Omentin-1 and microvascular Complications of Type 2 Diabetes

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Abstract:

Plasma omentin-1 is a relatively new biomarker that has anti-diabetogenic and its level is inversely related with insulin resistance and diabetes mellitus, thus, increasing the risk of diabetic complications.

Keywords: Omentin-1, microvascular Complications, Diabetes.

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Introduction:

Chronic intracellular hyperglycemia and genetic predisposition eventually affect the microvasculature, leading to complications mainly from the kidneys, the eyes and the nervous system. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD), diabetic retinopathy (DR) is the main cause of blindness in the developed world, diabetic neuropathy is the major risk factor for amputation and foot ulceration and finally, sexual dysfunction disproportionately affects diabetic patients ***(1)***

High clinical suspicion and early recognition of diabetic microvascular complications are mandatory, as it is estimated that up to 25% of newly diagnosed patients with T2DM have already developed one or more complications of DM **(2).**

1) Nephropathy (Diabetic Kidney Disease)

Diabetic nephropathy (DN), a chronic complication of diabetes, is the leading cause of end-stage renal disease (ESRD) in the western world. The complication is characterized by both albuminuria and progressive renal function loss **(3).** These functional alterations are primarily due to both excessive accumulation of extracellular matrix in the mesangium and podocyte damage **(4).**

<u>Pathogenesis of Diabetic Nephropathy</u>

Podocytes form the glomerular filtration barrier together with the glomerular basement membrane and the fenestrated glomerular endothelium **(5).** The junction between adjacent podocyte foot processes (FP), named slit diaphragm, is the major restriction site to protein filtration in the

glomeruli. Downregulation of slit diaphragm proteins, such as NPHS1/Nephrin and NPHS2/Podocin, FP effacement, and podocyte apoptosis are early features of DN and major determinants in the development of albuminuria **(6).**

Both hyperglycemia and Advanced glycated end products play an important role in the pathogenesis of the podocyte injury in DN by inducing both oxidative stress and inflammation **(7).** In addition, dysfunction of intracellular organelles also contributes to podocyte damage. However, the mechanisms underlying podocyte impairment in DN are not fully understood **(8).**

Risk factors for Diabetic Nephropathy

A variety of risk factors promotes the development and progression of diabetic nephropathy, including high glucose levels, obesity, dyslipidemia, elevated blood pressure, oxidative stress, and others. Most of these risk factors are modifiable. Therefore, their intensive management is essential for preventing and delaying the decline in renal function **(9).**

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage **(10).** CKD attributed to diabetes (diabetic kidney disease) in adults, occurs in 20–40% of patients with diabetes **(11).** Diabetic kidney disease (DKD) typically develops after a diabetes duration of 10 years in T1DM (the most common presentation is 5–15 years after the diagnosis of T1DM) but may be present at diagnosis of T2DM. CKD can progress to ESRD requiring dialysis or kidney transplantation **(12).**

The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR **(13).** However, signs of diabetic kidney disease may be present at diagnosis or without retinopathy in T2DM. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes mellitus and is becoming more common over time **(14).**

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection **(15).** Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration **(16).**

Thus, to be useful for patient screening, semiquantitative or qualitative (dipstick) screening tests should be >85% positive in those with moderately increased albuminuria (≥30 mg/g) and confirmed by albumin-to-creatinine values in an accredited laboratory **(17).** Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal albuminuria is defined as <30 mg/g creatinine, moderately elevated albuminuria is defined as ≥30–300 mg/g creatinine, and severely elevated albuminuria is defined as ≥300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes **(18).**

Furthermore, because of high biological variability of >20% between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have moderately or severely elevated albuminuria **(19).** Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage **(20).**

Traditionally, eGFR is calculated from serum creatinine using a validated formula **(21).** An eGFR persistently <60 mL/min/1.73 m^2 in presence of a urinary albumin value of >30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 years **(22).** Additionally, increased use of cystatin C (another marker of eGFR) is suggested in combination with the serum creatinine because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone **(23).**

For Staging of Chronic Kidney Disease, Stage 1 and stage 2 CKD are defined by evidence of high albuminuria with eGFR ≥60 mL/min/1.73 m^2, and stages 3–5 CKD are defined by progressively lower ranges of eGFR **(24) (Fig.1).** At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality **(18).**

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Fig. (1): Risk of chronic kidney disease progression, frequency of visits, and referral to a nephrologist according to glomerular filtration rate and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal estimated GFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient, must be taken into account. Adapted with permission from (25).

In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers ARBs) can reduce intravascular volume, renal blood flow, and/or glomerular filtration **(26).** There was a concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease **(27)** or high CVD risk with normal kidney function **(28).**

Complications of CKD generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy **(29).**

There is a clear need for annual quantitative assessment of urinary albumin excretion. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARBs therapy to maximum tolerated doses, and achievement of blood pressure targets. Early changes in kidney function may be detected by increases in albuminuria before changes in eGFR **(30),** and this also significantly affects cardiovascular risk. Moreover, an initial reduction of >30% from baseline, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the U.S. Food and Drug Administration **(31).**

Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARBs therapy. In addition, in clinical trials of ACE inhibitors or ARBs therapy in T2DM, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to maximize reduction in urinary albumin creatinine ratio. Data from post hoc analyses demonstrate less benefit on cardio-renal outcomes at half doses of renin angiotensin aldosterone system blockade (RAAS) **(32).**

The only proven primary prevention interventions for CKD are blood glucose and blood pressure control. There is no evidence that RAAS inhibitors or any other interventions prevent the development of diabetic kidney disease. Thus, the American Diabetes Association does not recommend routine use of these medications solely for the purpose of prevention of the development of diabetic kidney disease **(**33**).**

Omentin 1 and nephropathy

Diabetic nephropathy develops in 30% to 40% of type2 diabetic patients and has become the single most common microvascular complications of type 1 and type 2 diabetes mellitus and the leading cause of ESRD worldwide **(34)**

The development of sustained proteinuria is the major criterion for the diagnosis of DN, the risk of a progressive increase in albumin excretion to overt proteinuria within 6–14 years was 60–80% **(35)**

Adipose tissue actively participates in neuroendocrine, cardiovascular and immune systems by secreting proteins and other products (called adipokines), as well as responding to neural, hormonal, and nutritional signals **(36).**

Omentin-1 was shown to be predominantly expressed in visceral adipose tissue and was among the first molecules known to exhibit such a dramatic difference in gene expression between the two major fat depots. As a secretory factor, omentin-1 may be a novel hormone that is likely to act as both an endocrine factor to modulate systemic metabolism, including insulin action in subcutaneous adipocytes, and an autocrine and paracrine factor to regulate visceral adipose biology locally **(37).**

Omentin-1 is an adipokine preferentially produced by visceral adipose tissue with insulin-sensitizing effects and its expression was shown to be reduced in obesity, insulin resistance (IR) and type 2 diabetes **(38)**

It is associated with macro- and microvascular complications of diabetes mellitus. Interleukin-6, formerly called B-cell stimulatory factor- 2, is a multifunctional cytokine. IL-6 has a variety of functions, including growth and differentiation of hematopoietic cells and the immune and inflammatory responses. Recently, it was shown that IL-6 and omentin are implicated in glomerulonephritis, including mesangial proliferative glomerulonephritis. Its level is highly elevated in DN and associated with albumin excretion and renal hypertrophy **(39).**

Some evidence suggests an important role of inflammation in the pathogenesis and progression of diabetic nephropathy. There is a correlation between early markers of diabetic nephropathy, such as microalbuminuria and markers of inflammation in patients with type 2 DM **(40).**

Detection of serum omentin level may play an important role in early diagnosis and prevention of diabetic nephropathy in T2DM. Decreased serum level of omentin-1 and increased serum levels of IL-6 and insulin and raised HOMA-IR in cases suggest that insulin resistance and inflammation are important mechanisms in the pathogenesis of diabetic nephropathy in type 2 diabetes mellitus patients **(41).**

2) Diabetic Retinopathy

Diabetic retinopathy (DR), the most serious diabetic complication, is estimated to account for 4.8% of global blindness. Although major research has been concentrated on the elucidation of its pathogenesis, the clear mechanism of DR is still unknown. Within the factors involved in the mechanism of DR, inflammation is paid more attention during the past decade. Amultitude of inflammatory mediators have been demonstrated to be involved in the mechanism of diabetic retinopathy **(42).**

According to the epidemiological data shared by the American Academy of Ophthalmology, the global burden of diabetes mellitus is 387 million, which is estimated to increase to 592 million by 2035. Ninety-three million people are globally affected by diabetic retinopathy. Prevalence of diabetic retinopathy is 77.3% in type 1 diabetic patients and 25.1% in type 2 diabetic patients, out of which approximately 25% to 30% are expected to develop vision-threatening diabetic macular edema **(43).**

Diabetic retinopathy affects people with diagnosed or undiagnosed diabetes mellitus. The propensity to develop diabetic retinopathy is directly proportional to the patient's age and duration of diabetes, as well as poor glycemic control and fluctuating blood pressure levels **(44).**

Risk factors for diabetic retinopathy can be classified into:

- **Non-modifiable:** Puberty and Pregnancy
- **Modifiable:** Hypertension, Obesity, Dyslipidemia, Poor glycemic control, and Nephropathy
- **Newer risk factors:** Inflammation, Apolipoprotein, Hormonal influence - leptin and adiponectin, Vitamin D, Oxidative stress, and Genetic factors **(45).**

Classification of diabetic retinopathy (46)

a) **Mild non-proliferative retinopathy:** Microaneurysms i.e., small swellings in the tiny blood vessels of the retina will be formed.

b) **Moderate non-proliferative retinopathy**: As the disease progresses, some blood vessels that nourish the retina are blocked.

c) **Severe non-proliferative retinopathy**: More blood vessels are blocked, depriving several areas of the retina of their blood supply. The affected areas of the retina begin to show signs of ischemia such as blot hemorrhages, bleeding of the veins and intraretinal microvascular abnormalities.

d) **Proliferative retinopathy:** At this advanced stage, the Vaso proliferative factors produced by the retina begin to trigger the growth of new blood vessels. These new blood vessels are abnormal and fragile.

Retinopathy can also begin to develop as early as 7 years after diagnosis **(47).** The main characteristics of diabetic retinopathy are vascular leakage, angiogenesis and neuronal degeneration as described by **Zhang et al., (48).** Signs of diabetic retinopathy include; micro aneurysms dot and blot hemorrhages, flame shaped hemorrhages, retinal edema, hard exudates, cotton wool spots and macular oedema. Screening of diabetic retinopathy is done by Annual funduscopic examination and digital photography **(47).**

The ACCORD trial of medical therapies demonstrated that intensive glycemic control reduced the risk of progression of diabetic retinopathy in people with type 2 diabetes of 10 years duration **(49).**

Moreover, maintaining an intensive blood pressure control in patients with type 2 diabetes was found to reduce the incidence and progression of diabetic neuropathy over 4–5 years follow up. Although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit over targets of <140 mmHg **(50).**

Poor glycemic control, uncontrolled hypertension, dyslipidemia, nephropathy, male sex, and obesity are associated with worsening diabetic retinopathy **(51).**

Uncontrolled diabetes can lead to many ocular disorders like cataracts, glaucoma, ocular surface disorders, recurrent stye, non-arteritic anterior ischemic optic neuropathy, diabetic papillopathy, and diabetic retinopathy. Diabetic retinopathy eventually leads to blindness which is the most common and severe ocular complication (52).

Pathogenesis of Diabetic Retinopathy

Chronic hyperglycemia is considered to be the primary pathogenic agent in DR, Hyperglycemia leads to the activation of alternative pathways of glucose metabolism, including the polyol pathway. The oxidative stress, protein kinase activation, and non-enzymatic protein glycation lead to advanced glycation end products (AGEs) (53).

The result of these alternative pathways is the activation of cytokines along with the growth factors and vascular endothelial dysfunction, which eventually leads to increased vascular permeability and microvascular occlusion. Retinal ischemia, which occurs as a consequence of microvascular occlusion, leads to the formation of intraretinal microvascular abnormalities and neovascularization (54).

In the polyol pathway, glucose is reduced to sorbitol by the aldose reductase enzyme. The impermeability of sorbitol leads to its accumulation in all retinal cells leading to osmotic damage to the cells. Also, the use of NADPH during the reduction process leads to further oxidative damage. Oxidative stress results from increased levels of reactive oxygen species (ROS), leading to cell and tissue damage. Protein kinase C is involved in signal transduction. Its activation leads to basement membrane alterations and vascular changes like increased vascular permeability, the release of angiogenic growth factors, vascular stasis, and capillary occlusion (55).

In non-enzymatic protein glycation, reducing sugars react with free amino acids of nucleic acids, proteins, and lipids leading to the formation of advanced glycation end products responsible for the alterations in extracellular matrix proteins. The morphological changes seen in small retinal vessels in DR include early loss of pericytes, basement membrane thickening, loss of endothelial cells, increased vascular permeability, platelet aggregation, leukostasis, and capillary dropout (56).

Retinal ganglion cells (RGCs) are the only neurons that act as an action potential in the retina, playing an important role in the visual production. Diabetic retinopathy is often accompanied by neurodegeneration in the early stage in RGCs, leading to visual impairment. Moreover, it is also pointed out that the occurrence of neurodegeneration in DR is earlier than that of microvascular injury, which is the traditional pathological concept of DR, and it promotes the further development of microvascular diseases. Therefore, RGCs play a vital role in DR (57).

Like other nerve cells, the damage of RGCs cannot be repaired by regeneration. Although some researchers have realized the trans-differentiation of RGCs, its clinical application is still facing great challenges. Therefore, it is very important to delay the occurrence and development of DR by neuroprotective therapy (58).

Diabetic retinopathy does not only affect the micro vessels of the retina but also the Müller cells, which are the primary glial cells of the retina. The functions of Müller cells are maintaining the structural integrity of the retina, regulation of the blood-retinal barrier and retinal blood flow,

uptake and recycling of various neurotransmitters, retinoic acid compounds, and ions (such as potassium), regulation of metabolism and supply of nutrients to the retina **(59).**

In diabetes, there is continued potassium uptake leading to swelling of Müller cells, which leads to Muller cell dysfunction **(60).** Fluid accumulation inside the Muller cells is responsible for DME **(61).** Early inner retinal neuronal and Müller cell involvement may be noted in preclinical and early clinical DR **(62).** Activation of Müller cells and overexpression of glial fibrillary acidic protein are noted in DR **(59).**

Hyperglycemia leads to the release of growth factors and cytokines /chemokines. Growth factors as Vascular endothelial growth factor, Platelet-derived growth factor, Insulin-like growth factor, Erythropoietin and others. Cytokines and chemokines as Interleukin-1β, Interleukin-6, Tumor necrosis factor-α **(63).**

Omentin 1 and retinopathy

Omentin-1 could increase insulin stimulated glucose uptake and Akt phosphorylation in human adipocytes. Decreased omentin-1 concentrations were found in patients with insulin resistance (IR) and diabetes mellitus. Recently, omentin-1 was demonstrated to play an anti-inflammatory role in vascular smooth cells. Inflammation is correlated with the development of DR. Therefore, omentin-1 is hypothesized to play a role in DR development **(39).**

Omentin-1 plays an anti-inflammatory role through inhibition of tumor necrosis factor-alpha [TNf-a] induced superoxide production in vascular smooth cells. Angiogenesis is thought to be one of the underlying mechanisms of diabetic microvascular complications such as diabetic nephropathy and DR. It was found that omentin-1 decreases in vitro migration and angiogenesis in human endothelial cells induced by sera, C-reactive protein and VEGF. Thus omentin-1 appear to be a protective adipokine that it induces vasodilation and inhibit endothelial cell migration, vascular inflammation and angiogenesis as well as reducing endothelial dysfunction **(64).**

Omentin-1 treatment could enhance insulin-stimulated glucose uptake in human adipocytes. In addition, omentin increased Akt phosphorylation in human adipocytes. Serum omentin- 1 levels were lower in the impaired glucose regulation group than in the normal glucose tolerance (NGT) group **(65).**

Serum and vitreous omentin-1 levels in PDR patients were both significantly elevated compared with diabetic patients without DR, NPDR patients, and the controls. Vitreous omentin-1 concentrations are lower than serum omentin-1 concentrations. This indicates that vitreous omentin- 1 may be caused by bleeding from the vascular system of the eyes. This hypothesis could explain the similar reduction of plasma and vitreous omentin-1 concentrations. Omentin- 1 in eyes may protect the eyes against DR development. Serum/vitreous omentin-1 ratio was positively correlated with the presence and severity of DR. This indicates that serum/vitreous omentin-1 ratio may be utilized to predict or assess the development and progression of DR **(44).**

Angiogenesis is a key mechanism of DR. Omentin-1 could significantly decrease vascular endothelial growth factor (VEGF) induced endothelial cell migration and angiogenesis in human microvascular endothelial cells. This suggests that omentin-1 may serve as antiangiogenic mediator

and play an important protective role in the development of DR through the antiangiogenic effects **(66).**

Omentin was found to inhibit tumor necrosis factor- (TNF-) induced vascular inflammation in human endothelial cells and vascular smooth muscle cells. Serum omentin-1 was reported to be inversely associated with inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and C-reactive protein. These results indicate the anti-inflammatory role of omentin- 1. Inflammation has been suggested as a potential mechanism for DR. Omentin-1 may be involved in the mechanism of DR via the inhibitory role of inflammatory pathway. In short, serum and vitreous omentin-1 levels, as well as serum/vitreous omentin-1 ratio, are correlated with the presence and severity of DR **(67).**

3) Diabetic Neuropathy

Among the complications of DM, a group of clinical syndromes caused by damage to the peripheral and autonomic nervous systems generally referred to as different forms of neuropathy, these syndromes are caused by diffuse and focal nervous system damage and occur in up to half of all individuals with the most common form of diabetic neuropathy is Distal symmetric polyneuropathy (DSPN) **(68).**

The global epidemic of diabetes and its most common complication, neuropathy, requires a public health mandate to address modifiable risk factors with growing urgency. Without successful intervention, it is estimated that of the expected 9.7 billion individuals living in 2050, one-third will have DM and half of those will have neuropathy **(69).**

The duration of diabetes and hemoglobin A1c (HbA1c) levels are major predictors of diabetic neuropathy **(70).** These two predictors are commonly associated with other metabolic factors that are correlated with diabetic neuropathy, particularly in T2DM, such as insulin resistance and hypertension. Obesity is common in patients with neuropathy in population-based studies in multiple countries, including the United States, Denmark, China and the Netherlands **(71).** Independent of HbA_{1c} levels, the number of metabolic syndrome components, such as hypertriglyceridemia, hypertension, abdominal obesity and low high-density lipoprotein (HDL) levels, is consistently associated with diabetic neuropathy in patients with T2DM **(72).** Other independent risk factors for the development of diabetic neuropathy include smoking, alcohol abuse, increased height and older age **(68).**

Several genes are linked to diabetic neuropathy, but only ACE (angiotensin-converting enzyme) and MTHFR (methylene tetrahydrofolate reductase) polymorphisms have been studied in multiple populations including large cohorts. Much more research is needed to better understand the role of genetics in the development of diabetic neuropathy **(73).**

Risk factors for painful diabetic neuropathy

For assessing the risk factors for neuropathic pain in diabetic neuropathy there are a number of interesting factors that have emerged subsequently. Consistent with risk factors for many neuropathic pain disorders, female sex is a risk factor for painful diabetic neuropathy **(74).** Several metabolic factors are associated with painful diabetic neuropathy compared with painless diabetic

neuropathy, including poor glycaemic control (75), impaired renal function (76) and high body mass index (BMI) (77). These factors might be associated with neuropathy progression.

The diabetic neuropathies encompass a heterogeneous group of clinical syndromes. Typically, these syndromes are categorized according to their pattern of neurological involvement.

➢ ***Neuropathic syndromes occurring in DM, other than diabetic sensorimotor peripheral neuropathy: -***

- **Acute painful–distal sensory polyneuropathies**

These acute painful polyneuropathies are induced by hyperglycemia or treatment. Two distinct presentations exist, which occur either in the context of poor diabetes mellitus control, often associated with weight loss, or following rapid improvements in glucose control (treatment-induced neuropathy of diabetes). An acute 'stocking and glove' pattern of painful sensory neuropathy presents within weeks, with small-fiber neuropathic deficits. Management is focused on relieving pain and on the maintenance of optimal glycemic control (78).

- **Autonomic neuropathies**

Abnormalities of autonomic function are very common in patients with longstanding diabetes mellitus. Several systems might be affected, with cardiac autonomic neuropathy being the most prevalent. The cornerstone for the prevention or delay of progression of cardiac autonomic neuropathy is early achievement of tight glycemic control and multifactorial cardiometabolic risk reduction (79).

- **Focal or multifocal neuropathies**

Focal neuropathies are secondary to nerve compression or microvasculitis. The latter mainly affect middle-aged or older patients, are more common in men than in women and have a rapid onset (80).

- **Mononeuropathy and mononeuritis multiplex**

Cranial nerve palsies (for example, third cranial nerve palsy) are the most common mononeuropathies. Mononeuritis multiplex has also been described in diabetes mellitus, but this is rare (80).

- **Radiculoplexus neuropathy**

The most common disorder is lumbosacral radiculo-plexopathy. Patients present with subacute, painful, unilateral lower-limb neuropathy associated with weight loss. Proximal muscle weakness, often affecting the lower limbs (amyotrophy) is associated with neuropathic pain and can be profoundly disabling (81).

Truncal radiculopathy causes neuropathic pain in a radicular distribution and might be associated with pain and muscular weakness, classically causing out-pouching of the abdominal wall (82).

- **Entrapment neuropathies**

Entrapment neuropathies most commonly involve the median, ulnar and peroneal nerves. Diagnosis requires nerve conduction studies, although this might be challenging when there is concurrent diabetic sensorimotor peripheral neuropathy **(83).**

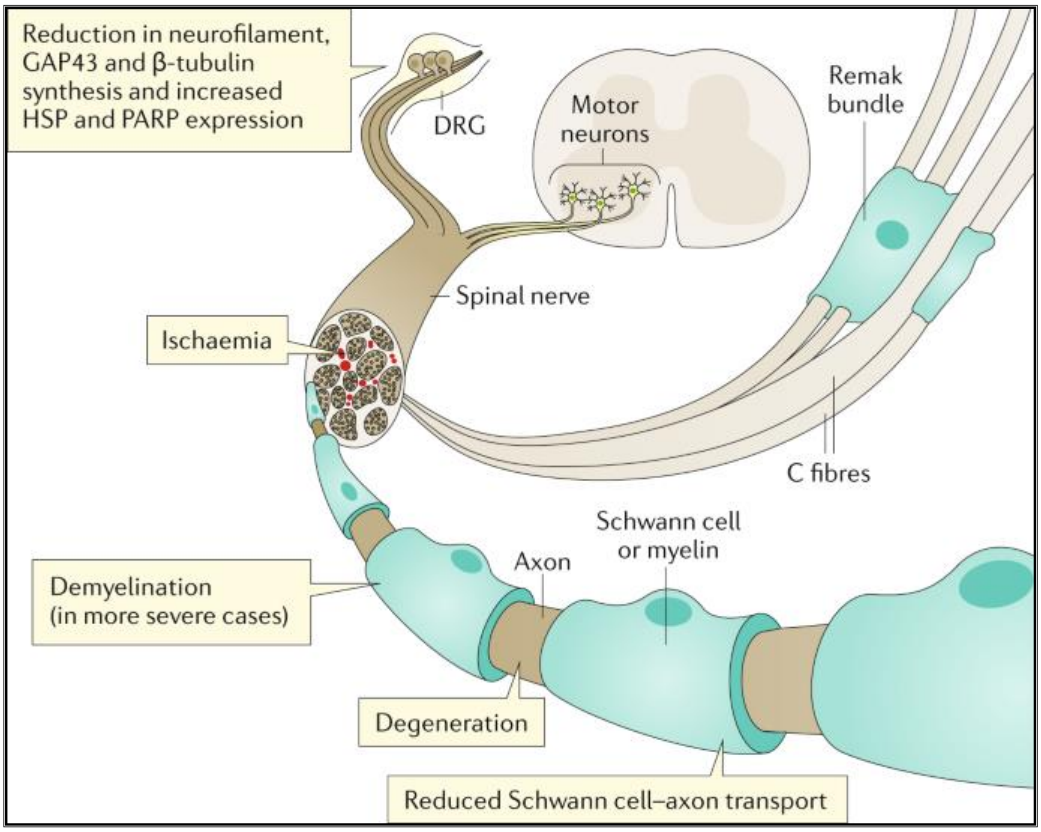
Pathogenesis of Diabetic Neuropathy

Diabetic neuropathy is a unique neurodegenerative disorder of the peripheral nervous system that targets sensory axons, autonomic axons and later, to a lesser extent, motor axons. How diabetes mellitus targets sensory neurons remains debated. Progressive diabetic neuropathy involves retraction and 'dying back' of terminal sensory axons in the periphery, with relative preservation of the perikarya (cell bodies). Its 'stocking and glove' pattern of involvement reflects damage to the longest sensory axons first with, for example, loss of distal leg epidermal axons preceding loss in more proximal limbs; for this reason, diabetic neuropathy is considered a length-dependent neuropathy **(84).**

Substantial experimental evidence supports the idea that the entire neuron, from the perikaryon to the terminal, is targeted by diabetes. However, whether damage first targets peripheral axons and their associated Schwann cells or the neuron perikarya that reside in the dorsal root ganglia and act to support the axons are debated as shown in **(Fig.2) (85).**

Whether diabetes promotes intrinsic programs within axons that facilitate axonal degeneration is unclear. Studies of Wallerian degeneration have identified intracellular signaling pathways that actively induce axonal degeneration, and mononucleotide adenyl transferase seems to be a key regulator of this pathway. However, whether these pathways are activated in diabetes is not yet clear **(86).**

Changes in axons, especially distal terminals, are associated with changes in the neuronal perikarya. Indeed, sensory neurons within the dorsal root ganglion (DRG) alter their phenotype in chronic



experimental diabetes, which might be critical in how they support distal axon branches. Preclinical studies in diabetic rodents also associate endoplasmic reticulum stress with diabetes-mediated peripheral nerve damagethat would affect nerve function **(87).**

Fig. (2): The peripheral nervous system and alterations in diabetic neuropathy. Sensory neurons relay sensory information from their nerve terminals (which are located throughout the periphery) to the dorsal horn of the spinal cord. The cell bodies of these sensory neurons are located in the dorsal root ganglia. Conversely, the cell bodies of motor neurons reside in the spinal cord ventral horn and transmit information from here to the periphery. Thin and unmyelinated sensory axons (C fibers or small fibers) are grouped together by non-myelinating Schwann cells into Remake bundles and represent a large portion of neurons of the peripheral nervous system. Adapted with permission from (88).

In vitro and in vivo experiments in rodent models have demonstrated that hyperglycemia alters the function of key plasticity molecules, such as growth-associated protein 43 (also known as neuromodulin) and β-tubulin, and the expression patterns of heat shock proteins **(89)** and poly ADP-ribose polymerase **(90)** in the DRG. Although the mechanisms of injury remain under investigation, data suggest that dysfunction in these pathways promotes abnormal protein processing, oxidative damage and mitochondrial dysfunction, leading to loss of peripheral nerve function **(88).**

Some studies have demonstrated a range of both mRNA and microRNA alterations in DRG sensory neurons exposed to chronic hyperglycemia **(91).**

Other specific changes in the DRG and nerve function can be linked to diabetic neuropathy, including altered spliceosome function, changes in expression of survival motor neuron protein and upregulation of GW-bodies (sites of mRNA processing) **(82).**

How the peripheral nervous system uses substrates for energy, especially in diabetes, is necessary to understand the pathogenesis of diabetic neuropathy. In Schwann cells, DRG neurons and axons, both glucose and fatty acids produce NADH and $FADH_2$ via glycolysis and the tricarboxylic acid cycle (glucose) and β-oxidation (fatty acids). When long-chain fatty acids are transported into Schwann cells to undergo β-oxidation, each β-oxidation cycle forms one molecule of acetyl-CoA, which is transported to the tricarboxylic acid cycle for NADH and $FADH_2$ formation. However, during substrate overload, such as in diabetes, the transport system becomes saturated, and acetyl-CoA molecules are converted to acyl carnitines. The accumulation of acyl carnitines is toxic to both Schwann cells and DRG neurons, adding to the ongoing nervous system injury in diabetic neuropathy. Accumulated acyl carnitines are released from Schwann cells and can induce axonal degeneration, which has been proposed to involve mitochondrial dysfunction and a maladaptive integrated stress response in Schwann cells **(93).**

NADH and $FADH_2$ are shuttled in the mitochondria through Complexes I–IV to produce ATP through oxidative phosphorylation. A byproduct of oxidative phosphorylation is the production of low levels of reactive oxygen species that are easily neutralized by innate cellular antioxidants, such as superoxide dismutase, glutathione and catalase **(94).** However, during excess substrate load, such as in diabetes, oxidative phosphorylation fails, leading to loss of ATP production and

increased ROS levels, which subsequently leads to mitochondrial failure and metabolic and oxidative damage of Schwann cells and DRG neurons **(95)**.

Dysfunctional mitochondria produce insufficient energy and lose the ability to normally traffic down axons, further promoting axonal disruption and injury **(96)**.

Increased glucose levels lead to glucose metabolism via the polyol and hexosamine pathways, resulting in increased ROS and inflammation, respectively, largely owing to mitochondrial injury **(88)** which contributes to ongoing nervous system dysfunction. Increased glucose levels lead to the glycation of numerous structural and functional proteins to produce AGEs. AGEs result in altered or loss of protein function and interact with AGE-specific receptor to modify gene expression and intracellular signalling and promote the release of pro-inflammatory molecules and free radicals **(97)**.

In parallel, the excessive free fatty acids catabolized by β-oxidation in response to hyperlipidemia can injure the peripheral nervous system, particularly Schwann cell **(98)**, through ROS generation and systemic and local inflammation via macrophage activation with subsequent cytokine and chemokine production **(99)** **(Fig. 3)**.

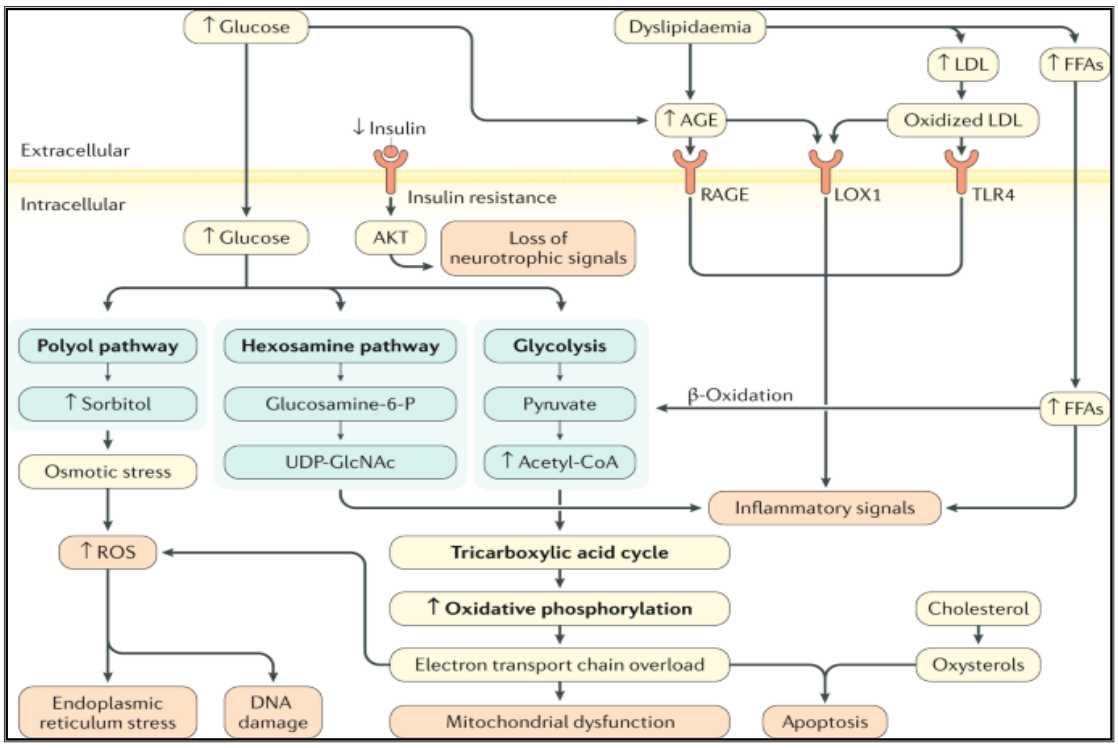


Fig. (3): Diabetic neuropathy pathogenesis. Hyperglycemia and dyslipidemia, together with altered insulin signaling, lead to several pathological alterations in neurons, glia and vascular cells that can lead to nerve dysfunction and ultimately, neuropathy, including DNA damage endoplasmic reticulum stress, mitochondrial dysfunction, neurodegeneration, and loss of neurotrophic signaling, and can trigger macrophage activation. The importance of these pathways in the development of neuropathy varies with cell type, disease profile and time, as distinct cell types are susceptible to injury depending on the metabolic impairments. Adapted with permission from (96).

Omentin 1 and neuropathy

Omentin inhibits TNF-a-induced vascular inflammation, correlates with adiponectin and exerts cardioprotective effects through 5' adenosine monophosphate-activated protein kinase and protein kinase B (Akt)-dependent mechanism. The anti-inflammatory properties of omentin may therefore contribute to the reduced risk of diabetic complications; however, our results indicate that TNF-a and adiponectin explain only a small proportion of the inverse association between omentin and polyneuropathy and therefore point towards the relevance of other pathophysiological pathways that are not directly related to inflammatory processes **(100).**

Regarding additional mechanisms that could link omentin and diabetic neuropathy, data are very scarce. A specific receptor on the surface of omentin-responsive cells has not yet been identified, and our knowledge of the intracellular signalling cascades that are affected by omentin is limited to the inflammation-related pathways mentioned above. Omentin binds to lactoferrin, an iron-binding protein that has been associated with insulin resistance; however, it is not known whether this interaction has any direct relevance for the development of neuropathic symptoms **(101).**

References:

1. Walinjkar, R. S., Khadse, S., Kumar, S., Bawankule, S., & Acharya, S. (2019). Platelet indices as a predictor of microvascular complications in type 2 diabetes. Indian Journal of Endocrinology and Metabolism, 23(2), 206.
2. Pivari, F., Mingione, A., Brasacchio, C., & Soldati, L. (2019). Curcumin and type 2 diabetes mellitus: prevention and treatment. Nutrients, 11(8), 1837.
3. Alicic RZ., Rooney MT. and Tuttle KR. (2017):Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol ;12(12):2032-2045
4. Thomas C.C. and Philipson L.H. (2015): Update on diabetes classification. Med Clin N Am ;99:1-16.
5. Reidy K., Hostetter T., Susztak K. et al., (2014): Molecular mechanisms of diabetic kidney disease. J Clin Invest ;124(6):2333-2340.
6. Kopp JB., Anders HJ., Susztak K. et al. (2020): Podocytopathies. Nat Rev Dis Primers ;6:68.
7. Brennan, E., Kantharidis, P., Cooper, ME. et al., (2021): Pro-resolving lipid mediators: regulators of inflammation, metabolism and kidney function. Nat Rev Nephrol ;17:725–739.
8. Audzeyenka I., Bierżyńska A., Lay AC. et al., (2022): Podocyte Bioenergetics in the Development of Diabetic Nephropathy: The Role of Mitochondria. Endocrinology ;163(1):bqab234.
9. Tziomalos, K., & Athyros, V. G. (2015). Diabetic nephropathy: new risk factors and improvements in diagnosis. The review of diabetic studies: RDS, 12(1-2), 110.
10. Tuttle KR., Bakris GL., Bilous RW. et al., (2014): Diabetic Kidney Disease: A Report From an ADA Consensus Conference. Diabetes Care ;37(10):2864–2883.
11. De Boer IH., Afkarian M., Rue TC. et al., (2014): Renal outcomes in patients with type 1 diabetes and macroalbuminuria. Journal of the American Society of Nephrology : JASN ;25(10):2342-2350.

12. Johansen KL., Chertow GM., Foley RN. et al., (2021): US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis ;77(4 Suppl 1):A7-A8.
13. Afkarian M., Zelnick LR., Hall YN. Et al., (2016): Clinical Manifestations of Kidney Disease Among US Adults With Diabetes 1988-2014. JAMA ;316(6):602-610.
14. He F., Xia X., Wu XF. et al., (2013): Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia ;56:457–466.
15. National Kidney Foundation (2013): KDIGO, Kidney Disease Improving Global Outcomes: Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. American Journal of Kidney Diseases ;3:1-24.
16. Yarnoff BO., Hoerger TJ., Simpson SK. et al., (2017): Centers for Disease Control and Prevention CKD Initiative. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. BMC Nephrol ;18(1):85.
17. Coresh J., Heerspink HJL., Sang Y. et al., (2019): Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. 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(2):115-127.
18. Fox CS., Matsushita K., Woodward M. et al (2012): Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet ;380(9854): 1662-1673.
19. Naresh CN., Hayen A., Weening A. et al., (2013): Day-to-day variability in spot urine albumin-creatinine ratio. Am J Kidney Dis ;62(6):1095-1101.
20. Tankeu AT., Kaze FF., Noubiap JJ. et al., (2017): Exercise-induced albuminuria and circadian blood pressure abnormalities in type 2 diabetes. World J Nephrol ;6(4):209-216.
21. Delanaye P. Ebert N., Melsom T. et al., (2016): Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol?. Clinical Kidney Journal ;9(5):682–699.
22. Kramer HJ., Nguyen QD., Curhan G. et al., (2003): Renal Insufficiency in the Absence of Albuminuria and Retinopathy Among Adults With Type 2 Diabetes Mellitus. JAMA ;289(24):3273–3277.
23. Benoit SW., Ciccia EA. And Devarajan P. (2020): Cystatin C as a biomarker of chronic kidney disease: latest developments. Expert Rev Mol Diagn ;20(10):1019-1026.
24. Flynn C. and Bakris GL. (2013): Noninsulin glucose-lowering agents for the treatment of patients on dialysis. Nat Rev Nephrol. ;9(3):147-153.
25. Vassalotti JA., Centor R., Turner BJ. et al., (2016): National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician. Am J Med ;129(2):153-162.
26. Harężlak T., Religioni U., Szymański FM. et al., (2022): Drug Interactions Affecting Kidney Function: Beware of Health Threats from Triple Whammy. Adv Ther ;39(1):140-147.
27. Perkovic V., Jardine MJ., Neal B. et al., (2019): Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med ;380(24):2295-2306.

28. Neuen BL., Ohkuma T., Neal B. et al., (2018): Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function. Circulation.;138(15):1537-1550.
29. Vaidya SR., Aeddula NR. and Doerr C. (2022): Chronic Renal Failure (Nursing). In: StatPearls. StatPearls Publishing, Treasure Island (FL), 11-43.
30. Zelniker TA., Raz I., Mosenzon O. et al., (2021): Effect of Dapagliflozin on Cardiovascular Outcomes According to Baseline Kidney Function and Albuminuria Status in Patients With Type 2 Diabetes: A Prespecified Secondary Analysis of a Randomized Clinical Trial. JAMA Cardiol ;6(7):801-810.
31. Levey AS., Eckardt KU., Dorman NM. et al., (2020): Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int ;97(6):1117-1129.
32. Epstein M., Reaven NL., Funk SE. et al., (2015): Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care ;21(11):S212-220.
33. Jain K. and Mottl AK. (2015): Comprehensive Care for People With Diabetic Kidney Disease. Diabetes Spectr ;28(3):187-192.
34. Korzh, O., Fylenko, Y., & Krasnokutskiy, S. (2023). Omentin-1 Levels and Endothelial Dysfunction in Diabetic Kidney Disease. Metabolism-Clinical and Experimental, 142.
35. Yan, P., Xu, Y., Zhang, Z., Zhu, J., Miao, Y., Gao, C., & Wan, Q. (2020). Association of circulating omentin-1 with osteoporosis in a Chinese type 2 diabetic population. Mediators of Inflammation, 2020.
36. Biscetti, F., Nardella, E., Rando, M. M., Cecchini, A. L., Angelini, F., Cina, A., Iezzi, R., Filipponi, M., Santoliquido, A., & Pitocco, D. (2020). Association between omentin-1 and major cardiovascular events after lower extremity endovascular revascularization in diabetic patients: a prospective cohort study. Cardiovascular Diabetology, 19(1), 1–11.
37. Devi, S., Sahu, S., Behera, K. K., Sahoo, D., & Priyadarshini, N. (2022). Assessment of the Diagnostic Utility of Serum Omentin 1 and IL-6 in Early Stages of Diabetic Nephropathy. The Journal of the Association of Physicians of India, 70(4), 11–12.
38. Zhao, A., Xiao, H., Zhu, Y., Liu, S., Zhang, S., Yang, Z., Du, L., Li, X., Niu, X., & Wang, C. (2022). Omentin-1: A newly discovered warrior against metabolic related diseases. Expert Opinion on Therapeutic Targets, 26(3), 275–289.
39. Mohammed, M. S., Abd Elbaky, R. S., Ali, H. M., & Naguib, T. A. (2021). Evaluation of Serum Omentin-1 Levels in Chronic Kidney Disease Patients with and without Type 2 Diabetes Mellitus. QJM: An International Journal of Medicine, 114(Supplement-1), hcab100-112.
40. Hayashi, M., Morioka, T., Hatamori, M., Kakutani, Y., Yamazaki, Y., Kurajoh, M., Motoyama, K., Mori, K., Fukumoto, S., & Shioi, A. (2019). Plasma omentin levels are associated with vascular endothelial function in patients with type 2 diabetes at elevated cardiovascular risk. Diabetes Research and Clinical Practice, 148, 160–168.
41. Kume, S., Tomita, I., Yamahara, K., Yasuda-Yamahara, M., Takeda, N., Osawa, N., Chin-Kanasaki, M., Kaneko, T., Pieper, M., & Araki, S.-I. (2019). SP430 Potential role for ketone body metabolism in an SGLT2 inhibitor-mediated anti-albuminuric effect in type 2 diabetic db/db mice. Nephrology Dialysis Transplantation, 34(Supplement_1), gfz103-SP430.

42. Gatev, T., Byalkova, V., Poromanski, I., Velikova, T., Vassilev, D., & Kamenov, Z. (2022). Omentin-1 and diabetic foot. The International Journal of Lower Extremity Wounds, 15347346211069812.
43. Hendrick AM., Gibson MV. and Kulshreshtha A. (2015): Diabetic Retinopathy. Prim Care ;42(3):451-464.
44. Wang, Y., Hu, Q., Luan, L., & Zhang, H. (2022). Omentin-1 ameliorates oxidative stress in model of diabetic ophthalmopathy via the promotion of AMPK function. Molecular & Cellular Toxicology, 18(4), 477–485.
45. Schreur V., van Asten F., Weeda J. et al., (2018): Risk factors for development and progression of diabetic retinopathy in Dutch patients with type 1 diabetes mellitus. Acta Ophthalmol ;96(5):459-464.
46. Yun WI., Acharya UR., Venkatesh YV. et al., (2008): Identification of different stages of diabetic retinopathy using retinal optical images. Information Sciences ;178(1):106-121.
47. Franklin SW. and Rajan SE. (2014): Diagnosis of diabetic retinopathy by employing image processing technique to detect exudates in retinal images. IET Image Process ;8:601–609.
48. Zhang X., Zeng H., Bao S. et al., (2014): Diabetic macular edema: new concepts in pathophysiology and treatment. Cell Biosci.;4:27.
49. Chew EY., Klein ML., Ferris FL. et al., (1996): Association of Elevated Serum Lipid Levels With Retinal Hard Exudate in Diabetic Retinopathy: Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol ;114(9):1079–1084.
50. Do DV., Wang X., Vedula SS. et al., (2015): Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev ;(1):CD006127.
51. Nittala M.G., Keane P.A., Zhang K. et al., (2014): Risk Factors for Proliferative Diabetic Retinopathy in a Latino American Population. Retina ;34(8):1594–1599.
52. Khan A. , Petropoulos I.N., Ponirakis G. et al., (2017): Visual complications in diabetes mellitus: beyond retinopathy. Diabet Med ;34(4):478-484.
53. Behl T. and Kotwani A. (2015): Exploring the various aspects of the pathological role of vascular endothelial growth factor (VEGF) in diabetic retinopathy. Pharmacol Res ;99:137-148.
54. Kador PF., Wyman M. and Oates PJ. (2016): Aldose reductase, ocular diabetic complications and the development of topical Kinostat(®). Prog Retin Eye Res ;54:1-29.
55. Kern TS., Antonetti DA. and Smith LEH. (2019): Pathophysiology of Diabetic Retinopathy: Contribution and Limitations of Laboratory Research. Ophthalmic Res ;62(4):196-202.
56. Wang W. and Lo ACY. (2018): Diabetic Retinopathy: Pathophysiology and Treatments. Int J Mol Sci ;19(6):56-64.
57. Maes ME., Schlamp CL. and Nickells RW. (2017): BAX to basics: How the BCL2 gene family controls the death of retinal ganglion cells. Progress in Retinal and Eye Research ;57:1-25
58. Hao M., Kuang HY., Fu Z. et al., (2012): Exenatide prevents high-glucose-induced damage of retinal ganglion cells through a mitochondrial mechanism. Neurochemistry International;61(1):1-6.
59. Coughlin B.A., Feenstra DJ. and Mohr S. (2017): Müller cells and diabetic retinopathy. Vision Res ;139:93-100.

60. Curtis TM., Hamilton R., Yong PH. et al., (2011): Müller glial dysfunction during diabetic retinopathy in rats is linked to accumulation of advanced glycation end-products and advanced lipoxidation end-products. Diabetologia ;54(3):690-698.
61. Pannicke T., Iandiev I., Wurm A. et al., (2006): Diabetes alters osmotic swelling characteristics and membrane conductance of glial cells in rat retina. Diabetes ;55(3):633-639.
62. Vujosevic S. and Midena E. (2013): Retinal layers changes in human preclinical and early clinical diabetic retinopathy support early retinal neuronal and Müller cells alterations. J Diabetes Res ;2013:905058.
63. Cai J. and Boulton M. (2002): The pathogenesis of diabetic retinopathy: old concepts and new questions. Eye (Lond) ;16(3):242-260.
64. Tuttolomondo, A., Del Cuore, A., La Malfa, A., Casuccio, A., Daidone, M., Maida, C. D., Di Raimondo, D., Di Chiara, T., Puleo, M. G., & Norrito, R. (2021). Assessment of heart rate variability (HRV) in subjects with type 2 diabetes mellitus with and without diabetic foot: correlations with endothelial dysfunction indices and markers of adipo-inflammatory dysfunction. Cardiovascular Diabetology, 20(1), 1–12.
65. Wang, H., Xu, J., Ding, G., Zheng, S., Han, Y., & Wu, X. (2023). The Potency of Serum Omentin-1 Quantification in Predicting Major Adverse Cardiac and Cerebrovascular Events Risk in Patients Receiving Hemodialysis. The Tohoku Journal of Experimental Medicine, 260(4), 283–291.
66. Tahmasebpour, N., Feizi, M. A. H., Ziamajidi, N., Pouladi, N., Montazeri, V., Farhadian, M., & Abbasalipourkabir, R. (2020). Association of omentin-1 with oxidative stress and clinical significances in patients with breast cancer. Advanced Pharmaceutical Bulletin, 10(1), 106.
67. Tatulashvili, S., Fagherazzi, G., Dow, C., Cohen, R., Fosse, S., & Bihan, H. (2020). Socioeconomic inequalities and type 2 diabetes complications: A systematic review. Diabetes & Metabolism, 46(2), 89–99.
68. Callaghan BC., Price RS., Chen KS. et al., (2015): The importance of rare subtypes in diagnosis and treatment of peripheral neuropathy: a review. JAMA Neurol ;72:1510–1518.
69. Boyle JP., Thompson TJ., Gregg EW. et al., (2010): Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr ;8:29.
70. Tesfaye S., Chaturvedi N., Eaton S. et al., (2005): Vascular risk factors and diabetic neuropathy. N Engl J Med ;352:341–350.
71. Callaghan BC., Xia R., Banerjee M. et al., (2016): Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. Diabetes Care ;39:801–807.
72. Callaghan BC., Gao L., Li Y. et al., (2018): Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. Ann. Clin. Transl Neurol ;5:397–405.
73. Prabodha LBL., Sirisena ND. and Dissanayake VHW. (2018): Susceptible and prognostic genetic factors associated with diabetic peripheral neuropathy: a comprehensive literature review. Int. J. Endocrinol ;2018:8641942.
74. Hebert HL., Veluchamy A., Torrance N. et al., (2017): Risk factors for neuropathic pain in diabetes mellitus. Pain ;158:560–568.

75. Themistocleous AC., Ramirez JD., Shillo PR. et al., (2016): The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. Pain ;157:1132–1145.
76. Raputova J., Srotova I., Vlckova E. et al., (2017): Sensory phenotype and risk factors for painful diabetic neuropathy: a cross-sectional observational study. Pain ;158:2340–2353.
77. Keller JN., Hanni KB. and Markesbery WR. (1999): Oxidized low-density lipoprotein induces neuronal death: implications for calcium, reactive oxygen species, and caspases. J Neurochem ;72:2601–2609.
78. Shillo, P., Sloan, G., Greig, M. et al., (2019): Painful and Painless Diabetic Neuropathies: What Is the Difference?. Curr Diab Rep ;19:32.
79. Spallone V. (2019): Update on the Impact, Diagnosis and Management of Cardiovascular Autonomic Neuropathy in Diabetes: What Is Defined, What Is New, and What Is Unmet. Diabetes Metab J ;43(1):3-30.
80. Greco D., Gambina F., Pisciotta M. et al., (2012): Clinical characteristics and associated comorbidities in diabetic patients with cranial nerve palsies. J Endocrinol Invest ;35(2):146-149.
81. Laughlin RS. And Dyck PJ. (2014): Diabetic radiculoplexus neuropathies. Clin Neurol ;126:45-52.
82. Selvarajah D., Kar D., Khunti K. et al., (2019): Diabetic peripheral neuropathy: Advances in diagnosis and strategies for screening and early intervention. Lancet Diabetes Endocrinol ;7(12):938–948.
83. Rota E. and Morelli N. (2016): Entrapment neuropathies in diabetes mellitus. World J Diabetes ;7(17):342-353.
84. Gumy LF., Bampton ET. and Tolkovsky AM. (2008): Hyperglycaemia inhibits Schwann cell proliferation and migration and restricts regeneration of axons and Schwann cells from adult murine DRG. Mol Cell Neurosci ;37:298–311.
85. Pan S. and Chan JR. (2017): Regulation and dysregulation of axon infrastructure by myelinating glia. J Cell Biol; 216:3903–3916.
86. Cashman CR. and Hoke A. (2015): Mechanisms of distal axonal degeneration in peripheral neuropathies. Neurosci Lett ;596:33–50.
87. Lupachyk S., Watcho P., Stavniichuk R. et al., (2013): Endoplasmic reticulum stress plays a key role in the pathogenesis of diabetic peripheral neuropathy. Diabetes ;62:944–952.
88. Feldman EL., Nave KA., Jensen TS. et al., (2017): New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. Neuron; 93:1296–1313.
89. Ma J., Pan P., Anyika M. et al., (2015): Modulating molecular chaperones improves mitochondrial bioenergetics and decreases the inflammatory transcriptome in diabetic sensory neurons. ACS Chem. Neurosci; 6:1637–1648.
90. Lupachyk S., Shevalye H., Maksimchyk Y. et al., (2011): PARP inhibition alleviates diabetes-induced systemic oxidative stress and neural tissue 4-hydroxynonenal adduct accumulation: correlation with peripheral nerve function. Free Radic Biol Med ;50:1400–1409.
91. Cheng C., Kobayashi M., Martinez J.A. et al., (2015): Evidence for epigenetic regulation of gene expression and function in chronic experimental diabetic neuropathy. J Neuropathol Exp Neurol; 74:804–817.

92. Kobayashi M., Chandrasekhar M., Cheng C. et al., (2017): Diabetic polyneuropathy, sensory neurons, nuclear structure and spliceosome alterations: a role for CWC22. Dis Model Mech ;10:215–224.
93. Viader A., Sasaki Y., Kim S. et al., (2013): Aberrant Schwann cell lipid metabolism linked to mitochondrial deficits leads to axon degeneration and neuropathy. Neuron ;77:886–898.
94. Vincent AM., Calabek B., Roberts L. et al., (2013): Biology of diabetic neuropathy. Clin. Neurol ;115:591–606.
95. Fernyhough P. (2015): Mitochondrial dysfunction in diabetic neuropathy: a series of unfortunate metabolic events. Curr. Diab. Rep ;15:89.
96. Rumora AE. Lentz SL., Hinder LM. et al., (2018): Dyslipidemia impairs mitochondrial trafficking and function in sensory neurons. FASEB J ;32:195–207.
97. Singh VP., Bali A., Singh N. et al., (2014): Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol ;18:1–14.
98. Padilla A., Descorbeth M., Almeyda AL. et al., (2011): Hyperglycemia magnifies Schwann cell dysfunction and cell death triggered by PA-induced lipotoxicity. Brain Res ;1370:64–79.
99. Legrand-Poels S., Esser N., L'homme L. et al., (2014): Free fatty acids as modulators of the NLRP3 inflammasome in obesity/type 2 diabetes. Biochem. Pharmacol ;92:131–141.
100. Bolignano, D., Greco, M., Arcidiacono, V., Presta, P., Caglioti, A., Andreucci, M., Dragone, F., Foti, D. P., & Coppolino, G. (2022). Circulating Omentin-1, Sustained Inflammation and Hyperphosphatemia at the Interface of Subclinical Atherosclerosis in Chronic Kidney Disease Patients on Chronic Renal Replacement Therapy. Medicina, 58(7), 890.
101. Pan, Y., Zhong, S., Zhou, K., Tian, Z., Chen, F., Liu, Z., Geng, Z., Li, S., Huang, R., & Wang, H. (2021). Association between diabetes complications and the triglyceride-glucose index in hospitalized patients with type 2 diabetes. Journal of Diabetes Research, 2021.