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Cutaneous manifestations of diabetic peripheral neuropathy

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ABSTRACT

There is a rise in number of people diagnosed with Diabetes Mellitus. The incidence is rising in modern Indian society because of Industrial development and drastically changing lifestyles. Diabetic neuropathies are microvascular disorders that are usually associated with the duration of Diabetes. Among the various forms, the most common is Diabetic Peripheral Neuropathy. The disease if neglected leads to chronic ulcer formation leading to amputations frequently. Hence the aim of this study is to document the early cutaneous changes and create an early awareness in the importance of controlling Diabetes. The study consisted of 205 patients with Type 2 DM. Participant's neuropathy status was determined based on Neuropathy Disability Score and Diabetic Neuropathy Symptom Score. Among the Skin changes documented, the common changes seen were: Peripheral hair loss in 185 (90.2%), Xerosis in 168 (82%), Anhydrosis in 162 (79%), Plantar Fissures in 136 (66.3%), Plantar Ulcer in 80 (39%), common nail changes documented were Onychomycosis in 165 (80.5%) and Onychauxis in 53 (25.8%) patients in relation to the occupation and duration of Diabetes mellitus. In conclusion, it is important to control glycemic levels in the all stages of Diabetes and institute foot care measures to prevent the complications of neuropathy.

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Introduction

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion and/or insulin action. If Diabetes is undiagnosed or poorly controlled, it can lead to a state of persistent hyperglycemia, resulting in complications and irreversible damage in a wide range of tissues, most notably the retina, the kidney glomeruli, neural tissue and blood vessels.[1] Due to these complications, patients with Diabetes often have a reduced life expectancy and quality of life.[2]

Among the various microvascular complications, such as Diabetic Retinopathy, Diabetic Nephropathy, Diabetic Neuropathy, Autonomic Neuropathy and Cranial Neuropathy; the most common form of Diabetic Neuropathy is Diabetic Peripheral Neuropathy. Diabetic Neuropathy exists as a disorder without any additional causes of peripheral neuropathy other than diabetes.

DPN leads to chronic manifestations such as ulcer formation and amputations. Worldwide, very few studies that have prospectively documented the skin changes of Diabetic Peripheral Neuropathy and very fewer in India. The aim of this study is to document the cutaneous changes in DPN in a South Indian population.

Materials and methods

Following ethics committee approval; Three year duration cross sectional study was done from the outpatient department of Endocrinology, Diabetes and Metabolism and department of Dermatology, Venereology and Leprosy at Sri Ramachandra University. Both genders above 30 years with T2DM with typical motor and sensory neuropathy symptoms and those willing to participate were included in the study. Subjects with clinical evidence of other known causes of Peripheral Neuropathy, Autoimmune Disorders, history of HIV, Hepatitis, Carcinomas and other psychological problems, those

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using alcohol, Narcotics, and those with Sexually transmitted diseases and with Vitamin B12 deficiency were excluded from the study. Recording of participant demographics, vital signs, BMI(kg/m2), FBS(mg/dl),, PPBS (mg/dl), Evaluate participant's neuropathy status based on Neuropathy Disability Score (NDS) and Diabetic Neuropathy Symptom Score (DNSS). Documentation of the Skin and Nail changes. The tools used were 10 g (5.07 Semmes-Weinstein) monofilament, Knee Hammer, 128 Hz Tunning Fork, and 2 Test Tubes for thermal examination. The severity of Neuropathy was detected based on the protocol for Diabetic Neuropathy Score and Neuropathy Disability Score.[3,4,5]

Documentation of cutaneous manifestations

Table 1 shows the classification of the cutaneous manifestations of diabetic peripheral neuropathy.[6]

Observations and results

The results were analyzed for 205 patients with DPN. The parameters and average statistics used for the study are shown in Table 2.

Majority of the study consisted of female (116) participants. Home makers, Farmers, manual labourers and street vendors working barefoot (Figure 1) were more at risk for complications due to ignorance of DM.

Upon categorization according to DNSS and NDS, we analyzed that 55% of our study group had severe DNSS and 49% had moderate NDS as shown in Figure 2.

The analysis for all the cutaneous manifestations documented in our study is summarized in Table 3.

Peripheral hair loss, Xerosis, and plantar fissures were the commonest initial manifestations of peripheral neuropathy exhibited in the study group. As the duration of diabetes, glycemic levels, and peripheral neuropathy increased; parameters such as Callosities, Diabetic blisters and Ulcers of various grades were observed as seen in Figure 3 and 4.

Table 2. Descriptive summary of all parameters.

Parameters	Number	Minimum	Maximum
Age	205	32	80
BMI	205	15	40
Duration of HTN	205	0	16
Duration of DM	205	5	43
FBS	205	107	329
PPBS	205	132	524
Duration of neuropathic symptoms	205	.01	17.00
Time taken for development of peripheral neuropathy Valid N(listwise)	205	2.00	37.94

Onychomycosis(80.5%) and claw toes(55%) were the predominant nail and anatomical foot changes documented. After complete analysis of all parameters in correlation to various factors; Statistical significance of P value < 0.05 was seen in Xerosis ($p = 0.001$), Varicose veins ($p = 0.000$), Anhidrotic skin ($p = 0.009$), and Plantar fissures ($p = 0.000$) with correlation to glycemic levels (PPBS). The correlation of DNSS with duration of DM, the statistical analysis was insignificant ($p = 0.142$); but significant with NDS ($p = 0.039$). Figure 5 shows the correlation of Duration of Diabetes with NDS, DNSS and NDS with Ulcer the statistical significance of $p = 0.000$; highly significant for both the parameters.

Lastly, as seen Figure 6; upon correlation of Barefoot during work along with Plantar skin changes; majority of the patients exhibited callosities and Ulcers.

Discussion

Distal Symmetric Polyneuropathy is the most prevalent form of Diabetic Neuropathy seen in clinical practice.

The term diabetic neuropathy includes either a clinical or subclinical disorder without any additional causes of peripheral neuropathy other than Diabetes. Damage to the microvasculature in peripheral nerves is as a major pathogenic factor in diabetic neuropathy. DPN is characterized by progressive loss of nerve fibres that predisposes the patients to painful,

Table 1. Classification of cutaneous manifestations of diabetic peripheral neuropathy.

Neuropathic Changes	Ischaemic Changes	Others	Nail Changes	Anatomical Foot Changes
Dry skin - Xerosis	Anhydrotic skin	Ulcer (with grade of ulcer)	Onychomycosis	Hallux Valgus
Dilated veins	Hair loss	Clavus	Paronychia	Charcot foot
Warm to touch	Cold to touch skin	Blister	Onychocryptosis	Hammer toes
Erythema	Pale skin	Plantar Fissures	Onychauxis	Claw toes
Callus		Candidal intertrigo of web spaces	Pincer nails	No foot deformities
		Previous ulcer		

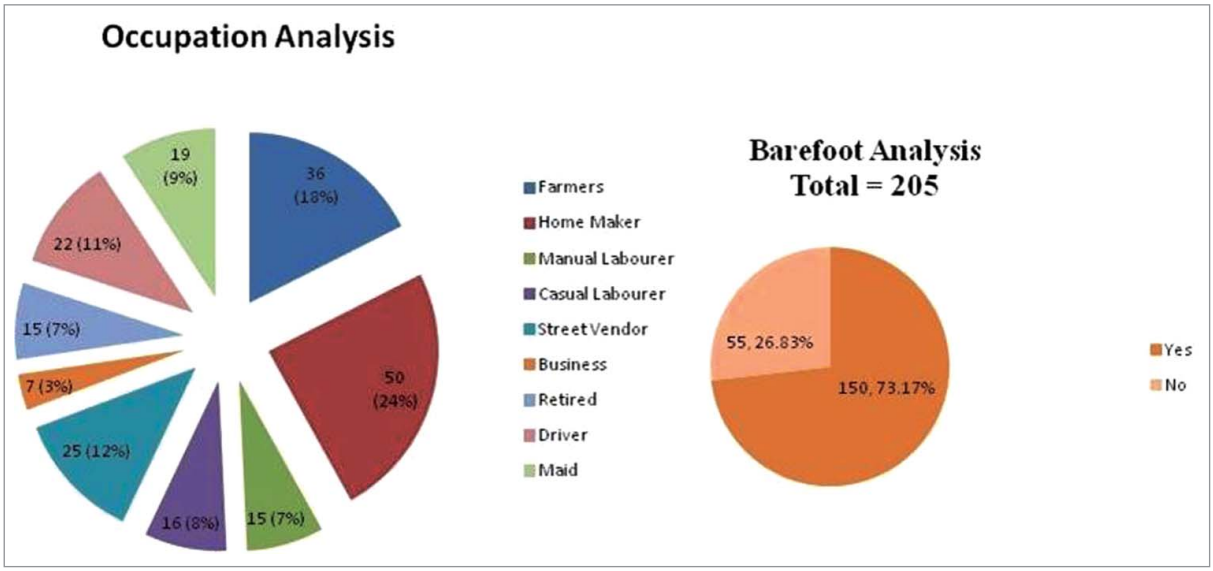

Figure 1. Occupation and barefoot analysis of study participants.

tingling/burning sensations or insensitive extremities, neuropathic ulcerations and amputations.[7]

The incidence of neuropathy is accelerated by degree of hyperglycemia, hyperlipidemia, and hypertension.[89] Retinopathy and nephropathy are highly associated with PN, occurring in 55% and 32% of type 2 diabetic patients, respectively.[10]

Damage to the microvasculature in peripheral nerves is a major contributing pathogenic factor in diabetic neuropathy. It may affect both sensory and autonomic nerves, but distal symmetric polyneuropathy is probably the most common consequence which, combined with peripheral vascular disease, is an important etiologic factor for foot ulcerations and lower limb amputations. Autonomic dysfunction is common in people with Diabetes, but is only clinically apparent in a small percentage. DN is encountered in about half of all people with Diabetes especially in patients over 60 years of age with T2DM either as polyneuropathy or mononeuropathy.[11]

Although exact prevalence depends on the diagnostic criteria used to identify neuropathy, most studies suggest that 50% of patients with a 20-years history of either type 1 or type 2 Diabetes have neuropathy. Diabetic PN is the most common peripheral polyneuropathy in the developed world countries.[11]

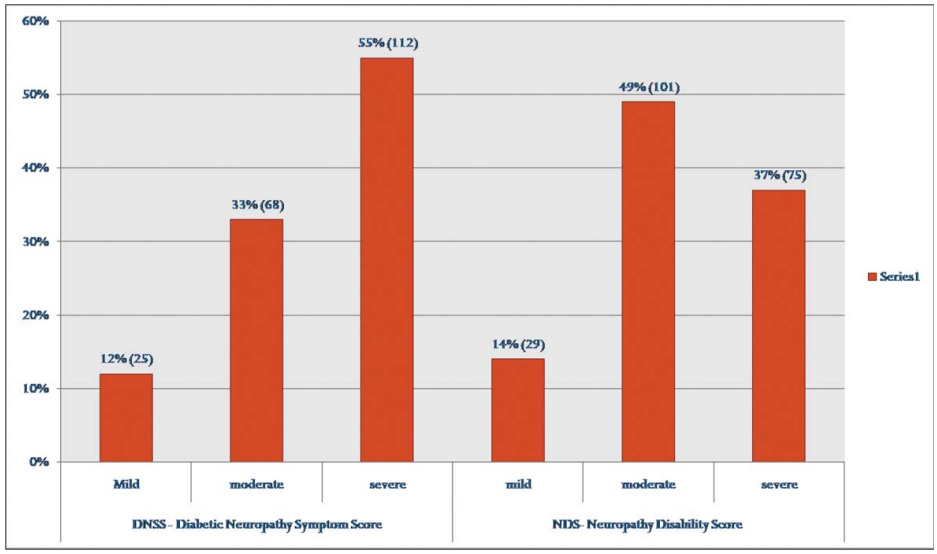

Figure 2. DNSS & NDS catergorization of patients.

Table 3. Analysis of all cutaneous manifestations of diabetic peripheral neuropathy of study participants. Type ischaemic changes nail changes anatomical foot changes.

Type	Changes	No.	%
Neuropathic Changes	Dry Skin- Xerosis	168	82%
	Varicose Veins	24	12%
	Warm to touch skin	29	14%
	Erythematous skin	31	15%
	Callus	73	36%
Ischaemic changes	Anhydrotic skin	162	79%
	Peripheral Hair loss	185	90%
	Cold to touch skin	10	5%
	Pale skin	12	6%
Others	Ulcers	80	39%
	Clavus (corn)	22	11%
	Blisters	25	12%
	Plantar Fissure	136	66%
	Candidallnertrigo of web spaces of toes	14	7%
	Previous ulcers	55	27%
Nail changes	Onychomycosis	165	80%
	Paronychia	19	9%
	Onychocryptosis	20	10%
	Onychauxis	101	49%
	Pincer nails	4	2%
Anatomical Foot changes	No Deformities	42	20%
	Hallux Valgus	24	12%
	Charcot Foot	7	3%
	Hammer toes	92	45%
	Claw toes	112	55%
	PesPlanus	74	36%
	Amputation of toes	33	16%

DPN is characterized by progressive loss of nerve fibres that predisposes the patients to painful, tingling/burning sensations or insensitive extremities, neuropathic ulcerations and amputations.[7]

The incidence of neuropathy increases with duration of Diabetes and is accelerated by degree of hyperglycemia, hyperlipidemia, and hypertension.[12,13]

The pathophysiological mechanisms for PN are not yet fully understood. Several different factors are thought to be involved, both metabolic and vascular[14–16] and immune factors are known to play a role in PN in Diabetes. The pathogenesis of DPN is shown in Figure 7.

Among the metabolic factors, hyperglycemia is the most important common initiator of metabolic nerve injury. Studies have shown that hyperglycemia leads to progression of micro- and macrovascular complications and increased risk for mortality in people with Diabetes.[17] Hyperglycemia in turn leads to activation of Protein Kinase C pathway. PKC is a family of serine-threonine kinases that plays an important role in signal transduction mechanisms. PKC is activated by the increased amounts of diacylglycerol (DAG), which are synthesized directly from glycolytic intermediates such as dihydroxyacetone phosphate and glyceraldehyde-3-phosphate. PKC is

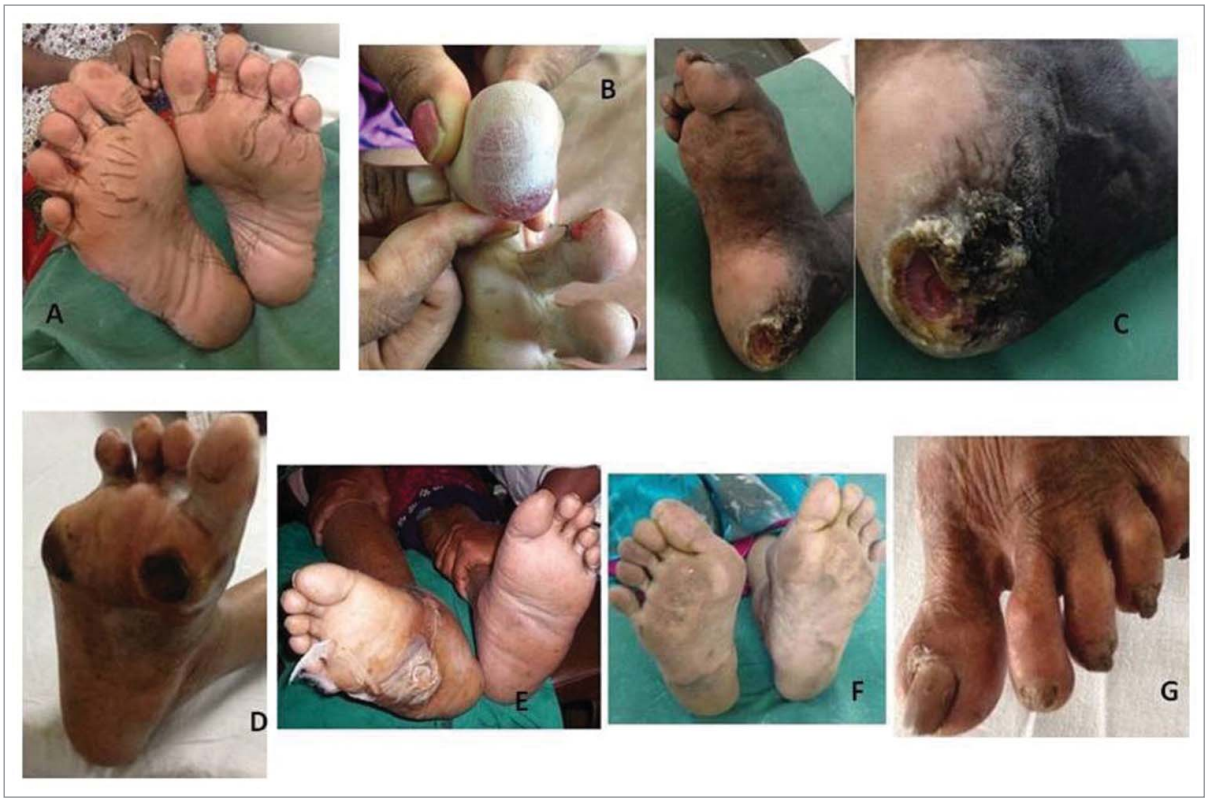

Figure 3. A: Plantar fissures B: Diabetic Blister C: Ulcer D: Ulcer with Squamous Cell Carcinoma E: Charcot Foot F: Hallux Valgus G: Claw toes.

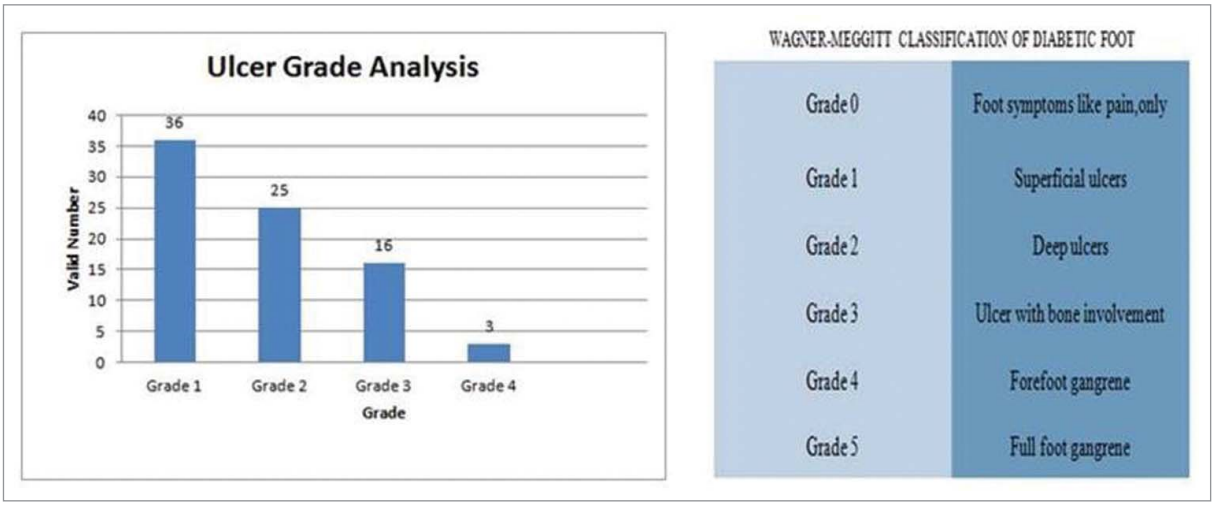

Figure 4. Ulcer grade analysis and categorization – majority of patients (36 patients) had superficial ulcers.

activated in diabetic tissues such as retina, kidney, heart and aorta. Activated PKC is implicated in processes relevant to diabetic complications, including regulation of vascular permeability and flow, increased production of cytokines, and increased synthesis of basement membranes.[18,19] For example, In Diabetes microvascular complications PKC affects the activation of a number of growth factors and changes the function of vasoactive factors. These vasoactive factors include vasodilators such as

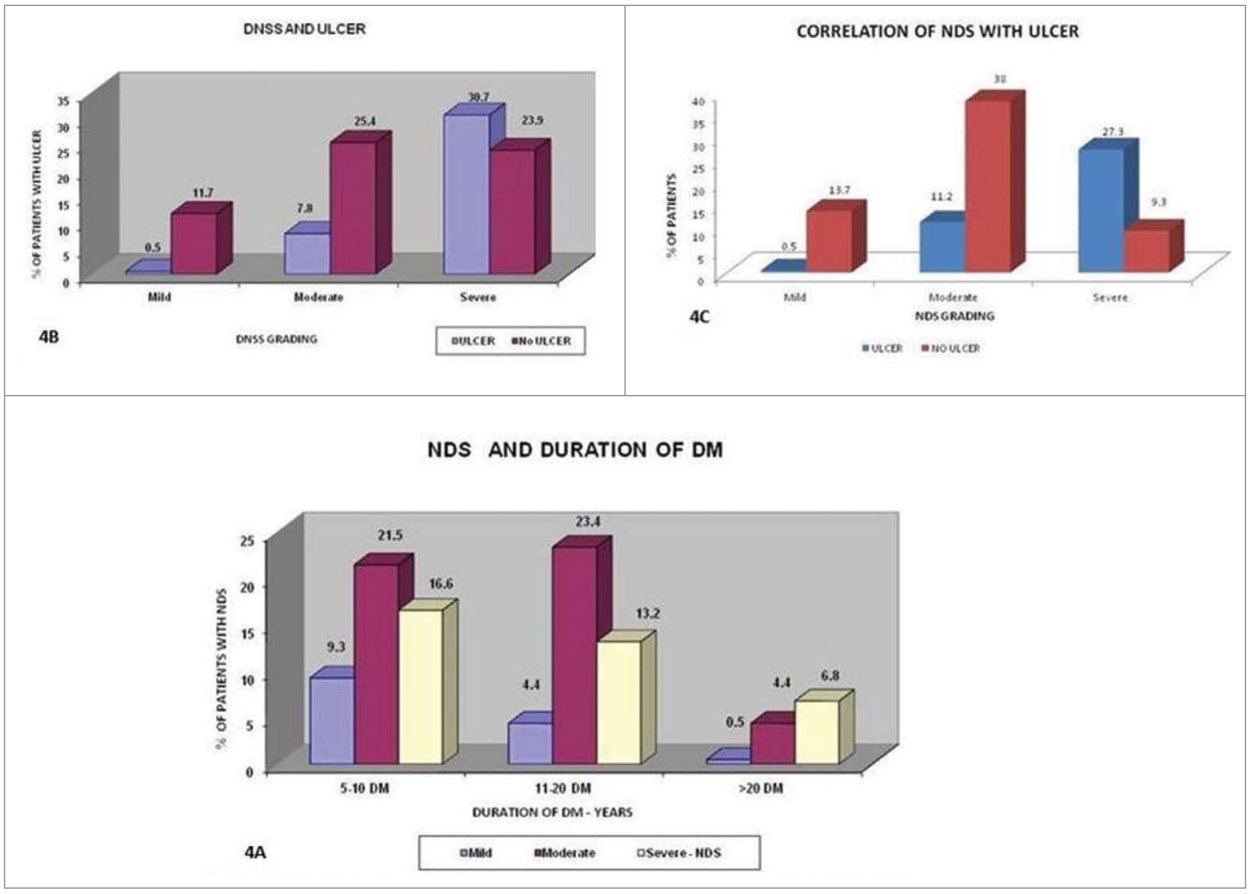

Figure 5. A: In correlation of NDS with duration of DM, the statistical analysis was significant (P = 0.039). B: DNSS with Ulcer the P value = 0.000 which was highly significant. C: NDS with Ulcer the P value = 0.000 which was highly significant.

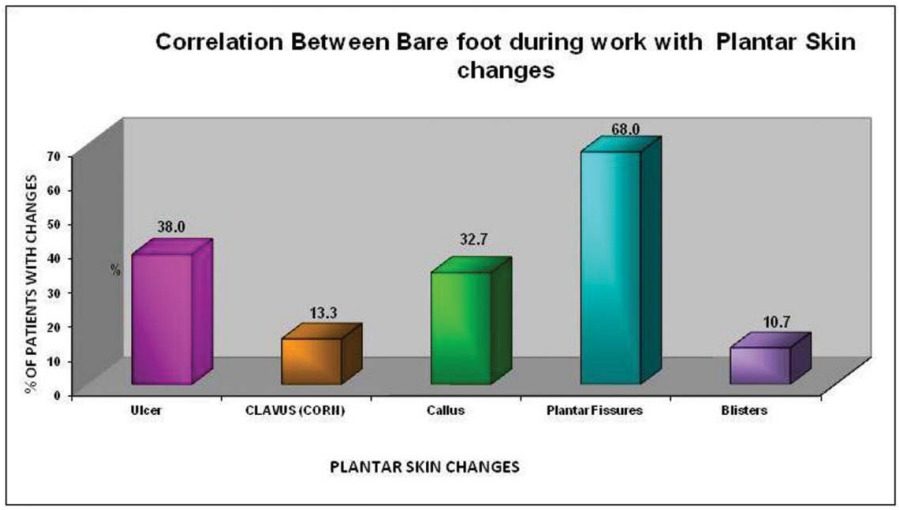

Figure 6. Shows the highest correlation between Plantar Fissures & Bare feet.

nitric oxide (NO) as well as vasoconstrictors such as angiotensin II and endothelin.[20]

In normoglycemic states, a small proportion of glucose is metabolized to sorbitol, while in hyperglycemia the enzyme aldose reductase is activated, leading to an accumulation of intracellular sorbitol and fructose that increases the flux through the polyol pathway. Sorbitols and other polyols accumulate intracellularily, leading to osmotic damage and swelling. Aldose reductase (AR) is the first and rate-limiting enzyme of the polyol pathway, which converts monosaccharides (e.g. glucose) to their polyols or sugar alcohols (e.g. sorbitol). This enzyme is widely distributed throughout the body, including those tissues that are susceptible to chronic diabetic complications (e.g. retina, lens, cornea, glomerulus, nervous system and the blood vessels). Alterations in sorbitol and fructose metabolism are implicated as factors contributing to vascular complications in Diabetes mellitus.[21]

The pathophysiologic event behind hyperglycemia-related alterations and in the pathophysiology of the

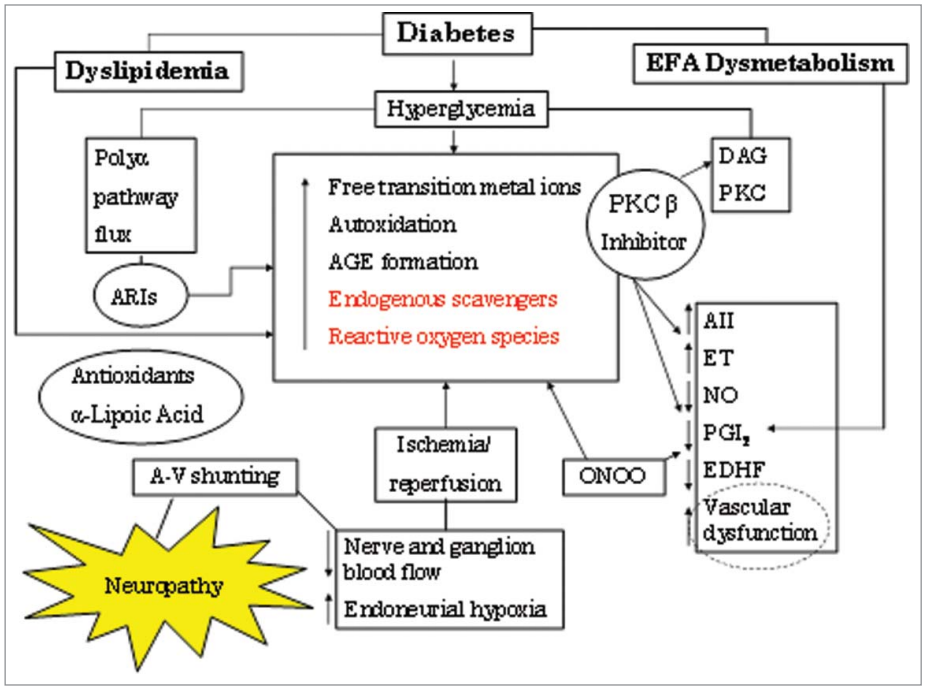

Figure 7. Pathogenesis of peripheral neuropathy. *Aaron I. Vinik et al Diabetes Mellitus: A Fundamental and Clinical Text: Ch. 91. Neuropathies: An Overview of Clinical Aspects, Pathogenesis, and Treatment 3rd Edition © 2004 Lippincott Williams & Wilkins.*

development of diabetic complications is Non-enzymatic glycation. Proteins and lipids exposed to aldose sugars go through non enzyme-dependent reactions, and generation of reversible Schiff bases or Amadori products take place. These early glycation products serve as a starting point for further rearrangements, which ultimately lead to the formation of advanced glycation end products (AGEs), a heterogeneous mixture of complex structures. The production of advanced glycation end products and free radicals are neurotoxic. Oxidative stress, in turn, may affect mitochondrial permeability leading to activation of programmed cell death caspase pathways, promoting apoptosis of neurons and Schwann cells.[22] A number of neuronal growth factors and insulin itself promote survival and outgrowth of neurons. Hence failed signaling from these factors and impaired nerve regeneration; may induce PN.[23]

Microangiopathy with endothelial dysfunction of the vasa nervorum is considered the vascular factor causing ischemia and hypoxia in nerves of diabetic patients.[23] Impaired vasodilatation of the vasa nervorum[23,24,25] may develop early and presage microangiopathic changes, subsequently leading to narrowing of the capillary lumen, resulting in reduced capillary blood flow, hypoxia, and progression of neuropathy. Degeneration of myelinated and unmyelinated nerve fibers may develop later and accompany the PN.[26]

Among the various pathogenic factors postulated for development of Diabetic Peripheral neuropathy; it is inconclusive whether autoimmunity plays a primary role., it accelerates PN initiated by metabolic or vascular injury. A significant greater activation of complement-independent calcium influx leading to apoptosis in cultured neuronal cells was shown in serum from type 2 diabetic patients with PN compared with serum from type 2 diabetic patients without PN. Autoimmune immunoglobulin was thought to induce apoptosis of the neuronal cells, and has been related to the severity of PN.[27,28] This suggests that autoimmune mechanisms may act in concert with hyperglycemia to damage sensory/autonomic neurons.

The number of patients with Diabetes mellitus is increasing by epidemic proportions in the world, particularly in India. Lower extremity disease, including peripheral neuropathy, foot ulceration, peripheral arterial disease, or lower extremity amputation, is twice as common in diabetic persons compared with non diabetic persons and it affects 30 per cent of diabetic persons who are older than 40 yr. In persons with Diabetes mellitus, the annual population-based incidence of foot ulcer ranges from 1.0 to 4.1 percent and the prevalence ranges from 4 to 10 per cent, this suggests that the lifetime incidence may be as high as 25 percent.[29,30]

In our study, the maximum number of patients with peripheral neuropathy, were in the age group of 51 – 60 years, which included 69 patients Similarly, in a multicentric study in India showed higher incidence for DPN in the elderly age group.[31]

In comparison to our study; Antonella caselli et al's study, the DNSS scores were absent (*n* – 20), mild (*n* – 66), moderate (*n* −95), and severe (*n* – 57) neuropathy.[32]

Similar to our study, Abbas Ali Mansour et al correlated that skin changes in patients with DPN were related to their work nature and type of footwear worn. As the dynamic and mechanical properties of the foot change depending on the pressure applied during the walk and the extent of pressure borne by the footwear; ill-fitting footwear can lead to cutaneous manifestations such as callosities, fissures, blisters, ulcers and nail changes.[33]

Wondwossen Amogne et al; identified antecedent risk factors for their foot problems such as; ill fitting and new shoes attributed in 48(44%). Neuro-ischaemic ulcers were seen in 113 (58%) of the cases and neuropathic ulcer in 63 (32%). Ulcer with cellulitis or gangrene was the most common mode of presentation seen in 92 (47%) of the patients. Ninety two (47%) patients had amputations. Re-amputation was necessary in 24 (26%) of these cases.[34]

In conclusion, Peripheral Neuropathy in Indian population is a delayed severe complication of Diabetes Mellitus most commonly affecting the middle aged and elderly individuals. DPN associated with long duration of DM, high glycemic levels and improper foot wear. Despite normal BMI, as Asian Indians have insulin resistance and are genetically predisposed to develop Type 2 DM. Most of these patients are unaware about the underlying complications due the loss of sensation. Peripheral hair loss, Xerosis, and Plantar fissures were the commonest initial manifestations of peripheral neuropathy in our patients. The incidence of skin changes increased with the duration of diabetes mellitus.

Hence, it is of great importance to control glycemic levels and diet control in the initial stages of Diabetes

and supplement Methylcobalamine along with oral antidiabetics to correct Metformin induced decline in serum B12 to avoid complications such as Peripheral Neuropathy, Diabetic Nephropathy, Diabetic Retinopathy and Diabetic Autonomic Neuropathy leading to Cardiac failure.

Once signs and symptoms of Peripheral Neuropathy initiate; it is mandatory to wear appropriate comfortable foot wear, regular lower limb care with proper moisturizer application on a regular basis and regular and proper trimming of nails and finally to approach a qualified medical practioner frequently to prevent morbidity and mortality associated with Diabetes Mellitus.

Abbreviations

BMI	Body Mass Index
DM	Diabetes mellitus
DPN	Diabetic Peripheral Neuropathy
DNSS	Diabetic Neuropathy Symptom Score
FBS	Fasting Blood Sugar
NDS	Neuropathy Disability Score
PPBS	Post Prandial Blood Sugar
PN	Peripheral Neuropathy
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

Conflict of interest

We hereby declare that; There is no conflict of interest regarding the publication of the article: " Cutaneous Manifestations of Diabetic Peripheral Neuropathy."

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