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ORIGINAL ARTICLE

Increased epidermal growth factor expression in amyotrophic lateral sclerosis patients: A potential protective mechanism against pressure ulcers

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ABSTRACT

Objectives: This study aimed to investigate epidermal growth factor (EGF) and keratinocyte growth factor (KGF) expression in proximal (gluteal) and distal (ankle) skin biopsies of individuals diagnosed with amyotrophic lateral sclerosis (ALS) compared to controls and to explore whether these factors may contribute to the relative sparing of pressure ulcers in ALS.

Patients and methods: In this prospective cohort study, 10 patients with limb-onset ALS and 16 age- and sex-matched controls with other neurological diseases underwent skin biopsies between April 2015 and December 2016. Immunohistochemical staining for EGF, KGF, and PGP9.5 was performed. Growth-factor expression was semiquantitatively scored; intraepidermal nerve fiber density quantification followed established protocol.

Results: The ALS group (7 male, 3 female; mean age: 52.9 ± 13.5 years; range, 31 to 72 years) and the control group (10 male, 6 female; mean age: 51.8 ± 12.8 years; range, 29 to 73 years) had similar demographic characteristics ($p > 0.05$). Proximal EGF expression was significantly higher in patients with ALS ($p < 0.05$). Distal EGF expression did not differ between groups. Across all participants, proximal EGF levels were higher compared to distal levels ($p < 0.05$). Expression of KGF showed no intergroup difference at either anatomical biopsy site. Patients with ALS demonstrated reduced intraepidermal nerve fiber density both in proximal and distal samples compared to established normative values consistent with small-fiber involvement. No associations were found between EGF and KGF levels and age, sex, or disease duration.

Conclusion: Increased EGF expression in pressure-prone gluteal skin of patients with ALS suggests that EGF-mediated wound-healing pathways may contribute to the unexpectedly low incidence of pressure ulcers in ALS. Larger prospective studies incorporating biochemical, histological, and functional assays are required to establish the mechanistic basis of this growth factor dysregulation in ALS.

Keywords: Amyotrophic lateral sclerosis, epidermal growth factor, keratinocyte growth factor, neurodegenerative process, pressure ulcers.

Amyotrophic lateral sclerosis (ALS) represents a rapidly advancing neurodegenerative condition in which the gradual deterioration of upper and lower motor neurons leads to severe muscular weakness, functional immobility, and complete reliance on external support.[1,2] Under normal circumstances, patients sharing a similar degree of motor restriction typically face significant vulnerability to pressure-induced tissue damage.[3] However, in clinical practice, pressure ulcers are strikingly uncommon in patients with ALS, a paradox that has intrigued clinicians.[4] This unexpected observation has encouraged researchers to look more closely at the biology of the skin in ALS. Previous studies have reported several distinctive cutaneous features, including altered collagen structure, changes in growth factor expression, and enhanced inflammatory signaling.[4,5] These

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converging findings suggest that the skin of patients with ALS may possess unique molecular responses that influence tissue resilience and wound-healing capacity. Furthermore, small fiber neuropathy has been increasingly recognized in this patient group, with reduced intraepidermal nerve fiber density (IENFD) suggesting a broader neuropathological involvement extending beyond the classical motor neuron degeneration.[6,7]

Among the molecular pathways involved in cutaneous repair, epidermal growth factor (EGF) is considered a critical regulator of tissue repair and wound healing. It acts as a critical mediator of epidermal regeneration, promoting keratinocyte proliferation, migration, and re-epithelialization while also enhancing collagen synthesis, angiogenesis, and extracellular matrix remodeling.[8,9] Through these mechanisms, EGF contributes to the maintenance of skin integrity and accelerates early phases of wound repair. Therefore, alterations in EGF signaling may have direct implications for susceptibility to pressure-induced tissue injury.

Keratinocyte growth factor (KGF) operates through a distinct mechanism. It is synthesized predominantly by dermal fibroblasts and acts on keratinocytes through paracrine signaling unlike EGF, which exerts its effects through direct receptor binding on epidermal cells.[10] It is particularly involved in epithelial differentiation, barrier restoration, and later stages of wound healing, including tissue remodeling and epithelial stabilization.[10] Thus, while both EGF and KGF contribute to skin homeostasis and repair, they operate through different cellular sources, signaling pathways, and temporal roles during the wound-healing process.

Despite the recognized importance of these growth factors, their expression and potential contribution to the unique cutaneous phenotype of ALS remain largely unexplored. Based on this rationale, the present study aimed to evaluate EGF and KGF expression in proximal (gluteal) and distal (ankle) skin regions in patients with ALS compared to individuals with other neurological conditions to elucidate potential biological mechanisms underlying the relative resistance to pressure ulcer development in ALS.

PATIENTS AND METHODS

In this prospective cohort study, 10 patients with limb-onset ALS and 16 patients with other neurological diseases were enrolled. Exclusion criteria included bleeding diathesis, anticoagulant/antiplatelet therapy, and active skin infection at biopsy site. Participants underwent skin biopsies at the Hacettepe University, Neuromuscular Diseases Research Laboratory between April 2015 and December 2016. Written informed consent was obtained from all participants. The study protocol was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Date: April 15, 2015, No. GO 15/283-14). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Under sterile conditions and local anesthesia, 4-mm punch skin biopsies were obtained from a proximal site overlying the gluteus maximus (typical region for pressure ulcers) and a distal site defined as 10 cm superior to the lateral malleolus. Tissue samples were immersed in 4% paraformaldehyde for fixation, subsequently transferred to 10% sucrose solution for cryoprotection, and stored at −80°C until processing. Serial 40-µm cryostat sections were processed for immunohistochemical staining using primary antibodies against EGF, KGF, and PGP9.5 (protein gene product 9.5) for intraepidermal nerve fiber analysis. Two investigators, blinded to clinical diagnosis and biopsy site, performed semiquantitative scoring of growth factor expression (EGF, 1-3; KGF, 1-4) according to staining intensity (EGF: 1, low; 3, high; KGF: 1, low; 4, high). For PGP9.5 staining, intraepidermal nerve fibers crossing the dermo-epidermal junction were counted per millimeter of epidermal length, and IENFD was calculated as fibers per millimeter, in line with the protocols outlined by the European Federation of Neurological Societies (EFNS).[7] For IENFD analysis, the results of patients with ALS were compared both with standardized normative data from our neuromuscular diseases research laboratory's healthy control group and with the established EFNS normative values.[7]

Statistical analysis

The statistical assessment of data was conducted using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Clinical and demographic features of enrolled patients were presented by means of descriptive statistics. Variable normality was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were shown as frequency and percentage. Continuous variables were given as mean ± standard deviation or median (minimum-maximum) based on data

distribution. Group comparisons employed the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. A *p*-value <0.05 was considered statistically significant.

RESULTS

The ALS group (7 male, 3 female; mean age: 52.9 ± 13.5 years; range, 31 to 72 years) and the control group (10 male, 6 female; mean age: 51.8 ± 12.8 years; range, 29 to 73 years) were similar in age ($p > 0.05$) and sex distribution ($p > 0.05$). The mean disease duration in the ALS group was 28.2 ± 17.2 months. All patients were ambulatory except for three individuals in the ALS group (two bedridden and one wheelchair-bound) and one bedridden patient in the control group. Serum albumin levels were similar in both groups. Diagnosis of patients in the control group (n = 16) included Parkinson's disease (n = 2), epilepsy (n = 2), myasthenia gravis (n = 2), multiple sclerosis (n = 2), dementia (n = 1), limbic encephalitis (n = 1), polyneuropathy (n = 1), dystonia (n = 1), neuromyelitis optica (n = 1), paraneoplastic cerebellar degeneration (n = 1), optic neuritis (n = 1), and normal pressure hydrocephalus (n = 1). In both groups comorbidities were similar and included hypertension and diabetes mellitus. A comprehensive overview of the demographic and clinical features of all groups is provided in Table 1.

Epidermal growth factor demonstrated a region-specific pattern. When all patients were

TABLE 1
Summary of demographic and clinical characteristics of the study groups

	ALS group (n = 10)					Control group (n = 16)					
	n	%	Mean ± SD	Median	Min-Max	n	%	Mean ± SD	Median	Min-Max	*p*
Age (year)			52.9 ± 13.5					51.8 ± 12.8			> 0.05
Sex											> 0.05
Male	7					10					
Female	3					6					
Albumin (g/dL)			3.90 ± 0.45					3.95 ± 0.40			> 0.05
Bedridden or wheelchair-bound patients	3	30				1	6				> 0.05
Disease duration in ALS (months)			28.2 ± 17.2			-	-				-
Prescence of medical comorbidities (hypertension and/or diabetes mellitus)	4	40				6	37.5				> 0.05
ALSFRS-R				32	11-46				-	-	-

ALS, amyotrophic lateral sclerosis; SD, standard deviation; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale.

TABLE 2
Summary of KGF, EGF, and IENFD in those with ALS and controls

		ALS group		Control group		Healthy controls*		
Parameter	Region	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
KGF score	Proximal	2	1-4	2	1-3			> 0.05[a]
	Distal	1	1-2	2	1-4			> 0.05[a]
EGF score	Proximal	2	1-3	1	1-2			**< 0.05**[a]
	Distal	1.5	1-3	1	1-3			> 0.05[a]
IENFD (fibers/mm)	Proximal	4.7	1.6-8.6	-	-	14.5	11.8-19.3	**< 0.05**[b]
	Distal	3.0	0.7-4.6	-	-	9.2	5.9-11.8	**< 0.05**[b]

KGF, keratinocyte growth factor; EGF, epidermal growth factor; IENFD, intraepidermal nerve fiber density; ALS, amyotrophic lateral sclerosis; * Age- and sex-matched standardized normative data from our neuromuscular diseases research laboratory's healthy control group; a, compared with neurological control group; b, compared with healthy controls.

analyzed together, proximal EGF expression was consistently higher than distal expression (p <0.05). Proximal EGF expression was significantly higher in the ALS group (median score: 2; range, 1 to 3) than in controls (median score: 1; p <0.05), whereas distal EGF levels were similar across groups. Epidermal growth factor levels were not associated with age, sex, or disease duration. Epidermal growth factor expression of the study groups are summarized in Table 2. Representative examples of EGF immunohistochemical staining in the ALS and control groups are shown in Figure 1.

No significant difference was detected between patients with ALS and controls at either of the two biopsy sites. Proximal KGF scores showed identical median values in both groups (median score: 2),

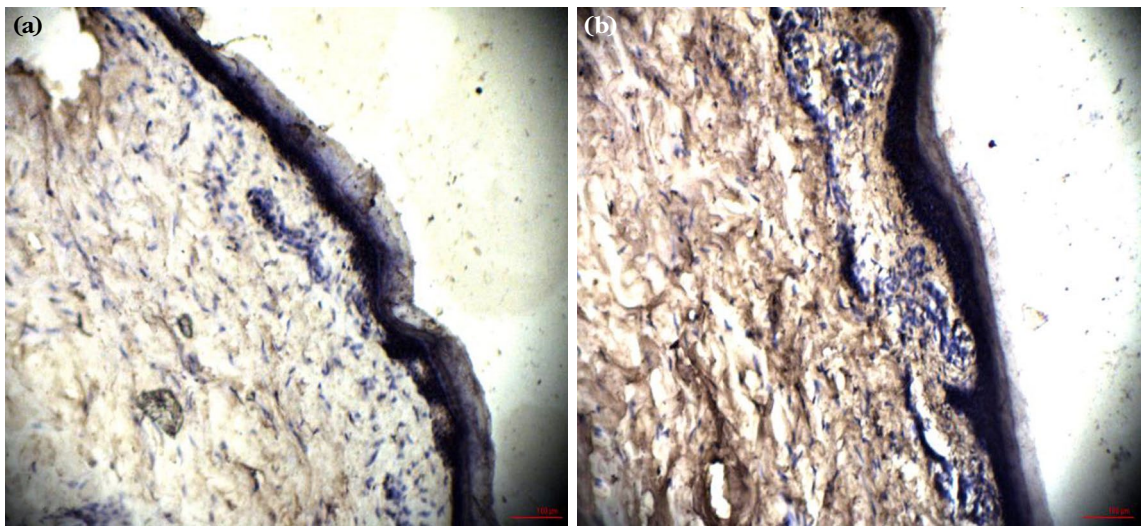

Figure 1. Epidermal growth factor immunohistochemical staining patterns in the ALS and control groups. **(a)** Epidermal growth factor staining in a proximal biopsy from the control group (staining score: 1); **(b)** Epidermal growth factor staining in a proximal biopsy from the ALS group (staining score: 3; ×20 magnification).

ALS, amyotrophic lateral sclerosis.

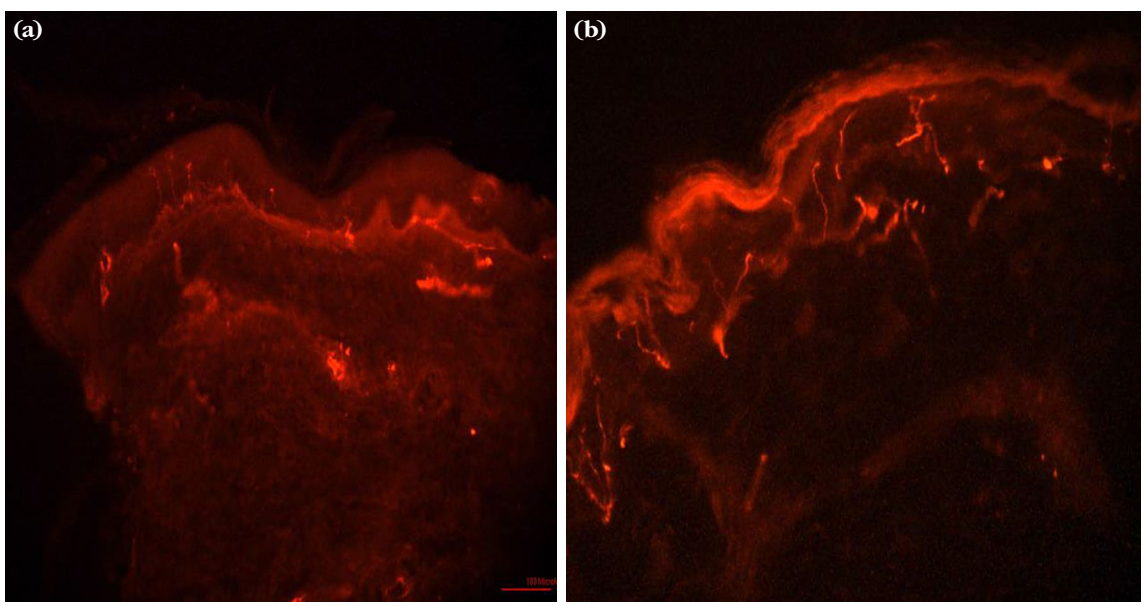

Figure 2. Representation of intraepidermal nerve fibers in a patient with ALS and a healthy individual. **(a)** ALS patient, **(b)** healthy control. Note the reduced IENFD in the patient with ALS.

ALS, amyotrophic lateral sclerosis; IENFD, intraepidermal nerve fiber density.

while distal KGF expression was slightly lower in the ALS group (median score: 1) compared to controls (median score: 2), although this difference was not statistically significant ($p > 0.05$ for all comparisons). Keratinocyte growth factor levels showed no correlation with age or disease duration, suggesting that KGF expression remained largely preserved in ALS and comparable to that observed in other neurological disorders. Keratinocyte growth factors expression in the study groups is summarized in Table 2.

Intraepidermal nerve fiber density was reduced in both proximal and distal sites of patients with ALS (median proximal IENFD: 4.7 fibers/mm; median distal IENFD: 3 fibers/mm). These values were significantly lower than both our laboratory's standardized healthy control database and the EFNS normative data,[7] consistent with small-fiber involvement. Intraepidermal nerve fiber density values of the groups are presented in Table 2 and illustrated in Figure 2.

DISCUSSION

This study evaluated EGF and KGF expression in gluteal skin of patients with ALS, a region directly relevant to the development of pressure ulcers. Among our findings, the most clinically striking was the significantly higher expression of EGF in the proximal skin of patients with ALS compared to the controls with other neurological diseases. This pattern was uniquely observed in the gluteal region and was not paralleled by changes in KGF expression. The selective elevation of EGF in the gluteal region, despite most patients being ambulatory, warrants careful interpretation. Rather than a response to prolonged immobility, this region-specific finding suggests that the skin in patients with ALS may possess an inherent molecular hypersensitivity or a primed adaptive response to the physiological mechanical stress typically encountered in the gluteal area during daily sitting and movement. Epidermal growth factor is a primary mediator of the skin's response to mechanical strain; therefore, its higher expression in ALS may reflect a specialized compensatory mechanism. This baseline resilience could potentially explain why these patients are remarkably resistant to pressure ulcers when they eventually become bedbound in the later stages of the disease.

The biological plausibility of this hypothesis is further supported by the well-established role of EGF as a proximal regulator of skin homeostasis and wound repair.[11] In this context, the higher EGF expression observed in our ALS cohort may serve as a critical physiological advantage. Epidermal growth factor is known to accelerate re-epithelialization by enhancing keratinocyte migration and proliferation.[12] Epidermal growth factor-driven EGF receptor signaling also promotes extracellular matrix remodeling and modifies fibroblast behavior, leading to more effective repair.[13] The clinical relevance of this pathway is evidenced by studies showing that intralesional or topical EGF can improve closure rates and durability of healing in chronic ulcers.[11] Taken together, these data support the notion that an intrinsically higher EGF tone in the gluteal skin of patients with ALS may represent a preactivated regenerative state, providing a protective molecular shield at pressure-prone sites before clinical skin breakdown occurs.

Additionally, proximal EGF upregulation also contextualizes previously reported dermatopathological findings in ALS. While increased matrix metalloproteinase activity and altered collagen structures typically suggest a compromised skin matrix, the concomitant elevation of EGF may act as a critical counter-regulatory signal.[5] Given that EGF signaling can stimulate vascular endothelial growth factor expression and modulate inflammatory cascades,[14] its higher expression in pressure-prone gluteal skin likely reflects a coordinated, adaptive response. By promoting keratinocyte proliferation and strengthening epidermal barrier integrity, EGF may help maintain tissue resilience despite the underlying metabolic alterations observed in cutaneous tissues of those with ALS.[2] Thus, the enhanced EGF tone may provide a necessary molecular counterbalance that confers protection against ulcer formation.

In contrast to the findings regarding EGF, KGF expression appeared unchanged across groups, irrespective of the skin region sampled. While both growth factors promote re-epithelialization, they govern distinct phases of the repair process. Epidermal growth factor more strongly couples to integrin activation, cytoskeletal reorganization, and early keratinocyte motility,[12] whereas KGF often acts later on epithelial differentiation and barrier restoration.[10] The absence of significant KGF alterations in our cohort, despite proximal EGF elevation, may indicate that early mechanosensitive EGF receptor pathways, rather than later

KGF-dependent remodeling, are preferentially engaged in the primed adaptive response of the gluteal skin in ALS.

Furthermore, several factors may account for the lack of observed KGF differences. Keratinocyte growth factor levels are known to be influenced by immune activation; since our control cohort included patients with autoimmune conditions such as multiple sclerosis and myasthenia gravis, subtle disease-specific differences might have been obscured by the inflammatory background of these disorders. Alternatively, it is possible that KGF does not play a substantial role in the unique cutaneous biology of ALS or in its relative resistance to pressure-related injury.[15] Future studies utilizing larger, more homogeneous cohorts and longitudinal assessments of these growth factors during different stages of tissue stress are necessary to clarify whether KGF contributes to later phases of skin stability in ALS.

Another important finding of this study is the reduction in IENFD in patients with ALS. This observation aligns with previous evidence of small-fiber pathology in ALS and suggests that sensory axonal involvement may contribute to altered skin physiology.[16] Reduced trophic support from small fibers may influence local immune responses, wound-healing dynamics, and barrier function and could therefore interact with growth-factor-mediated mechanisms in complex ways.[17]

The current study had some limitations. The sample size was relatively small, particularly for bedridden individuals, who represent the highest-risk group for pressure ulcers. Quantitative densitometric analysis of growth-factor expression could not be performed. In addition, quantitative protein analysis methods such as Western blotting were not feasible due to technical constraints, which may have limited the detection of subtle differences. The heterogeneity of the control group, which included multiple neurological diagnoses, may have introduced variability that obscured disease-specific patterns. Furthermore, biochemical analysis of EGF or KGF levels in serum or cerebrospinal fluid was not performed, and patients with active pressure ulcers were not included, preventing direct assessment of how these growth factors behaved during active tissue breakdown. Notably, none of the patients with ALS enrolled in this cohort had developed pressure ulcers at the time of biopsy, which limited our ability to directly correlate EGF and KGF expression with clinical ulcer status. Future studies comparing patients with ALS who have active or healed pressure ulcers with those who remain ulcer-free may help clarify this relationship. Body mass index, which may influence skin trophism, was not systematically recorded in this study; however, serum albumin levels, a surrogate marker of nutritional status, were comparable between groups. Genetic characterization was not performed in our cohort, precluding exploration of potential genotype-phenotype correlations with IENFD or growth factor expression. Future studies incorporating genetic testing are warranted. Nonetheless, the present study highlights the value of examining site-specific growth factor expression in neurodegenerative diseases. Unlike systemic biomarker studies, regional skin biopsy analysis may capture spatially restricted molecular adaptations that would otherwise remain undetected. The gluteal region, chosen here for its direct clinical relevance to pressure ulcer development, proved to be biologically distinct from distal skin in ALS. Future studies should therefore consider multi-site sampling strategies when investigating cutaneous biology in motor neuron diseases, as regional heterogeneity may carry both diagnostic and prognostic significance.

In conclusion, markedly elevated EGF immunoreactivity was demonstrated in the gluteal dermis of those with ALS. This region-specific finding suggests that the skin may possess a proactive compensatory mechanism that contributes to the remarkably low incidence of pressure ulcers in ALS. Keratinocyte growth factor levels showed no meaningful variation across groups, and reduced IENFD is consistent with known small-fiber involvement in ALS. Future studies integrating simultaneous assessment of EGF and KGF in serum, CSF, and skin, together with functional experimental models such as EGF-knockout or receptor-inhibition systems, are needed to elucidate the mechanistic basis of ulcer resistance in ALS and to explore the therapeutic relevance of these pathways.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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