2015, 408:25–35. https://doi.org/10.1007/s11010-015-2479-y
29. Brownlee M: The Pathobiology of Diabetic Complications: A Unifying Mechanism. Diabetes. 2005, 54:1615–25. https://doi.org/10.2337/diabetes.54.6.1615
30. Vincent AM, Russell JW, Low P, Feldman EL: Oxidative Stress in the Pathogenesis of Diabetic Neuropathy. Endocrine Reviews. 2004, 25:612–28. https://doi.org/10.1210/er.2003-0019
31. Cameron NE, Ma C, Horrobin DH, Tritschler H: Effects of α-lipoic acid on neurovascular function in diabetic rats: interaction with essential fatty acids. Diabetologia. 1998, 41:390–9. https://doi.org/10.1007/s001250050921
32. Tesfaye S, Boulton AJM, Dyck PJ, et al.: Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. Diabetes Care. 2010, 33:2285–93. https://doi.org/10.2337/dc10-1303
33. Gregg EW, Sorlie P, Paulose-Ram R, et al.: Prevalence of Lower-Extremity Disease in the U.S. Adult Population >=40 Years of Age With and Without Diabetes: 1999-2000 National Health and Nutrition Examination Survey. Diabetes Care. 2004, 27:1591–7. https://doi.org/10.2337/diacare.27.7.1591
34. Vinik AI, Erbas T, Casellini CM: Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. Journal of Diabetes Investigation. 2013, 4:4–18. https://doi.org/10.1111/jdi.12042
35. Freeman R: Autonomic Peripheral Neuropathy. Neurologic Clinics. 2007, 25:277–301. https://doi.org/10.1016/j.ncl.2007.01.001
36. Malik VS, Popkin BM, Bray GA, Després J-P, Hu FB: Sugar-Sweetened Beverages, Obesity, Type 2 Diabetes Mellitus, and Cardiovascular Disease Risk. Circulation. 2010, 121:1356–64. https://doi.org/10.1161/circulationaha.109.876185
37. Bates DW: Effect of Computerized Physician Order Entry and a Team Intervention on Prevention of Serious Medication Errors. JAMA. 1998, 280:1311. https://doi.org/10.1001/jama.280.15.1311
38. Kluding PM, Pasnoor M, Singh R, et al.: The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. Journal of Diabetes and its Complications. 2012, 26:424–9. https://doi.org/10.1016/j.jdiacomp.2012.05.007
39. Boulton A, Armstrong D, Albert S, et al.: Comprehensive Foot Examination and Risk Assessment. Endocrine Practice. 2008, 14:576–83. https://doi.org/10.4158/ep.14.5.576
40. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai K-S, Stacey B: Pain Severity in Diabetic Peripheral Neuropathy is Associated with Patient Functioning, Symptom Levels of Anxiety and Depression, and Sleep. Journal of Pain and Symptom Management. 2005, 30:374–85. https://doi.org/10.1016/j.jpainsymman.2005.04.009
41. Bertsch T, Kuehl S, Muehlhauser F, et al.: Source of Endothelin-1 in Subarachnoid Hemorraghe. Clinical chemistry and laboratory medicine. 2001, 39: https://doi.org/10.1515/cclm.2001.053
42. Ramasamy R, Yan SF, Schmidt AM: The RAGE connection to diabetes and atherosclerosis: an intertwined web of advanced glycation and inflammation. Future Lipidology. 2007, 2:239–50. https://doi.org/10.2217/17460875.2.2.239