Review Article

Navigating the Landscape of Diabetic Microvascular Complications: Strategies for Prevention and Management

Anastasia V. Poznyak[1*], Elizaveta Romanovna Korchagina[2], Olesya Olegovna Galanova[3], Sergey Alekseevich Protasov[4], Alexander N. Orekhov[1]

[1]*Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia*

[2]*Department of Systemic Rheumatic Diseases, Nasonova Research Institute of Rheumatology, 34A, Kashirskoe Shosse, 115522 Moscow, Russia*

[3]*Moscow Center for Advanced Studies, 20, Kulakova Street, 123592 Moscow, Russia*

[4]*Talrose Institute for Energy Problems of Chemical Physics, Semenov Federal Research Center for Chemical Physics, 38-2, Leninsky Prospekt, 119334 Moscow, Russia*

*Address Correspondence to: Anastasia V. Poznyak, Email: tehhy_85@mail.ru

Abstract

As the global prevalence of Diabetes Mellitus (DM) continues to rise, projected to affect nearly 700 million individuals by 2045, the burden of associated macro-and Micro-Vascular Complications (MVCs) is escalating markedly. This review synthesizes current knowledge regarding the development, risk factors, prognostic implications, and preventive strategies for key diabetic MVCs, including Diabetic Retinopathy (DR), nephropathy, peripheral neuropathy, and autonomic neuropathy. Evidence underscores a significant link between these complications and cardiovascular risk, revealing that MVCs often predict cardiovascular events with greater accuracy than traditional risk factors such as hypertension and glycemic control. Through a comprehensive exploration of epidemiological findings, clinical trials, and treatment strategies, this review highlights the importance of early detection and rigorous management of diabetic MVCs. Key interventions, including angiotensin-converting enzyme inhibitors, statins, and effective glycemic control, are discussed as vital measures to mitigate the progression of diabetic complications. Additionally, we emphasize the necessity for routine screening, particularly for high-risk populations, to enable timely intervention and improve patient outcomes. By integrating clinical guidelines with advancements in diabetes care, our findings propose a multifaceted approach to reducing the burden of diabetic microvascular diseases.

Keywords: Diabetes mellitus; Retinopathy; Nephropathy; Glycemic control

Introduction

Evidence from the year 2019 indicate that the number of individuals suffering from DM was 463 million, which is prognoses to be up to seven hundred million by 2045. Raising rates of the disease and elevation of time periods spent with DM affected the progression of macro-and micro-vascular complications considerably. Healthcare systems hereby are experiencing an enormous burden worldwide [1,2]. Whereas decrease in CV complications, CV deaths and limb amputation frequency were observed in the past twenty years, especially in developed countries, the worldwide burden of CVD, DR, and renal failure in patients with DM has elevated drastically [3,4]. The Discover trial demonstrated that the highest rates of MVCs in subjects with T2DM were found in Europe, and the lowest in Africa, 23.5% and 14.5% of the total 18.8%, respectively. In subjects with average disease duration of 4.1y. The rates of peripheral nerve disorders were 7.7%, Chronic Kidney Disease (CKD) 5%, high levels of albumin in urine 4.3% [5,6].

Epidemiological trials show a connection between various MVCs of DM. E.g., DR is linked to the risk of diabetic nephropathy progression and can predict ischemia and CVD. Moreover, in subjects with T2DM, different MVCs predict CV risk with higher precision than traditional predictors e.g., hypertension, glycated hemoglobin, Low-density Lipoprotein Cholesterol (LDL-C), while some MVCs are connected to two-fold higher risk of CVD and CV death [7-9]. These discoveries indicate that screening for MVCs could become a useful instrument to boost

CV risk predicting in subjects with DM, as well as that application of CV treatments might help avoid or curb the detrimental CV events [10-12].

MVCs usually progress during years of disease, although the onset can coincide with the moment the individual is diagnosed, especially in case of T2DM. While high blood sugar is a prerequisite for the development of MVCs, the processes underlying the impairment of healthy microvascular structure and functioning are intricate and not fully known [13,14]. Moreover, high blood pressure, reduced LDL-C, high TGs, tobacco use, and DM duration together remarkably affect its pathogenesis. In the past years, the interconnections of genetic and lifestyle factors have been considered a possible way of diabetic MVCs progression. In fact, DR and moderately increased urine albumin are frequently observed in pre-DM and pre-hypertension [15,16].

This review is focused on the development, risk factors, prognoses and preventing of such diabetic MVCs as retinopathy, renal disorders, peripheral neuropathy and autonomic neuropathy. The review also concentrates on the optimal clinical approaches which can be applied to treat individuals with said disorders (Table 1).

Table 1: Prevention and Management Strategies for Microvascular Complications (MVCs).

Complication	Prevention strategy	Management / Treatment
Diabetic Retinopathy (DR)	Regular screening exams with an ophthalmologist	Tight glycemic control
	Maintain blood pressure <140/80 mmHg	Advanced treatments such as Panretinal Photocoagulation (PRP)
Diabetic Nephropathy (DKD)	Annual assessment of eGFR and urine albumin levels	ACE inhibitors / ARBs for renal protection
	Maintain HbA1c <6.5%	Statins for lipid management
Peripheral Neuropathy (PN)	Annual foot exams for risk assessment	Tight glycemic control
	Patient education on foot care	Pain management and physical therapy
Autonomic Neuropathy (AN)	Monitor cardiovascular risk factors	Cardiovascular autonomic function assessment
	Screening for other diabetic complications	Addressing lifestyle factors (diet, exercise)

Preventing Microvascular Disease (MVD)

Risk factors: In order to prevent MVD, it is important to monitor exacerbating risk factors and apply screening methods to ameliorate early diagnosis. The UK prospective diabetes study and the diabetes control and complications trial showed that development of DR and diabetic kidney disease is associated with glycemic regulation, as well as that it is vital to retain glycated hemoglobin not higher than 6.5% to alleviate the condition. However, the connection between blood pressure/glucose and diabetic kidney disease is less clear [17,18].

Blood Pressure (BP): The blood pressure should be maintained lower than 140/80 mmHg to avoid development of MVCs. Although, when these levels are reached, it should be further decreased to levels lower than 125/75 mmHg [19,20].

Angiotensin-Converting Enzyme Inhibitors (ACEI): Angiotensin-converting enzyme inhibitors and Angiotensin Receptor Blockers (ARBs) are the treatment of choice. Studies showed their effectiveness in decreasing levels of protein in urine and in suppressing development of kidney failure [21-23]. The Heart outcomes prevention evaluation trial revealed that ramipril decreased evident kidney disease by twenty-four percent [24]. The Reduction of endpoints in NIDDM with the angiotensin II antagonist losartan study showed a twenty-five percent decrease in development of DR and a 28% decrease in the End-stage renal disease risk [25]. Inhibition of angiotensin with angiotensin-converting enzyme inhibitors can also help avoid DR and decrease its

severity by fifty percent. Although, these compounds are possibly teratogenic and this should be taken into account when female subjects of reproductive age are treated with it [26,27].

Statins: Diabetic kidney disease can be alleviated with statins which decrease levels of protein in urine and can ameliorate kidney functioning. In subjects with diabetic kidney disease, concentrations of LDL-C should be decreased to be lower than 2 mmol/l. In animal trials, statins have shown an ability to alleviate DR [28-31]. However, results of clinical trials are not as reliable. The Fenofibrate intervention and event lowering in diabetes trial study demonstrated that fibrates have beneficial impact on DR [32].

Screening: MVD has to be detected early with application of reliable screening programs. National screening program for DR began in the nineties and has been crucial for decreasing DM-associated eye diseases [33-35]. Subjects with severe DR should be referred as recommended by national guidelines. Diabetic kidney disease may be detected early by monitoring urine albumin levels, and diabetic nerve disorders can be identified by thoroughly examining lower limbs as part of the annual checkup for subjects with DM [36,37].

Diabetic nephropathy: Diabetic nephropathy is a frequent MVC of diabetes which affects about twenty-five percent of subjects with diabetes. Furthermore, diabetes is one of the main reasons of end-stage renal disease development and it is responsible for a half of the cases. There has been found a connection between presence of albumin in urine and CVD [38,39]. Particularly, moderate elevation of urine albumin concentrations is believed to be a risk factor for cardiovascular disease, whereas treatment which reduces albumin levels has a beneficial impact on CV system. Consistently, early detection and treatment of diabetic nephropathy is vital [40-43].

Diabetic Kidney Disease (DKD) is characterized by changed kidney functioning in subjects with DM, given that other explanations for Chronic kidney disease have been ruled out. Newest ADA's guidelines state that the diagnosis of diabetic nephropathy should be based on the reduced estimated Glomerular Filtration Rate (eGFR) with levels less than 60 ml/minute/1.73m2 or levels of albumin in urine higher than or equal to 30 mg/g creatinine, which

last over three months [44-47].

Since type 2 diabetes is an insidious disease, it is important to check DM subjects for diabetic nephropathy when they are diagnosed and perform annual checkups. The screening has to involve the assessment of estimated glomerular filtration rate following the evaluation of creatinine in serum and the evaluation of Urinary albumin-to-creatinine ratio [48-51]. A number of formulas were suggested for measurement if estimated glomerular filtration rate, among which the CKD Epidemiology Collaboration equation appears to be the most precise. At the early phases of DKD, estimated glomerular filtration rate can be within normal limits or increased because of glomerular hyperfiltration, even though renal functioning is altered. Hereby, more precise markers are needed to determine diabetic nephropathy at early stage and avoid its development [52-56].

Detection of abnormal urinary albumin levels can be conducted by measuring urinary albumin to creatinine ratio or by measuring albumin excreted over a certain amount of time (e.g., twenty-four hours). Evaluation of urinary albumin to creatinine ratio from a spot sample is commonly applied because it is easy and convenient, albeit limited [57,58]. These levels can vary from day to day and the differences may be up to forty percent. Additionally, some disorders can induce an elevation in albuminuria, e.g., Urinary tract infections, pyrexia, Congestive heart failure, hypertension, physical activity, high sugar or protein consumption. Hereby, increased urinary albumin to creatinine ratio needs to be checked again in the following three to six months with two analyses of first-void urine. For diagnosis confirmation, two or three samples must meet the albuminuria criteria. Classic stratification of this condition to micro- and macroalbuminuria were changed lately. In Kidney disease: Improving global outcomes 2012 clinical practice guidelines, this condition is broken down into three groups [59,60]. The first group, A1, is characterized by normal to slightly elevated urinary albumin to creatinine ratio, lower than 30 mg/g creatinine. The second group, A2, is characterized by moderately elevated urinary albumin to creatinine ratio, from 30 to 300 mg/g creatinine. The third group, A3, is characterized by high urinary albumin to creatinine ratio, higher than 300 mg/g creatinine [61-63].

High occurrence rates of type 2 diabetes in adults indicates that not all subjects with DM and changes in renal functioning have diabetic nephropathy, while non-diabetic

kidney disease can be accountable for it. Recent research demonstrated that occurrence of non-diabetic kidney disease in subjects with DM varies between 3-82.9%, which could be explained by heterogeneous property of the population [64-67]. Diagnosing DKD requires kidney biopsy, however, it is not often conducted since there are no enough standard criteria. It is mainly preserved for disorders that point to different etiology of CKD. In particular, quickly reducing estimated glomerular filtration rate, active urine sediment, systemic disorders or quickly elevating levels of proteins in urine typically mean that kidney biopsy is necessary [68-70]. Systolic BP, diabetes mellitus duration, diabetic retinopathy and glycated hemoglobin range are in negative correlation with non-diabetic renal disease. Furthermore, decreased estimated glomerular filtration rate with no albuminuria can mean that non-diabetic renal disease is developing [71-74].

Usually, DKD development involves five well-studied phases, drawing on evidence obtained from trials in subjects with T1DM. The initial phase of diabetic nephropathy is hyperfiltration which causes albuminuria, which progresses from micro-albuminuria to macro-albuminuria, with consequent reduction in glomerular filtration rate and increase in BP [75-78]. The advanced stage is end-stage renal failure with negative impact on life quality and a risk of death. Although, recent studies showed that this is not always the case and micro-albuminuria may not develop into macro-albuminuria, and sudden remissions were detected [79,80]. Steno 2 study included more than 7 years of observation and showed that just in 47 patients of 151 macro-albuminuria developed into macro-albuminuria, while 58 patients still had micro-albuminuria and 46 patients had remission [81]. Alleviation of micro-albuminuria is in correlation with anti-hypertension therapy and a reduction in glycated hemoglobin because of ameliorated glucose regulation. At the same time, subjects with DM can exhibit kidney dysfunction with elevated creatinine concentrations, but no albuminuria [82-84]. The United Kingdom prospective diabetes trial showed that in 38% of subjects with DM albuminuria progressed over fifteen years, and kidney dysfunction was observed in 29% of subjects, among which fifty-five percent showed normal levels of urinary albumin [85]. Similar findings were observed in the Renal insufficiency and cardiovascular events study study in 15773 subjects with type 2 diabetes. At baseline, 56.6% of subjects had kidney dysfunction (glomerular filtration rate lower than 60 mL/minute/1.73 m2) and normal levels of albumin, 30.8% of subjects had micro-albuminuria and 12.6% of subjects had macro-albuminuria [86]. Kidney dysfunction with normal levels of albumin was observed in women with reduced glycated hemoglobin, but the connection to diabetic retinopathy and high BP was not as strong in comparison to subjects with albuminuria. It is noteworthy that the occurrence of cardiovascular events in this group of subjects was higher than in subjects with only albuminuria and lower than in subjects with kidney dysfunction and albuminuria (OR 1.66, 1.21 and 2.27 respectively) [87]. Therapy with Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blocker (ARB) and enhanced management of high BP and diabetes are believed to be responsible for the elevated occurrence rates of that phenotype in subjects with DM. Additionally, the probable physiologic mechanism of progression of diabetic nephropathy without albuminuria is macro-angiopathy and not micro-angiopathy. However, recurrent or not resolved AKI could also be responsible for development of that condition [88,89].

Accordingly, estimated glomerular filtration rate and albumin levels are presently utilized markers for diagnosis and observation of diabetic nephropathy. Although, not all chronic kidney disease in subjects with DM can be explained by diabetes. More accurate markers and standard criteria for kidney biopsy are necessary for early diagnosis and treatment of patients with diabetes [90,91].

Diabetic retinopathy

Globally, diabetic retinopathy is the most frequent cause of Vision Impairment (VI). In diabetic retinopathy VI is mostly due to diabetic macular edema, which affects central vision, and proliferative diabetic retinopathy, which causes angiogenesis and dense connective tissue formation which leads to retinal detachment or pre-retinal hemorrhage [92-95]. Whereas diabetic retinopathy is usually believed to be a primary vascular disease, new evidence indicate that it might be due to DM retinal nerve degeneration. Although, further study is necessary to determine the causality [96-99].

A meta-analysis of thirty-five studies from 1980 to 2008 was performed and it demonstrated that 25.16% of subjects with type 2 diabetes had diabetic retinopathy, 2.97% had proliferative diabetic retinopathy and 5.57% had diabetic macular edema. Another systematic review showed that

global annual occurrence of diabetic retinopathy is from 2.2 to 12.7%, and the development rates vary between 3.4% and 12.3% [100,101].

Blood glucose, BP and lipid levels are well-known diabetic retinopathy risk factors. The UK prospective diabetes study revealed that effective management of blood glucose levels leads to a decrease in MVCs in comparison to traditional therapy. Particularly, there was a twenty-five percent decrease in the risk of the necessity for Panretinal Photocoagulation (PRP) was detected in the glucose management group [102,103]. Another important discovery of that study is that intensive BP control led to a thirty-four percent decrease in the diabetic retinopathy development rates, with 47% decrease in vision impairment. The necessity of PRP was decreased by 35%. The FIELD trial showed that fenofibrate can decrease the necessity for laser therapy for diabetic retinopathy in comparison to the placebo group (3.4% and 4.9%, p=0.0002), mostly because of a decrease in the diabetic macular edema incidence [104-107]. Beneficial impact of fenofibrate was confirmed in the Action to control cardiovascular risk in diabetes trial [108]. Combined therapy with simvastatin and fenofibrate led to an amelioration in diabetic retinopathy in comparison to the placebo group (6.5% and 10.2%). This study also demonstrated that subjects who underwent tight glucose control showed reduced rates of diabetic retinopathy development in comparison to subjects who were treated with traditional methods (7.3% and 10.4%). Although a correlation between tight BP control and diabetic retinopathy development rates was not found [109,110].

As in DKD, all subjects must be assessed by an ophthalmologist when they are diagnosed with type 2 diabetes. A thorough eye exam is required to find early symptoms of diabetic retinopathy. Ophthalmoscopic examination with dilated fundus enables diagnosis of diabetic retinopathy and determination of its phase [111,112]. Stereoscopic 7F photographs give the same results with the benefit of providing information on subject's conditions that may be utilized for future comparing. NMDSRI is another accurate instrument which can be applied to evaluate the subjects and detect diabetic retinopathy. However, it is not able to replace thorough eye exam. In subjects with diabetic retinopathy, UWFA may be performed to visualize the vessel leaking, RNP and formation of new blood vessels [113]. OCT is also a useful noninvasive method to assess thickness of the retina, which gives valuable data on the retinal vessels. Additionally, new methods are becoming available, e.g., smartphone fundoscopy. However, the accuracy and precision of this method are yet to be confirmed [114-116].

ADA guidelines suggest to examine the eyes two years in a row, after which the exams can be performed with lower frequency (once in one to three years) provided that the results of the two were normal and the is tight glucose maintenance. In other cases, the time periods are defined by the phase of the disorder to make sure that its development is quickly noticed, since early treatment provides better results [117].

Diabetic retinopathy and Diabetic macular edema classification are drawing on the International clinical diabetic retinopathy disease severity scale severity scale which involves five phases. Diabetic macular edema can be found in any phase of diabetic retinopathy. However, the occurrence rates are higher as diabetic retinopathy develops to advanced stages [118-120]. Diabetic retinopathy is divided into two main groups, non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. Non-proliferative diabetic retinopathy is also broken down into groups: mild non-proliferative diabetic retinopathy, moderate non-proliferative diabetic retinopathy and severe non-proliferative diabetic retinopathy [121-123].

Mild non-proliferative diabetic retinopathy is featured by micro-aneurysms, i.e., bulgings of vascular walls, and retinal dot and blot hemorrhages. Hard exudates are another symptom of this phase of the disease. Such exudates are formed when Lp is leaking from the aneurysms. Subjects with these symptoms must be checked every nine to twelve months [124,125]. As non-proliferative diabetic retinopathy develops, hypoxia of the retina and alterations in circulation can enable serious lesions to be formed. More severe hemorrhages happen, and Intraretinal microvascular abnormalities, venous beadings and Cotton wool spots are typical for advanced phases of non-proliferative diabetic retinopathy [126-128]. In moderate non-proliferative diabetic retinopathy, subjects must be checked every four to six months, and in severe non-proliferative diabetic retinopathy, which involves ischemia and a high risk of proliferative diabetic retinopathy, the subjects must be referred to an ophthalmologist for immediate treatment [129,130].

Diabetic retinopathy develops to the Proliferative diabetic retinopathy, in which formation of new retinal vasculature presents a risk of ruptures, leading to pre-retinal hemorrhage. Such individuals have to be referred to an ophthalmologist to be treated, since there is a high risk of blindness. After the stage of new vessels formation, remission comes with the consequent formation of dense connective tissue and a risk of detachment of the retina [131,132].

To sum up, diabetic retinopathy is a MVC of type 2 diabetes which occurs often. If this condition is not monitored and managed, it will progress into a grave disease. Tight control, examinations by an ophthalmologist and management of risk factors are vital in diabetic retinopathy. Treatments which might abolish the complications of diabetic retinopathy in early phases are scarce, hereby further study is necessary [133].

Diabetic Neuropathy (DN)

Diabetic nerve diseases are pathological conditions that occur in subjects with DM and have various manifestations. This diagnosis is made in subjects with DM and peripheral neuropathy when other diagnoses have been excluded. This MVC of type 2 diabetes occurs often in approximately half of subjects with DM after ten years of living with the disorder [134]. Approximately twenty percent of the subjects with DM already have this complication when they are diagnosed. Although, almost half of the DM subjects with this complication do not show symptoms of it, hereby this MVC is frequently overlooked. When it is not noticed and managed appropriately, it can progress into Charcot arthropathy (diabetic foot), ulcers and a need for amputation [135-137].

A number of classifications were suggested for DN, depending on the anatomical location, prevalence, progression, physiology and properties. Usually, Peripheral DN (DPN) are classified into three groups: symmetric motor polyneuropathy, autonomic and somatic symptoms, focal and multi-focal DN, and combined forms. Recent studies divided peripheral DN into groups: typical peripheral DN, distal symmetric polyneuropathy, and non-typical versions (e.g., MNM, thoracic radiculopathy) [138,139].

Distal symmetric polyneuropathy is the most common form of the complications which constitutes seventy-five percent of all DN. It is a chronic length-dependent condition characterized by symmetry. It can be induced by high blood glucose levels together with CV risk factors [140-142]. No therapies for this condition presently exist that could abolish axonal degeneration and demyelinating of neural tissues, which emphasizes the necessity for early diagnosis which would allow to prevent progression of this MVC [143,144].

Intensive glucose control is believed to be the most important part of the prevention of this MVC. Although, different RCTs showed contradicting results on the distal symmetric polyneuropathy development. The first RCT performed in Japan confirmed that intensive glucose control directly correlated with positive results in context of DN. The same findings were reported in the Accord trial [145,146]. Although, The UK prospective diabetes study could not confirm beneficial impact of tight glucose control on DN. Furthermore, the Veterans affairs diabetes study showed that remarkable difference between glycated hemoglobin levels in intensive and in standard therapies did not lead to different results regarding occurrence of DN [147-149]. Analogously, the Anglo-Danish-Dutch study of intensive treatment in people with screen-detected diabetes in primary care trial involved 5.9 year-long observation and did not demonstrate any considerable differences in the results of two cohorts [150]. It is possible that the two cohorts reached similar levels of glycated hemoglobin by the end of the trial, and the observation period has not been prolonged enough to detect positive impacts. Except glucose control, alterations in life style also could help prevent development of DN. The University of Utah type 2 diabetes study involved subjects with no symptoms of DPN underwent a treatment that included exercise and consumption modifications. Density of Intra-Epidermal Neural Tissues (IENFD) in the lower limb was elevated in this cohort, and it was mildly reduced in the cohort receiving standard treatment. This implies that metabolism amelioration can drive dermal axons to regenerate [151-154].

Similar to other MVCs in type 2 diabetes, such subjects must be evaluated for distal symmetric polyneuropathy when they are diagnosed and then annually checked. NCS are believed to be the best assessment tool for this complication, although its applications in clinical settings are confined and preserved for subjects with non-typical symptoms evident during physical exam [155,156]. Diagnosis of distal symmetric polyneuropathy is mostly clinical.

Different neural tissues are involved in distal symmetric polyneuropathy which exhibit various symptoms. In small fibers, the most frequent manifestations are night pain and dysesthesia. There can also be such symptoms as allodynia and hyperalgesia. In large fibers, the most common symptoms are numbness and LOPS [157]. Small fibers are estimated by checking of sensitivity to temperature and pinprick. Large fibers are assessed by measuring sensitivity to vibration, kinesthesia, ankle reflex, sensitivity to light touch. The latter is assessed with application of 10g monofilament, an important instrument to predict risk of ulcers and need for amputation [158-160]. Toronto Consensus Panel (TCP) on DN conducted in 2009 showed that there are four groups of diagnosis certainty drawing on evident manifestations: Possible distal symmetric polyneuropathy, probable distal symmetric polyneuropathy, confirmed distal symmetric polyneuropathy, subclinical distal symmetric polyneuropathy [161,162]. A number of tools were suggested for the assessment of subjects with suspected distal symmetric polyneuropathy, that are mostly foot exam combined with questionnaire. Chronic care management and Intraepidermal nerve fiber density can also be useful for assessment of distal symmetric polyneuropathy. They were validated in clinical studies for evaluation of small fibers, although they have not yet been suggested for routine clinical assessment [163,164].

Distal symmetric polyneuropathy should be diagnosed after exclusion of other DPN etiologies. High alcohol consumption, high blood levels of urea, environmental factors, human immunodeficiency virus, thyroid disorders, paraproteinemia, connective tissue diseases, paraneoplastic neurological disorders and hereditary neural disorders can also induce DPN, and these factors must be excluded with thorough evaluation of family and health history [165,166]. Another study showed that distal symmetric polyneuropathy coincides with different causes of neural disorders in 53% of cases. Hand sensor aberrances in these subjects were detected more often which implies that this symptom might indicate the need to look for other causes of DPN. Most frequent additional symptom in these subjects was excessive alcohol consumption, use of drugs with neurotoxicity, B-12 deficit, and renal disorders [167,168]. Electrodiagnostics and neuraxis magnetic resonance imaging are not commonly applied due to their modest usefulness. Although, these patients should be referred to a neurologist if their symptoms indicate another etiology

apart from DN, e.g., fast development, motor neuropathy higher than sensor, non-symmetrical symptoms [169-171].

Diabetes frequently induces autonomic neural disorders with high variety. It has an impact on SNS and PSNS, resulting in inducing various symptoms, e.g., CV, GI, submotor and genitourinary [172].

CV autonomic neuropathy is a well-explored form of DM-associated autonomic neural disorder. It is characterized by impaired CV autonomic regulation, given that other reasons for the condition were excluded. It is present in about sixty percent of subjects with type 2 diabetes fifteen years following the diagnosis [173-175]. It is a major risk factor for CV death and Silent Myocardial Ischemia (SMI). The ACCORD study demonstrated that CV autonomic neuropathy elevated overall mortality by 1.55 to 2.14 times [176]. Tachycardia, aberrant BP regulating, inability to perform physical exercise and postural hypotension are typical signs of this condition, which though often does not show symptoms in early phases. Reduced Heart rate variability is the first sign of cardiovascular autonomic neuropathy, but as the disorder develops, tachycardia and inability to perform physical exercise, postural hypotension, Silent myocardial ischemia and left sided heart failure can progress [177,178].

Screening programs should be applied when a patient is diagnosed with type 2 diabetes, particularly in case of other diabetic MVCs, CV risk factors and high blood sugar present. CV autonomic neuropathy assessment involves Classification and regression trees, heart rate variability, postural HR, Valsalva maneuver HR, standing systolic BP and isometric exercise diastolic BP [179,180]. Time- and frequency domain heart rate variability testing are also good instruments for assessment of cardiovascular autonomic neuropathy. One aberrant cardiovascular autonomic reflex test is enough to diagnose cardiovascular autonomic neuropathy. To confirm the diagnosis, two or three tests should be present [181-183].

Sexual dysfunction

Sexual dysfunction in type 2 diabetes is frequently missed, while it greatly affects life quality. Development of Erectile Dysfunction (ED) in subjects with DM is intricate and involves vascular, neural and hormonal alterations due to diabetes. It represents a manifestation of autonomic DN, micro- and macro-angiopathy. Consistently, erectile

dysfunction can probably be used as a biomarker of DM-associated MVCs allowing early treatment [184-186].

Erectile dysfunction is a condition characterized by inability to achieve penile erection of enough durability and rigidity to perform sexual activity. This symptom has to persist for three months or longer to diagnose this disorder. Numerous researches showed that erectile dysfunction occurs in 35 to 90 percent of male patients with DM [187,188]. Such broad range can be explained by variations in methods and populational properties in the researches. Erectile dysfunction occurs three times more frequently in subjects with DM. During ten years after the DM diagnosis, more than a half of subjects with DM exhibit this complication. Another multi-center study involved subjects who were recently diagnosed with type 2 diabetes [189,190]. These subjects were assessed for erectile dysfunction which was observed in one third of the subjects, among which there were mild cases, mild to moderate cases, moderate cases and severe cases (19.4%, 15.4%, 10.4%, 21.6% respectively). These findings emphasize that erectile dysfunction can be a part of early phases of type 2 diabetes [191-193].

Connection between erectile dysfunction and CAD progression is well-known. Erectile dysfunction occurs three to five years prior to the coronary heart disease progression. Hereby, screening programs for erectile dysfunction can provide a possibility to prevent coronary heart disease, particularly in young subjects [194-196]. These discoveries apply to male patients with DM, since erectile dysfunction was validated as a predictor of coronary artery disease in subjects without evident cardiovascular disease. Erectile dysfunction is in correlation with DKD, DR and DN. However, presently there are no ways to apply it as a screening instrument, and more study is required [197,198].

Diagnosis of erectile dysfunction can be made applying questioning. IIEF questionnaire is the most common tool for such diagnostics. It involves fifteen items that explore four main aspects of sexual activity in male subjects: erectile functioning, orgasm functioning, sexual desire and sexual satisfaction. In addition, this can be a useful instrument for evaluation of response to therapy [199-201]. The next stage of evaluation of erectile dysfunction is a thorough review. Diabetes frequently coincides with accompanying disorders which are involved in the erectile dysfunction progression,

e.g., high BP, abnormal lipid levels, depression, CVD. Furthermore, alterations of such risk factors as adiposity, lack of exercise, tobacco use, alcohol abuse, can lead to positive results in context of erectile dysfunction [202-204]. In diabetes, occurrence of erectile dysfunction is related to the duration of diabetes, whereas reducing alcohol consumption, inactivity and rest had beneficial effect on erectile functioning. Anti-hypertension and anti-depression drugs can induce erectile dysfunction. Although, such medications are different, and ARBs can exhibit beneficial effect on erectile functioning, but other agents, e.g., Ca2+ antagonists and ACEI do not show such impact [205,206]. Diuretic medications and betablockers can induce erectile dysfunction. Physical exam might not help explain the cause of erectile dysfunction, although, particular signs can be useful for diagnostics, e.g., gynecomastia, changes in patterns of hair growth, absent DP or PT pulses. Subjects with erectile dysfunction have to be evaluated for hypogonadism with application of testosterone tests, since it is often observed in subjects with type 2 diabetes. Approximately twenty percent of male subjects diagnosed with type 2 diabetes have hypogonadism, and as diabetes develops occurrence rates of hypogonadism rise up to fifty percent [207,208].

Specific testing is not typically applied and are preserved for particular cases. Assessment of NPTR tests with application of Rigiscan gives important information on the condition of erectile neural and vascular mechanisms. Duplex ultrasound testing of cavernous arterial circulation following the intracavernosal administration of vasoactive agent can confirm the artery insufficiency. Penile arteries and veins may be investigated following the intracavernosal administration of vasoactive agent. In case of a corporal venoocclusive function impairment, DICC may be applied [209,210].

Female sexual dysfunction is a condition characterized by reduced sexual desire and arousal, painful sexual intercourse and impaired orgasmic function. Recent research demonstrated that female sexual dysfunction occurs more often in subjects with type 2 diabetes in comparison to the control group (OR:2.49). Previous studies showed that in subjects with type 2 diabetes occurrence rates of female sexual dysfunction are from 12 to 88 percent [211-213]. In female subjects with DM depression occurred more often, and body mass index has been the only one parameter that

was in correlation with female sexual dysfunction. Female sexual dysfunction can be assessed with application of FSFI, which involves six aspects: Sexual arousal, desire, orgasmic function, vaginal lubrication, intercourse satisfaction, and pain [214,215].

Development of female sexual dysfunction is yet to be fully explored. The risk factors for this condition are not yet identified. Although, female patients with female sexual dysfunction must be screened for type 2 diabetes, since they have higher risk of glucose changes (Table 2).

Table 2: Epidemiological insights on diabetic microvascular complications.

Complication	Prevalence	Associated risks	Screening recommendations
Diabetic Retinopathy (DR)	Affects ~25% of patients with Type 2 DM	Higher risk of cardiovascular disease	Ophthalmologic exams annually
		Vision impairment	
Diabetic Nephropathy (DKD)	Affects ~25% of DM patients	Major contributor to End-Stage Renal Disease (ESRD)	Annual urine albumin measurement
		Correlates with cardiovascular mortality	eGFR evaluation (annually)
Peripheral Neuropathy (PN)	Affects ~50% of DM patients after 10 years	Increased risk of foot ulcers, amputations	Annual foot exams
Autonomic Neuropathy (AN)	~60% of DM patients within 15 years of diagnosis	Silent Myocardial Ischemia (SMI)	Autonomic function testing as needed

Conclusion

In summary, the staggering rise in diabetes mellitus incidence and its associated microvascular complications underscores the urgent need for comprehensive strategies aimed at prevention, early detection, and effective management. Our review highlights that diabetic retinopathy, nephropathy, peripheral neuropathy, and autonomic neuropathy not only significantly affect patient quality of life but also increase cardiovascular risks. It is crucial to recognize the interconnected nature of these complications, as early identification of one may facilitate the diagnosis and management of others.

Adherence to tight glycemic control, regular screening, and targeted therapeutic interventions such as the use of angiotensin-converting enzyme inhibitors and statins can substantially mitigate the progression of MVCs. Furthermore, lifestyle modifications should be emphasized as integral components in the management of diabetes to enhance patient outcomes.

Ultimately, a multidisciplinary approach involving healthcare providers, patients, and caregivers is essential for optimizing care and empowering individuals with diabetes to manage their health effectively. Future research should aim at refining screening protocols and exploring emerging therapies that can further diminish the burden of microvascular complications. By prioritizing these strategies, we can hope to significantly improve prognosis and quality of life for millions affected by diabetes worldwide.

Funding

References

1. P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition, Diabetes Res Clin Pract, 157(2019):107843.

2. M.J. Hossain, M. Al-Mamun, M.R. Islam. Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused, Health Sci Rep, 7(2024):e2004.

3. M. Kropp, O. Golubnitschaja, A. Mazurakova, L. Koklesova, N. Sargheini, et al. Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications-risks and mitigation, EPMA J, 14(2023):21-42.

4. E. Dal Canto, A. Ceriello, L. Rydén, M. Ferrini, T.B. Hansen, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and microvascular complications, Eur J Prev Cardiol, 26(2019):25-32.

5. K. Khunti, H. Chen, J. Cid-Ruzafa, P. Fenici, M.B.

Gomes, et al. Glycaemic control in patients with type 2 diabetes initiating second-line therapy: Results from the global DISCOVER study programme, Diabetes Obes Metab, 22(2020):66-78.

6. T.R. Einarson, A. Acs, C. Ludwig. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017, Cardiovasc Diabetol, 17(2018):83.

7. L. Sacchetta, M. Chiriacò, L. Nesti, S. Leonetti, G. Forotti, et al. Synergistic effect of chronic kidney disease, neuropathy, and retinopathy on all-cause mortality in type 1 and type 2 diabetes: A 21-year longitudinal study, Cardiovasc Diabetol, 21(2022):233.

8. V. Natesan, S.J. Kim. Diabetic nephropathy-a review of risk factors, progression, mechanism, and dietary management, Biomol Ther, 29(2021):365-372.

9. J. Fang, C. Luo, D. Zhang, Q. He, L. Liu. Correlation between diabetic retinopathy and diabetic nephropathy: A two-sample Mendelian randomization study, Front Endocrinol, 14(2023):1265711.

10. H.E. Bays, P.R. Taub, E. Epstein, E.D. Michos, R.A. Ferraro, et al. Ten things to know about ten cardiovascular disease risk factors, Am J Prev Cardiol, 5(2021):100149.

11. P. Gourdy, F. Schiele, J.M. Halimi, S. Kownator, S. Hadjadj, et al. Atherosclerotic cardiovascular disease risk stratification and management in type 2 diabetes, Front Cardiovasc Med, 10(2023):1227769.

12. C.X. Ma, X.N. Ma, C.H. Guan. Cardiovascular disease in type 2 diabetes mellitus: Progress toward personalized management, Cardiovasc Diabetol, 21(2022):74.

13. S.I. Sherwani, H.A. Khan, A. Ekhzaimy, A. Masood, M.K. Sakharkar, et al. Significance of HbA1c test in diagnosis and prognosis of diabetic patients, Biomark Insights, 11(2016):95-104.

14. W.T. Cade. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting, Phys Ther, 88(2008):1322-1335.

15. J.R. Petrie, T.J. Guzik, R.M. Touyz. Diabetes, hypertension, and cardiovascular disease: Clinical insights and vascular mechanisms, Can J Cardiol, 34(2018):575-584.

16. V. Calcaterra, J.P. Winickoff, C. Klersy. Smoke exposure and cardio-metabolic profile in youth with type 1 diabetes, Diabetol Metab Syndr, 10(2018):53.

17. D.K. McGuire, R.P. Busui, J. Deanfield, S.E. Inzucchi, J.F.E. Mann, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial, Diabetes Obes Metab, 25(2023):1932-1941.

18. M. Marassi, G.P. Fadini. The cardio-renal-metabolic connection: A review of the evidence, Cardiovasc Diabetol, 22(2023):195.

19. R.M. Carey, P.K. Whelton. Evidence for the universal blood pressure goal of <130/80 mm Hg is strong, Hypertension, 76(2020):1384-1390.

20. L.C. Saiz, J. Gorricho, J. Garjón, M.C. Celaya, J. Erviti, et al. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease, Cochrane Database Syst Rev, 11(2022):CD010315.

21. M. Zhao, R. Wang, Y. Yu, M. Chang, S. Ma, et al. Efficacy and safety of angiotensin-converting enzyme inhibitor in combination with angiotensin-receptor blocker in chronic kidney disease, Front Pharmacol, 12(2021):638611.

22. S. Alshahrani. Renin-angiotensin-aldosterone pathway modulators in chronic kidney disease, Front Pharmacol, 14(2023):1101068.

23. H. Sawaf, G. Thomas, J.J. Taliercio, G. Nakhoul, T.J. Vachharajani, et al. Therapeutic advances in diabetic nephropathy, J Clin Med, 11(2022):378.

24. P. Sleight. The HOPE study (Heart Outcomes Prevention Evaluation), J Renin Angiotensin Aldosterone Syst, 1(2000):18-20.

25. S. Shahinfar, P.A. Lyle, Z. Zhang, W.F. Keane, B.M. Brenner. Losartan: Lessons learned from the RENAAL study, Expert Opin Pharmacother, 7(2006):623-630.

26. L.L. Herman, S.A. Padala, I. Ahmed. Angiotensin-converting enzyme inhibitors (ACEI), StatPearls, (2024).

27. B.T. Bateman, E. Patorno, R.J. Desai, E.W. Seely, H. Mogun, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations, Obstet Gynecol, 129(2017):174-184.

28. T.S. Huang, T. Wu, Y.D. Wu, X.H. Li, J. Tan, et al. Long-term statins administration exacerbates diabetic nephropathy via ectopic fat deposition in diabetic mice, Nat Commun, 14(2023):390.

29. J. Lv, C. Ren, Q. Hu. Effect of statins on early diabetic nephropathy: A meta-analysis, Ann Palliat Med, 10(2021):11548-11557.

30. Y. Kong, W. Feng, X. Zhao, P. Zhang, S. Li, et al. Statins ameliorate cholesterol-induced inflammation by inhibiting NLRP3 activation in the kidney, Theranostics, 10(2020):10415-10433.

31. T.S. Huang, T. Wu, Y.D. Wu, et al. Long-term statins administration exacerbates diabetic nephropathy via ectopic fat deposition, Nat Commun, 14(2023):390.

32. J.C. Ansquer, C. Foucher, P. Aubonnet, K. Le Malicot. Fibrates and microvascular complications in diabetes, Curr Pharm Des, 15(2009):537-552.

33. L.S. Weerasinghe, H.P. Dunn, A.T. Fung, G. Maberly, N.W. Cheung, et al. Diabetic retinopathy screening at the point of care, BMJ Open Diabetes Res Care, 11(2023):e003376.

34. A. Abou Taha, S. Dinesen, A.S. Vergmann, et al. Present and future screening programs for diabetic retinopathy: A narrative review, Int J Retin Vitr, 10(2024):14.

35. A.R. Elam, V.L. Tseng, T.M. Rodriguez, E.V. Mike, A.K. Warren, et al. Disparities in vision health and eye care, Ophthalmology, 129(2022):e89-e113.

36. E.A. Christofides, N. Desai. Optimal early diagnosis and monitoring of diabetic kidney disease, J Prim Care Community Health, 12(2021):21501327211003683.

37. O. Gheith, N. Farouk, N. Nampoory, M.A. Halim, T. Al-Otaibi. Diabetic kidney disease: Worldwide difference of prevalence and risk factors. J Nephropharmacol, 5(2015):49-56.

38. R.T. Varghese, I. Jialal. Diabetic nephropathy, StatPearls, (2024).

39. V. Natesan, S.J. Kim. Diabetic nephropathy-risk factors, progression, mechanism, and dietary management, Biomol Ther, 29(2021):365-372.

40. B.M. Scirica, O. Mosenzon, D.L. Bhatt, J.A. Udell, P.G. Steg, et al. Cardiovascular outcomes according to urinary albumin and kidney disease, JAMA Cardiol, 3(2018):155-163.

41. P.C. Pafundi, C. Garofalo, R. Galiero, S. Borrelli, A. Caturano, et al. Role of albuminuria in detecting cardio-renal risk in diabetic subjects, Diagnostics, 11(2021):290.

42. M.S. Khan, I. Shahid, S.D. Anker, G.C. Fonarow, M. Fudim, et al. Albuminuria and heart failure: JACC state-of-the-art review, J Am Coll Cardiol, 81(2023):270-282.

43. A.V. Poznyak, V.A. Orekhova, V.N. Sukhorukov, V.A. Khotina, M.A. Popov, et al. Atheroprotective aspects of heat shock proteins, Int J Mol Sci, 24(2023):11750.

44. I.H. de Boer, K. Khunti, T. Sadusky, K.R. Tuttle, J.J. Neumiller, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO), Diabetes Care, 45(2022):3075-3090.

45. R.I. Farah, M.Q. Al-Sabbagh, M.S. Momani. Diabetic kidney disease in patients with type 2 diabetes mellitus, BMC Nephrol, 22(2021):223.

46. N.M. Selby, M.W. Taal. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines, Diabetes Obes Metab, 22(2020):3-15.

47. R. Ravender, M.E. Roumelioti, D.W. Schmidt, M.L. Unruh, C. Argyropoulos. Chronic kidney disease in the older adult patient with diabetes, J Clin Med, 13(2024):348.

48. P.K. Dabla. Renal function in diabetic nephropathy, World J Diabetes, 1(2010):48-56.

49. K. Vijay, B.L. Neuen, E.V. Lerma. Heart failure in patients with diabetes and chronic kidney disease, Cardiorenal Med, 12(2022):1-10.

50. T.A. Dejenie, E.C. Abebe, M.A. Mengstie, M.A. Seid, N.A. Gebeyehu, et al. Dyslipidemia and serum cystatin C levels as biomarker of diabetic nephropathy, Front Endocrinol, 14(2023):1124367.

51. N.G. Nikiforov, T.V. Kirichenko, M.V. Kubekina, Y.S. Chegodaev, A.D. Zhuravlev, et al. Macrophages derived from LPS-stimulated monocytes from individuals with subclinical atherosclerosis were characterized by increased pro-inflammatory activity, Cytokine, 172(2023):156411.

52. D. Giavarina, D.N. Cruz, G. Soffiati, C. Ronco, Comparison of estimated Glomerular Filtration Rate (eGFR) using the MDRD and CKD-EPI equations for CKD screening in a large population, Clin Nephrol, 74(2010):358-363.

53. L. Tonneijck, M.H. Muskiet, M.M. Smits, E.J. van Bommel, H.J. Heerspink, et al. Glomerular hyperfiltration in diabetes: Mechanisms, clinical significance, and treatment, J Am Soc Nephrol, 28(2017):1023-1039.

54. M. Provenzano, L. Hu, C. Abenavoli, G. Cianciolo, G. Coppolino, et al. Estimated glomerular filtration rate in observational and interventional studies in chronic kidney disease, J Nephrol, 37(2024):573-586.

55. KDIGO CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease, Kidney Int, 105(2024):S117-S314.

56. C. Abenavoli, M. Provenzano, S.H. Ksiazek, L. Hu, V. Cuna, et al. Role of estimated glomerular filtration rate in clinical research: The never-ending matter, Rev Cardiovasc Med, 25(2024):1.

57. Y. Hayashi. Detection of lower albuminuria levels and early development of diabetic kidney disease using an artificial intelligence-based rule extraction approach, Diagnostics, 9(2019):133.

58. N. Younes, P.A. Cleary, M.W. Steffes, I.H. de Boer, M.E. Molitch, et al. Comparison of urinary albumin-creatinine ratio and albumin excretion rate in the DCCT/EDIC study, Clin J Am Soc Nephrol, 5(2010):1235-1242.

59. L. Ming, D. Wang, Y. Zhu. Association between urinary albumin-to-creatinine ratio within normal range and hypertension among adults in the United States, Clin Cardiol, 46(2023):622-631.

60. Y.J. Chou, C.C. Yang, S.J. Chang, S.S. Yang, Albuminuria is affected by urinary tract infection: A comparison between biochemical quantitative method and automatic urine analyzer, Diagnostics, 13(2023):3366.

61. T.K. Chen, D.H. Knicely, M.E. Grams. Chronic kidney disease diagnosis and management: A review, JAMA, 322(2019):1294-1304.

62. C. García-Carro, A. Vergara, S. Bermejo. How to assess diabetic kidney disease progression? From albuminuria to GFR, J Clin Med, 10(2021):2505.

63. A. Chagnac, A.N. Friedman. Measuring albuminuria in individuals with obesity: Pitfalls of the urinary albumin-creatinine ratio, Kidney Med, 6(2024):100804.

64. M. Basu, S. Pulai, S. Neogi, N.P. Bhattacharyya, S. Sengupta, et al. Prevalence of non-diabetic kidney disease and inability of clinical predictors to differentiate it from diabetic kidney disease, BMJ Open Diabetes Res Care, 10(2022):e003058.

65. R.I. Farah, M.Q. Al-Sabbagh, M.S. Momani, A. Albtoosh, M. Arabiat, et al. Diabetic kidney disease in patients with type 2 diabetes mellitus, BMC Nephrol, 22(2021):223.

66. K.S. Wan, N.N. Hairi, F. Mustapha, M.F.M. Yusoff, H.M. Rifin, et al. Prevalence of diabetic kidney disease and associated factors among patients with type 2 diabetes in a multi-ethnic Asian country, Sci Rep, 14(2024):7074.

67. A.V. Poznyak, V.N. Sukhorukov, M.A. Popov, Y.S. Chegodaev, A.Y. Postnov, et al. Mechanisms of the Wnt pathways as a potential target pathway in atherosclerosis, J Lipid Atheroscler, 12(2023):223-236.

68. C. Plattner, S. Sallaberger, J.P. Bohn, C. Zavadil, F. Keller, et al. Rationale and design of the Innsbruck diabetic kidney disease cohort, Clin Kidney J, 17(2024):sfae109.

69. R.C. Stanton, Clinical challenges in diagnosis and management of diabetic kidney disease, Am J Kidney Dis, 63(2014):S3-S21.

70. E. Kardalas, A. Paikopoulou, D.A. Vassiliadi, D. Kounatidis, N.G. Vallianou, et al. The role of kidney biopsy in deciphering diabetic versus non-diabetic origin of kidney disease among patients with type 2 diabetes mellitus and nephrotic range proteinuria: A retrospective study, Metabol Open, 23(2024):100313.

71. C.C. Hung, H.Y. Lin, D.Y. Hwang. Diabetic retinopathy and clinical parameters favoring the presence of diabetic nephropathy could predict renal outcome in patients with diabetic kidney disease, Sci Rep, 7(2017):1236.

72. L. Fabre, É.B. Rangel. Age-related markers and predictors of diabetic kidney disease progression in type 2 diabetes patients: A retrospective cohort study, Ther Adv Endocrinol Metab, 15(2024):20420188241242947.

73. Q. Wang, H. Cheng, S. Jiang, L. Zhang, X. Liu, et al. The relationship between diabetic retinopathy and diabetic nephropathy in type 2 diabetes, Front Endocrinol, 15(2024):1292412.

74. Y. Sun, Y. Ren, P. Lan, X. Yu, J. Feng, et al. Clinico-pathological features of diabetic and non-diabetic renal diseases in type 2 diabetic patients: A retrospective study from a 10-year experience in a single center, Int Urol Nephrol, 55(2023):2303-2312.

75. S. Scilletta, M. Di Marco, N. Miano, A. Filippello, S. Di Mauro, et al. Update on diabetic kidney disease: Focus on non-albuminuric DKD and cardiovascular risk, Biomolecules, 13(2023):752.

76. H.J. Kim, S.S. Kim, S.H. Song. Glomerular filtration rate as a kidney outcome of diabetic kidney disease: a focus on new antidiabetic drugs, Korean J Intern Med, 37(2022):502-519.

77. A. Mazzieri, F. Porcellati, F. Timio, G. Reboldi. Molecular targets of novel therapeutics for diabetic kidney disease: A new era of nephroprotection, Int J Mol Sci, 25(2024):3969.

78. A.V. Poznyak, D.A. Kashirskikh, A.Y. Postnov, M.A. Popovet, V.N. Sukhorukov, et al. Sialic acid as the potential link between lipid metabolism and inflammation in the pathogenesis of atherosclerosis, Braz J Med Biol Res, 56(2023):e12972.

79. J. Coresh, H.J.L. Heerspink, Y. Sang, K. Matsushita, J. Arnlov, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: An individual participant-level consortium meta-analysis of observational studies, Lancet Diabetes Endocrinol, 7(2019):115-127.

80. N.M. Selby, M.W. Taal, An updated overview of diabetic nephropathy, Diabetes Obes Metab, 22(2020):3-15.

81. P. Gæde, J. Oellgaard, B. Carstensen, P. Rossing, H.L. Andersen, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial, Diabetologia, 59(2016):2298-2307.

82. N. Al-Waili, H. Al-Waili, T. Al-Waili, K. Salom. Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials, Redox Rep, 22(2017):99-118.

83. Y.C. Lin, Y.H. Chang, S.Y. Yang, K.D. Wu, T.S. Chu, et al. Update of pathophysiology and management of diabetic kidney disease, J Formos Med Assoc, 117(2018):662-675.

84. X.C. Zeng, Y. Tian, X.M. Liang, X. Wu, C. Yao, et al. SGLT2 inhibitors relieve proteinuria in diabetic nephropathy, Diabetol Metab Syndr, 16(2024):46.

85. A.I. Adler, R.L. Coleman, J. Leal, W.N. Whiteley, P. Clarke, et al. Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91), Lancet, 404(2024):145-155.

86. G. Pugliese, A. Solini, E. Bonora, C. Fondelli, E. Orsi, et al. Chronic kidney disease in type 2 diabetes: Lessons from the RIACE study, Nutr Metab Cardiovasc Dis, 24(2014):815-822.

87. Y.M. Hsieh, W.J. Lee, W.H. Sheu, Y. Li, S. Lin, et al. Inpatient screening for albuminuria and retinopathy to predict long-term mortality in type 2 diabetic patients: A retrospective cohort study, Diabetol Metab Syndr, 9(2017):29.

88. C. Xue, K. Chen, Z. Gao, T. Bao, L. Dong, et al. Common mechanisms underlying diabetic vascular complications: Focus on the interaction of metabolic disorders, immuno-inflammation, and endothelial dysfunction, Cell Commun Signal, 21(2023):298.

89. M. Thomas, M. Brownlee, K. Susztak, et al. Diabetic kidney disease, Nat Rev Dis Primers, 1(2015):15018.

90. F. Persson, P. Rossing, Diagnosis of diabetic kidney disease, Kidney Int Suppl, 8(2018):2-7.

91. E. Kardalas, A. Paikopoulou, D.A. Vassiliadi, D. Kounatidis, N.G. Vallianou, et al. The role of kidney biopsy in deciphering diabetic versus non-diabetic origin of kidney disease among patients with type 2 diabetes mellitus and nephrotic range proteinuria: A retrospective study, Metabol Open, 23(2024):100313.

92. U.V. Shukla, K. Tripathy. Diabetic retinopathy, StatPearls, (2024).

93. R. Lee, T.Y. Wong, C. Sabanayagam, Epidemiology of diabetic retinopathy and related vision loss, Eye Vis, 2(2015):17.

94. W.M. Amoaku, F. Ghanchi, C. Bailey, S. Banerjee, S. Banerjee, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group, Eye, 34(2020):1-51.

95. Z. Yang, T.E. Tan, Y. Shao, T.Y. Wong, X. Li, et al. Classification of diabetic retinopathy: Past, present and future, Front Endocrinol, 13(2022):1079217.

96. Z. Yang, T.E. Tan, Y. Shao, T.Y. Wong, X. Li, et al. Classification of diabetic retinopathy: Past, present and future, Front Endocrinol (Lausanne), 13(2022):1079217.

97. S.K. Lynch, M.D. Abràmoff. Diabetic retinopathy is a neurodegenerative disorder, Vision Res, 139(2017):101-107.

98. A.V. Blagov, V.N. Sukhorukov, S. Guo, D. Zhang, M.A. Popov, et al. Impaired mitochondrial function in T-lymphocytes, Cells, 12(2023):1072.

99. T.E. Tan, T.Y. Wong. Diabetic retinopathy: Looking forward to 2030, Front Endocrinol, 13(2023):1077669.

100. S.D. Solomon, E. Chew, E.J. Duh, L. Sobrin, J.K. Sun, et al. Diabetic retinopathy: A position statement by the American Diabetes Association, Diabetes Care, 40(2017):412-418.

101. R. Lee, T.Y. Wong, C. Sabanayagam. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss, Eye Vis, 2(2015):17.

102. J.B. Vasilijević, I.M. Kovačević, Z.M. Bukumirić, G.D. Marić, N.A. Slijepčević, et al. Vision-related quality of life and treatment satisfaction following panretinal Photocoagulation in diabetic retinopathy-A panel study, Medicina, 58(2022):1741.

103. L. Denadai, V. Mozetic, R.A. Moore. Pain control during panretinal photocoagulation for diabetic retinopathy, Cochrane Database Syst Rev, 2022(2022):CD014927.

104. B. Corcóstegui, S. Durán, M.O. González-Albarrán, C. Hernández, J.M.R. Moreno, et al. Update on diagnosis and treatment of diabetic retinopathy: A consensus guideline of the working group of ocular health (Spanish Society of Diabetes and Spanish Vitreous and Retina Society), J Ophthalmol, 2017(2017):8234186.

105. T.A. Bahr, S.J. Bakri. Update on the management of diabetic retinopathy: Anti-VEGF agents for prevention of complications, Life, 13(2023):1098.

106. Z. Yang, T.E. Tan, Y. Shao, T.Y. Wong, X. Li, et al. Classification of diabetic retinopathy: Past, present and future, Front Endocrinol, 13(2022):1079217.

107. A.N. Orekhov, V.I. Summerhill, V.A. Khotina, M.A. Popov, J.K. Uzokov, et al. Role of mitochondria in the chronification of inflammation: Focus on dysfunctional mitophagy and mitochondrial DNA mutations, Gene Expr, 22(2023):329-344.

108. E.Y. Chew, M.D. Davis, R.P. Danis, J.F. Lovato, L.H. Perdue, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, Ophthalmology, 121(2014):2443-2451.

109. J.E. Knickelbein, A.B. Abbott, E.Y. Chew. Fenofibrate and diabetic retinopathy, Curr Diab Rep, 16(2016):90.

110. D. Preiss, J. Logue, E. Sammons, M. Zayed, J. Emberson, et al. Effect of fenofibrate on progression of diabetic retinopathy, NEJM Evid, 3(2024):EVIDoa2400179.

111. R. Raman, K. Ramasamy, R. Rajalakshmi, S. Sivaprasad, S. Natarajan, et al. Diabetic retinopathy screening guidelines in india: all india ophthalmological society diabetic retinopathy task force and Vitreoretinal Society of India Consensus Statement, Indian J Ophthalmol, 69(2021):678-688.

112. 112. N.M. Alali, A. Albazei, H.M. Alotaibi, A. M. Almohammadi, E. K. Alsirhani, et al. Diabetic retinopathy and eye screening: Diabetic patients standpoint, their practice, and barriers; A cross-sectional study, J Clin Med, 11(2022):6351.

113. N.V. Nguyen, E.M. Vigil, M. Hassan, M.S. Halim, S.C. Baluyot, et al. Comparison of montage with conventional stereoscopic photographs for DR severity, Int J Retina Vitreous, 5(2019):51.

114. R.F. Spaide, J.G. Fujimoto, N.K. Waheed, S.R. Sadda, G. Staurenghi, et al. Optical coherence tomography angiography, Prog Retin Eye Res, 64(2018):1-55.

115. S. Muchuchuti, S. Viriri. Retinal disease detection using deep learning techniques: A comprehensive review, J Imaging, 9(2023):84.

116. L.J. Coan, B.M. Williams, V.K. Adithya, S. Upadhyaya, A. Alkafri, et al. Automatic detection of glaucoma via fundus imaging and artificial intelligence, Surv Ophthalmol, 68(2023):17-41.

117. S.D. Solomon, E. Chew, E.J. Duh, J.K. Sun, B.L. VanderBeek, et al. Diabetic retinopathy: A position statement by the American Diabetes Association, Diabetes Care, 40(2017):412-418.

118. L. Wu, P. Fernandez-Loaiza, J. Sauma, E.H. Bogantes, M. Masis, et al. Classification of diabetic retinopathy and diabetic macular edema, World J Diabetes, 4(2013):290-294.

119. S.R. Cohen, T.W. Gardner, Diabetic retinopathy and diabetic macular edema, Dev Ophthalmol, 55(2016):137-146.

120. F.C. Gundogan, U. Yolcu, F. Akay, A. Ilhan, G. Ozge, et al. Diabetic macular edema, Pak J Med Sci, 32(2016):505-510.

121. W. Wang, A.C.Y. Lo, Diabetic retinopathy: Pathophysiology and treatments, Int J Mol Sci, 19(2018):1816.

122. T.Y. Wong, C.M. Cheung, M. Larsen, S. Sharma, R. Simó, et al. Diabetic retinopathy, Nat Rev Dis Primers, 2(2016):16012.

123. W.M. Amoaku, F. Ghanchi, C. Bailey, S. Banerjee, S. Banerjee, et al. Diabetic retinopathy and diabetic macular oedema pathways and management, Eye, 34(2020):1-51.

124. A.N. Kollias, M.W. Ulbig. Diabetic retinopathy: Early diagnosis and effective treatment, Dtsch Arztebl Int, 107(2010):75-83.

125. A.A. Alghadyan. Diabetic retinopathy-an update, Saudi J Ophthalmol, 25(2011):99-111.

126. D. An, E. Chandrasekera, D.Y. Yu, C. Balaratnasingam. Non-proliferative diabetic retinopathy and peripapillary capillary alterations, Invest Ophthalmol Vis Sci, 61(2020):39.

127. W.M. Amoaku, F. Ghanchi, C. Bailey, S. Banerjee, S. Banerjee, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group, Eye, 34(2020):1-51.

128. E.J. Duh, J.K. Sun, A.W. Stitt. Diabetic retinopathy: Mechanisms and treatment strategies, JCI Insight, 2(2017):e93751.

129. L.A. Everett, Y.M. Paulus. Laser therapy in diabetic retinopathy and diabetic macular edema, Curr Diab Rep, 21(2021):35.

130. Y. Yonekawa, Y.S. Modi, L.A. Kim, D. Skondra, J.E. Kim, et al. American Society of Retina Specialists Clinical Practice guidelines on the management of nonproliferative and proliferative diabetic retinopathy without diabetic macular edema, J Vitreoretin Dis, 4(2020):125-135.

131. G.B. Arden, D.J. Ramsey. Diabetic retinopathy and a novel treatment based on rod photoreceptors, Webvision, (2015).

132. A.A. Alghadyan, Diabetic retinopathy-an update, Saudi J Ophthalmol, 25(2011):99-111.

133. M.M. Nentwich, M.W. Ulbig. Diabetic retinopathy: Ocular complications of diabetes mellitus, World J Diabetes, 6(2015):489-499.

134. V. Bansal, J. Kalita, U.K. Misra, Diabetic neuropathy, Postgrad Med J, 82(2006):95-100.

135. B. Stancu, T. Ilyés, M. Farcas, H.F. Coman, B.A. Chiș, et al. Diabetic foot complications: A retrospective cohort study, Int J Environ Res Public Health, 20(2022):187.

136. C. Gooday, F. Game, J. Woodburn, F. Poland, E. Sims, et al. A randomised feasibility study of serial magnetic resonance imaging to reduce treatment times in Charcot Neuroarthropathy In People With Diabetes (CADOM): A protocol, Pilot Feasibility Stud, 6(2020):85.

137. E. Gouveri, N. Papanas. Charcot osteoarthropathy in diabetes: A brief review with an emphasis on clinical practice, World J Diabetes, 2(2011):59-65.

138. H. Yang, G. Sloan, Y. Ye, S. Wang, B. Duan, et al. New perspective in diabetic neuropathy: From the Periphery to the Brain, a Call for Early Detection, and Precision Medicine, Front Endocrinol, 10(2020):929.

139. S. Smith, P. Normahani, T. Lane, et al. Pathogenesis of distal symmetrical polyneuropathy in diabetes, Life, 12(2022):1074.

140. V. Maeda-Gutiérrez, C.E. Galván-Tejada, M. Cruz, A.V. Salgado, et al. Distal symmetric polyneuropathy identification using random forest, Healthcare, 9(2021):138.

141. A. Anandhanarayanan, K. Teh, M. Goonoo. Diabetic neuropathies, Endotext, (2022).

142. Z.Z. Chong, D.L. Menkes, N. Souayah. Targeting neuroinflammation in diabetic polyneuropathy, Drug Discov Today, 29(2024):104087.

143. M. Errede, T. Annese, V. Petrosino, G. Longo, F. Girolamo, et al. Microglia-derived CCL2 in neocortex neuroinflammation, Fluids Barriers CNS, 19(2022):68.

144. Peripheral Nerve Society, 2017 peripheral nerve society meeting, J Peripher Nerv Syst, 22(2017):226-414.

145. J. Poonoosamy, P. Lopes, P. Huret, R. Dardari, A. Penfornis, et al. Impact of intensive glycemic treatment on diabetes complications, Pharmaceutics, 15(2023):1791.

146. L. Ang, M. Jaiswal, C. Martin. Glucose control and diabetic neuropathy, Curr Diab Rep, 14(2014):528.

147. J.S. Skyler, R. Bergenstal, R.O. Bonow, J. Buse, P. Deedwania, et al. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA diabetes trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association, Diabetes Care, 32(2009):187-192.

148. T. Funamizu, H. Iwata, Y. Nishida, K. Miyosawa, S. Doi, et al. Increased risk of cardiovascular mortality by strict glycemic control (pre-procedural HbA1c < 6.5%) in Japanese medically-treated diabetic patients following percutaneous coronary intervention: A 10-year follow-up study, Cardiovasc Diabetol, 19(2020):21.

149. K. Umanath, J.B. Lewis. Update on diabetic nephropathy, Am J Kidney Dis, 71(2018):884-895.

150. N.R. Waugh, D. Shyangdan, S. Taylor-Phillips. Screening for type 2 diabetes, Health Technol Assess, 17(2013):35.

151. A.P.D.B. Batalha, I.C. Ponciano, G. Chaves, D.C. Felício, R.R. Britto, et al. Behavior change interventions in patients with type 2 diabetes: a systematic review of the effects on self-management and A1c, J Diabetes Metab Disord, 20(2021):1815-1836.

152. M.J. Davies, V.R. Aroda, B.S. Collins, R.A. Gabbay, J. Green, et al. Management of hyperglycaemia in type 2 diabetes, 2022: A consensus report by the ADA and EASD, Diabetologia, 65(2022):1925-1966.

153. S.M. Chen, F.C. Shen, J.F. Chen, W.D. Chang, N.J. Chang, et al. Effects of resistance exercise on glycated hemoglobin and functional performance in older patients with diabetes and knee osteoarthritis, Int J Environ Res Public Health, 17(2019):224.

154. E. Afsaneh, A. Sharifdini, H. Ghazzaghi, M.Z. Ghobadi, et al. Recent applications of machine learning and deep learning models in the prediction, diagnosis, and management of diabetes, Diabetol Metab Syndr, 14(2022):196.

155. J. Kasznicki. Advances in the diagnosis and management of diabetic distal symmetric polyneuropathy, Arch Med Sci, 10(2014):345-354.

156. J. Carmichael, H. Fadavi, F. Ishibashi, A.C. Shore, M. Tavakoli, et al. Advances in screening, early diagnosis and accurate staging of diabetic neuropathy, Front Endocrinol, 12(2021):671257.

157. A.K. Schreiber, C.F. Nones, R.C. Reis, J.G. Chichorro, J.M. Cunha, et al. Diabetic neuropathic pain: Physiopathology and treatment, World J Diabetes, 6(2015):432-444.

158. R. Galiero, A. Caturano, E. Vetrano, D. Beccia, C. Brin, et al. Peripheral neuropathy in diabetes mellitus: Pathogenetic mechanisms and diagnostic options, Int J Mol Sci, 24(2023):3554.

159. S. Baraz, K. Zarea, H.B. Shahbazian. Comparison of the accuracy of monofilament testing at various points of feet in peripheral diabetic neuropathy screening, J Diabetes Metab Disord, 13(2014):19.

160. V. Aithal, S. Bhat. Semmes Weinstein monofilament test for detection of diabetic peripheral neuropathy: sensitivity and specificity, Egypt J Neurol Psychiatry Neurosurg, 60(2024):6.

161. T.S. Jensen, P. Karlsson, S.S. Gylfadottir, S.T. Andersen, D.L. Bennett, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management, Brain, 144(2021):1632-1645.

162. P.J. Dyck, J.W. Albers, H. Andersen, J.C. Arezzo, G.J. Biessels, et al. Diabetic polyneuropathies: Update on research definition and diagnostic criteria, Diabetes Metab Res Rev, 27(2011):620-628.

163. J. Carmichael, H. Fadavi, F. Ishibashi, A.C. Shore, M. Tavakoli, et al. Advances in screening, early diagnosis and accurate staging of diabetic neuropathy, Front Endocrinol, 12(2021):671257.

164. T.S. Jensen, P. Karlsson, S.S. Gylfadottir, S.T. Andersen, D.L. Bennett, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management, Brain, 144(2021):1632-1645.

165. B.C. Callaghan, R.S. Price, E.L. Feldman. Distal symmetric polyneuropathy: A review, JAMA, 314(2015):2172-2181.

166. B.C. Callaghan, K. Kerber, A.L. Smith. Evaluation of distal symmetric polyneuropathy: A physician survey, Arch Neurol, 69(2012):339-345.

167. V. Maeda-Gutiérrez, C.E. Galván-Tejada, A.V. Salgad.o M. Cruz, J.I. Galván-Tejada, et al. Distal Symmetric Polyneuropathy Identification in Type 2 Diabetes Subjects: A Random Forest Approach, Healthcare, 9(2021):138.

168. D. Menon, H.D. Katzberg, V. Bril. Treatment approaches for atypical CIDP, Front Neurol, 12(2021):653734.

169. J. Kollmer, M. Bendszus. Magnetic resonance neurography: Improved diagnosis of peripheral neuropathies, Neurotherapeutics, 18(2021):2368-2383.

170. E.G. Hasankhani, F. Omidi-Kashani. MRI versus electrophysiologic tests in radicular pain diagnosis, ISRN Neurosci, 2013(2013):952570.

171. C. Yen, C.L. Lin, M.C. Chiang. Exploring the frontiers of neuroimaging: a review of recent advances in understanding brain functioning and disorders, Life, 13(2023):1472.

172. A.I. Vinik, T. Erbas, C.M. Casellini. Diabetic cardiac autonomic neuropathy and cardiovascular disease, J Diabetes Investig, 4(2013):4-18.

173. V.A. Serhiyenko, A.A. Serhiyenko. Cardiac autonomic neuropathy: Diagnosis and treatment, World J Diabetes, 9(2018):1-24.

174. K. Nabrdalik, K. Irlik, Y. Meng, H. Kwiendacz, J. Piaśnik, et al. Artificial intelligence-based classification of cardiac autonomic neuropathy from retinal fundus images in patients with diabetes: The silesia diabetes heart study, Cardiovasc Diabetol, 23(2024):296.

175. G. Dimitropoulos, A.A. Tahrani, M.J. Stevens. Cardiac autonomic neuropathy in patients with diabetes mellitus, World J Diabetes, 5(2014):17-39.

176. H.N. Ginsberg. ACCORD lipid trial subgroup analyses, Diabetes Care, 34(2011):S107-S108.

177. J.M. Stewart. Common syndromes of orthostatic intolerance, Pediatrics, 131(2013):968-980.

178. C. Rukadikar, A. Rukadikar, S. Kishore. A review on autonomic functional assessment in diabetic patients, Cureus, 15(2023):e34598.

179. B.K. Koo. Screening of autonomic neuropathy in patients with type 2 diabetes, Diabetes Metab J, 38(2014):346-348.

180. S. Agashe, S. Petak. Cardiac autonomic neuropathy in diabetes mellitus, Methodist Debakey Cardiovasc J, 14(2018):251-256.

181. A.H. Zinglersen, K.K. Iversen, H.C.B. Leffers, E. Laugesen, J. Fleischer, et al. Characteristics of cardiovascular autonomic dysfunction and association with quality of life in patients with systemic lupus erythematosus, Lupus Sci Med, 8(2021):e000507.

182. Y.B. Atala, M.R. De Matos, D.E. Zantut-Wittmann, A.R. Castillo, D.P. Santos-Bezerra, et al. Cardiovascular autonomic reflex tests and 7 heart rate variability indices for early diagnosis of cardiovascular autonomic neuropathy in type 2 diabetes individuals, Curr Diabetes Rev, 18(2022):e270821195908.

183. J. Hayano, E. Yuda. Pitfalls of assessment of autonomic function by heart rate variability, J Physiol Anthropol, 38(2019):3.

184. A. Bahar, F. Elyasi, M. Moosazadeh, G. Afradi, Z. Kashi, et al. Sexual dysfunction in men with type II diabetes, Caspian J Intern Med, 11(2020):295-303.

185. G. Defeudis, R. Mazzilli, M. Tenuta, G. Rossini, V. Zamponi, et al. Erectile dysfunction and diabetes: A melting pot of circumstances and treatments, Diabetes Metab Res Rev, 38(2022):e3494.

186. D. Dilixiati, A. Waili, A. Tuerxunmaimaiti. Risk factors for erectile dysfunction in diabetes mellitus: a systematic review and meta-analysis, Front Endocrinol, 15(2024):1368079.

187. S.W. Leslie, T. Sooriyamoorthy. Erectile dysfunction,

StatPearls, (2024).

188. A.W. Shindel, T.F. Lue. Medical and surgical therapy of erectile dysfunction, Endotext, (2022).

189. G. Defeudis, R. Mazzilli, M. Tenuta, G. Rossini, V. Zamponi, et al. Erectile dysfunction and diabetes: A melting pot of circumstances and treatments, Diabetes Metab Res Rev, 38(2022):e3494.

190. G. Defeudis, R. Mazzilli, A.M. Di Tommaso, V. Zamponi, F. Carlomagno, et al. Effects of diet and antihyperglycemic drugs on erectile dysfunction: A systematic review, Andrology, 11(2023):282-294.

191. V. Zamponi, G. Defeudis, F. Federico, A. Faggiano, R. Mazzilli , et al. Erectile dysfunction severity: The role of glycometabolic compensation and antihyperglycemic drugs, J Clin Med, 11(2022):7214.

192. P. Calleja Hermosa, F. Campos-Juanatey, R. Varea Malo. Sexual function after anterior urethroplasty, Transl Androl Urol, 10(2021):2554-2573.

193. Y. Liu, X. Hu, M. Xiong. Association of BMI with erectile dysfunction: A cross-sectional study of men from an andrology clinic, Front Endocrinol, 14(2023):1135024.

194. H. Hamur, H. Duman, E. Keskin, Z. Kucuksu. Erectile dysfunction and coronary artery disease, Int J Clin Exp Med, 8(2015):21295-21302.

195. Q. Li, Q. Long, B. Ren, S. Bing. Causal association between cardiovascular disease and erectile dysfunction: Mendelian randomization, Front Cardiovasc Med, 10(2023):1094330.

196. E.S. Polomski, M.L. Antoni, J.W. Jukema, J.R. Kroep. Nuclear medicine imaging of cardiotoxicity, Semin Nucl Med, 52(2022):597-610.

197. S.C. Dsouza, O. Rahman. Erectile dysfunction and coronary artery disease in type 2 diabetes, Ghana Med J, 57(2023):43-48.

198. S.J. Turek, S.M. Hastings, J.K. Sun, G.L. King. Sexual dysfunction as cardiovascular marker in type 1 diabetes, Diabetes Care, 36(2013):3222–3226.

199. M.D. González-Gutiérrez, Á. López-Garrido, I. Cortés-Pérez, E. Obrero-Gaitan. Effects of non-invasive radiofrequency diathermy in pelvic floor disorders, Medicina, 58(2022):437.

200. F.A. Yafi, L. Jenkins, M. Albersen, G. Corona. Erectile dysfunction, Nat Rev Dis Primers, 2(2016):16003.

201. S. De Vincentis, G. Tartaro, V. Rochira, D. Santi. HIV and sexual dysfunction in men, J Clin Med, 10(2021):1088.

202. G. Defeudis, R. Mazzilli, M. Tenuta, G Rossini. Erectile dysfunction and diabetes: A melting pot of circumstances and treatments, Diabetes Metab Res Rev, 38(2022):e3494.

203. D. Dilixiati, A. Waili, A. Tuerxunmaimaiti, L. Tao. Risk factors for erectile dysfunction in diabetes mellitus: A systematic review and meta-analysis, Front Endocrinol, 15(2024):1368079.

204. B.K. Pedersen, B. Saltin. Exercise as medicine-evidence for prescribing exercise as therapy in 26 different chronic diseases, Scand J Med Sci Sports, 25(2015):1-72.

205. M.C. Carella, C. Forleo, A. Stanca, E. Carulli. Heart failure and erectile dysfunction: a review of the current evidence and clinical implications, Curr Heart Fail Rep, 20(2023):530-541.

206. P.K. Whelton, R.M. Carey, W.S. Aronow. ACC/AHA guideline for hypertension management, Hypertension, 71(2018):1269-1324.

207. E. Kaplan-Marans, A. Sandozi, M. Martinez, J. Lee. Medications most commonly associated with erectile dysfunction: evaluation of the Food and Drug Administration National Pharmacovigilance Database, Sex Med, 10(2022):100543.

208. C. Zhao, J.L. Feng, S. Deng, X.P Wang. Genetically predicted hypertension, antihypertensive drugs, and risk of erectile dysfunction: A Mendelian randomization study, Front Cardiovasc Med, 10(2023):1157467.

209. Chung E. Contemporary and novel imaging studies for the evaluation of erectile dysfunction, Med Sci, 7(2019):87.

210. S.W. Leslie, T. Sooriyamoorthy. Erectile dysfunction, StatPearls, (2024).

211. M.I. Maiorino, G. Bellastella, K. Diabetes and sexual dysfunction: current perspectives, Diabetes Metab Syndr Obes, 7(2014):95-105.

212. F. Elyasi, Z. Kashi, B. Tasfieh, A. Bahar. Sexual dysfunction in women with type 2 diabetes mellitus, Iran J Med Sci, 40(2015):206-213.

213. E. Bąk, C. Marcisz, S. Krzemińska, et al. Relationships of sexual dysfunction with depression and acceptance of illness in women and men with type 2 diabetes mellitus, Int J Environ Res Public Health, 14(2017):1073.

214. E. Cichocka, M. Jagusiewicz, J. Gumprecht. Sexual dysfunction in young women with type 1 diabetes, Int J Environ Res Public Health, 17(2020):4468.

215. K. Stechova, L. Mastikova, K. Urbaniec, M. Vanis, S. Hylmarova, et al. Sexual dysfunction in women treated for type 1 diabetes and the impact of coexisting thyroid disease, Sex Med, 7(2019):217-226.