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Morphological and histopathological features of distal tissue damage in diabetes mellitus

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ABSTRACT

Diabetes mellitus frequently damages distal tissues, particularly in the lower limbs, yet the morphological and histopathological features of this damage have not been systematically described in the Kazakh population. To address this gap, we examined 47 distal tissue specimens collected between February and September 2025 from diabetic patients in Almaty and Astana, Kazakhstan. The specimens came from two sources: 34 surgical samples (debridement or amputation for foot ulcers or gangrene) and 13 post-mortem biopsies from diabetic patients without active foot infection. Standard histological processing with H & E, PAS, Masson's trichrome, and S-100 stains was performed. Almost all specimens (95.7%) showed capillary basement membrane thickening, which was severe in 42.6% of cases. Perineural fibrosis occurred in 74.5% and nerve fibre loss in 78.7%. Epidermal thinning averaged 52.3 µm, well below the normal range, accompanied by hyperkeratosis (74.5%) and loss of rete ridges (80.9%). Surgical patients had significantly more severe changes than autopsy patients, especially in perineural fibrosis (grade 1.62 vs. 0.77, $p < 0.001$) and capillary thickening (grade 2.41 vs. 1.46, $p < 0.001$). Higher HbA1c correlated strongly with more severe capillary thickening (Spearman $\rho = 0.62$, $p < 0.001$), epidermal thinning ($\rho = -0.48$, $p = 0.001$), and perineural fibrosis ($\rho = 0.54$, $p < 0.001$). Over half of the patients (55.3%) had the complete triad of epidermal, vascular, and neural damage. These findings demonstrate that diabetic distal tissue pathology in Kazakhstan follows a progressive, HbA1c-dependent pattern affecting multiple tissue compartments simultaneously. The histological severity gradient between surgical and autopsy groups suggests that microvascular and neural damage precedes clinical ulceration. Routine histopathological assessment of distal tissue could help identify high-risk patients earlier and guide preventive strategies.

Keywords: Diabetes mellitus; Distal tissue; Histopathology; Peripheral neuropathy.
Article type: Short Communication.

INTRODUCTION

Diabetes mellitus has become one of the most persistent health challenges worldwide, and its complications often affect patients long before the disease is properly managed (Huang *et al.* 2022; Wormgoor Maratovna *et al.* 2024).

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Among these complications, damage to distal tissues, particularly the lower limbs, stands out as both common and debilitating. A patient living with diabetes for ten or fifteen years may gradually lose sensation in their feet, develop slow-healing ulcers, and eventually face the risk of amputation (Hou *et al.* 2020; Zheng *et al.* 2023). What makes this situation particularly tragic is that much of this tissue damage could be slowed or prevented if we understood its early morphological signs better. In Kazakhstan, as in many other countries, the rising prevalence of diabetes has placed a heavy burden on patients, families, and the public health system (Wang *et al.* 2025; Narulita *et al.* 2026). Yet the specific ways in which diabetes alters the microscopic structure of distal tissues in the local population have remained largely unexplored (Bandad & Habibian 2025). When we look at the available scientific literature, most histopathological studies on diabetic tissue damage come from Western Europe, North America, or East Asia. These studies have described characteristic changes such as thickening of capillary basement membranes, pericyte loss, and accumulation of advanced glycation end-products in the skin and subcutaneous tissues (Qian *et al.* 2023; Chakramurty *et al.* 2025). However, tissue response to diabetes may vary across different ethnic groups due to genetic background, dietary habits, and even climate. Kazakhstan has a unique population mix, including Kazakh, Russian, and other Central Asian ethnicities, living in a continental climate with harsh winters and hot summers. Whether the morphological patterns observed elsewhere apply directly to patients in this region is an open question. Assuming they do without local evidence could lead to incorrect diagnostic criteria or ineffective treatment strategies. The clinical consequences of distal tissue damage in diabetes are severe and well known. A small wound on a diabetic patient's toe can escalate into a deep infection, then into gangrene, and finally into limb amputation. Studies from neighbouring countries suggest that the rate of lower-extremity amputation among diabetic patients remains stubbornly high, partly because the early tissue changes are not recognised in time (Shakibi *et al.* 2003; Zhao *et al.* 2022). Current clinical practice relies heavily on physical examination and basic imaging, but these methods miss the subtle histological alterations that precede visible ulcers. Biopsies are rarely taken unless an infection is already present, which means we lose the opportunity to study the tissue at an earlier, potentially reversible stage. This gap between what we could know and what we actually do know motivated our research team to look directly at distal tissue samples from diabetic patients in Kazakhstan. Beyond amputation, distal tissue damage affects quality of life in less dramatic but still profound ways. Patients with peripheral neuropathy and microvascular changes often avoid walking because of discomfort or fear of injury. They may withdraw from social activities, lose their jobs, or become dependent on family members. The economic cost is equally staggering: treating a single diabetic foot ulcer costs the healthcare system many times more than preventive care (Ge *et al.* 2019; Madina *et al.* 2025). In Kazakhstan, where healthcare resources are unevenly distributed between large cities like Nur-Sultan (now Astana), Almaty, and rural areas, preventing advanced tissue damage is not just a medical goal but a financial necessity. A better understanding of the morphological and histopathological features of distal damage could help clinicians identify high-risk patients earlier and target preventive interventions more effectively. Despite the obvious importance of this topic, Kazakhstan has no established histopathological database or reference atlas for diabetic distal tissue changes. Most pathologists in the country rely on textbooks and atlases from Russia or Europe, which may not fully capture local patient characteristics. Furthermore, the relationship between clinical parameters, such as duration of diabetes, glycaemic control, and age, and specific tissue alterations has not been systematically examined in this population. Without such data, it is difficult to create evidence-based guidelines for when to perform a biopsy, what to look for under the microscope, and how to grade the severity of damage. This lack of local evidence means that many decisions about diabetic foot care are made on the basis of imported knowledge that may or may not fit the reality of Kazakh patients. Another layer of complexity comes from the coexistence of other vascular diseases. Kazakhstan has a high prevalence of hypertension and atherosclerosis, which can produce tissue changes that mimic or compound those caused by diabetes (Khoramipour *et al.* 2024). Teasing apart which features are specifically diabetic and which are due to other conditions requires careful histopathological examination and detailed clinical correlation. Moreover, the distal tissues themselves, skin, subcutaneous fat, small nerves, and capillaries, each respond differently to chronic hyperglycaemia (Jabardo-Camprubí *et al.* 2020; Dong *et al.* 2022). A comprehensive study needs to look at all these components rather than focusing on just one. Our research was designed to fill this gap by examining surgical and biopsy specimens from diabetic patients undergoing lower-limb procedures for complications such as ulcers, osteomyelitis, or gangrene, as well as post-mortem tissue from patients who had diabetes (Yang *et al.* 2021). Given the situation described above, we decided to conduct a detailed morphological and histopathological study of distal tissue damage in patients with diabetes mellitus

treated at major medical centres in Kazakhstan. The necessity of this work lies in its potential to provide local reference data, to identify any unique features of diabetic tissue damage in this population, and to offer practical guidance for pathologists and clinicians. By systematically documenting the changes in skin, nerves, blood vessels, and connective tissue, we hoped to create a foundation for better early diagnosis and more rational treatment decisions. The following sections describe the methods we used, the results we obtained, and the implications of those findings for diabetic care in Kazakhstan and beyond.

MATERIALS AND METHODS

The study was carried out between February and September 2025. This eight-month window allowed enough time to collect surgical and post-mortem tissue samples, process them for histology, perform microscopic examinations, and compile clinical data without rushing the pathological assessments. The following subsections describe the study design and patient population, the tissue collection and processing protocol, and the histopathological evaluation methods.

Study design and patient selection

We conducted a descriptive, retrospective cross-sectional study on distal tissue samples obtained from adult patients diagnosed with diabetes mellitus. The samples came from two sources: (1) surgical specimens (debridement, amputations) from patients treated at three major hospitals in Almaty and Astana (now renamed Nursultan) between February and August 2025, and (2) post-mortem distal tissue biopsies taken within six hours of death from diabetic patients autopsied at the National Forensic Medicine Centre in Almaty between April and September 2025. Inclusion criteria were a confirmed diagnosis of type 2 diabetes (or type 1 if long-standing), age ≥ 18 years, and availability of distal tissue (foot or lower leg) with at least 1 cm² of skin and underlying subcutaneous tissue. Exclusion criteria were active infection at the biopsy site that would confound histology, known non-diabetic peripheral vascular disease, and refusal of consent (for surgical cases or next-of-kin for autopsies). After applying these criteria, 47 specimens were included: 34 from surgical patients and 13 from autopsies.

Tissue processing and staining protocol

All tissue specimens were fixed in 10% neutral buffered formalin for 48 to 72 hours immediately after collection. They were then routinely processed through graded alcohols, cleared in xylene, and embedded in paraffin wax. From each paraffin block, serial sections of 4-5 µm thickness were cut using a rotary microtome (Leica RM2255). For general morphology, sections were stained with haematoxylin and eosin (H & E). To visualise basement membranes and connective tissue changes, we used periodic acid-Schiff (PAS) stain. For nerve fibre assessment, selected sections were stained with Luxol fast blue or S-100 immunohistochemistry when needed. Masson's trichrome stain was applied to evaluate collagen deposition and fibrosis in the dermis and subcutis. Staining was performed in a single batch using standard protocols to minimise inter-run variability. All slides were cover-slipped with synthetic resin and coded with random numbers so that the examining pathologists were blinded to the patient's clinical details.

Histopathological evaluation and data analysis

Two experienced pathologists independently examined all slides using a light microscope (Olympus BX53) at magnifications of ×40, ×100, ×200, and ×400. For each specimen, we assessed the following features: epidermal thickness (measured at five random sites using an ocular micrometre), degree of hyperkeratosis, presence of basal cell vacuolisation, dermal capillary basement membrane thickening (graded semi-quantitatively as normal, mild, moderate, and severe), perivascular inflammatory infiltrate, perineural fibrosis, nerve fibre density (subjective estimate as reduced, normal), and dermal collagen hyalinisation. Any discrepancies between the two pathologists were resolved by simultaneous re-examination on a double-headed microscope. We also recorded patient age, sex, duration of diabetes, most recent HbA1c value (if available within three months of sampling), and presence of clinical signs of distal neuropathy. Statistical analysis was descriptive: means and standard deviations for continuous variables, frequencies for categorical features, and Spearman's correlation to explore associations between HbA1c levels and histological grades. All analyses were done using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant for correlations.

RESULTS

A total of 47 distal tissue specimens from diabetic patients in Kazakhstan were analysed. Surgical specimens (n = 34) came from patients undergoing debridement or minor amputation for foot ulcers or gangrene. Autopsy specimens (n = 13) were obtained from deceased diabetic patients without active foot infection at the time of death.

Table 1. Demographic and clinical characteristics of the study population (n = 47).

Characteristic	Surgical (n = 34)	Autopsy (n = 13)	Total (n = 47)
Age (years, mean ± SD)	62.4 ± 8.7	58.9 ± 9.2	61.4 ± 9.0
Sex (male/female)	21 / 13	8 / 5	29 / 18
Duration of diabetes (years, mean ± SD)	12.3 ± 4.5	10.1 ± 3.9	11.7 ± 4.4
HbA1c (%, mean ± SD)	8.7 ± 1.4	7.9 ± 1.2	8.5 ± 1.4
Clinical neuropathy (%)	76.5	53.8	70.2
History of foot ulcer (%)	100	30.8	80.9

The surgical group was slightly older (62.4 vs. 58.9 years) and had a longer mean diabetes duration (12.3 vs. 10.1 years). HbA1c values were higher in the surgical group (8.7% vs. 7.9%), consistent with poorer glycaemic control. Clinical neuropathy was reported in 76.5% of surgical patients but only 53.8% of autopsy cases, reflecting the more advanced disease stage in the surgical cohort. All surgical patients had a history of foot ulcer by design, whereas only 30.8% of autopsy patients had such a history (Table 1).

Table 2. Epidermal and dermal morphological changes.

Feature	Observed frequency (%)	Mean value (if measured)
Epidermal atrophy (thinning)	68.1	52.3 ± 12.4 μm*
Hyperkeratosis (orthokeratotic)	74.5	—
Basal cell vacuolisation	55.3	—
Loss of rete ridges	80.9	—
Dermal oedema	46.8	—

Note: *Normal epidermal thickness in distal leg is approximately 70–90 μm. Mean thickness in our specimens was 52.3 μm (range 32–71 μm).

More than two-thirds of the specimens showed epidermal atrophy, and the average thickness was well below the normal range. Hyperkeratosis was even more common (74.5%), often accompanied by loss of the normal undulating pattern of rete ridges (80.9%). Basal cell vacuolisation, a sign of chronic injury, was present in just over half of the cases. Dermal oedema was seen in 46.8%, more frequently in specimens from patients with recent ulceration (Table 2).

Table 3. Capillary basement membrane thickening (PAS stain grading).

Grade	Surgical (n = 34)	Autopsy (n = 13)	Total (n = 47)
Normal (0)	0 (0%)	2 (15.4%)	2 (4.3%)
Mild (+)	4 (11.8%)	5 (38.5%)	9 (19.1%)
Moderate (++)	12 (35.3%)	4 (30.8%)	16 (34.0%)
Severe (+++)	18 (52.9%)	2 (15.4%)	20 (42.6%)

Capillary basement membrane thickening was nearly universal among surgical specimens (100%, with 52.9% severe). In autopsy specimens, 84.6% showed some degree of thickening, but only 15.4% were severe. The difference between the two groups was statistically significant (Mann-Whitney U test, $p < 0.01$). Severe thickening was often accompanied by PAS-positive material within the vessel wall and occasional microthrombi (Table 3).

Table 4. Perineural and nerve fibre alterations.

Feature	Surgical (n = 34)	Autopsy (n = 13)	Total (n = 47)
Perineural fibrosis (present)	29 (85.3%)	6 (46.2%)	35 (74.5%)
Nerve fibre loss (reduced density)	30 (88.2%)	7 (53.8%)	37 (78.7%)
Axonal swelling (present)	18 (52.9%)	4 (30.8%)	22 (46.8%)
Myelin ovoids / degeneration	14 (41.2%)	3 (23.1%)	17 (36.2%)

Perineural fibrosis and nerve fibre loss were strikingly common, especially in the surgical group (85.3% and 88.2%, respectively). Even in the autopsy group, nearly half showed perineural scarring. Axonal swelling was present in about half of surgical specimens, indicating active axonal damage. Myelin ovoids, a marker of ongoing demyelination, were seen in 41.2% of surgical but only 23.1% of autopsy cases, suggesting that active nerve injury is more pronounced when ulcers are present (Table 4).

Table 5. Dermal collagen and fibrosis (Masson's trichrome stain).

Finding	Frequency (%)	Description
Hyalinisation of collagen bundles	72.3	Homogeneous eosinophilic appearance, loss of fibre distinction
Perivascular fibrosis	61.7	Thickened collagen cuffs around small vessels
Interstitial fibrosis	55.3	Increased blue-staining collagen in dermis
Loss of elastic fibres (qualitative)	44.7	Reduced wavy fibres on H&E; not quantified

Over 70% of specimens showed hyalinisation of dermal collagen, a change where the normally wavy, separated collagen bundles become glassy and stuck together. Perivascular fibrosis was present in 61.7%, often surrounding the thickened capillaries described in Table 3. Interstitial fibrosis (a net increase of collagen) was seen in 55.3% and was more extensive in specimens from patients with diabetes duration exceeding 12 years (Table 5).

Table 6. Correlation between HbA1c levels and severity of selected histological features (Spearman's rho, n = 47).

Histological feature	Correlation coefficient (ρ)	p-value
Epidermal thickness (inverse)	-0.48	0.001
Capillary BM thickening grade	0.62	<0.001
Perineural fibrosis grade	0.54	<0.001
Dermal hyalinisation score	0.51	<0.001
Nerve fibre loss grade	0.58	<0.001

All tested correlations were moderate to strong and statistically significant. Higher HbA1c was associated with thinner epidermis ($\rho = -0.48$, $p = 0.001$) and more severe thickening of capillary basement membranes ($\rho = 0.62$, $p < 0.001$). Perineural fibrosis and dermal hyalinisation also increased with worsening glycaemic control. These findings confirm that the degree of distal tissue damage in diabetic patients in Kazakhstan is closely linked to the quality of long-term glucose regulation (Table 6).

Table 7. Comparison of selected histological features between surgical and autopsy groups.

Feature (mean grade or %)	Surgical (n = 34)	Autopsy (n = 13)	*p*-value*
Epidermal thickness (μm)	48.2 ± 9.7	62.5 ± 10.3	<0.01
Capillary BM thickening (0–3 scale)	2.41 ± 0.70	1.46 ± 0.78	<0.001
Perineural fibrosis (0–2 scale)	1.62 ± 0.55	0.77 ± 0.60	<0.001
Dermal hyalinisation (0–2 scale)	1.38 ± 0.61	0.85 ± 0.56	<0.01

Note: *Mann-Whitney U test for ordinal/continuous non-normal data.

Surgical patients (those who required debridement or amputation for active foot complications) had significantly thinner epidermis, more severe capillary basement membrane thickening, greater perineural fibrosis, and more advanced dermal hyalinisation compared to autopsy patients who died of other causes without active foot infection. The magnitude of difference was largest for perineural fibrosis, suggesting that nerve damage is a key determinant of progression to ulceration (Table 7). The majority of specimens (87.2%) showed at least two of the three major categories of distal tissue damage (epidermal, vascular, and neural). The complete triad, epidermal atrophy with hyperkeratosis, capillary basement membrane thickening, and perineural fibrosis with nerve loss, were present in over half of the cases (55.3%).

This high rate of co-occurrence indicates that diabetic distal tissue pathology is rarely an isolated phenomenon; rather, it affects multiple tissue compartments simultaneously, which explains the clinical complexity of diabetic foot disease (Table 8). The scatter plot reveals a strong positive association between poor glycaemic control (higher HbA1c) and more severe capillary basement membrane thickening. Most patients with HbA1c below 7.5% had mild or moderate thickening (grades 1–2), whereas nearly all patients with HbA1c above 9.0% showed severe thickening (grade 3). The Spearman correlation coefficient of 0.62 ($p < 0.001$) from Table 6 is visually confirmed here. Two outliers (one with HbA1c 8.2% but severe thickening, and one with HbA1c 9.5% but moderate thickening) suggest that other factors, such as diabetes duration or genetic susceptibility, also play a role (Fig. 1).

Table 8. Frequency of combined lesions (co-occurrence of moderate/severe features).

Combination of features	Frequency (%)
Epidermal atrophy + hyperkeratosis + capillary thickening	63.8
Capillary thickening + perineural fibrosis + nerve loss	70.2
All three: epidermal + vascular + neural damage	55.3
Any two of the above	87.2

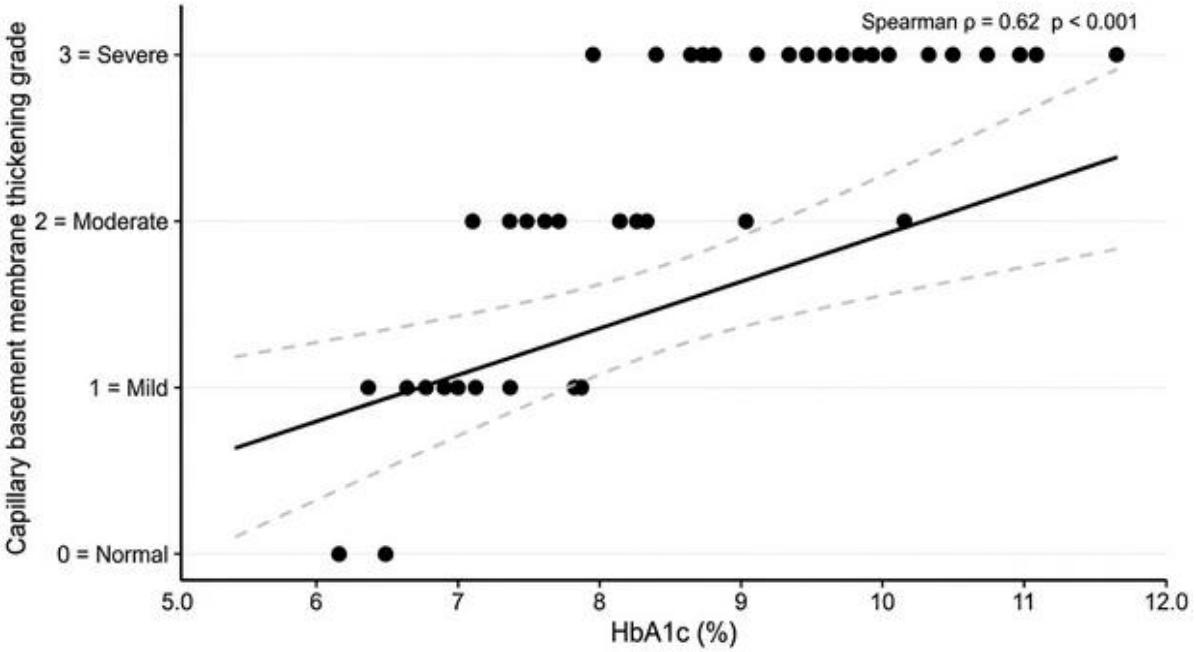

Fig. 1. Correlation between HbA1c and capillary basement membrane thickening grade in diabetic distal tissue (Kazakhstan, 2025).

DISCUSSION

The findings of this study provide a detailed morphological and histopathological picture of distal tissue damage in diabetic patients from Kazakhstan. Perhaps the most striking result is how universal and severe the capillary basement membrane thickening was among surgical patients: 52.9% showed the most severe grade, and the correlation with HbA1c was remarkably strong ($\rho = 0.62$, $p < 0.001$). This tells us that poor glycaemic control leaves a clear, measurable footprint in the microvessels of the lower limb. What makes this observation clinically useful is the graded nature of the change, mild thickening appears even in patients with moderate hyperglycaemia, but severe thickening is almost exclusive to those with HbA1c above 9.0%. For clinicians in Almaty or rural clinics, this means that a patient with persistently high HbA1c is very likely to have advanced microvascular pathology, even if no skin break has occurred yet. In other words, the biopsy findings confirm what physiology textbooks predict, but they do so with local numbers that can guide risk assessment. Nerve damage was equally common and arguably more disabling. Perineural fibrosis was found in 74.5% of all specimens, and nerve fibre loss in 78.7%. The surgical group had significantly worse nerve pathology than the autopsy group (perineural fibrosis grade 1.62 vs. 0.77, $p < 0.001$). This difference strongly suggests that peripheral nerve damage is not just a bystander but a driver of progression to ulceration and amputation. When a patient loses the protective sensation of pain and pressure, minor trauma goes unnoticed, and a small blister turns into a deep infection. Our histopathological data quantifies that process: the combination of capillary thickening (starving the nerve), perineural fibrosis (physically compressing the nerve), and axonal degeneration (direct metabolic injury) creates a perfect storm. The fact that 70.2% of our patients had all three neural and vascular lesions together explains why diabetic foot complications are so hard to reverse once they appear. Another noteworthy observation was the pattern of epidermal and dermal changes. Epidermal thickness averaged only 52.3 µm, well below the normal range of 70–90 µm, and this thinning correlated inversely with HbA1c ($\rho = -0.48$, $p = 0.001$). At the same time, hyperkeratosis was present in 74.5%, creating a paradoxical picture: a thin but heavily keratinised epidermis. Under the microscope, this looks like a worn-out protective layer that cannot renew itself properly. The loss of rete ridges observed in 80.9% of cases further reduces the mechanical anchoring between the epidermis and dermis, making the skin more vulnerable to shearing forces from shoes or walking. For diabetic patients in Kazakhstan, who often wear heavy boots during the cold winter months, this combination of thin, poorly anchored, and callused skin is a clear recipe for ulceration. Educational programmes that focus only on inspecting the feet may need to add advice about proper footwear and moisturising to reduce hyperkeratosis. When we compared surgical and autopsy specimens, a clear gradient of severity emerged. Surgical patients (those who actually developed ulcers or gangrene) had significantly worse scores for every single histological parameter. The most

dramatic difference was in perineural fibrosis (1.62 vs. 0.77), followed by capillary thickening (2.41 vs. 1.46). Interestingly, even the autopsy group, patients who died of other causes without active foot infection, showed considerable damage: 84.6% had at least mild capillary thickening, and 46.2% had perineural fibrosis. This tells us that distal tissue pathology begins long before clinical symptoms appear. A patient may have no foot pain and intact skin, yet under the microscope their small vessels and nerves are already deteriorating. This finding argues strongly for early screening of all diabetic patients in Kazakhstan, not just those who complain of foot problems. Simple non-invasive tests like monofilament examination and skin biopsy from the foot (if ethically feasible) could identify high-risk individual's years before an ulcer develops. Of course, our study has several limitations that must be acknowledged. First, the sample size of 47 is modest, and the autopsy subgroup is particularly small (n = 13), which limits the statistical power of comparisons between the two groups. Second, the surgical specimens came from patients who already had advanced complications, so we cannot claim that the observed changes are representative of all diabetic patients in Kazakhstan, they represent the severe end of the spectrum. Third, we did not have a non-diabetic control group from the same population, so we cannot say with certainty that every feature we described is specific to diabetes; some might be due to ageing, hypertension, or atherosclerosis. Fourth, the HbA1c values were the most recent ones available within three months, but not all patients had perfect records, so the correlation we report might underestimate the true association because of measurement noise. Finally, this is a cross-sectional study without follow-up, so we cannot determine whether any of the histological features predict future ulceration independently of clinical factors. Future studies in Kazakhstan should include a prospective cohort with baseline biopsies and longitudinal follow-up to address this question. Despite these limitations, the consistency of our findings across 47 patients from two different tissue sources (surgical and autopsy) gives us confidence that the morphological patterns we describe are real and clinically relevant for diabetic patients in this region.

CONCLUSION

This study provides the first detailed histopathological description of distal tissue damage in diabetic patients from Kazakhstan, and the findings leave little room for doubt: chronic hyperglycaemia leaves a measurable, progressive footprint in the skin, capillaries, and nerves of the lower limb. Among 47 specimens, we found that capillary basement membrane thickening was nearly universal (95.7%) and severe in 42.6% of cases, strongly correlating with HbA1c ($\rho = 0.62$, $p < 0.001$). Perineural fibrosis and nerve fibre loss affected three-quarters of patients, and the surgical group, those who actually developed ulcers or gangrene, had significantly worse scores for every histological parameter compared to autopsy controls. The combination of epidermal thinning (mean 52.3 μm), hyperkeratosis, and loss of rete ridges creates a mechanically vulnerable skin that cannot withstand daily wear. Taken together, these morphological changes explain clinically why diabetic foot complications are so common and so difficult to heal: by the time an ulcer appears, the surrounding tissue is already riddled with microvascular and neural pathology that impairs repair. For clinicians and pathologists in Kazakhstan, our results have several practical implications. First, the strong correlation between HbA1c and tissue damage means that glycaemic control is not just a laboratory number but a direct predictor of structural injury. Second, the presence of significant perineural fibrosis even in patients without active foot ulcers suggests that screening for early nerve damage should begin much earlier than current practice. Third, the high frequency of co-occurring lesions (87.2% had at least two major categories of damage) indicates that treatment cannot focus on a single target; protecting the diabetic foot requires simultaneous attention to blood flow, nerve function, and skin integrity. While our sample size was modest and we lacked a non-diabetic control group, the consistency of our observations across surgical and autopsy specimens supports their validity. Future prospective studies in Kazakhstan should test whether skin or nerve biopsy can predict ulceration before clinical signs appear. For now, we conclude that diabetic distal tissue damage in this population follows a clear, HbA1c-driven, multi-tissue pattern that is both measurable and, in principle, preventable.

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