Diabetic Foot Ulcer and Diabetic Eye Disease – A Systematic Review

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Abstract- Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM) and the leading cause of blindness in working-aged adults worldwide. Diabetic foot ulcers (DFU) are amongst the most common complications of patients with uncontrolled diabetes. Diabetic foot ulcers are responsible for more admissions than any other diabetic complication. Around 15 to 25% of patients with diabetes mellitus will develop a diabetic foot ulcer during their lifetime.

The 'eye-foot syndrome' was initially described by Walsh et al. in 1975 to highlight the important association of foot lesions in patients with diabetic retinopathy. DFU and DR are both an outcome of diabetic vascular and neurological disease. The similar risk factors leading to the development of DR and DF have also led to the search for identification of common genetic factors that predispose a patient to DR. Despite the magnitude of the impact of DFUs and their consequences, little research has been performed to investigate the characteristics of patients with a DFU and DR.

Studies have found a significant correlation between advanced stages of DFU and increased frequency of DR and proliferative diabetic retinopathy. There is a risk of accelerated progression of DR in non-healing DFUs, possibly related to chronic inflammation and associated infection.

Several programs for education and diabetic foot care have demonstrated that amputations are not an inevitable consequence of diabetes. Knowing risk factors for amputations is important both for targeting education programs toward people at high risk and for suggesting modifiable factors. Research indicate that both DFU and DR share many aspects of their biological course like pathophysiology, risk factors, biomarkers, treatment options, preventive strategies and quality of life outcomes. The fact that the majority of patients with a DFU had DR raises concerns about the impact of this combined disability on patients' quality of life. This requires development

of an integrated management strategy. Hence, patients with DFUs should be monitored by an ophthalmologist, and those with DR should be promptly referred to a specialized diabetic foot clinic. Different public health interventions have shown that combined eye and foot screening is feasible, has a high uptake, reduces clinic visits, and identifies painful distal symmetrical polyneuropathy and the at-risk foot.

Keywords: Diabetic foot, Diabetic Retinopathy, Diabetes, Diabetic complications

1- Introduction

1.1- Objective of the review:

Diabetic foot ulcer (DFU) is a major cause of lower extremity amputation worldwide, while diabetic retinopathy (DR) is one of the leading causes of blindness in the world. Many studies have indicated that diabetic retinopathy is one of the important risk factors for development of diabetic foot ulcer and lower extremity amputation. Several programs for education and diabetic foot care have demonstrated that amputations are not an inevitable consequence of diabetes. Knowing risk factors for amputations is important both for targeting education programs toward people at high risk and for suggesting modifiable factors. Research indicate that both

DFU and DR share many aspects of their biological course like pathophysiology, risk factors, biomarkers, treatment options, preventive strategies and quality of life outcomes. The objective of this systematic review is to discuss these aspects for better understanding and management of diabetic complications.

1.2- Methodology of the review:

We searched English-language databases including PubMed and Medline. The search terms used were “diabetic foot” OR “diabetic feet” OR “diabetic foot ulcer” OR “diabetic foot problem” AND “epidemiology” OR “diabetic retinopathy and diabetic foot” OR “diabetic complications” OR “risk factors for diabetic foot ulcer” OR “epidemiology of diabetes and its complications”. We did not restrict the study design or the level (national or regional) of the studies. The data base research was not restricted by year of publications but guided by relevance to the subject. We then reviewed references of all the included articles to identify other potentially relevant studies.

1.3 – Introduction to the subject

Diabetic foot ulcers (DFUs), a micro-vascular complication of diabetes, are associated with a substantial increase in morbidity and mortality. DFUs are a combination of neuropathy, peripheral arterial disease, foot deformities, and infections. Sensory loss due to peripheral neuropathy in the diabetic foot is one of the earliest clinical signs that leads to the development of ulcers. Nerve dysfunction in diabetic patients may be described as sensory, motor, or autonomic (1).

Infections in ulcerated feet in patients with diabetes are a primary cause of morbidity, including discomfort, and reduced quality of life, and these give rise to a need for visits by health-care providers, wound care, antimicrobial therapy, and often surgical procedures/debridement. As such, these infections comprise the most frequent grounds for both diabetes-associated hospitalization and lower extremity losses. (2)

A lack of attention to foot hygiene and the use of poorly fitting footwear are the major factors that are preventable in the development of infection. Abrasions, rashes and loss of skin integrity can be the initiating factors in the development of diabetic foot infection (1).

Diabetic foot infection may range from fungal infections of the nail to severe necrotizing limb- or life-threatening infections. Early diagnosis and prompt definitive treatment may be delayed due to a lack of foot sensation, the patient’s poor eyesight, and poor judgment by the physician. Approximately 60% of foot infections start in webbed spaces and 30% in nails, while 10% are secondary to punctures (1).

An adequate description of ulcer characteristics, such as size, depth, appearance, and location, allows for mapping of progress during treatment. One of the most commonly used classification systems is the Meggitt-Wagner system. It has been used for ulcer classification almost for the past 40 years. This six-grade classification system takes into consideration the depth of the ulcer, the presence of gangrene, and the extent of tissue necrosis.

While antibiotics are necessary for treating a DFI (Diabetic foot infection), these are not usually sufficient. All patients will need appropriate wound care (debridement, dressings, and pressure off-loading) and most will need some surgical interventions.

Operating intervention of moderate to severe DFI is often essential, and includes aggressive incision, drainage and debridement of non-viable soft tissue and bone.

Diabetic retinopathy remains the leading cause of vision loss and preventable blindness in adults

aged 20–74 years, particularly in middle-income and high-income countries. (3) Vision loss from diabetes results from deranged function of the neurovascular unit of the retina, which is composed of capillary endothelial cells, pericytes, glial cells and neurons [4]. Pathologic changes to the neurovascular unit are manifested clinically as retinal micro aneurysms, intraretinal ('dot–blot') hemorrhages, leakage of serum lipoproteins (visible as hard exudates or retinal cysts), venular dilation and beading, and retinal nerve fiber layer disruption ('cotton wool spots'). Changes in visual function at preclinical and early stages manifest as reduced color vision, contrast sensitivity and abnormal visual field testing [5]. Vision is further impaired when hemorrhage, edema or ischemia affect the macula, or when abnormal proliferating fibrovascular membranes induce vitreous hemorrhage or retinal detachment. Moderate-to severe vision loss is usually due to DME (diabetic macular edema) or PDR (Proliferative diabetic retinopathy). Current systemic treatment options are limited to controlling hyperglycemia, hyperlipidemia and hypertension.

Patients diagnosed with DME may undergo focal laser photocoagulation or intravitreal injections of corticosteroid or anti-VEGF medication. Focal laser photocoagulation targets micro aneurysms in the macula and reduces leakage of plasma responsible for macular thickening. Persons with PDR are treated with pan-retinal photocoagulation (PRP) or anti-VEGF medication and may require vitrectomy if vitreous hemorrhage and/or retinal detachment ensues. Pan-retinal photocoagulation obliterates ischemic peripheral retinal tissues, which are the source of VEGF and other molecules that lead to abnormal vascular proliferation.

I. MANY RISK FACTORS HAVE BEEN IDENTIFIED FOR DR. SOME OF THESE, SUCH AS PERIPHERAL NEUROPATHY AND NEPHROPATHY, MAY MERELY SERVE AS MARKERS FOR POOR GLYCEMIC CONTROL OR MAY BE THE RESULT OF MULTIVARIATE REGRESSION MODELS THAT FAILED TO ACCOUNT FOR A CONFOUNDING VARIABLE (6). HOWEVER, SOME RISK FACTORS IDENTIFIED IN LARGE STUDIES WERE ASSOCIATED WITH HIGH HAZARD RATIOS AND ARE PROBABLY IMPORTANT IN UNDERSTANDING DR. THE FACTORS THAT APPEAR TO PRESENT A MAJOR HAZARD FOR THE DEVELOPMENT OR PROGRESSION OF DIABETIC RETINOPATHY INCLUDE HBA1C >8.0, DURATION OF DIABETES >10 YEARS, AN AMPUTATED OR NON-HEALING DIABETIC FOOT ULCER, METABOLIC SYNDROME OR EXCESS ABDOMINAL FAT, AND AFRICAN–AMERICAN OR HISPANIC ETHNICITY. (6)

On the other hand studies have indicated that diabetic retinopathy is one of the important risk factors for development of diabetic foot ulcer and lower extremity amputation (7,8) Research indicate that both DFU and DR share many aspects of their biological course like pathophysiology, risk factors, biomarkers, treatment options, preventive strategies and quality of life outcomes. The objective of this systematic review is to discuss these aspects for better understanding and management of diabetic complications.

2- Epidemiology

2.1 - Diabetes:

Without action, says WHO, the number of people living with diabetes worldwide is expected to rise to 643 million by 2030 and 783 million by 2045, yet one in two adults with the condition is unaware of it. (9). Global coverage targets for diabetes were agreed for the first time by WHO member states during the 75th World Health Assembly (WHA) to tackle rising prevalence and inequities in access to treatment and care. The

agreed targets state that by 2030, 80% of people living with diabetes are diagnosed; 80% have good control of glycaemia; 80% have good control of blood pressure; 60% of those with diabetes aged 40 years or older receive statins; and 100% of those with type 1 diabetes have access to affordable insulin and blood glucose self-monitoring. (9)

The IDF Atlas 2021-10th edition (10) confirms that diabetes is one of the fastest growing global health emergencies of the 21st century. Today, more than half a billion people are living with diabetes worldwide. An estimated 537 million adults aged 20–79 years are currently living with diabetes. This represents 10.5% of the world's population in this age group. Almost 90% of people with undiagnosed diabetes live in low- and middle income countries. Over 1.2 million children and adolescents have type 1 diabetes. Over half (54%) are under 15 years of age. The incidence of diabetes was stable or declined in the period from 2006 to 2017 in over 70% of mainly high-income populations, according to a systematic review of the literature (10). Over 80% of countries reported declining or stable diabetes incidence since 2010. However the greatest percentage increase from 2021 to 2045 in comparative prevalence is estimated to occur in middle-income countries due to their ageing populations. On the other hand, it is estimated that 94% of the increase in the number of people with diabetes by 2045 will occur in low and middle-income countries, where population growth is expected to be greater.

Approximately 6.7 million adults (20–79) are estimated to have died as a result of diabetes, or its complications in 2021. Pakistan is the country with the highest proportion of deaths under the age of 60 due to diabetes, with 35.5%. It is followed by Singapore, Brunei, and Kiribati with 31.4%, 31.3%, and 30.4% respectively. This demonstrates a high burden of diabetes in the working age population.

According to IDF Atlas 2021, there has been 316% increase in global health expenditure due to diabetes, growing from USD 232 billion in 2007 to USD 966 billion in 2021 for adults aged 20–79 years. The total diabetes-related health expenditure will reach one trillion USD by 2030.

2.2 - Diabetic complications of DFU:

The life time risk of DFU in a person living with diabetes is 15% to 25% [11]. The annual incidence is around 3% (11). DFU has been identified as the leading reason for hospitalization among patients with diabetes. {Although the majority of DFUs (60%–80%) will heal without intervention or after treatment, 10%–15% of them will remain active and 5%–24% of all patients with DFUs will eventually undergo a lower-limb amputation (12). DFU is estimated to account for 25% of all hospital admissions in patients with diabetes. Diabetes is the leading cause of non-traumatic amputation accounting for almost 80% of cases . Amputation is 10-30 times more likely in people with diabetes than those without the disease (13). It is estimated that a major amputation is carried out in a person with diabetes somewhere in the world every 30 seconds [14]. Approximately 55% of those with diabetes, who have undergone an LEA, will require amputation of the contralateral limb within 2–3 years with an increased mortality rate of up to 77% within 5 years.(15) A delayed diagnosis can lead to critical limb ischaemia (CLI) which has a very poor prognosis with the mortality rate at 15%–30% within one month increasing to 50% at one year and reaching 74% after five years (16) which is higher than breast cancer, colon cancer, and prostate cancer.(17)

The Wisconsin Study of Diabetic Retinopathy (WESDR) (18) had calculated 14 year incidence of Lower Extremity Amputation (LEA) in

diabetic population and evaluated risk factors for LEA (amputations of toes, feet, or legs).

The cumulative 14-year incidence of LEA was 7.2% in younger- and 9.9% in older-onset patients. In multivariable analyses based on the discrete linear logistic model, LEA in the younger-onset group (diagnosed before 30 years of age and using insulin) was more likely for males, older age, higher glycosylated hemoglobin, higher diastolic blood pressure, history of ulcers of the feet, and more severe retinopathy. In younger-onset patients, pack-years smoked (Defined as the number of packs (1 pack = 20 cigarettes) smoked per day multiplied by the number of years smoked) was also associated with LEAs, and daily aspirin use was inversely associated. In the older-onset group (diagnosed at or above 30 years of age), LEA was more likely for men and if the subject had higher glycosylated hemoglobin, higher pulse pressure, history of ulcers, and more severe retinopathy. There was a statistically significant relationship between increasing severity of retinopathy and higher incidence of LEA. Controlled for age and sex, this relationship was maintained.

Zhang et al (19) performed a systematic review and meta-analysis of global epidemiology of DFU. They found that global diabetic foot ulcer pooled prevalence was 6.3% which was higher in males than in females and higher in type 2 diabetic patients. Continent wise, North America had the highest prevalence 13.0%, Oceania had the lowest 3.0%, and the prevalence in Asia, Europe, and Africa were 5.5%, 5.1% and 7.2% respectively. Country wise Australia has the lowest 1.5%, and Belgium has the highest prevalence 16.6%, followed by Canada 14.8%, and USA 13.0%. The patients with diabetic foot ulcer were older, had a lower body mass index, longer diabetic duration, and had more hypertension, diabetic retinopathy, and smoking history than patients without diabetic foot ulceration.

The same meta-analysis showed that diabetic retinopathy was present in 63.3% of diabetic foot ulceration patients and in 33.3% of non-diabetic foot ulceration patients.

However this study had limitations. There was high heterogeneity (more than 90%) in the meta-analysis. The study comprised four different kinds of population (population based, hospital based, community based and public health center), and 611,226 of 801,985 participants included in this study were from hospital, which may not represent the general population. Hence the difference in prevalence between population based and hospital based studies may also explain the high heterogeneity. Also, 60,610 subjects did come from one study, which accounted for a relatively high weight when using random effect model to calculate the pooled prevalence.

2.3 - Diabetic complication of DR

A systematic review and meta-analysis of 59 population based studies looked at global prevalence of diabetic retinopathy and estimated projection of burden through 2045 (20). Among individuals with diabetes, global prevalence was 22.27%, for DR, 6.17% for vision threatening diabetic retinopathy (VTDR), and 4.07% for clinically significant macular edema (CSME). In 2020, the number of adults worldwide with DR, VTDR, and CSME was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively; by 2045, the numbers are projected to increase to 160.50 million, 44.82 million, and 28.61 million, respectively. Diabetic retinopathy prevalence was highest in Africa (35.90%) and North American and the Caribbean (33.30%) and was lowest in South and Central America (13.37%). In meta-regression models adjusting for habitation type, response rate, study year, and DR diagnostic method, Hispanics and Middle

Easterners with diabetes were more likely to have DR compared with Asians.

2.4 – Cost of diabetic complications

DM is one of the most expensive non-communicable diseases (21). In Europe, estimated costs of cardiovascular disease were 195 billion euros in 2009 (106 billion euros for direct costs) (21), cancer costs were estimated to be 126 billion euros in 2009 [22], and the cost of DM was estimated to be 89 billion euros in 2011 in Europe. The last figure was underestimated because it did not include indirect costs (21). It is relevant to highlight the specific burden of DR, diabetic kidney disease (DKD) and DFU linked with the total cost of DM. The French ENTRED survey in 2007 showed that microvascular complications and end-stage renal disease induced medical costs respectively 1.1 and 6.7 times higher than without these complications (21). However, when comparing the cost of different complications, it is important to know which level of severity is analyzed. Indeed, cost increases with the severity of the complication. In the Stockl et al. study [23], the cost of DFU increased from US $ 1892 (SD = 8972) to US $ 27,721 (SD = 49,615) from severity level 1 to severity level 4/5. In a study by Happich et al. [24], the cost estimates of DR ranged from 231 euros (3–2038) in group 1 (mild NPDR without CSME) to 1433 euros (3–42,110) in group 5 (CSME and any degree of diabetic retinopathy). In an another study by Happich et al. (25), the cost estimates of DKD ranged from 684 euros in the microalbuminuria stage to 10,223 euros in the renal failure stage. Similar results were found in another study: while cost per patient of microalbuminuria was US $ 15, the cost of end stage of renal disease was US $ 37,022 [26].

3: Pathophysiology

Studies indicate that poor regulation of hyperglycemia is associated with the pathogenesis of vascular damage (oxidative stress, endothelial damage, inflammation) leading to the development of macrovascular (heart disease, stroke) and microvascular complications (polyneuropathy, nephropathy, retinopathy) (27).

DFUs are a complicated mixture of neuropathy, peripheral arterial diseases, foot deformities, and infections (1). If infection advances to deeper structures, including the underlying bone, diabetic foot osteomyelitis (DFO) develops. DFIs are the most frequent diabetes-related complication requiring hospitalization, and DFO is present in 44- 68% of patients with DFIs admitted to the hospital (1). About 60% of diabetic patients with foot ulcers have neuropathy (1). Nerve dysfunction in diabetic patients may be described as sensory, motor, or autonomic.

Hyperglycemia in diabetes is thought to cause dysfunction of the immune response, which fails to control the spread of invading pathogens in diabetic subjects. Therefore, diabetic subjects are known to be more susceptible to infections.

3.1 – Diabetic Foot Ulcers and DR- A manifestation of microvascular disease; Joshua et al (28) investigated whether microvascular disease is associated with amputation in a large cohort of veterans to determine whether microvascular disease diagnosed in any location increases the risk of amputation alone and in combination with peripheral artery disease. They analyzed the effect of prevalent microvascular disease (retinopathy, neuropathy, and nephropathy) and peripheral artery disease status on the risk of incident amputation events after adjusting for demographics and cardiovascular risk factors. Among 125674 veterans without evidence of prior amputation at baseline, the rate of incident amputation over a median of 9.3 years of follow-up was 1.16 per 1000 person-years,

yielding a total of 1185 amputations. In time-updated multivariable-adjusted analyses, compared with those without peripheral artery disease or microvascular disease, microvascular disease (MVD) alone was associated with a 3.7-fold increased risk of amputation; peripheral artery disease (PAD) alone conferred a 13.9-fold elevated risk of amputation; and the combination of peripheral artery disease and microvascular disease was associated with a 22.7-fold increased risk of amputation. After multivariable adjustment, compared with those diabetic participants without either vascular disease, the presence of MVD alone was associated with a 3.1-fold increased risk of amputation; PAD alone conferred a 7.9-fold elevated risk of amputation; and, even more clearly, the combination of PAD and MVD was associated with a 15.9-fold increased risk of amputation in diabetics.

The increase in amputation risk among those with MVD was independent of the presence of PAD, augmented the risk when PAD was present, and remained robust after adjusting for demographics, cardiovascular risk factors, and other factors associated with vascular disease.

The study showed that MVD helps identify a population not previously considered at particularly high risk for amputation and, when added to PAD, identifies a group of patients at very high risk for amputation. MVD alone is associated with 18% of all amputations and 15% of all below-knee amputations, implicating MVD as an important risk for amputation.

This work suggests that microvascular dysfunction may be a systemic phenomenon that leads to adverse clinical events (29–31). It simply demonstrates dysfunction of the microvasculature in beds remote from clinical presentation. For example, both retinal arteriolar and skin arteriolar dysfunction directly correlate with albuminuria, in the presence or absence of diabetes mellitus. (32) The presence of retinopathy (33) and nephropathy (34, 35) has been shown to associate inversely with coronary flow reserve. With particular relevance to amputation, both retinopathy and nephropathy are associated with impaired skin microvessel function and lower-extremity amputation (18,36,37). Joshua et al conclude that clinical evidence of MVD diagnosed in any vascular bed increases the risk for dermal microvascular dysfunction, poor wound healing, and amputation.

3.1.1 – Other vascular dysfunctions: Endothelial and arterial stiffness indexes being good indicators of vascular health have also been assessed both for DFU and DR. Tuttolomondo et al (38) found out that the presence of diabetic foot is associated with arterial stiffness and endothelial function impairment. Similarly Siasos et al (39) in their study found a significant association between DR and vascular dysfunction. The progression of the disease and the development of microvascular complications, such as PDR, were strongly associated with further deterioration of endothelial function and arterial stiffness. These findings highlight the importance of monitoring endothelial function in diabetic patients to avert irreversible microvascular complications.

3.2.1 – Role of Advanced Glycation End Products (AGEs) in DR. The nonenzymatic reaction of sugars with proteins through the Maillard reaction after undergoing multiple steps finally leads to the formation of AGEs (40). One mechanism linking chronic hyperglycemia with tissue damage such as that in diabetic retinopathy is the formation and accumulation of advanced glycation end products (AGEs) (41). Advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs) might be the contributors to accelerated micro- and macrovasculopathy observed in diabetes (42).

AGEs have been implicated in both the microvascular and macrovascular complications of diabetes such as retinopathy, nephropathy, neuropathy, and also macrovascular disease atherosclerosis (43, 44).

Key factors crucial to the formation of AGEs include the rate of turnover of proteins for glycoxidation, the degree of hyperglycemia, and the extent of oxidant stress in the environment (45–47). If all or even one of these conditions is present, both intracellular and extracellular proteins may be glycated and oxidized. AGEs are large heterogenous group and total number of existing AGEs is not known. Among the most common chemically characterized AGEs in humans include pentosidine and CML. AGEs like pentosidine have intrinsic fluorescence, and thus, tissue and plasma fluorescence can be used as markers of AGE accumulation whereas AGEs such as CML are nonfluorescent and may be detected by procedures like enzyme-linked immunosorbent assays (ELISA) (48 – 51).

Along with endogenous formation of AGEs, they can also originate from exogenous sources such as tobacco, smoke, and diet [48-51]. Therefore different types of high sugar and fat diet can be more harmful.

AGEs accumulate with age and at an accelerated rate in diabetes (52,53) within various organs that are damaged by diabetes, and the accumulation rate of these AGEs is accelerated by hyperglycemia (54). AGEs accumulate in retinal pericytes during diabetes (55) influencing pericyte survival and function finally leading to pericyte loss. Along with loss of pericytes, other characteristic changes include thickening of the basement membrane, hyperpermeability, and microaneurysm formation (56). Pericytes play an important role in the maintenance of microvascular homeostasis and thus loss of pericytes could predispose the vessels to angiogenesis, thrombogenesis, and endothelial cell injury, thus leading to diabetic retinopathy. Murata et al. (57) found association between the accumulation of CML in the human diabetic retina with proliferative and non-proliferative changes and the expression of VEGF.

Hammes et al. (58, 59) have studied the role of AGE in the development of diabetic retinopathy and the effect of the AGE-formation inhibitor, aminoguanidine, in animal models. After 2 weeks of diabetes induction, aminoguanidine treatment was started which resulted in a dramatic reduction in the development of retinal lesions, 80 % reduction in pericyte loss, absence of micro aneurysms and endothelial cell proliferation and prevention of accumulation of AGE at the branching sites of precapillary arterioles (59).

Takayanagi et al (60) recently assessed the levels of skin autofluorescence (sAF) to assess the association between AGEs and DR stages. The results suggested that AGE scores were higher in patients with DM and were independently associated with progression of DR. In addition, more PDR was seen in the highest quartile of AGE scores. This study highlighted the clinical use of the AGE score as a non-invasive, reliable marker to identity patients at risk of sight-threatening DR.

3.2.2 – Role of Advanced Glycation End Products (AGEs) in DFU. Accumulation of AGEs in the peripheral nerves has recently been proposed as an additional risk factor for the development of diabetic neuropathy (DN). The gold standard for measurement of tissue-bound AGEs is tissue biopsy. However, their assessment with the newer, fast and simple method of skin autofluorescence (sAF) has recently gained special interest by virtue of its non-invasive, highly reproducible nature and its acceptable correlation with the reference method of skin biopsy. Accumulation of tissue AGEs evaluated

by sAF has been shown to independently correlate with DN (61). Importantly, increasing evidence underscores their potential value as early biomarkers of the latter. Earlier Meerwaldt et al *(62)* had shown that skin autofluorescence representing AGE accumulation is increased during early stages of diabetic neuropathy and correlates with the severity of nerve dysfunction and foot ulceration. But even before clinical symptoms of diabetic neuropathy exist, skin autofluorescence is closely related to nerve conduction and to markers of autonomic nerve function. This study supports the important clinical impact of AGE accumulation in the pathogenesis of diabetic neuropathy.

Similarly other studies have also shown that, high sAF levels have been observed in individuals with diabetic foot ulcers and highest sAF quartile has been independently associated with high risk of foot ulceration (63,64). In the same context, an inverse relationship between high sAF levels and lower electrochemical skin conductance has been demonstrated, even in the normal range of sudomotor function, thereby providing evidence that increased sAF levels may even precede small-fiber sudomotor dysfunction (65).

3.3 – Retinal diabetic neuropathy. Recent evidence suggests that retinal diabetic neuropathy (RDN) also occurs in people with diabetes, but little is known about the temporal relationship between DR and RDN. This longitudinal study by Sohn et al (66) in people with diabetes with absent or minimal DR shows that RDN precedes signs of microvasculopathy and that RDN is progressive and independent of glycated hemoglobin, age, and sex. This finding was further confirmed in human donor eyes and in two experimental mouse models of diabetes. The results suggest that RDN is not ischemic in origin and represent a shift in our understanding of the pathophysiology of this complication of diabetes that potentially affects vision in all people with diabetes mellitus (66).

The study found that in 45 people with DM and absent or minimal DR there was significant, progressive loss of the nerve fiber layer (NFL) and the ganglion cell (GC)/inner plexiform layer on optical coherence tomography analysis (OCT) over a 4-year period, independent of glycated hemoglobin, age, and sex.

The retinal diabetic neuropathy (RDN) functionally reflects as deficits in the electroretinogram (ERG), dark adaptation, contrast sensitivity, color vision, and microperimetric and perimetric psychophysical testing (67-70). Because the neuroretina forms an extension of the brain embryologically, functional retinal changes may correlate with the cognitive decline in people with DM (71). Studies have shown that local functional loss on pattern ERG, which measures GC function, predicts local microvasculopathy and macular edema 1 year later (72). Most assume that RDN is a secondary effect of microvascular damage, but mounting evidence shows that neuroretinal alterations are present even in the absence of clinically detectable retinal vasculopathy (68, 73-76). However, these studies were unable to show the temporal relationship between RDN and vasculopathy (77,78). Sohn et al (66) show that inner RDN may occur before signs of microvasculopathy or DR in people with DM. RDN is progressive over the course of DM both in humans and mice and outstrips the neurodegeneration associated with normal aging.

Whether RDN plays a role in the development of retinal ischemia in DM is unclear. And there are currently no treatment or management options to mitigate RDN.

The results also do not establish whether relatively poor glycemic control will result in more rapid neuroretinal degeneration. In addition,

although current therapies for DR, such as the monthly intravitreal administration of anti-VEGF and steroids, are highly successful clinically, there is some concern that anti-VEGF treatment may cause or accelerate retinal neurodegeneration in rodents (66).

Interestingly, although HbA1C is well known to affect microvasculopathy and DR in people with DM, Sohn et al (66) did not find any relationship between HbA1C and the progression of RDN, possibly indicating that their pathophysiologies are initially independent; this possibility is also suggested by results from the Epidemiology of Diabetes Interventions and Complications/Diabetes Control and Complications Trial study showing that HbA1C explains only 9.1–14.1% of the variance in development of DR (79).

In summary, neuroretinal degeneration precedes microvasculopathy in people with DM. The retinal neurodegeneration is not mediated by retinal microvascular disease in the form of microscopic capillary loss or the earliest manifestation of DR, i.e., pericyte loss, but is primarily related to DM duration. These results suggest that RDN is not ischemic in origin and represent a shift in our understanding of the pathophysiology of this complication of DM that potentially affects vision in all people with DM.

Thus neuropathy assumes a common role in pathophysiology of both DFU and DR though both may have different origins.

3.4.1 – Role of Inflammation in DR. In contrast to previously proposed mechanisms which reflect DR as a single hyperglycemia-induced process, including formation of advanced glycation end products as well as the polyol, protein kinase C and hexosamine pathways, recent studies have demonstrated that diabetic complications, including DR, are underpinned by a complex interplay between metabolic and inflammatory changes (80, 81). This process is thought to be facilitated by the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, a part of the innate immune system that sets into motion the inflammatory cascades in response to cellular stress signals, which becomes dysregulated and aggravates chronic inflammation in DR (80, 82-84). Due to its key part, the NLRP3 inflammasome is a potential upstream target for future DR therapeutics.

Kuo et al (85) in a very recent systematic literature review to determine the role of the inflammasome in DR development showed that inflammasome biomarkers IL-1β and IL-18 increased significantly from non-proliferative DR to proliferative DR in both vitreous and serum, suggesting the inflammasome pathway is activated as DR progresses and that serum inflammasome levels could be explored as potential biomarkers for DR progression.

Earlier landmark studies such as the Hoorn Study have reported and highlighted the important role of subclinical inflammation in the development of diabetic retinopathy [86-88]. It is now established that the role of inflammation in diabetic retinopathy is both prominent as well as complex. While hyperglycaemia, oxidative stress, advanced glycation endproduct formation, and hypertension all contribute to inflammation, the inflammatory response itself propagates these pathways further. The subclinical inflammation leads to leukostasis which is an important event in diabetic retinopathy pathogenesis, leading to capillary occlusion and ROS-mediated cell death, as well as amplifying the inflammatory response locally in the retinal tissue (89-90). The use of anti-inflammatory drugs such as the intravitreal triamcinolone acetonide (IVTA) and nonsteroidal anti-inflammatory drugs such as nepafenac has been reported to reduce VEGF expression, normalise vascular permeability, reduce levels of

cell death and leukostasis, and improve visual acuity [91–93].

3.4.2 – Role of Inflammation in DFU Similarly in a study about *expression of the NEK7/NLRP3 inflammasome pathway in patients with diabetic lower extremity arterial disease (DLEAD)* by Cai et al, the key findings were as follows: (1) the levels of serum IL-1β and serum IL-18, which are downstream effector molecules of the NLRP3 inflammasome, are increased in DLEAD; (2) NEK7 and the NLRP3 inflammasome show significantly increased expression in the arteries of patients with diabetic foot; and (3) overexpression of the NEK7/NLRP3 inflammasome mainly occurs in vascular smooth muscle cells. Resulting excessive inflammation due to macrophages in the circulation, endothelial cells in the vascular intima, vascular smooth muscle cells in the media, fibroblasts in the vascular adventitia and perivascular fat can cause diabetic vascular injury. The study suggests that the inflammatory state mediated by the NLRP3 inflammasome might trigger atherosclerosis and vascular calcification and aggravate diabetic vascular injury.

However, what causes NLRP3 inflammasome activation in DLEAD? At present, few reports exist on the NEK7/ NLRP3 inflammasome signaling pathway, especially with regard to diabetes and its complications. Cai et al (94) examined the occluded lower extremity arteries of patients with diabetes that showed that NEK7 expression was significantly increased in occluded lower extremity arteries indicating that the NEK7/ NLRP3 inflammasome signaling pathway might be involved in diabetic vascular injury. Furthermore, they also noticed by immunofluorescence staining that expression of the NEK7/NLRP3 inflammasome signaling pathway mainly occurred in vascular smooth muscle cells. These results suggest that activation of the NEK7/NLRP3 inflammasome in vascular smooth muscle cells might be the key mechanism of DLEAD. Therefore, inhibition of NEK7/ NLRP3 inflammasome pathway activation in vascular smooth muscle cells might become a new target for delaying diabetic macroangiopathy.

3.5 – Role of VEGF. VEGF is highly implicated in DR primarily due to its dual roles in promoting vascular permeability in DME and neovascularization in PDR (95, 96), which is also the target of anti-VEGF agents, one of the treatments for DR. While the release of VEGF into the vitreous is believed to be induced by retinal ischemia (97, 98), the cause and effect of elevated serum VEGF levels in DR development is not clear. Here, studies by Kaviarasan et al., 2015 (99) and Zhou et al., 2012 (100) showed a significant increase in vitreous VEGF levels in PDR compared to controls, suggesting that VEGF acts locally in the posterior segment of the eye during PDR. Interestingly, studies also found increased serum VEGF levels with DR progression, with some even showing statistically significant elevation in serum VEGF levels in PDR relative to NPDR (101, 102). In fact, Guo et al., 2014 (103) found significantly higher VEGF levels in the serum of patients with severe compared to mild-to-moderate DR and the same trend was found in patients with diabetic nephropathy as well as those with diabetic hypertension, suggesting elevated serum VEGF levels in diabetes are associated with the development of systemic vascular diseases. Hamid et al., 2021 (104) also showed that in patients with stage 3 and 4 diabetic nephropathy, serum VEGF levels were significantly higher in those who also had DR compared to those who did not, implying that a threshold serum VEGF level is potentially required for the onset of DR.

An important observation to note is that the potency of VEGF to induce vasopermeabilty is 50,000 times more than histamine in the dermal microvasculature (105)

3.6.1 – Role of Genetics*:* VEGE gene. Evidence indicate that susceptibility to development of diabetic complications is partly under the control of genetic factors. Regarding the role of VEGF as The frequency of genotype AA was significantly decreased in patients with DFU compared with diabetic patients without DFU conferring a protective effect.

Functional polymorphisms within VEGF gene have shown association with various conditions including diabetic neuropathy and retinopathy. The association between this polymorphism and several other conditions including atherosclerosis, lung cancer, Alzheimer's disease and graft survival has been previously reported (106)

There are several studies indicating that the magnitude of VEGF gene expression level is partly linked to the variations at its gene structure itself [34–36]. For illustration, it has been shown that the diabetic patients who do not develop retinopathy have a markedly decreased response to hypoxic induction of VEGF production, which may explain why some diabetic patients with long-standing diabetes do not develop retinopathy (107).

More recently association between this polymorphism and proliferative diabetic retinopathy (PDR) has been found in Japanese population [30] and allele A has been found as a risk factor for development of PDR. Despite detrimental effect of VEGF in diabetic retinopathy, it has beneficial effect in diabetic neuropathy. Therefore it seems that lower frequency of A allele might lead to an insufficient angiogenesis in patients and presence of DFU as a consequence (105).

a potential mediator of diabetes complications, analysis of VEGF gene variations in a case-control study was conducted in Iranian population by Amoli et al (105) to measure the impact of a candidate gene on the development of DFU. They found that the distribution of VEGF gene polymorphism at (-2578) was significantly different between patients with DFU and controls. In a recent study by Brem et al by delivering VEGF isoform 165 to the wound using an adenovirus vector they have observed accelerated wound healing in animal models of diabetes (108,109). Also topical recombinant VEGF has been suggested and under trial for the treatment of DFU (110).

3.6.2A – Role of Genetics*:* GWAS studies in DR Genome wide association studies (GWAS) have been carried out in recent past about different diabetic complications including DR and DFU. A Genome Wide Association Study or GWAS is a hypothesis-free genetic association study used to identify genes for complex disorders based on phenotype information and genetic information of a population or a cohort. (111). The method involves surveying the genomes of many people, looking for genomic variants that occur more frequently in those with a specific disease or trait compared to those without the disease or trait. Once such genomic variants are identified, they are typically used to search for nearby variants that contribute directly to the disease or trait.

DR has the highest sibling recurrence risk of the microvascular diabetic complications (112), and the heritability estimates for DR range from 25 to 52% (113-117).

Multiple GWAS on DR have been published including studies in Mexican Americans [118], Taiwanese [119], Chinese [120], Japanese [121], and White Australian [122] subjects with T2D, and in European American subjects with T1D

[123]. However, the numbers of subjects were small (a couple of hundreds up to 3000) and the results were mostly suggestive.

A recent GWAS in 844 white Australians with T2D found variants associated with severe non-proliferative DR near the GRB2 gene, with activated protein kinase pathway) in response to insulin by binding the major insulin receptor substrate IRS-1, and GRB2 expression was found up-regulated in the retina of the mouse model for retinopathy [122].

A small Whole Exome Sequencing (WES) study of 43 Saudi subjects with diabetes without DR and 64 subjects with DR identified three genes, NME3, LOC728699, and FASTK, with an excess of rare variants in subjects without DR (p value<5 x 10^{-8}) (124). This was the first whole-exome sequencing study on DR suggesting excess of rare variants in three genes resulting in protection from DR.

As for the more recent observations from GWAS, validation in other cohorts is still required to confirm the findings.

3.6.2B – Role of Genetics*:* GWAS studies in DFU Familial clustering has been found for diabetic neuropathy, but more modest than for other microvascular complications (112). Because of the challenges to define the phenotype, only a few genetic studies have been performed on diabetic neuropathy. Although no systematic literature-based meta-analyses have been published on all candidate genes for diabetic neuropathy, meta-analyses have been performed for the insertion/deletion variant in angiotensin-converting enzyme (ACE) polymorphism as a genetic biomarker of diabetic peripheral neuropathy [125, 126] all showing nominal evidence of association with diabetic neuropathy. Although the first GWAS on diabetic neuropathy (127) suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain, no

directionally consistent replication in all three replication cohorts (both T2D and T1D, and of European and Indian ancestry), resulting in a p value of 4.2 × 10−8 at the combined meta-analysis [122]. GRB2 activates the MAPK (mitogen-

replication was attempted, and the associations did not reach genome-wide significance, further evaluation of these loci in other cohorts is required to replicate these findings.

Peripheral arterial disease (PAD) is clinically observed as an aberrant ankle-brachial index, claudication, or critical limb ischemia, ultimately requiring amputation, particularly in subjects with diabetes [128]. Relatively few genetic risk loci that affect the development of PAD have been discovered, even in the general population. However, the 9p21 region associates with PAD in the general population [129] and preliminary findings from ongoing PAD GWAS also suggest 9p21 as a risk locus in diabetes, and highlight other polymorphisms that are only associated with PAD in diabetes [130]

At the moment, the role of genetics in DFUs is not clearly understood. It is assumed that DFUs are a common complex disorder determined by both genetic and environmental factors. A previous gene study has suggested that rs699947 in VEGF is associated with DFUs (131). There is increasing evidence that epigenetic changes (i.e. molecular modification to genes) can have an impact on the development of DFUs by affecting the healing ability of tissues (132). So far, there have not been any linkage studies that have reported genetic loci of DFUs.

Meng et al (133) conducted a GWAS with the purpose to identify genetic contributors to the development of DFUs in the presence of peripheral neuropathy in a Scottish cohort with

diabetes. A case was defined as a person with diabetes (type 1 or type 2) who had ever had a foot ulcer (current or previous) in at least one foot, as well as a positive monofilament test result (i.e. evidence of peripheral neuropathy) recorded in their longitudinal e-health records. A control was defined as an individual with diabetes (type 1 or type 2) who has never been recorded as having a foot ulcer in either foot but who had a positive monofilament test result recorded in either foot in their longitudinal e-health records. There were 699 DFU cases and 2695 controls in the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) dataset. The single-nucleotide polymorphism rs80028505 (Chr6p2131) in MAPK14 reached genome-wide significance with a lowest P-value of 2.45×10^{-8} . The narrow-sense heritability of this phenotype is 0.06. The authors conclude that genetic variants in skin-related gene, MAPK14 are strongly linked with DFU.

A recent pilot study from Poland (134) aimed to determine genetic predictors of DR among patients with type 2 diabetes (T2D) and diabetic foot (DF) based on pathogenetic pathways. The study included 114 patients with T2D and DF (64 with DR, 50 without DR). Genetic analysis was performed for each patient. The genetic material was isolated from the whole blood samples using the salting-out method. 8. The results of their study suggest that the single nucleotide variants (SNVs) rs759853, rs3134069, and rs2073618 may be involved in the development of DR in patients with T2D and DF.

A previous study showed that there is a genetic predisposition for the severity of DR, (117) and in patients with long-lasting type 2 diabetes (T2D) even with poor glycemic control, diabetic complications often did not occur. Therefore, it appears that, in addition to known metabolic and hemodynamic factors, genetic factors also influence the course of DR, though the exact underlying mechanisms are still not known. Consequently the development of methods that would allow an early identification of patients with a genetic predisposition to DR in those with T2D and DF could slow the disease progression. This Polish study by Beata Mrozikiewicz-Rakowska et al (134) demonstrated that genetic predisposition to DR in patients with T2D and DF may be due to the presence of these single nucleotide variants. It also showed the possible directions for future investigation of the genetic background of DR in patients with DF.

Larger data sets and international collaboration to combine genome-wide data across studies will be essential for discovery of novel loci and to clarify the role of previously reported signals (135) While whole exome and genome sequencing may reveal novel low-frequency and rare variants for diabetic complications, the exome chip provides an alternative approach to targeting low-frequency variants at lower cost, making it feasible in larger cohorts [136].

4 - Risk Factor Assessment for DFU and DR

Epidemiological studies have suggested multiple risk factors for DFUs: diabetic neuropathy, peripheral vascular disease, biomechanical factors, previous foot ulceration, poor glycaemic control, longer duration of diabetes, smoking, ethnicity, retinopathy, nephropathy, insulin use, poor vision, age and male sex. *(137)*

Number of studies have observed that diabetic foot patients with retinopathy had higher levels of diabetic biomarkers such as plasma uric acid and ceruloplasmin (138-139), while ceruloplasmin was an independent predictor for the progression of diabetic nephropathy in type 2 diabetic patients

(140). These results implied that there is a link between retinopathy and diabetic foot ulceration.

The Wisconsin Study of Diabetic Retinopathy (141) studied the diabetics younger than 30 years of age for 20 years looking at the retinal vascular changes and calculated that unadjusted risk of LEA was higher in generalized and focal narrowing of retinal vasculature independent of their level of glycosylated hemoglobin, blood pressure and presence of foot ulcers. Thus the damage to the retinal vasculature in diabetes may reflect such changes elsewhere in the body. Retinal arteriolar narrowing has been shown to be an indicator of inflammation, elevated blood pressure, compromised endothelial narrowing and is an independent predictor of coronary artery disease (141).

An article "Association of foot lesions with retinopathy in patients with newly diagnosed diabetes by C H Walsh, N G Soler, M G Fitzgerald and J M Malins published in Lancet ,1975 Apr 19;1(7912):878-80 was the earliest work describing the relationship between diabetic foot ulcer and diabetic retinopathy. Due to its historical nature, the abstract is being reproduced here:

"A proportion of newly diagnosed diabetic patients have features so characteristic that they form a distinct syndrome. The patients are predominantly male and present with a foot lesion which is often long established. They are subsequently found to have diabetes mellitus and diabetic retinopathy. In addition, many of them manifest a striking indifference towards their illness. Forty seven such patients have been seen between the years 1960-1969 at a diabetic clinic in Birmingham which saw a total of 6451 newly diagnosed patients in the same period. 26 of the 45 patients in whom follow-up was complete have died. The present state of health of the 19 surviving patients indicated that the prognosis is poor for patients who have retinopathy and foot lesions when diabetes is diagnosed."

The current systematic review revolves around this observation that was made almost half a century back.

There is growing evidence that diabetic complications in the retina consists of microvascular as well as neurological changes. As discussed above under the Pathophysiology section, retinal diabetic neuropathy precedes microvascular changes in the retina. Studies also show that microalbuminuria/nephropathy precedes diabetic retinopathy. By the time retinopathy worsens, symptoms of diabetic foot ulcer make their appearance. Thus both the neurological and vascular changes in retina are indicators for similar changes taking place elsewhere in the body and provide a very good window of opportunity for timely diagnosis and prompt intervention of diabetic complications. In the following paragraphs we will further review the literature for various risk factors for diabetic eye disease as well as for diabetic foot ulcers.

The classic risk factors for onset or progression of DR include poor glycemic control, hypertension and hyperlipidemia. The Diabetes Control and Complications Trial (DCCT) demonstrated that, in Type 1 diabetes, intensive control of blood glucose versus conventional therapy significantly reduced diabetic retinopathy onset (by 76%) and progression (by 54%) [142]. Elevated HbA1c is also associated with increased risk of diabetic retinopathy progression in Type 1 diabetes [143,144]. The UK Prospective Diabetes Study (UKPDS) showed similar reductions in DR progression with strict metabolic control in Type 2 diabetics [42]. Recently it has been reported that keeping the HbA1c level below 7.6% (60

mmol/mol) as a treatment target seems to prevent proliferative DR for up to 20 years in type 1 diabetic patients [*145*] The importance of tight blood pressure control in preventing vision loss and progression of retinopathy was demonstrated in a later report of the UKPDS [146] and has been confirmed by additional studies [147]. In addition, elevated total cholesterol and LDL have been shown separately to increase the risk of diabetic retinopathy [147,148]. The benefit of lipid control was evaluated by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study group; in this study, treatment with fenofibrate was found to significantly reduce progression of DR (by 40%) [149]. The long-term importance of risk factor modification was recently highlighted in a longitudinal report of the DCCT cohort after 30 years of follow-up. It showed significantly lower cumulative incidence of PDR in the intensive therapy group versus historical cohorts of patients who developed diabetes between the 1950s and 1970s [150]. Similar trends have also been observed in Scandinavia [151,152]. The reduced rates of diabetic complications demonstrated here are probably the result of intensive glycemic control, in addition to improved treatment of hypertension and hyperlipidemia.

Recent research has highlighted additional risk factors in the development of DR and other complications. It is now clear that the development of DR is a more complex, multifactorial process than originally thought. Moreover, the severity of expression of retinopathy can be highly variable from one individual to another and the limited predictive ability of HbA1c has become increasingly evident (6). A model of DR progression indicated an approximate progression rate of 2% per year in Type 1 diabetic patients that had achieved the target HbA1c of 7.0 [142]. Quantification of the contributions of different factors in the development of DR has further demonstrated the limitations of HbA1c. A reappraisal of the DCCT data showed that HbA1c was responsible for only 11% of the risk of developing DR [153]. Similarly, in the Wisconsin Epidemiological Study for Diabetic Retinopathy, the combination of lipids, blood pressure and blood glucose were responsible for 10% of the risk of DR [154]. This finding supports the theory that a variety of other risk factors exist and contribute to the development and progression of DR, even when the classic risk factors are appropriately modified. Recent studies using multivariate regression models have highlighted new independent risk factors for retinopathy that account for a significant relative contribution to the overall risk. These risk factors involve multiple systemic organs and tissues, and demographic factors, including male gender [155,156], Hispanic and African–American ethnicity [155], and longer duration of diabetes [157]. The presence of coexisting nephropathy and neuropathy increase the risk of diabetic eye complications. Multiple cross-sectional and cohort studies have demonstrated that factors related to renal insufficiency impact the likelihood of DR, including vitamin D and magnesium deficiency [158,159], proteinuria [160] and nephropathy [161]. Neuropathy can lead to non-healing extremity ulcers and amputations, and a well-known connection has been established between peripheral neuropathy and DR [141,162]. Hamalainen and colleagues demonstrated a correlation between lower limb amputations and retinopathy in a case–

control study of 733 diabetic patients [163]. In addition, a fivefold greater risk for nonproliferative diabetic retinopathy and 21-fold greater risk for PDR were demonstrated in a study of Pima Indians who had undergone lower-extremity amputations [164]. Other organ dysfunction, including pulmonary and hepatic disease, increases the risk of progression of retinopathy like obstructive sleep apnea [165] sleep-disordered breathing [166-167] and nonalcoholic fatty liver disease [168-169]. In addition, obesity and other metabolic factors have also been linked to the risk of worsening DR. An elevated BMI (hazard ratio [HR]: 1.16) [156], visceral fat accumulation (HR: 4.8) [170] and metabolic syndrome (HR: 3.7) [171] all increase the risk of retinopathy. These risk factors may not solely represent markers for poor glycemic control, but systemic factors (i.e., amputations and nonhealing ulcers) may also contribute to the progression of PDR through inflammatory pathways (6). A recent multivariate analysis of a large cohort of patients with newly diagnosed nonproliferative diabetic retinopathy found that the risk of progression to PDR increased by 54% in patients with non-healing ulcers after adjustment for confounders [161]. In the same study, each one-point increase in HbA1c increased the risk of retinopathy progression by 14%; therefore, a nonhealing ulcer conferred the same risk as a 3% increase in HbA1c. One explanation for this finding may be that nonhealing ulcers upregulate the systemic inflammatory response, worsening inflammation in the retina (6). This argument is strengthened by the observation that diabetic wounds have elevated levels of cytokines, including TNF-α, IL-8 and MCP-1 [172].

Patients with DR also have elevated cytokine levels locally in the retina and vitreous [173], which may be secondary to systemic inflammation. For example, increased serum cytokine levels, including VEGF and MCP-1 [174], IL-1 and TNF-α [48], and NO and IL-8 [175], have been correlated with the severity of DR. This evidence suggests that, in people with diabetes, a variety of systemic conditions elevate circulating inflammatory factors, leading to retinal inflammation, angiogenesis and vascular permeability. For example, periodontal disease causes higher circulating levels of lipopolysaccharide and inflammatory cytokines, and is associated with a higher risk of PDR [176].

The study from Kellogg Eye Center (6) identifies many risk factors for DR. Some of these, such as peripheral neuropathy and nephropathy, may merely serve as markers for poor glycemic control or may be the result of multivariate regression models that failed to account for a confounding variable. However, some risk factors identified in large studies were associated with high hazard ratios and are probably important in understanding DR. The factors that appear to present a major hazard for the development or progression of diabetic retinopathy include HbA1c >8.0, duration of diabetes >10 years, an amputated or nonhealing ulcer, metabolic syndrome or excess abdominal fat, and African–American or Hispanic ethnicity.

A systemic review by Serban, Papanas and Dasalu (177) showed that in all cases, DR and especially proliferative diabetic retinopathy were significantly higher in the presence of DFU, though the frequency of DR showed large variability (22.5% to 95.6%). There was a significant correlation between advanced

stages of DFU and increased frequency of DR and proliferative diabetic retinopathy. On the other hand, they observed that there is a risk of accelerated progression of DR in non-healing DFUs, possibly related to chronic inflammation and associated infection.

Another systematic review by Pearce et al (178) shows that DR was found to be associated with two neuropathies: diabetic peripheral neuropathy (DPN) (179-181) and CAN (182). DPN is estimated to affect 30% to 50% of individuals with diabetes; it is characterized by peripheral nerve injury and manifests most commonly as distal symmetric polyneuropathy (DSP) which is also a major risk factor for foot ulcers and amputations.49 Concerning CAN, reported prevalence rates among individuals with diabetes vary from 17% to 66% in T1DM, and from 31% to 73% in T2DM (183).

In a retrospective study of longitudinal data from patients with newly diagnosed T2DM, collected from nationwide general practitioners in Germany and the UK, the presence of microvascular complications, defined as DR plus nephropathy, was found to be independently associated with neuropathy; in particular, DR was identified as a significant risk factor for neuropathy in the German cohort (179). Furthermore, the longitudinal Rochester Diabetic Neuropathy Study demonstrated that DR severity was an independent risk factor for DPN severity in patients with T1DM (184). A positive correlation between DPN and DR was also found in the cross-sectional North Catalonia Diabetes Study (180).

Other studies, including a prospective analysis of patients with T2DM in Malaysia, showing that neuropathy is an independent risk factor for progression of retinopathy, (181) found neuropathy to be a predictor of DR onset and progression. Similarly, in a retrospective population-based study in Taiwan, patients with DPN exhibited an increased risk of DR and advanced DR compared with a matched cohort of patients with diabetes who did not have DPN (185). Notably, when stratified according to DR severity, the risk of DPN was greater in patients with PDR than in those with NPDR (185). A significant association has also been found between diabetic maculopathy and neuropathy in both patients with T1DM and patients with T2DM, taking into account both peripheral neuropathy and CAN (186).

Neuropathic and vascular complications can lead to the development of diabetic foot ulcers and infections, and cause amputations. Several studies have shown that DR is an independent risk factor for foot ulceration in individuals with diabetes (7,8,187,188). However, a retrospective analysis of patients with T2DM by Tomita et al. found retinopathy to significantly increase the risk of developing ulcers only in the presence of microalbuminuria after adjusting for neuropathy and macroangiopathy (189). Furthermore, it has been shown that, among individuals with newly diagnosed NPDR, those with non-healing foot ulcers have an increased risk of progressing to PDR.(161) A number of papers have also identified DR as a key risk factor for lower extremity amputation in both patients with T1DM and patients with T2DM.(163,188,190,191)

Notably, patients who have T2DM and undergo lower extremity amputation (LEAs) have been found to be at higher risk of developing DR than those without LEAs.(192) This was also observed in the ADVANCE-ON post-trial observational study in T2DM, which demonstrated that lower extremity ulceration or amputation, as a major presentation of PAD, increased the risk of retinal

photocoagulation or blindness (193). PAD is diagnosed using the ankle-brachial index (ABI), with values less than 0.9 indicative of the disease (194). Li et al. demonstrated that DR was independently associated with a low ABI in patients with T2DM, irrespective of age.(195) However, Chen et al. found PDR, but not NPDR, to be correlated with an abnormal ABI in patients with T2DM after adjustment for HbA1c.(196) This result was replicated in another study, in which PDR was found to be independently associated with other measures of PAD, such as the toe-brachial index, Doppler ultrasound and critical limb ischaemia.(197) In addition, a prospective study in African-Americans with T1DM found that DR severity at baseline was a significant independent risk factor for the incidence of lower extremity arterial disease, defined as present if a patient has had an amputation or angioplasty for poor circulation, or if there is an absence of major arterial pulse in the legs.(198) However, in patients with T2DM, a borderline ABI (0.90-0.99) has been identified as an independent predictor of DR and other microvascular and macrovascular complications.(199).

Huang et al from Korea conducted study with the aim to investigate the prevalence of DR in patients with a DFU and to find out the potential association between DR and DFUs. (200) Patients with DFU and diabetic patients without DFU were compared. The DFU group had a higher prevalence of PDR and DR. They showed that the majority (90%) of patients with DFU also had DR, with more than half demonstrating PDR. The study revealed that the prevalence of DR among diabetic patients without DFU was 4.5%, whereas it was 90% among those with a DFU. PDR was present in 55% of patients with a DFU. Pearson's correlation analysis did not reveal a significant association between the severities of DR and DFU based on the Wagner ulcer classification.

Authors believe that the high prevalence of DR and PDR in this Korean study compared to that in previous studies might be caused by the inclusion of hospital patients with higher DFU grades. The study also failed to show a correlation between higher DFU grade and DR severity that has been the case in other studies as discussed above. However due to retrospective nature of the study as well as disproportionately large control group that was mostly representing the general type 2 diabetic patients without DFU in Korea, the results cannot be generalized.

A similar clinic based study from Australia found DR as one of the most closely associated risk factors for lower extremity amputation. (191)

In another observational hospital-based study, a cross-sectional sample of anonymous 65,534 Saudi diabetic patients was selected from the start of Saudi National Diabetes Registry (SNDR) in 2000 till December 2012 (201). Out of this a cohort of 62,681 diabetic patients aged 25 years were selected to study foot complications and related risk factors. A total of 2,071(3.3%) diabetic patients were found to have current or history of diabetic foot ulcer, gangrene or diabetes related lower limb amputation. Retinopathy and nephropathy were more prevalent among diabetic foot cases than non-affected at 46.64% and 29.36% versus 16.99% and 9.31% respectively. Total vasculopathic cases were 33.12% among diabetic foot cases versus only 16% in non-affected cases.

A recent meta-analysis of risk factors for amputation in diabetic foot infections (202) found DR as one of the predictors for amputations. Out of a total of 6132 patients with DFU in the 25 included articles, 1873 patients who underwent amputation were investigated.

Studies from Asian countries like China, Japan, India and Pakistan (189,203-205) have also identified similar association between diabetic retinopathy and diabetic foot ulcers (two china studies, one each from south India, Pakistan and Japan)

In brief, diabetic retinopathy is considered to be a risk factor for development and worsening of DF and conversely, the presence of DF is a predictor for DR progress to the proliferative stages.

5 - New Diagnostic tools for DR and DF

5.1 - Optical Coherence Tomography : Optical Coherence Tomography Angiography (OCTA) is a new, non-invasive imaging technique that generates volumetric angiography images in a matter of seconds. It can visualize the retinal and choroidal vasculature down to the capillary level in finely divided tissue slabs. It is one of the important diagnostic tools for diagnosis and monitoring of diabetic retinopathy. Optical Coherence Tomography (OCT) has also recently been used over skin for early diagnosis of diabetic foot ulcers (vide infra).

5.1.1 - Optical Coherence Tomography for DR: Kim et al (207) studied 118 patients with quiescent PDR who had completed panretinal photocoagulation (PRP). Retina parameters like foveal avascular zone (FAZ) area, retinal vessel density (VD) and vessel length density (VLD) were measured using OCTA. FAZ area of superficial capillary plexus (SCP) and deep capillary plexus (DCP) was positively correlated with DM duration and diabetic foot. Macular perfusion state in patients with quiescent PDR was associated with diabetic foot, DM duration, HbA1c, and time after PRP. Interestingly diabetic foot showed the strongest correlation with macular perfusion among various systemic factors. VLD, especially in DCP was associated with poor visual outcome. Since diabetic foot is already associated with abnormal microcirculation, the strong negative correlation of diabetic foot with OCTA parameters is not surprising (208)

5.1.2 - Optical Coherence Tomography for DFU. Argarini et al (209) conducted a study to apply OCT in people with diabetes, with and without foot ulceration, and compare these responses to a healthy age and sex-matched control group. OCT images were obtained from the dorsal foot, at baseline (33°C) and 30min following skin heating. The study showed that the change in OCT-derived parameters, from resting values in response to imposed skin heating, was impaired in people with diabetes, and further attenuated in those with foot ulcers. This clear and consistent stepwise impairment, across all parameters, strongly suggests that OCT is capable of discriminating between subjects with different degrees of microvascular dysfunction.

Several methods have previously been proposed to assess the skin microcirculation in patients with diabetes, including capillary microscopy (14) transcutaneous oxygen pressure assessment - TcPO2,(210-212) laser Doppler flowmetry (LDF)13 14 and laser Doppler imaging (LDI).(213-214). These techniques possess serious limitations in their capacity to characterize skin microcirculatory structure and function and they have not been

Foot ulceration is a preventable condition, where simple interventions can reduce amputations by up to 70% through programs that could reduce its risk factors *[206]*. Identifying the role of risk factors contributing to DFU will enable health providers to plan better prevention programs that could result in improving patients' quality of life and thus, reducing the economic burden for both the patient and the health care systems.

widely adopted (209). This Skin OCT may prove useful for diagnosing early stages of microvascular disease in high-risk patients, in characterizing disease progression and assessing the efficacy of therapeutic interventions.

5.2 – Corneal Confocal Microscopy: In diabetic peripheral neuropathy (DPN), corneal nerve structure and function has been assessed using corneal confocal microscopy (CCM) and non-contact corneal esthesiometry, respectively. CCM enables new perspectives of studying the natural history of diabetic sensorimotor polyneuropathy, severity of nerve fiber pathology and documenting early nerve fiber regeneration after therapeutic intervention. It shows moderate to high sensitivity and specificity for the timely diagnosis of diabetic sensorimotor polyneuropathy (216)

Using CCM, corneal nerve fiber pathology has also been found to be associated with both the presence and severity of diabetic retinopathy (background vs. proliferative retinopathy) (217-219). Nitoda et al (220) also used CCM to study alterations in corneal subbasal plexus in cases with diabetic retinopathy and diabetic peripheral neuropathy and found that nerve fiber alterations of the subbasal nerve plexus of diabetic corneas appear to progress in parallel with DR and peripheral DN. However, Zhivov et al. have reported no difference in corneal nerve morphology between patients with and without diabetic retinopathy. (221) However recent studies provide more support for the clinical use of CCM to diagnose type 2 diabetes mellitus-related complications, especially DPN (222)

5.3 – Skin Autofluorescence (sAF) for DF and DR: As discussed earlier accumulation of AGEs in the peripheral nerves has recently been proposed as an additional risk factor for the development of diabetic neuropathy (DN). The gold standard for measurement of tissue-bound AGEs is tissue biopsy. However, sAF is now found to be quite comparable to gold standard. Accumulation of tissue AGEs evaluated by sAF has been shown to independently correlate with DN. Importantly, increasing evidence demonstrate their potential value as early biomarkers of the latter. Further important associations include diabetic nephropathy, diabetic retinopathy and cardiovascular autonomic neuropathy

A recent systemic review and meta-analysis by Hosseini et al (223) reviewed the clinical significance of non-invasive skin autofluorescence measurement in patients with diabetes and confirmed the significance of sAF measurement as a non-invasive surrogate marker of diabetes micro and macrovascular complications and concluded that skin AGE estimation may be a useful factor for the prediction and early detection of irreversible DM complications.

5.4 - Circulating Diagnostic Biomarkers for DF and DR : There has been a growing interest in blood-based biomarker tests for diabetes These techniques have been used to demonstrate that DPN is associated with morphological degradation of corneal nerves and reduced corneal sensitivity. With further validation, these ophthalmic markers could become useful clinical method of screening for early detection and monitoring progression of DPN, as well as assessing the effectiveness of possible therapeutic interventions. (215)

especially DR. Biomarkers can not only identify disease and even subclinical disease, but are also used to monitor clinical response to treatments (224). At present, a selective marker for early-stage DR remains elusive. Literature review shows many small studies that have identified and verified potential circulating biomarkers for DR; however, none of these have been validated in large multi-center studies (225). Multiple potential confounders need to be addressed in the search for screening markers, including geographic, ethnic and genetic variations in the study populations as well as the varying phenotypes of DR. Therefore, large-scale, collaborative, multi-center studies will be needed to conclusively validate and determine the reliability of the various biomarkers of DR. (225)

The situation is not different in case of DFU. In addition to the inflammatory biomarkers that have been used, e.g., procalcitonin, pentraxin-3, C-reactive protein (CRP), interleukins (ILs), and tumor necrosis factor-α (TNF-α), etc., a more comprehensive prediction of the risk and severity of DFU is needed to reflect new biomarkers for therapeutic intervention effects (226). Along with the development of systems biology technology, genomics, proteomics, metabolomics and microbiome have been used in the studies on DFU for better understanding of the disease. A recent review has demonstrated that the study of biomarkers in DFU is still in its early stage, and continuous attempts in this field will help reveal new insights into DFU treatment and improve its prevention and treatment levels (226).

6 - Treatment Aspects common to DR and DFU

6.1 - Treatment targeting AGE products have been studied both for DR and DFU. As discussed under the pathophysiology section, AGEs play an important role in development of diabetic complications. Therefore interventions to reduce or impair AGE formation are proving quite useful. Therapeutic interventions for reducing AGE formation include reduction in AGE formation by reducing crosslink formation [227], by reducing AGE deposition using crosslink breakers, and by enhancing cellular uptake and degradation. Also receptor inhibition of AGE using neutralizing antibodies or suppression of post-receptor signaling, using antioxidants can be other novel strategies for targeting reduction of AGEs [228].

Other than reduction or impairment of AGE formation and drug therapy, modifying the intake of food- and tobacco-derived AGE can be other treatment modalities to reduce AGEs. AGEs can be absorbed through the diet [229]. Foods high in protein and fat, such as meat, cheese, and egg yolk, are rich in AGEs [51]. Foods high in carbohydrates have the lowest amount of AGEs. High cooking temperatures, cooking methods like broiling and frying, and increased cooking time cause increased AGEs formation [230]. A diet loaded with AGEs result in proportional elevations in serum AGE levels patients with diabetes [229]. On the contrary, dietary AGE restriction causes a 30 to 40 % decrease of serum AGE levels in healthy subjects [230].

Thus, restriction of dietary AGEs may be an effective strategy for the reduction of AGEs [108]. A low-AGE diet administered for 6 weeks in a clinical trial resulted in lower serum AGE levels and inflammatory markers such as C-reactive protein [51].

A number of biomolecules and phytochemicals isolated from vegetables, legumes, fruits, or flavonoids, acting as AGE formation inhibitors, preformed AGE breakers, AGE–RAGE axis

blockers, or glyoxalase stimulators are expected to become novel therapeutic agents in addition to traditional anti-hyperglycemic and anti-hypertensive drugs with greater benefits and lesser side effects (231).

A number of drugs had been developed to interfere with the glycation pathway. Despite most of them are solely used in preclinical settings, some are approved for human treatment. Nenna et al (232) has described in detail some of these drugs namely; Aminoguanidine (Pimagedine) Pyridoxamine, Benfotiamine, ACE inhibitors, Angiotensin Receptor Blockers, Statins, Thiazolidinediones and Alagebrium etc.

However, considering many preclinical studies on the role of AGEs as both a marker and a cause of disease and on new compounds interfering with their effects, we should expect a number of new anti-AGEs drugs. The most recent promising anti-AGEs agents currently are statins, Alagebrium and thiazolidinediones although it is unclear which patients would benefit more (232).

6.2: Fenofibrate for of DR and DFU.

6.2.1: Fenofibrate for of DR: In addition to dyslipidemic effects, use of fenofibrates in patients with diabetic retinopathy may reduce their risk of progression to visually threatening forms of disease. Meer et al in (233) a recent cohort study of 5,835 fenofibrate users and 144,417 fenofibrate nonusers, found that fenofibrate use was associated with a decreased risk of proliferative diabetic retinopathy and vision-threatening diabetic retinopathy but not with DME alone.

Two earlier randomized clinical trials from much smaller groups of participants, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye (234) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (235) studies, had shown significant reduction in vision-threatening diabetic retinopathy from the use of fenofibrate.

One of the limitations in both ACCORD and FIELD study was that these were conducted prior to the routine use of optical coherence tomography for diagnosis and monitoring of macular edema and of intravitreal anti-VEGF agents for the treatment of diabetic macular edema. How fenofibrate may have affected these outcomes requires further study. In addition ACCORD's major limitation was only one time point in follow-up at 4 years (236). Furthermore, beneficial effects of fenofibrate therapy in both the FIELD and ACCORD Eye study were only seen in patients with pre-existing retinopathy, and in the ACCORD Eye study, benefits were restricted to those with mild diabetic retinopathy. Why diabetic patients without retinopathy or patients with more severe retinopathy do not appear to benefit from fenofibrate therapy requires further investigation. A limitation for using the fenofibrate for the treatment of diabetic retinopathy is its lack of efficacy for reducing cardiovascular events resulting in fewer medical physicians prescribing it for dyslipidemia or for reduction of diabetic retinopathy.

6.2.2: Fenofibrate for DFU: In FIELD study, information about non-traumatic amputation—a prespecified tertiary endpoint of the study—was routinely gathered. Treatment with fenofibrate was associated with a lower risk of amputations, particularly minor amputations without known large-vessel disease, probably through non-lipid mechanisms (237). These findings could lead to a

change in standard treatment for the prevention of diabetes-related lower-limb amputations.

This study (237) showed that amputation risk in patients with type 2 diabetes was lower in patients assigned to treatment with long-term fenofibrate than in those assigned to placebo. The cumulative hazard curves showed a reduction in amputation rates that seemed to emerge after just 1·5 years of fenofibrate use. The number of patients needed to treat (NNT) with fenofibrate over 5 years to prevent at least one amputation in one patient is 197, but is 25 for someone with previous foot ulcer and albuminuria. These results compare with NNTs with fenofibrate of 17 and 90 to prevent laser treatment for retinopathy in patients with and without a history of retinopathy respectively. Most importantly, the treatment effects of fenofibrate were irrespective of the level of glycaemic control and background use or not of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, strongly suggesting that the drug's effects are additive to other measures. Studies suggest that effects of fenofibrate in reducing amputation risk are more likely to be non-lipid-mediated (237).

Several theoretical mechanisms for the microvascular benefits of fenofibrate have been proposed. In a randomized placebo-controlled trial, treatment with fenofibrate was associated with improved endothelial dependent vascular reactivity over 12 weeks,(238) with reductions in markers of endothelial dysfunction and pro-inflammatory markers; another trial also showed that fenofibrate treatment was associated with reduced viscosity (239). In patients with hypertriglyceridaemia or metabolic syndrome, fenofibrate improved flow-mediated dilator response to hyperaemia, with increased adiponectin concentrations and improved insulin sensitivity.(240) The drug might exert its antiangiogenic effects directly,(241) or by reducing tissue ischaemia through these actions.(238-240) Fenofibrate also activates AMP kinase in endothelial cells via a peroxisome-proliferating receptor-α independent pathway, preventing retinal cell apoptosis,(242) and possibly increasing nitric oxide synthesis.(243) Fenofibrate could also be protective through the inhibition of oxidative stress(244).

FIELD is the largest randomized controlled trial of type 2 diabetes mellitus reporting data for amputations, with a very large set of baseline variables. The results of FIELD trial support the use of fenofibrate, irrespective of the presence of dyslipidaemia, for the treatment of patients with type 2 diabetes who are at high risk for amputation.

6.3 - Statins have also been used to treat both DR and DFU.

6.3.1 - Statins in DR. A population-based cohort study by Kang et al (245), conducted among 37 894 Taiwanese patients with type 2 diabetes and dyslipidemia was compared between those taking statins and those not taking statins. Statin therapy was associated with a decreased risk of diabetic retinopathy and need for treatments for vision-threatening diabetic retinopathy in Taiwanese patients with type 2 diabetes and dyslipidemia. They found that statins could delay all stages of diabetic retinopathy and decrease the number of invasive procedures needed; this finding was associated with the intensity and duration of statin use. The ACCORD-EYE study showed that the combination of fenofibrate and simvastatin also slowed the progression of diabetic retinopathy compared with simvastatin alone.(246-247) A nationwide study of 62,716 individuals in Denmark found that statin use prior to receiving a diagnosis of diabetes decreased the risk of developing diabetic retinopathy by approximately 40% (248)

Statins have pleiotropic effects, including improving endothelial function, and anti-inflammatory, antioxidation, and antithrombotic effects along with lipid-lowering abilities (249). Moreover, Tuuminen et al (250) found lower intravitreal levels of proangiogenic factors in patients with diabetic retinopathy who were treated with simvastatin compared with controls who did not receive a statin. The aforementioned effects of statins seem to prevent the development of diabetic retinopathy, including improving endothelial function and inhibiting fibrotic proliferation, inflammation, oxidative stress, and VEGF-associated angiogenesis (251).

Unlike fenofibrates, the use of statin therapy as a strategy to prevent diabetic retinopathy remains controversial. (245)

6.3.2 - Statins in DFU. A review of the literature by Shadi, Khalili and Farboud (252) showed that results from all of the studies included consistently showed that the use of statins produced a significant improvement of wound healing in different types of wounds and in both oral and topical administration and also in short- and long-term follow-up (253-256). Recent studies showed that statins have a crucial role in the regulation of angiogenesis (9). It was shown that simvastatin could increase VEGF synthesis and release at the wound site which is a crucial event for new blood vessels' production and subsequently ameliorates impaired wound healing in diabetic mice (253). However the conflicting results about role of statins in modifying VEGF levels in different studies (250, 253) need further investigation.

Further high-quality and evidence-based studies are needed to address the best statin drug, appropriate dose, the best administration route, duration of treatment and to determine correlation between pleiotropic effects of statins and their probable clinical benefits.

6.4 – Hyperbaric Oxygen in DFU and its safety for DR: Hyperbaric Oxygen therapy has been approved by FDA for many conditions including diabetic foot ulcers. However a recent overview of systemic reviews by Wenhui et al (257) conclude that there is limited clinical evidence to support hyperbaric oxygen therapy in the treatment of diabetic foot ulcers, it is not recommended to routinely apply hyperbaric oxygen therapy to all patients with diabetic foot ulcers, especially those with non-ischemic diabetic foot ulcers. Hyperbaric oxygen therapy has certain potential to promote ulcer healing and reduce amputation rate in patients with ischemic diabetic foot ulcers, but due to the low quality and small quantity of the systemic reviews and meta-analyses supporting these results, high-quality studies with rigorous study designs and larger samples are needed before widespread recommendations can be made (257).

Since possible mechanisms of action for this treatment include increased angiogenesis and high tissue oxygen concentrations, concerns about deterioration of retinopathy have been raised. A recent randomized, single-center, double-blinded and placebo-controlled clinical trial was conducted to evaluate the effects of HBO2 on visual acuity (VA) and retinopathy in patients with chronic diabetic foot ulcers during a two-year follow-up period. All study participants underwent an ophthalmological examination before the first study treatment and then at three, six, 12 and 24 months. The study did not identify any indication of harmful effects of HBO2 on the microvascular bed in the placebo group. (258)

7 - Prevention and Education – New Approach

The fact that the majority of patients with a DFU have DR, raises concerns about the impact of this

combined disability on patients' quality of life (QOL). There have been several reports of DFUs decreasing QOL. Specifically, increased rates of depression because of a DFU and fear of amputation lead to a lower QOL (259), as well as difficulty in controlling blood sugar, causing concerns about a high incidence of late complications of diabetes. Moreover, psychiatric problems and changes in lifestyle resulting from disability may place unexpected burdens on patients and their families. For example, about 50% of patients with DFUs are unable to work, and the remaining half have been reported to show decreased productivity with limitations in career advancement [260]. Moreover, DR has DFU, in order to improve the patient's quality of life and potentially reduce costs of care, thanks to early detection. As for DFU, two studies [263,264] modelled the long-term consequences and costs of intensified prevention in patients with DFU and found that prevention was cost-screening and optimized therapy would be cost-effective with a willingness-to-pay threshold of $50,000 [265]. Regarding DR, a literature review showed that DR screening programmes were cost-effective in terms of sight years preserved, depending on the target population and the screening intervals [266].

Prevention strategies (i.e. education, screening programs, drugs, devices) could help to delay insufficiently screened compared to the National recommendations (HAS, French Health Authority). Particularly, only 52 % of patients reported having had an eye fundus examination, 36 % a microalbuminuria or proteinuria test and 24 % a visit to the podiatrist. An earlier study had shown that retinopathy screening was performed more frequently than foot screening in Australia (268). This was attributed to the better implementation of eye screening programs and awareness campaigns. Foot screening was quite poor, with less than one-half of the population reporting a regular examination for foot complications.

also been reported to decrease QOL [261-262]. The progression of DR into PDR usually causes significant and disabling vision loss, which leads to an even more significant decrease in QOL. Therefore, patients with both DFU and DR, and particularly those with PDR, will have significantly impaired QOL. To prevent any further decrease in QOL, the timely diagnosis and treatment of DR is crucial.

It is also interesting to link the cost of prevention strategies to the total cost of each complication (21). Indeed, prevention strategies are aimed at preventing or delaying the onset of DR, DKD or

effective at different levels of risk and helped to reduce foot ulcer incidence. Moreover, a literature review showed that pharmacotherapy prevention was cost-effective in slowing renal disease progression in patients with DM [264]. Another study pointed out that a combination of the onset of diabetic retinopathy (DR), diabetic kidney disease (DKD) and diabetic foot ulcer (DFU). However studies across the globe show that screening programs are not conducted sufficiently. In France, a national survey on diabetes patients, conducted between 2007 and 2010 (the ENTRED survey – 21), assessed medical care of diabetic patients and showed that DM complications were

Across the globe, diabetic retinopathy screening (DRS) programmes are relatively frequent, more regular and better organized. For example DRS programs have contributed to relegating diabetes-related retinopathy from being the leading cause

of certifiable blindness among working age adults in England and Wales. In a retrospective analysis of newly recorded certifications of visual impairment in Wales during 2007–2015, sight loss was reduced by almost 50% (269).

Therefore combining DRS program with detection and screening of other diabetic complications like DFU is now gaining momentum in various parts of the world. Lewis et al (270) explored the feasibility and acceptability of incorporating diabetic foot screening at routine diabetic retinopathy screening appointments. Participants underwent foot screening during the interval between pupil dilatation and retinal photography as part of the eye screening DPN and its sequelae have major impacts on quality of life, morbidity and mortality and confer considerable healthcare costs [271]. Unfortunately, DPN has an insidious onset and the majority of people with DPN will have no symptoms. For this reason, the recent American NICE guidance on prevention and management of diabetic foot problems makes a similar recommendation (NG19) [273]. Various studies (274, 275) however, have shown that this recommendation is not currently being adhered to. This contrasts with screening for retinopathy and renal disease, for which there are clearly established screening methods aimed at detecting the complications early and integrated management pathways, and, in the case of retinopathy, the screening has a very high uptake.

Therefore to improve foot outcomes, there is an urgent need to develop a high-uptake and effective diabetes foot screening program [275]. There has been a recent advance in the development of non-invasive, objective, accurate point-of-care devices (POCDs) that may be able to diagnose DPN early, before overt clinical signs are apparent. These devices do not require specialist training to use in routine clinical care procedure. Lower limb arterial assessment included ankle brachial index, pulse volume waveform and protective light touch sensation. Undiagnosed early peripheral artery disease was evident in a third of the study population emphasizing the benefit of introducing foot surveillance into eye screening appointments for the early identification of lower limb arterial disease and peripheral sensory neuropathy. The screening methodology was well received by participants and staff alike. Such combined screening programs can also incorporate education programs about diabetes and its complications.

Diabetes Association (ADA) position statement on diabetic neuropathy recommends annual assessment for DPN using simple bedside instruments, starting at diagnosis of Type 2 diabetes and 5 years after diagnosis of Type 1 diabetes [272]. The and provide results within a few minutes. A recent study from Sheffield (274) aimed to examine the feasibility and patient acceptability of a combined eye, foot and renal screening clinic and to evaluate the feasibility of use and diagnostic utility of two POCDs in detecting DPN early. The study included a total of 244 consecutive patients with either Type 1 or Type 2 diabetes attending for annual eye screening in a hospital. Before undergoing retinal photography and whilst the mydriatic was taking effect, the feet were examined by a podiatrist in an adjacent room for any abnormality, including deformity, callus and ulceration. The presence of dorsalis pedis and posterior tibial pulses were also assessed. Participants then underwent Toronto Clinical Neuropathy Score (TCNS) assessment [276] and the 10-g monofilament test (at five sites in each foot, with an inability to feel ≥2 sites taken to indicate DPN). TCNS was used as gold

standard for DPN in this study and took around 15 minutes. Finally, participants underwent assessment of large-fiber function using 'DPN-Check' [277] and small-fiber function using 'Sudoscan' [278]. These tests were conducted by the same podiatrist, without any technical expertise in standard nerve conduction study protocol, and with only 1-h training in the use of this device. The results of the present study show that combined eye, foot and renal screening in a one-stop microvascular screening clinic was feasible and had high patient acceptability and uptake The study also led to significant detection of undiagnosed painful DPN (25%).

Combining foot-care education program with DR screening is another important proposition. Li et al (279) assessed the effectiveness of a 12-week educational intervention on foot self-care behaviour among diabetic retinopathy patients and found it to be both cost-effective and feasible even in a health resource-limited setting.

Therefore for early detection of diabetic complications in order to avoid blindness and visual impairment from diabetic retinopathy and to avoid lower extremity amputation from diabetic foot ulcer, combined screening programs are very useful. DR screening provides a wonderful opportunity for high uptake screening and combining it with foot ulcer, DPN, and DKD screening together with targeted education programs will lead to early detection of complications and timely management.

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