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Clinical Complications of Type-2 Diabetes: Opportunities and Challenges. A Case Report

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Abstract

Type 2 diabetes mellitus (T2DM) has become a major global health challenge, with its prevalence increasing substantially since 1990. The burden is particularly pronounced among South Asian populations, who develop T2DM at younger ages and at lower body mass indices than many other ethnic groups. The South Asian phenotype is characterized by visceral adiposity, insulin resistance, dyslipidemia, and a heightened susceptibility to cardiometabolic disease. Despite increasing recognition of these risks, current clinical strategies remain largely focused on identifying and treating established risk factors and maintaining glycemic targets, particularly HbA1c, rather than detecting early microvascular dysfunction and preventing progressive end-organ injury. We describe the longitudinal clinical profile of an 89-year-old South Asian individual with longstanding hypertension, left ventricular hypertrophy, and T2DM. Contemporary diagnostic modalities, including ambulatory cardiac rhythm monitoring, stress electrocardiography/echocardiography, and technetium-99 myocardial perfusion imaging, were used to evaluate cardiovascular function and ischemic risk. Although transient ST-segment depressions were observed during ambulatory and stress ECG monitoring, myocardial perfusion imaging demonstrated no inducible ischemia but revealed a fixed perfusion defect consistent with myocardial scar. The patient subsequently developed persistent foot discomfort for which conventional podiatric evaluation did not adequately distinguish among impaired peripheral circulation, neuropathic or inflammatory mechanisms, and immune-mediated processes. This case illustrates an important gap in the current management of diabetes and its complications. HbA1c provides an important measure of glycemic exposure but does not adequately characterize tissue-level microvascular perfusion, inflammation, immune activation, or the evolving mechanisms responsible for end-organ injury. In particular, the absence of readily available methods for assessing peripheral microvascular flow dynamics makes it difficult to determine whether symptoms such as foot pain reflect vascular insufficiency, inflammation, neuropathy, or a combination of these processes. The case highlights the need to move beyond HbA1c-centered diabetes management toward an integrated approach incorporating early detection of microvascular dysfunction, assessment of peripheral microcirculation, and identification of inflammatory and immune biomarkers. Development and clinical validation of accessible tools for monitoring microvascular flow and tissue-level inflammatory responses may improve risk stratification, enable earlier intervention, and reduce progressive microvascular and end-organ complications in South Asian individuals with T2DM..

Keywords: Type 2 diabetes, metabolic diseases, microvascular diseases, peripheral artery disease.

1. Introduction

The global burden of type 2 diabetes mellitus (T2DM) has increased dramatically over the past several decades [1]. Since 1990, the worldwide prevalence of diabetes has more than quadrupled, with much of this increase occurring in low- and middle-income countries. More than 830 million people are now estimated to be living with diabetes worldwide, making T2DM one of the most important global public-health challenges of our time [2]. In the United States, approximately 12% of the population has diabetes, the vast majority being T2DM, while an additional 115 million adults are estimated to have prediabetes [3]. The burden is particularly concerning among individuals of South Asian ancestry. The South Asian phenotype is characterized by a distinctive cluster of metabolic abnormalities, including increased visceral adiposity, hypertriglyceridemia, elevated low-density lipoprotein cholesterol (LDL-C), insulin resistance, and a marked susceptibility to T2DM [4]. Importantly, these metabolic abnormalities may occur despite a body mass index (BMI) that would not necessarily be considered obese by conventional Western standards. Individuals of South Asian ancestry may develop T2DM at a substantially younger age and at a lower BMI than many other ethnic populations, reflecting both genetic and environmental susceptibility [5,6].

South Asians have been reported to have a several-fold greater risk of developing T2DM than many other populations [7]. A combination of greater visceral fat accumulation, increased insulin resistance, impaired pancreatic β-cell function, and

genetic predisposition contributes to this heightened vulnerability [8]. The earlier onset of diabetes also means that individuals may be exposed to hyperglycemia and associated metabolic abnormalities for a longer period of their lives [9]. Consequently, cardiovascular and cerebrovascular disease may develop at an earlier age, while prolonged metabolic injury can progressively damage the microvasculature and vital organs [10]. Despite growing recognition of the South Asian phenotype, conventional healthcare guidelines and risk-assessment strategies may fail to identify metabolic abnormalities at a sufficiently early stage in this population [11]. Reliance on BMI, fasting glucose, HbA1c, and conventional lipid measurements may underestimate the underlying metabolic risk [12]. By the time overt diabetes is diagnosed, substantial metabolic and vascular injury may already have occurred [13]. This has led to increasing emphasis on earlier and more aggressive identification and modification of cardiovascular and metabolic risk factors. Initiatives such as the American Heart Association's efforts directed toward cardiovascular health in South Asian populations emphasize the importance of recognizing risk at an earlier stage and addressing modifiable factors before clinical disease becomes established [14].

Nevertheless, contemporary clinical management remains predominantly focused on treating risk factors after they have been identified rather than preventing the biological processes that give rise to them. In diabetes, management frequently becomes centered on achieving an acceptable HbA1c level. Although glycemic control is critically important, HbA1c represents only one dimension of the disease. It does not fully capture glycemic variability, duration of metabolic injury, vascular inflammation, endothelial dysfunction, microvascular abnormalities, or tissue-specific responses to metabolic stress [15]. Consequently, even individuals whose HbA1c values are considered satisfactory may continue to develop neuropathy, peripheral vascular abnormalities, renal disease, retinal disease, and other complications [16,17]. This raises an important question: Are we adequately monitoring the biological consequences of diabetes, or are we primarily monitoring a surrogate marker (HbA1c) of the disease?

2. A Longitudinal Case Study

This case study describes the longitudinal clinical course of an 89-year-old individual of South Asian ancestry with a long history of hypertension, left ventricular hypertrophy, and T2DM [18-20]. The subject of this study at the super age of 89, apart from his metabolic disease and the slow progression of vascular dysfunction and atherosclerosis, is otherwise healthy, active and productive. He follows a heart-healthy American (American Heart Association Diet) diet, exercises regularly, and walks at least 7,000 steps per day. The case provides an opportunity to examine the limitations of conventional approaches to chronic cardiometabolic disease management and, in particular, the difficulties encountered when assessing vascular and inflammatory complications involving the peripheral microcirculation.

The subject a male individual of South Asian descent arrived in the USA for higher studies in 1965. At that time, he was in good health, weighed 125 pounds and was 5 ft 8 inches in height. In 1994, during a visit to India he noticed shortness of breath, while climbing a small hill. Primary physician at Minneapolis Minnesota performed ECG tests and diagnosed right ventricular hypertrophy (LVH). The blood pressure of this individual at that time was 160/80. He was recommended the use of Vasotec 5Mg initially and later changed to 50 Mgs of Atenolol. In 2005 in addition to ambulatory blood pressure monitoring a complete transthoracic cardiac ultrasound study was done to follow the progression or regression of LVH. Left atrium was found to be enlarged at 46mm. A mild concentric LVH was observed. Cardiac ejection fraction was 75%. In 1998 the subject developed type 2 diabetes (fasting blood glucose of 170 Mgs) and suffered considerable loss of weight (from 153 lbs. to 130 lbs.). In addition to the antihypertensives drugs Glucophage (750 Mgs/day) was recommended to manage the blood glucose levels.

In 2007, his blood chemistry was as follows: Cholesterol 140, Triglycerides 137, Cholesterol 76, VLDL-cholesterol 27, Cholesterol-HDL ratio 3.7, Fasting glucose 164, HbA1c 7.0 and Blood pressure 140/70. Medication included Metformin ER 500Mg two tablets/twice daily, Enalapril 10 Mg twice daily, Carvedilol 6.5 Mg twice daily and Cyanocobalamin 1 ml twice a month. In 2012, postretirement the subject permanently moved to Potomac, Maryland. Medication at this time included Metformin HCL 500 Mgs twice daily, Lisinopril 20Mg twice daily, Carvedilol 6.25 Mg twice daily, Glipizide 10 Mg twice daily, Jardiance 120 Mg once daily. Atorvastatin 10Mg once daily and cyanocobalamin injections as per previous recommendations.

In 2024 the subject at the age of 87 underwent specific tests to follow the progress of atherosclerotic arterial disease of the blood vessels. 1) Lower limb vascular assessment by ultrasound, 2) Bilateral lower limb arterial doppler study, bilateral peroneal and posterior nerve conduction study. 3) carotid calcium score. 4) bilateral carotid (neck) doppler studies and echocardiography of the heart. Current medications include Metformin ER 500Mg two tablets twice daily, Lisinopril 20Mg Twice daily, Carvedilol 6.25 Mg twice daily, Glipizide 10Mg twice daily, Jardiance 10 Mg once daily, Rybelsus 7Mg once daily, Atorvastatin 10 Mg once daily, Cyanocobalamin 1000mcg twice a month. Vitamin D 1000 IU daily. During his yearly visits to India, he used to consult cardiologists as well as endocrinologists in Bengaluru, India. During his 2024 visit to India, the endocrinologist suggested additional tests to follow the progress of atherosclerosis of the regional vascular beds, bone density, nerve conduction and vascular flow dynamics in the lower limbs.

Bilateral iliac, common femoral, popliteal arteries showed diffuse wall thickening, calcification with mild narrowing of lumen. Despite these lesions, blood flow studies showed normal velocity waveforms. Left femoral artery showed wall irregularity and calcified plaques causing 20-30% luminal stenosis. Bilateral anterior tibial and dorsalis pedis arteries showed biphasic waveform, diffused wall thickening, calcification with mild narrowing of the lumen. In the motor nerve, bilateral common peroneal nerve studies showed mildly prolonged latency with mildly reduced compound muscle action potential (CMAP) amplitude and reduced motor conduction velocity. Bilateral posterior tibial nerve studies showed mildly prolonged latency with reduced motor conduction velocity and normal CMAP amplitude. These studies indicate electrophysiological evidence of bilateral lower limb mild sensorimotor axonal with secondary demyelinating neuropathy. Risk assessment of coronary artery calcium (CAC) score showed significant calcification of the coronary arteries. Number of calcifications in right coronary artery was 3 [Agatston Score (AS) 1007], left main coronary artery 0, Left anterior descending artery 2 (AS 54), left circumflex artery 2 (AS 1748). Current medications remain same as before except Glipizide and Rybelsus are dropped and 48 units of Sanofi long acting once daily insulin (Toujeo Max SoloStar) is included. Daily average glucose as determined by Abbott Libre 3 Plus is presented in Fig 1.

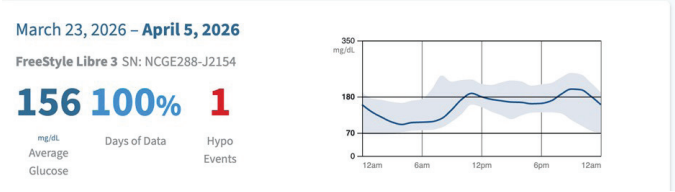

Figure 1. Daily glucose profile as determined by continuous Glucose Monitor

In 2024, the patient discovered during a routine testing of a Cardiac Rhythm measuring device that during daily activity multiple times ST-segment depression occurred. This study was further followed (2025) up in Washington DC by Cardio Care specialists. The Bruce exercise test showed a normal heart rate and blood pressure response to exercise [21]. However, the possible ST-segment depression in Stage 3 exercise is suggestive of ischemia, which may indicate coronary artery disease or inadequate blood flow to parts of the heart under stress. The Burce test as well as Technetium scans revealed no ischemia under Burce test as well as nuclear stress tests indicating no disturbances in the flow of blood in the arteries [20-22]. However, the ST-segment depression observed in these studies (Fig 2) above heart rate of 135 cannot be explained at this point. The Bruce Stress Test and the nuclear test were repeated in May of 2026. The Cardiologist reported that the overall quality of the study was excellent. There was no significant attenuation artifact. RV uptake was normal. LV size was normal at rest and following stress L/H ratio was 0.11. TID was 0.99. Left ventricular ejection was 68%. Compared to previous 2025 study there was no change.

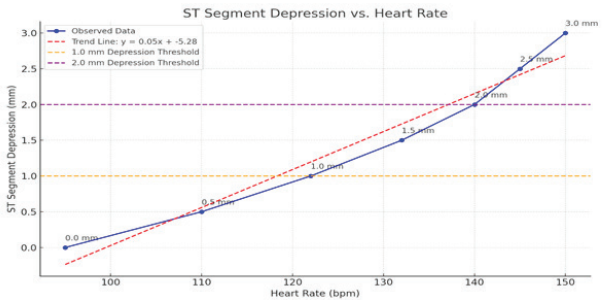

Figure 2. Open AI computed Plotting of ST- segment depression with increased heart rate. (Combined data from Padma Cardiac Device [Cardiac Design Laboratory, Bengaluru, India] and measurements shared by Cardio Care of Washington DC, post Bruce Tread Mill Test).

Legend Figure 2: The patient was monitored by Padma Cardiac Rhythm Device (Cardiac Design Laboratoires, Bengaluru, India) continuously for five days. Average heart rate was 72bpm. Minimum heart rate was 53 and maximum was 120bpm. ST-segment depression was observed on 9 separate occasions at heart rates 90-112bpm. Whereas in a relatively short Bruce Stress Test the ST -segment depression was noticed only at the heart rate above 135bpm).

Nerve conduction studies done in India showed mildly prolonged latency with reduced motor conduction velocity. The experts reported evidence of bilateral lower limb sensory motor axonal with demyelinating neuropathy. Furthermore, ultrasound imaging of the lower limb vessels showed diffuse plaques which the clinicians thought age related but no ischemia was detected in the lower limbs. Despite these observations the subject started noticing tingling of the toes, pain in the lower front surface of foot and heaviness of the foot during sleep. In view of these development primary physician referred the patient to a Podiatrist. Based on the X-ray studies as well as ultrasound measurement, the studies by the podiatrist suggested swelling of the plantar nerves, nerve entrapment, especially at the tarsal tunnel possibly related to neuroma formation (Table 1 and 2). He suggested soaking the feet in hot water containing Epsom salt daily. Patient has followed his suggestions as well as used many commercially available creams to get relief from pain during walking or during sleeping.

Table 1. Patient's Nerve Web space as measured by Ultrasound

Location	Measured Nerve/web space (mm)	Normal range	Interpretation
Right 1st web	Normal	< 5 mm	✅ Normal
Right 2nd web	9.24 mm	< 5 mm	⚠️ Abnormally enlarged
Right 3rd web	7.82 mm	< 5 mm	⚠️ Abnormally enlarged
Right 4th web	Normal	< 5 mm	✅ Normal
Left 1st web	Normal	< 5 mm	✅ Normal
Left 2st web	6.86 mm	< 5 mm	⚠️ Mildly enlarged
Left 3rd web	10.73 mm	< 5 mm	⚠️ Significantly enlarged
Left 4th web	Normal	< 5 mm	✅ Normal

(**Legend for the Table 1:** Right 1st web, right 4th web,-left 1st web and left 4th web were normal. Left 2nd web was mildly enlarged. Left 3rd web significantly enlarged. Right 2nd web and 3rd web were abnormally enlarged).

Table 2. Normal Plantar Nerve Measurements.

Normal Plantar Nerve Measurements Tough values can vary slightly depending on equipment and patient size, typical reference rangers are:		
Nerve	**Typical CSA (cross-sectional area)**	**Possible indication if enlarged**
Medial Plantar nerve	2–4 mm^2	Compression or entrapment near tarsal tunnel or arch
Lateral plantar nerve	2–3 mm^2	Entrapment under the abductor hallucis muscle
Tibial nerve (before division into plantar branches)	10–12 mm^2	Tarsal tunnel syndrome
Common plantar digital nerve (between toes)	< 2 mm^2	If enlarged (≥ 3–5 mm^2), may suggest Morton's neuroma

(**Legend for the Table 2**: Shows typical plantar nerve measurements. If enlarged > 3.5 mm^2 may suggest Morton's Neuroma. Patients Ultrasound measurements suggested indications of Morton's Neuroma).

3. Discussion

The Framingham Heart Study, a landmark long-term, population-based epidemiological investigation, fundamentally transformed our understanding of cardiovascular disease and established the modern concept of risk factors for coronary artery disease (CAD) [23]. Early reports from the study demonstrated that habitual physical activity, cigarette smoking, hypertension, diabetes, elevated blood cholesterol, and obesity were important risk factors for CAD. Despite these seminal findings, more than 75 years later, clinical practice worldwide continues to focus predominantly on managing these established modifiable risk factors rather than identifying the underlying metabolic disturbances that precede and contribute to their development [24-30]. The sequence of cellular and molecular abnormalities that ultimately manifests as these conventional risk factors is complex and progressive.

It includes oxidative stress, endothelial injury and dysfunction, vascular remodeling, increased intimal thickness, arterial narrowing, subclinical atherosclerosis, vascular and myocardial inflammation, and activation of platelet and coagulation pathways. Since the identification of the major modifiable risk factors for CAD, extensive research has elucidated many of the cellular and molecular mechanisms underlying cardiometabolic disease [30]. Nevertheless, clinical practice has been relatively slow to incorporate emerging diagnostic approaches that can detect these early metabolic and vascular disturbances through biomarker assessment. Earlier identification of such abnormalities could provide an opportunity to intervene before conventional risk factors become established and thereby enable more effective, mechanism-based strategies for the prevention of CAD.

This case study illustrates the complex and often discordant cardiovascular and neurological manifestations of long-standing cardiometabolic disease in an older South Asian man. The principal finding is the coexistence of extensive subclinical and clinical vascular disease, preserved ventricular systolic function, apparently adequate resting large-vessel perfusion, negative stress-perfusion imaging, and electrophysiological evidence of peripheral neuropathy. Taken together, these observations underscore an important limitation of conventional cardiometabolic assessment: the absence of hemodynamically significant large-vessel obstruction or inducible myocardial ischemia does not imply the absence of substantial atherosclerotic disease or tissue-level vascular dysfunction [31]. In this patient, the lower-extremity symptoms are most appropriately interpreted as multifactorial, reflecting the interaction of diffuse atherosclerosis, diabetes-associated neuropathy, possible focal nerve entrapment, age-related changes, and potentially impaired microvascular function [32].

4. Long-Term Cardiometabolic Exposure and Cumulative Vascular Injury

The patient's vascular phenotype is best understood in the context of several decades of exposure to hypertension and type 2 diabetes mellitus [33]. Hypertension was recognized in the 1990s and was associated with ventricular hypertrophy and subsequent evidence of mild concentric left ventricular hypertrophy and left atrial enlargement. These structural changes are consistent with chronic pressure loading and represent more than incidental echocardiographic findings. Left ventricular hypertrophy is an established marker of cumulative cardiovascular risk and is associated with myocardial stiffness, impaired relaxation, atrial remodeling, arrhythmia, and eventual heart failure, even when systolic function remains preserved.

The reported ejection fraction of 75% demonstrates preserved left ventricular systolic function but should not be interpreted as evidence of completely normal cardiac function. In older individuals with hypertension, diabetes, and ventricular hypertrophy, abnormalities of relaxation and increased ventricular stiffness may precede any reduction in ejection fraction. Left atrial enlargement may provide an additional indirect marker of chronically elevated filling pressures. Consequently, a contemporary assessment of cardiac status should consider left ventricular mass, relative wall thickness, trans mitral and tissue-Doppler indices, left atrial volume, pulmonary pressures, and other measures of diastolic function rather than relying on ejection fraction alone.

Diabetes, diagnosed in 1998, adds a second major pathway of cumulative vascular and neurological injury [34]. The available historical measurements, including fasting glucose of 164 mg/dL and an HbA1c of 7.0% in 2007, suggest that hyperglycemia was present over an extended period. Even relatively modest chronic hyperglycemia can contribute to endothelial dysfunction, oxidative stress, advanced glycation, vascular stiffness, microvascular injury, and peripheral nerve damage. Importantly, the relatively lean body habitus sometimes observed in South Asian individuals should not be interpreted as evidence of low metabolic risk. South Asians may develop insulin resistance, visceral adiposity, dyslipidemia, and type 2 diabetes at lower BMI than many other populations [4]. The patient's phenotype therefore illustrates the importance of considering metabolic risk beyond body weight alone.

5. Extensive Atherosclerotic Burden Despite Relatively Preserved Large-Vessel Hemodynamics

One of the most striking features of the case is the discrepancy between the extensive arterial wall disease demonstrated by ultrasound and the relatively modest degree of luminal obstruction [35,36] Diffuse wall thickening and calcification were present in the iliac, femoral, popliteal, tibial, and dorsalis pedis arteries, while the reported focal left femoral stenosis was only approximately 20–30% [37]. Normal proximal velocities and the absence of a major focal velocity increase indicate that there was no critical flow-limiting stenosis at rest. This distinction between atherosclerotic burden and hemodynamic obstruction is clinically important [38]. Atherosclerosis is a systemic disease of the arterial wall, whereas duplex ultrasonography primarily identifies its consequences for vessel anatomy and blood flow. A heavily calcified arterial tree can therefore represent advanced systemic vascular disease without producing a discrete stenosis severe enough to cause resting flow limitation. The patient should consequently not be classified as having minimal vascular disease merely because no major obstructive lesion was identified.

Arterial calcification also creates technical challenges in the assessment of lower-extremity perfusion [39]. In patients with diabetes and advanced age, medial arterial calcification may make ankle arteries poorly compressible and can lead to falsely elevated ankle-brachial index measurements. Where symptoms raise concern for impaired distal perfusion, complementary assessments such as toe-brachial index, toe systolic pressure, pulse-volume or Doppler waveform analysis, exercise ABI, transcutaneous oxygen pressure, or skin-perfusion pressure may provide additional information. These measurements address different aspects of tissue perfusion and may detect abnormalities not evident on routine resting duplex examination. Nevertheless, the clinical presentation does not strongly support severe flow-limiting peripheral arterial disease as the primary cause of the patient's foot symptoms. There is no clear description of typical exertional calf claudication, critical limb ischemia, tissue loss, or ischemic rest pain. Thus, the vascular imaging should be interpreted primarily as evidence of substantial systemic arterial disease and increased cardiovascular risk rather than as proof that the patient's neurological symptoms are caused by peripheral ischemia.

6. Extreme Coronary Calcium Burden and The Meaning of a Negative Stress Study

The coronary calcium score provides perhaps the strongest evidence of the patient's extensive systemic atherosclerotic burden [40]. A reported Agatston score of approximately 2,809, with particularly high calcium deposition in the right coronary and left circumflex distributions, represents an exceptionally high level of coronary calcification. Such a score indicates a very large burden

of established coronary atherosclerosis and identifies a patient at markedly elevated long-term cardiovascular risk. Importantly, coronary calcium scoring and stress myocardial perfusion imaging answer different clinical questions. Coronary calcium quantifies calcified plaque burden but does not determine the degree of luminal narrowing or whether a lesion produces ischemia. Conversely, a nuclear stress study primarily evaluates whether myocardial perfusion becomes impaired under the physiological conditions of the test. Thus, a negative stress study should not be interpreted as evidence that the coronary arteries are free of significant atherosclerosis.

The apparently discordant combination of extreme coronary calcium and negative stress imaging is therefore not inherently contradictory [41]. It may indicate extensive nonobstructive plaque, disease that does not produce ischemia during the test, limitations of stress testing, or less commonly, diffuse or balanced disease that is not readily detected by relative perfusion imaging. The appropriate clinical interpretation depends on symptoms, exercise capacity, electrocardiographic findings, ventricular function, and the patient's overall risk profile. This distinction has direct therapeutic implications. The calcium score itself does not establish an indication for invasive coronary angiography or revascularization in an asymptomatic patient. It does, however, reinforce the importance of aggressive and individualized cardiovascular risk reduction.

7. Interpreting Exercise-Induced ST-Segment Depression

The exercise-associated ST-segment depression occurring predominantly at a heart rate of approximately 135 beats per minute represents another important area of apparent discordance [42]. Exercise-induced ST depression may indicate myocardial ischemia, but its specificity is reduced in the presence of left ventricular hypertrophy, baseline repolarization abnormalities, conduction disturbances, medication effects, electrolyte abnormalities, or technical factors. Rate-related repolarization changes may also occur at higher heart rates. The negative nuclear perfusion study reduces, but does not completely eliminate, the likelihood of clinically important inducible ischemia. The findings should therefore be interpreted as complementary rather than mutually exclusive: the electrocardiogram suggests an abnormal physiological response to exercise, whereas perfusion imaging did not demonstrate a corresponding regional perfusion defect.

8. Peripheral Neuropathy as A Major Contributor to The Foot Symptoms

The neurological findings provide a compelling alternative and potentially complementary explanation for the patient's lower-extremity symptoms [43-46]. Nerve-conduction studies demonstrated mild bilateral sensorimotor neuropathy with predominantly axonal involvement and secondary slowing or demyelinating features. In the context of long-standing diabetes, this pattern is compatible with distal symmetric diabetic polyneuropathy, although the electrophysiological pattern is not specific for diabetes. The clinical symptoms of toe tingling, nocturnal discomfort, and heaviness are also consistent with peripheral neuropathy. Chronic hyperglycemia can damage peripheral nerves through multiple mechanisms, including oxidative stress, mitochondrial dysfunction, advanced glycation, impaired axonal transport, microvascular injury, and abnormalities of the polyol pathway. Importantly, neuropathy can persist or progress even when contemporary glycemic control appears satisfactory because cumulative metabolic exposure may produce relatively irreversible structural injury.

9. Superimposed Focal Nerve Entrapment

The podiatric and ultrasound findings suggest that generalized polyneuropathy may not be the entire explanation for the patient's symptoms [47]. Focal nerve enlargement raises the possibility of superimposed entrapment involving the tibial or plantar nerve system, including tarsal tunnel syndrome or a localized plantar nerve lesion. Such focal neuropathies can coexist with diabetic polyneuropathy and may account for symptoms that are asymmetric, anatomically localized, or related to particular pressure points. However, nerve enlargement on ultrasound is supportive rather than diagnostic. The significance of this finding depends on its correlation with the anatomical distribution of symptoms, physical examination, provocative maneuvers, footwear-related pressure, and electrodiagnostic findings. This distinction is important because structural abnormalities may be present without being the principal source of pain.

10. Macrovascular Disease, Microvascular Dysfunction, And Neuropathy: An Integrated Model

The case is particularly informative because it demonstrates the limitations of dividing vascular disease into a simple macrovascular-versus-microvascular dichotomy [48]. The patient clearly has extensive macrovascular atherosclerosis, demonstrated by widespread arterial calcification and an extremely high coronary calcium score. At the same time, diabetes may have produced abnormalities at the level of the microcirculation, including impaired endothelial function, altered autoregulation, capillary dysfunction, and reduced tissue oxygen delivery. Peripheral neuropathy may further disturb autonomic regulation of skin blood flow. Routine duplex ultrasonography cannot adequately characterize these processes. It primarily evaluates arterial anatomy and macroscopic blood flow and does not directly measure capillary recruitment, endothelial-dependent vasodilation, tissue oxygenation, or neurovascular regulation. Thus, apparently satisfactory arterial velocities do not necessarily imply completely normal tissue-level perfusion.

At the same time, the available data do not establish a specific inflammatory microvascular disorder. There are no reported skin-biopsy findings, microvascular reactivity measurements, inflammatory biomarkers, or clinical features establishing vasculitis or another primary inflammatory vascular process. Accordingly, terms such as "vascular inflammation" or "microvascular ischemia" should be used cautiously unless supported by additional evidence. The strongest evidence in this case supports diffuse atherosclerosis and peripheral neuropathy, with microvascular dysfunction remaining a plausible but incompletely characterized contributor.

11. Distinguishing Neuropathic Symptoms from Ischemic Symptoms

An important clinical challenge is distinguishing neuropathic pain from ischemic pain when both vascular disease and neuropathy are present [49,50]. Classic ischemic rest pain generally involves the distal foot or toes, is often aggravated by elevation, and improves when the limb is placed in a dependent position. It is usually accompanied by objective evidence of impaired perfusion in more advanced disease. By contrast, burning, tingling, nocturnal discomfort, altered sensation, and pain distributed along a nerve territory are more characteristic of neuropathic disease. In this patient, the symptom pattern and electrophysiological findings favor a substantial neuropathic component. However, diabetes-associated neuropathy may blunt the perception of ischemic pain, making clinical assessment more difficult. Consequently, the

absence of typical ischemic pain should not be interpreted as evidence that clinically important ischemia is absent. This case emphasizes that cardiometabolic disease in advanced age is not adequately characterized by blood pressure, glucose concentration, ventricular ejection fraction, resting arterial flow, or stress-test results considered individually. Long-standing hypertension and diabetes can produce extensive arterial wall disease, coronary calcification, peripheral neuropathy, and tissue-level vascular dysfunction while conventional tests continue to show preserved function in selected domains.

The patient's symptoms are therefore best understood through a multifactorial model incorporating diffuse atherosclerosis, diabetic peripheral neuropathy, possible focal nerve entrapment, age-related mechanical factors, and potentially impaired microvascular regulation. The absence of critical peripheral stenosis makes severe flow-limiting peripheral arterial disease an unlikely sole explanation for the foot symptoms, while the extreme coronary calcium score demonstrates that a negative stress study should not be equated with absence of coronary atherosclerosis. The central clinical lesson is that atherosclerotic burden, hemodynamic impairment, ischemia, neuropathy, and symptoms represent related but distinct dimensions of cardiometabolic disease. A comprehensive evaluation that integrates vascular imaging, tissue perfusion, electrophysiology, metabolic risk, medication safety, and clinical phenotype is therefore more informative than any single diagnostic test. This integrated approach may be particularly important in older adults and in South Asian populations, in whom substantial cardiometabolic risk may occur despite relatively modest conventional anthropometric measures.

12. Toward A New Approach to Diabetes Complications

This case highlights the need to move beyond a management strategy centered primarily on HbA1c and conventional cardiovascular risk factors [51]. Glycemic control remains fundamental to diabetes management, but it should not be considered a complete measure of disease control [52-54]. A patient can have an acceptable HbA1c while continuing to experience progressive vascular, neural, inflammatory, and tissue-level injury. Future diabetes management should therefore incorporate tools capable of detecting functional vascular injury before irreversible structural damage occurs. In particular, there is a need for practical, reproducible methods capable of measuring peripheral microvascular flow dynamics and tissue perfusion longitudinally [55-58].

Such technologies could potentially answer several clinically important questions:

- Is peripheral tissue perfusion adequate at rest and during physiological stress?
- Is the microcirculation capable of appropriately increasing blood flow when tissue demand increases?
- Is endothelial function impaired despite apparently normal large-vessel circulation?
- Can early microvascular dysfunction be detected before clinical complications become apparent?
- Can changes in microvascular function be used to monitor the effectiveness of therapeutic interventions?
- Is diabetes mediated neuropathy due to circulatory dysfunction demyelination of nerves, inflammation or immune mediated?
- Is cellular and molecular mechanisms leading microvascular neuropathy same for the peripheral neuropathy of the lower limbs, nephropathy and retinopathy?

At the same time, there is a need for biomarkers that can distinguish the biological mechanisms underlying peripheral microvascular symptoms60. Biomarkers of inflammation, endothelial activation, immune responses, oxidative stress, and tissue injury could complement measurements of blood flow and provide a more comprehensive picture of macrovascular/microvascular disease activity.

Conclusion

This longitudinal case illustrates a fundamental limitation of current cardiometabolic disease management. Modern medicine has developed remarkably sophisticated technologies for evaluating the heart and large blood vessels, yet our ability to assess the dynamic function of the peripheral microcirculation remains comparatively limited. The South Asian phenotype makes this issue particularly important because metabolic and vascular injury may develop at younger ages and at lower BMI, often before conventional risk assessment identifies substantial disease. By the time overt diabetes is diagnosed, pathological processes involving the cardiovascular system, microcirculation, peripheral nerves, and other organs may already be well established. The clinical objective should therefore evolve from simply controlling diabetes to understanding and monitoring the biological consequences of diabetes. HbA1c should remain an important component of disease monitoring, but it should not be regarded as a comprehensive measure of vascular health. This case emphasizes the need for a new generation of diagnostic technologies capable of assessing peripheral microvascular flow dynamics and tissue perfusion, together with biomarkers that can identify inflammatory and immune-mediated mechanisms of tissue injury. Such approaches could help determine whether symptoms such as foot pain are primarily vascular, neuropathic, inflammatory, immune-mediated, or multifactorial. Ultimately, the goal should be to identify microvascular dysfunction earlier, understand its underlying mechanisms, and intervene before functional abnormalities progress to irreversible structural damage and end-organ failure. The future of diabetes care may therefore depend not only on how effectively we control blood glucose, but also on how effectively we can see, measure, and monitor the microvascular consequences of metabolic disease.

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