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REVIEW ARTICLE

Biomechanical Factors in Psoriatic Disease: Defective Repair Exertion as a Potential Cause. Hypothesis Presentation and Literature Review

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Joining main clinical manifestations of psoriatic skin disorder are inflammatory arthritis and nail lesions. Repetitive microdamage has been postulated as a main triggering factor in lesions of psoriatic arthritis. This concept of psoriatic disease might also be admissible for triggering nail lesions because the nail is a frequently traumatized structure. Here, we aimed to describe the conjectural injury mechanisms of nail complex with regard to acting biomechanical factors. Tissue repair response to physical microdamage may be altered in psoriatic disease. It is plausible to consider that a defective repair process in the dysregulated prepsoriatic tissue may lead to innate immune activation and further development of autoinflammatory lesions, although excessive inflammation is known to impair wound healing. Recently published data have revealed the importance of mechanosensitive Wingless-type (Wnt) signaling in the pathophysiology of psoriasis and ankylosing spondylitis. The Wnt signaling system is involved in morphogenesis, repair, and regeneration as a biologic process main regulator. Wnt5a seems to be a dominating mediator in both psoriatic plaques and during the spondylitis process that might also be a linking molecule of psoriatic response to mechanical stress. Future studies should focus on complex responsive interactions of tissue repair regulators regarded in psoriatic disease.

Introduction

Psoriasis is a nonscarring, inflammatory, and hyperproliferative chronic skin disease, likely unique to humans with a varied adult prevalence of 0.9% in the United States to 8.5% in Norway, as it probably depends on geographic factors (1). Interactions between genetic and immunologic variations with certain and unclear affecting environmental factors have supposed to result in psoriatic lesions. Trauma is a well-known triggering factor for psoriatic skin lesions. Development of new lesions in the apparently normal skin secondary to trauma in patients with certain dermatoses has been called Koebner phenomenon after the German dermatologist Heinrich Koebner (2). Although it is typified as true Koebnerization along with lichen planus and vitiligo, psoriasis is most likely to have the highest incidence of the Koebner phenomenon (3,4). Besides, psoriatic lesion development is also a frequent consequence of localized trauma, including friction, shearing, stretching, and pressure (5–7). Therefore, tissue-specific biomechanical triggering factors other than direct external injury should also be considered in terms of lesion development. Psoriatic lesions appear mostly on frequently stretched extensor skin surfaces during daily activities, bony promontories of the knee and elbow, where the joint flexion range of motion is excessive. Friction that occurs during lumbar movements due to waistbands may also traumatize the sacral skin. Another frequently involved site, the scalp is also a stretched skin tissue (8). Flexion of the cervical spine may also lead to an increase in tension, particularly on the occipital skin. All of the aforementioned dermal areas have insufficient subcutaneous support tissue.

Approximately, 20.0% to 30.0% of psoriasis patients are accompanied by psoriatic arthritis (PsA). PsA is classified as seronegative spondyloarthritis (SpA). The prototype disease of SpA is ankylosing spondylitis (AS). Researchers have put forth a role for mechanical stress and repetitive microdamage in triggering musculoskeletal lesions in both PsA and AS (9–13). While axial spinal involvement is much less common and clinically more moderate in PsA, AS is characterized mainly

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by symmetric and ascending spinal involvement. This finding might point to the fact that the spine is exposed to a stronger or perpetual stimulus in AS compared with psoriatic spondylitis but that it might not be segmental. In contrast, PsA is characterized mainly by peripheral manifestations such as inflammatory arthritis, enthesitis, and dactylitis. Even in the presence of psoriatic spondylitis, peripheral involvement is observed more frequently compared with AS (14). Therefore, PsA is an inflammatory disorder of more mobile musculoskeletal structures, unlike AS. This situation might also apply to the axial spine. The cervical spine, probably because of increased mobility during daily activities compared with the lumbosacral region, is more commonly involved in PsA. Mechanical stress–related chronic process of psoriatic lesion development in musculoskeletal structures may substantially be motion dependent (13,15).

Biomechanical factors and nail involvement

The average prevalence of nail lesions in patients with psoriasis can estimated to be more than 50%. The prevalence is much higher among patients with PsA. To date, it has been debated whether trauma is an actual cause of psoriatic nail lesions. Together with the consideration of the physical disuse of nail apparatus in modern humans, applied forces may contribute to the development of specific nail lesions. Pitting, onycholysis, and splinter hemorrhages are the most frequently detected changes in fingernails, whereas onycholysis, crumbling, and subungual hyperkeratosis are the most frequently detected nail changes in toenails (16). It is known that matrix trauma that is due to manicure induces leukonychia (5). Furthermore, injury to the nail matrix in the transverse plane that occurs during nail cutting or nail filing may result in leukonychia, depending on the extent of shearing or the targeted site of applied pressure (17).

While working with hands, friction between the nail plate and nail bed may cause chronic mechanical trauma, leading to onycholysis and thickness. Parts of the nail, including the matrix, can also be repetitively exposed to compressive forces. As a specific injury mechanism of the proximal matrix, impacts between the harder dorsal nail plate layer and solid objects might theoretically lead to development of pitting that is due to Koebnerization by the high-rated mechanical energy transmission (18). However, the density and Young's modulus values of each nail plate layer may not be significantly different, and typewriting typifies this injury mechanism in desk workers, leading to chronic damage of the whole matrix and thereby resulting in the development of crumbling (19,20).

Considering this conjectural injury mechanism may be reasonable because it can explain the co-existence of distal interphalangeal (DIP) joint involvement in patients with nail lesions on the same finger as well as accompanying extensor tendon inflammation because the compressive stress wave may stand on further to the DIP joint–related structures through the fibers of the

extensor tendon, which envelopes the nail root, thereby leading to the co-Koebnerization of the nail root and DIP joint (10,11,21,22). The Shearing effect of pulse on the nail matrix and, additionally, the reflection (tensile stress) should also be taken into consideration because the transmitted energy advances in different contiguous tissues with different densities. Impact speed is the main determinant (19,23–28). However applied force during a pinch grip may be a more influental mechanical factor for the development of DIP arthritis overall. Nail involvement in the hand is less common in the little finger compared with other fingers, possibly because it is rarely used during working.

Psoriatic toenail involvement is most frequently detected in the big toe, which lacks the anatomic envelope mechanism of long fingers (21,29). Toes bear much larger mechanical forces compared with fingers. The toenails may be exposed to repetitive mechanical stress during walking, particularly at the end of the stance phase of the gait cycle. As the heel rise starts, the ground reaction force (GRF) vector (center of pressure) moves medially to the big toe, which is forced to an accelerated extension along with the other toes by the lever arm of the ankle propels the body forward. Overload of the big toe concomitant with the generated extension force applied to a repelling force to the extensor side structures leads to displacement toward the nail plate and increased in tissue pressure, particularly in the nail matrix contiguous to the hard nail plate and might result in time-dependent development of crumbling. Toward toe off, the eccentric contraction of the musculus flexor hallucis longus fixes the big toe in full floor contact to undertake the second lever arm function to maintain the forward motion of the body (push-off phase) and thus bears most of the applied forces in comparison with other toes (30). Both lever arms pull the soft tissues to inferoposterior as the toes become hyperextended with a compression of the nail bed by the GRF. Repetitive shearing between the nail bed and the hard nail plate during this phase may cause the development of onycholysis and subungual hyperkeratosis in severe cases. Although individual gait patterns may differ slightly, the human bipedal walking can be considered as an uniform movement. Thus, this biomechanical conjecture may be compatible with the involvement patterns of both toenail lesions and metatarsophalangeal arthritis (16,30–32).

Footwear can alter certain parameters of the gait cycle, such as decreased forefoot spreading and increased stance time. Shoes may decrease force dispersion, particularly during the push-off phase, by limiting the natural motion of the barefoot through application of external pressure and additional weight and however, also limits the toe extension range of motion in a variable degree, depending on the rigidity of the footwear. Although the second peak value of vertical GRF in the push-off phase does not differ, the propulsive GRF may be altered (33). Ill-fitted or narrow-toed shoe wearing further decreases the weight bearing area, changes force distribution, and causes impingement of the nail complex. Static shearing of the nail bed occurs in women who wear high-heeled shoes.

Shoes also traumatize the big toenail repetitively by impulsive forefront contact that may result in onycholysis (34). Collectively, all of the aforementioned mechanical factors may explain why the big toenail is exposed to more repetitive microdamage and, consequently, might explain the higher frequency of developing psoriatic nail lesions in the big toe compared with other toes.

Further evidence

It has been revealed by imaging techniques that the main event in PsA may be enthesitis (35). In psoriasis patients without musculoskeletal symptoms, ultrasonographic enthesitis is quite frequent regardless of physical examination (36,37). It has been demonstrated in cadaveric studies that the changes associated with microdamage and inflammation are observed in SpA patients even in their normal joints and entheses (38). As the connections of the skeleton, enthesis-related structures bear excessive tensile load, especially during movement. Overweight is more common in psoriatic patients than in the healthy population, causing higher mechanical stress in both lower limb joints and entheses. This condition is supported by the evidence that species with large body mass have increased incidence of axial SpA (39).

The persistent repair exertion in prepsoriatic tissue under continuous mechanical stress might result in either aberrant innate immune activation or a decreasing ability to terminate inflammation that occurs during the wound healing process, which further develops autoinflammatory lesions, although excessive inflammation is known to impair wound healing (10,40–42). This assumption may point to a vulnerability to chronic physical damage in psoriasis patients, which may also be indicated by disruption of the basement membrane laminin layer as a specific feature, especially at the apex of dermal papillae in both involved and uninvolved skin (43–45). The main function of laminin is to aid anchoring and stabilization of the basal keratinocytes. As the earliest event in the lesion development process, this structural disorder leads to proliferation of unstable keratinocytes before the onset of inflammation and hyperkeratosis (46). Dysfunctionality in tissue laminin synthesis should be taken into consideration (47). Secondly, laminins are the extracellular macromolecules that play a regulatory role during wound healing. Application of laminin-derived peptides promote re-epithelization, angiogenesis, and cell migration during wound healing as well as decrease inflammation and granulation (48).

The defective repair exertion as a potential cause

Cumulative tissue damage that is particularly due to biomechanical factors that may trigger psoriatic lesion development might result from person-specific tissue dysregulation. If this alternative concept of psoriatic disease is true, it is plau-

sible to consider that a defective wound healing process in the dysregulated psoriatic tissue may lead to a vulnerability to chronic damage (13). Psoriatic plaques resemble the wound healing response with regard to many cellular and molecular mediators (41). Furthermore, the wound healing rate may be accelerated in both involved and uninvolved skin (49). Many genes activated during the wound healing process may be differentially involved either similarly or inversely in the molecular pathophysiology of psoriasis. Expressions of late cornified envelope (LCE)-3 genes are upregulated in psoriatic skin which undertake an important role in the epidermal barrier repair following superficial injury of healthy skin (50). Other known psoriasis susceptibility genes consist of upregulated myeloid related protein (MRP) 8 (S100A8), MRP14 (S100A9), MRP8/MRP14 heterodimer, and nuclear factor-ĸ-B-inhibitor α (NFK-BIA/IĸBα) as well as downregulated jun B proto-oncogene and all were demonstrated to be significantly upregulated during a short-termed incisional wound model of neonatal mice (51–55). Based on this model, the early growth factor (Egr)-1, c-myc, FOS-like antigen-1 (Fra-1), the mitogen-activated protein kinases (MAP4K4), c-Jun N-terminal kinase (JNK) pathway, retinol binding protein-1, keratins (KRT6), plexins, osteopontin (deep dermal), cathepsin S, ephrin receptor B1 (ephA2 in psoriasis), C-X-C motif chemokines (CXCL10), C-C motif chemokine ligand family (CCL2/MCP-1, CCL7), and C-C motif chemokine receptors (CCR1) can additionally be listed as expressed genes of wound healing related similarly with psoriasis. However, the notch signaling, C-fos, and mitogen-activated protein kinase phosphatase (MKP)-1 may be downregulated in psoriatic lesions, contrary to what happens with wounds (56–73). It is worth noting that MRP8, MRP14, and MRP8/MRP14 expression was reported to be higher in the synovial sublining layer of PsA patients compared with rheumatoid arthritis (RA) and SpA (74).

Investigation of the effects of pharmacotherapeutic agents may offer some clues. Systemic treatment with certain drugs, such as β-blockers, statins, corticosteroids, antimalarial drugs, and lithium, may flare or worsen psoriatic skin lesions. These drugs may also affect wound healing. Beta adrenergic blockades delay cutaneous wound healing, whereas propranolol improves wound healing in streptozotocin-induced diabetic rats (75,76). Topical simvastatin improves wound healing in rats by its anti-inflammatory properties, increasing fibroblast proliferation and epithelization (77). Corticosteroids delay repair by affecting proinflammatory cytokines, and they have catabolic effects particularly in the skin and connective tissue. To our knowledge, there is no relevant information in the literature regarding the effects of antimalarial drugs on wound healing. Lithium activates β-catenin signaling through Wingless-type (Wnt) signaling pathway mediated mechanism, enhances tissue healing, increases cutaneous wound strength, and stimulates local mineralization after bone fracture (78–80). It inhibits cell migration as a specific effect.

Wnt signaling system is required in all phases of wound healing. β-Catenin has been shown to inhibit keratinocyte migration and activate fibroblast proliferation in cutaneous healing. It mediates the effects of transforming growth factor (TGF)-β during healing (78). β-Catenin can either inhibit or enhance the wound healing process, indicating the complex interactive responses. A previously published work has revealed a correlation between in vivo β-catenin level and the tensile strength of the wound in mice after irradiation and lithium treatment increases wound strength in those expressing null alleles for β-catenin as well (79). Psoriatic plaques are characterized distinctly with decreased extensibility and elasticity in both uninvolved and involved skin (81). Whether this structural finding might be associated with tissue Wnt system interactions have not yet been investigated. Decreased extensibility may lead to further mechanical stress to the tissues exposed to repetitive stretching. After dithranol treatment, mechanical parameters of psoriatic plaques have improved markedly (81).

Activated Wnt5a signaling in plaques and syndesmophytes

The Wnt signaling molecules are involved in crucial functions, including cellular proliferation and regeneration, tissue regulation, and immune development. The Wnt5a is differentially expressed in psoriatic plaques and is known as a suppressor of notch-1 signaling (82,83). In cultured keratinocytes, Wnt5a can be induced by proinflammatory cytokines interleukin (IL)-1α, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, as well as TGF-α (84). Induction of Wnt5a in mesenchymal cells was supposed to adjust the accurate localization and timing of the TGF-β signalization during injury repair (85). TGF-β and nerve growth factor may be the key regulatory molecules of the Koebner phenomenon (42,86). In psoriasis, homeostatic inhibition of Wnt signaling is impaired, and a shift away from canonical Wnt signaling toward noncanonical system driven mainly by interactions of increased Wnt5a may exist. Moreover, circulating Wnt5a was reported to be significantly higher in psoriasis patients than in controls, especially in the obese patients (84,87). Theoretically, chronic injury may cause inappropriately prolonged Wnt signaling (88).

The Wnt signaling is also likely to play an important role in the syndesmophyte formation. Certain cytokines are capable of inducting Wnt proteins (84,89). It was suggested that pro-inflammatory cytokines released during chronic inflammation in SpA may lead to subsequent new bone formation by upregulating β-catenin (90). Recently, Wnt3a, Wnt4, Wnt5a, Wnt7b, and Wnt10b were detected to be highly expressed in spinal ligaments of AS patients with syndesmophytes as osteoinductive Wnts, and their significantly elevated levels in the sera were reported to be correlated with syndesmophyte progression as well (91). Wnt5a seems to be a master regulator of spondylitis response in AS because its serum level increases earlier, along with the Wnt9b and Wnt16b, in the patients without syndesmophytes. As the new bone formation process starts, the Wnt5a level continues to increase in conjunction with the distinct activation of other osteogenic Wnts. However, the process of syndesmophyte formation that could be driven mainly by the Wnt signaling system may be related to the intensity of inflammatory stimulus. *In vitro* stimulation of a monocyte cell line by low dosage of TNF-α was demonstrated to induce persistent Wnt activity, whereas high dosage stimulation has no effect on Wnts with an increase in expression of canonical Wnt inhibitor dickkopf-related protein (Dkk)-1, also known as a suppressor of bone formation. Thus, excessive release of TNF-α in AS may impair the osteogenic Wnt activity and as well as repair response compatible with the TNF brake hypothesis (41,91,92). Besides that, Wnt5a may also have a role in the augmentation of psoriatic skin inflammation by forming a positive feedback loop with the inflammatory cytokines, thereby enabling the occurrence of cytokine storm (83).

Offering clues of Wnt5a

High circulating levels of Dkk-1 were detected in the patients with axial SpA. Thus, Dkk-1 measurement was suggested to be a good indicator of the presence and severity of osteoproliferative radiologic changes of spondylitis in PsA (93). However, capacity of Dkk-1–mediated inhibition of active β-catenin was demonstrated to decrease in AS; this dysfunctionality could be related to the strong activity of Wnt5a, as resembled in psoriatic plaques (82,84,94–96). Wnt5a signaling suppresses keratinocyte proliferation in normal skin, whereas it is required in perichondrium for regulating longitudinal skeletal outgrowth of developing long bones (84,97). However, as similar functions, while Wnt5a likely stimulates the anabolic new bone formation along with the canonical Wnts in axial SpA, it seems to partially suppress canonical Wnts in psoriatic plaques and stimulates keratinocyte proliferation in conjunction with the absence of increased expression of Dkk-1 in psoriatic plaques contrary to the increased expression in the nonlesional psoriatic skin of unknown importance (98,99). However, it was reported that increased expression of Wnt5a alone does not have a psoriasiform effect in transgenic mice, although biologic systems in rodent dermal tissue may differ from humans (100). In contrast with canonical Wnts, activation of Wnt5a signaling also fails to induce cartilage lesions in experimental osteoarthritis induced by collagenase and destabilization of the medial meniscus (101). Therefore, induction of Wnt5a might be related to a compensatory repair process in the aforementioned conditions rather than primary damage. Prolonged activation of noncanonical pathway via Wnt5a signaling was demonstrated to form regenerative changes evidently in cutaneous wound healing (102). Interestingly, despite the absence of frizzled-4 (FZD4) receptor, overexpressed Wnt5a triggering the Wnt/β-catenin signaling pathway may also play an important role in the keloid pathogenesis, which is an aberrant wound healing process that responds to deep skin trauma (103).

Molecular response to mechanical stretching of skin

Interactions of mechanical input with Wnt signaling system may promote tissue regulation. Wnt signaling systems, including the noncanonical pathway, have been revealed as being mechanosensitive (104). Biomechanical stimuli are required for cell behaviors during skeletal, joint, tendon, and ligament development through activating Wnt genes (105). Wnt5a or N-cadherin–mediated β-catenin signaling is essential to mechanically induced mesenchymal stem cell (MSC) osteogenic differentiation *in vitro* (106).

Mechanical stretching of skin may promote skin tissue regeneration by upregulating the expression of genes related to hypoxia, vascularization, and cell proliferation (107). Mechanical stretching of the expanded skin leads to upregulated mRNA expressions of stromal-derived factor (SDF)-1α, hypoxia-inducible factor (HIF)-1α, and matrix metalloproteinase (MMP)-2 in a rat model of tissue implantation. *In vitro* mechanical stretching of human MSCs causes upregulation of the genes of Janus kinase/signal transducers and activators of transcription (JAK-STAT), cyclin D2, secreted frizzled-related protein4 (SFRP4), and Wnt5b (107). SDF-1α, HIFs, and MMP-2 are highly expressed in psoriatic lesions (108–110). Upregulated C-X-C chemokine receptor type 4 (CXCR4)/SDF-1α axis may also have potential proinflammatory effects in the pathophysiology of RA and SpA, including PsA (111). JAK1 and JAK3 upregulated in psoriasis are probably concomitant with overexpression of cyclins (82,112). However, expression of Wnt signaling inhibitor SFRP4 is diminished in psoriatic skin, which inhibits excessive keratinocyte proliferation evoked by proinflammatory cytokines *in vitro* and decreases the severity of psoriasiform lesions in imiquimod-induced mouse model (113). Wnt5b gene expression also tends to be lower in psoriatic plaques (84). Consequently, main molecular behavioral difference that exist in psoriatic skin resulting from mechanical stress may occur in the Wnt signaling system. Thus, the probability that Wnt5a may be a key regulatory molecule of psoriatic response to mechanical stress has emerged. Whether Wnt5a induction in psoriasis is defective or compensatory should be elucidated (82). A proposed paradigm of the altered repair response to chronic mechanical stress through Wnt5a signaling is shown in Figure 1.

Molecular response to mechanical stretching of tendon

Chronic tendinopathies are characterized with inflammation and matrix destruction. Repetitive mechanical stretching of tendons can change the gene expression and protein synthesis of tenocytes and fibroblasts. Low-magnitude stretching is regarded as anti-inflammatory, whereas high-magnitude stretching is proinflammatory (114). Cyclic stretching or mechanical load can induce gene expressions of IL-1β, bone morphogenetic protein (BMP)-2, cyclooxygenase (COX)-2, MMP-1, and MMP-9 in conjunction with the increase in production of IL-6 and PGE2 (114–118). Apart from mechanical load, the inflammatory cytokine response was suggested as another factor for matrix destruction in overuse tendinopathies (119). Cyclic tensile strain can also induce an immediate but transient stress response by activating the stress-activated protein kinase (SAPK)/JNK pathway and extracellular signal-regulated kinase 2 (ERK2/MAPK-1). The JNK activity is suppressed in a time-dependent manner possibly because of the adaptation of fibroblasts. Therefore, insufficient ability to suppress JNK activity may lead to apoptosis (120–122).

Molecular response to vibration and hypergravity

It should be noted that both changes in gravity and exposure to vibration may cause molecular response. Exposure to long-term whole body vibration (WBV), particularly at low frequencies, is a widely accepted etiologic cause of low back pain and disc herniation (123). Moreover, WBV is also associated with spinal radiographic damage in AS patients (124). Molecular changes secondary to an increase in gravity may also reflect the long-term effects of gravitational acceleration on musculoskeletal system. Short-term hypergravity of 1.8*g* was reported to induce IL-6 release from chondrocytes and to be capable of regulating genes *in vitro* related with cartilage integrity including downregulated BMP-4, MMP-3, MMP-10, Wnt5a, and upregulated endothelin (EDN)-1, whereas vibration within a broad spectrum of frequency upregulates IL-6 and IL-8 accompanied with the downregulation of growth factors such as epidermal growth factor (EGF), vascu-
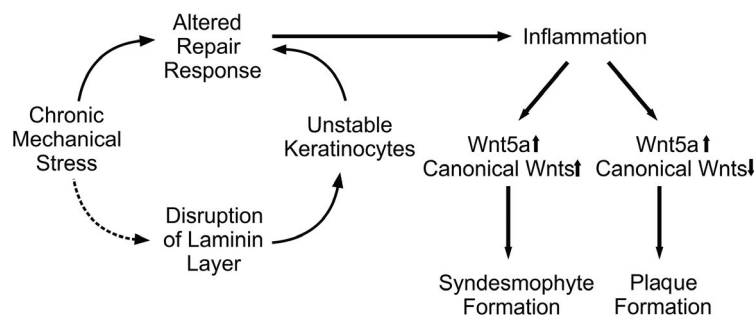
Figure 1. A proposed paradigm of altered repair response to chronic mechanical stress through Wnt5a signaling

lar endothelial growth factor (VEGF), and fibroblast growth factor (FGF)-17 (125). Low-frequency vibration was demonstrated to cause diffuse cellular neuroimmune response in the rat spinal cord possibly through activating the MAPKs indicated by the decrease in expressions of anti-inflammatory cytokines concomitantly with the increase of some proinflammatory cytokines such as TNF-α and IL-6 (126,127). Besides, higher-frequency WBV may lead to a decrease in systemic IL-17 positive Th cell count counteracted with an increase of forkhead box P3 (FoxP3) positive Treg cells (128). All mentioned factors may be involved in axial SpA pathophysiology (129–133).

Biomechanical factors in AS

We think that assessment of AS in terms of biomechanical factors should also be briefly mentioned. The bamboo spine characteristics may not be a frequently encountered feature of axial SpA in nonhuman primates (134,135). The thoracolumbar spinal musculature usually functions in humans with isometric contractions both consciously and unconsciously for balance control and trunk stabilization, rather than intentional motion requiring motor planning. The spinal insertions are exposed to constant stretching in AS, a consequence of axial myofascial hypertonicity that might also point to a subclinical neural disorder (136). Interestingly, the neuropathic pain component was detected in patients with AS and accompanied with cortical thinning in specific areas, including primary somatosensory cortex (perception of proprioception), insula (visceral sensation processing and autonomic regulation, vestibular function), supplementary motor area (learning and planning self-initiated complex movements), and gray matter abnormalities in the putamen (motor learning) and thalamus (sensory signal processing, preparation of voluntary movement, alertness) (137). Available evidence in the literature might not suggest a decrease in postural control of neural origin or a proprioceptive deficit because this impairment is largely attributed to the mechanic changes secondary to the spondylitis process such as kyphosis, pelvic tilt, and flexion contracture of the hip (138,139). As a recent observation, eyes-closed rehabilitation programs were reported to improve more marked balance impairment in AS and therefore might be admissible as a clue for the favorable effect of rehabilitation on proprioceptive acuity (140). Besides, potential significance of the reported vestibular dysfunction in AS patients should additionally be taken into consideration (141,142).

CONCLUSION

Biomechanical factors primarily affect musculoskeletal and dermal tissue integrity as well as functions. Lesion-specific injury mechanisms of the nail apparatus should be discussed. While soft-tissue mobility may contribute to the development of nail

bed lesions, frequent increases in tissue pressure might result in time-dependent development of crumbling. Offered postulations indicate that psoriatic patients may have a vulnerability to chronic physical damage in both skin and musculoskeletal tissues, particularly to the tissue-specific kinetic factors. However, robust evidence is needed. Investigations regarding disruption of the basement membrane laminin layer or strong activation of mechanosensitive Wnt5a may provide direct evidence to support the concept of mechanical stress in the pathophysiology of psoriatic disease.

AUTHOR CONTRIBUTIONS

All authors drafted the article or critically revised the manuscript for important intellectual content, and both authors approved the final version of the article to be published.
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Acquisition of data. Tönük.
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REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377–85.

2. Köbner H. Zur aetiologie der psoriasis. Vjschr Dermatol 1876;3:559.

3. Boyd AS, Neldner KH. The isomorphic response of Koebner. Int J Dermatol 1990;29:401–10.

4. Thappa DM. The isomorphic phenomenon of Koebner. Indian J Dermatol Venereol Leprol 2004;70:187–9.

5. Farber EM, Roth RJ, Aschheim E, Eddy DD, Epinette WW. Role of trauma in isomorphic response in psoriasis. Arch Dermatol 1965;91:246–251.

6. Tagami H. Triggering factors. Clin Dermatol 1997;15:677–85.

7. Bernstein EF, Kantor GR. Treatment-resistant psoriasis due to a mastectomy sleeve: an extensive Koebner response. Cutis 1992;50:65–7.

8. Inaba M, Inaba Y. Etiologic factors in male pattern baldness. In: Androgenetic alopecia. Modern concepts of pathogenesis and treatment. Tokyo: Springer Japan; 1996. p. 171.

9. McGonagle D, Ash Z, Dickie L, McDermott M, Aydin SZ. The early phase of psoriatic arthritis. Ann Rheum Dis 2011;70 Suppl 1:71–6.

10. McGonagle D. Enthesis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. J Eur Acad Dermatol Venereol 2009;23 Suppl 1:9–13.

11. McGonagle D, Tan AL, Benjamin M. The nail as a musculoskeletal appendage–implications for an improved understanding of the link between psoriasis and arthritis. Dermatology 2009;218:97–102.

12. Masi AT. Might axial myofascial properties and biomechanical mechanisms be relevant to ankylosing spondylitis and axial spondyloarthritis? [research support]. Arthritis Res Ther 2014;16:107.

13. Tönük ŞB, Ramadan B, Yorgancıoğlu ZR. Kinetic factors may trigger lesion development in the patients with psoriatic arthritis. Int J Rheum Dis 2016;19:1032–4.

14. Pérez Alamino R, Maldonado Cocco JA, Citera G, Arturi P, Vazquez-Mellado J, Sampaio-Barros PD, et al. Differential features between primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease. J Rheumatol 2011;38:1656–60.

15. Arslan Alhussain F, Kasapoglu Gunal E, Kurum E, Bakirci S, Ozturk AB, McGonagle D, et al. Greater magnitude of entheseal microdamage and repair in psoriatic arthritis compared with ankylosing spondylitis on ultrasound. Rheumatology (Oxford) 2019;58:299–303.

16. Brazzelli V, Carugno A, Alborghetti A, Grasso V, Cananzi R, Fornara L, et al. Prevalance, severity and clinical features of psoriasis in fingernails and toenails in adult patients: Italian experience. J Eur Acad Dermatol Venereol 2012;26:1354–9.

17. Baran R, Perrin C. Transverse leukonychia of toenails due to repeated microtrauma. Br J Dermatol 1995;133:267–9.

18. Forslind B, Thyresson N. On the structure of the normal nail. A scanning electron microscope study. Arch Dermatol Forsch 1975;251:199–204.

19. Sihota P, Yadav RN, Dhiman V, Bhadada SK, Mehandia V, Kumar N. Investigation of diabetic patient's fingernail quality to monitor type 2 diabetes induced tissue damage. Sci Rep 2019;28;9:3193.

20. Manhart R, Rich P. Nail psoriasis. Clin Exp Rheumatol 2015;33 Suppl 93:S7–13.

21. Tan AL, Benjamin M, Toumi H, Grainger AJ, Tanner SF, Emery P, et al. The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis—a high-resolution MRI and histological study. Rheumatology (Oxford) 2007;46:253–6.

22. Lai TL, Pang HT, Cheuk YY, Yip ML. Psoriatic nail involvement and its relationship with distal interphalangeal joint disease. Clin Rheumatol 2016;35:2031–7.

23. Beer FP, Johnston ER Jr, DeWolf JT, Mazurek DF. Mechanics of materials. New York: McGraw Hill; 2009. p. 1–131.

24. Johnson W. Impact strength of materials. London: Hodder Arnold; 1972. p. 5–36.

25. Meyers MA, Chen P-Y, Lin AY-M, Seki Y. Biological materials: structure and mechanical properties. Prog Mater Sci 2008;53:1–206.

26. Artuc M, Reinhold C, Stüttgen G, Gazith J. A rapid method for measuring drug enrichment in epidermis. Arch Dermatol Res 1980;268:129–40.

27. Van Kuilenburg J, Masen MA, van der Heide E. Contact modelling of human skin: what value to use for the modulus of elasticity? [research article]. Proc Inst Mech Eng Part J J Eng Tribol 2013;227:349–361.

28. Liang X, Boppart SA. Biomechanical properties of in vivo human skin from dynamic optical coherence elastography. IEEE Trans Biomed Eng 2010;57:953–9.

29. Palomo López P, Becerro de Bengoa Vallejo R, López López D, Prados Frutos JC, Alfonso Murillo González J, Losa Iglesias ME. Anatomic relationship of the proximal nail matrix to the extensor hallucis longus tendon insertion. J Eur Acad Dermatol Venereol 2015;29:1967–71.

30. Hayafune N, Hayafune Y, Jacob HA. Pressure and force distribution characteristics under the normal foot during the push-off phase in gait. The Foot 1999;9:88–92.

31. Delle Sedie A, Riente L, Filippucci E, Scirè CA, Iagnocco A, Meenagh G, et al. Ultrasound imaging for the rheumatologist. XXXII. Sonographic assessment of the foot in patients with psoriatic arthritis. Clin Exp Rheumatol 2011;29:217–22.

32. Freeston JE, Coates LC, Nam JL, Moverley AR, Hensor EM, Wakefield RJ, et al. Is there subclinical synovitis in early psoriatic arthritis? A clinical comparison with gray-scale and power Doppler ultrasound. Arthritis Care Res (Hoboken) 2014;66:432–9.

33. Franklin S, Grey MJ, Heneghan N, Bowen L, Li FX. Barefoot vs common footwear: a systematic review of the kinematic, kinetic and muscle activity differences during walking. Gait Posture 2015;42:230–9.

34. Zaias N, Escovar SX, Zaiac MN. Finger and toenail onycholysis. J Eur Acad Dermatol Venereol 2015;29:848–53.

35. McGonagle DG, Helliwell P, Veale D. Enthesitis in psoriatic disease. Dermatology 2012;225:100–9.

36. Ash ZR, Tinazzi I, Gallego CC, Kwok C, Wilson C, Goodfield M, et al. Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. Ann Rheum Dis 2012;71:553–6.

37. Acqualcalda E, Albert C, Montaudie H, Fontas E, Danre A, Roux CH, et al. Ultrasound study of entheses in psoriasis patients with or without musculoskeletal symptoms: a prospective study. Joint Bone Spine 2015;82:267–71.

38. Benjamin M, Toumi H, Suzuki D, Redman S, Emery P, McGonagle D. Microdamage and altered vascularity at the enthesis-bone interface provides an anatomic explanation for bone involvement in the HLA-B27–associated spondylarthritides and allied disorders. Arthritis Rheum 2007;56:224–33.

39. Nunn CL, Rothschild B, Gittleman JL. Why are some species more commonly afflicted by arthritis than others? A comparative study of spondyloarthropathy in primates and carnivores. J Evol Biol 2007;20:460–70.

40. Mansbridge JN, Knapp AM. Changes in keratinocyte maturation during wound healing. J Invest Dermatol 1987;89:253–63.

41. Nickoloff BJ, Bonish BK, Marble DJ, Schriedel KA, DiPietro LA, Gordon KB, et al. Lessons learned from psoriatic plaques concerning mechanisms of tissue repair, remodeling, and inflammation. J Investig Dermatol Symp Proc 2006;11:16–29.

42. Raychaudhuri SP, Jiang WY, Raychaudhuri SK. Revisiting the Koebner phenomenon: role of NGF and its receptor system in the pathogenesis of psoriasis. Am J Pathol 2008;172:961–71.

43. Mondello MR, Magaudda L, Pergolizzi S, Santoro A, Vaccaro M, Califano L, et al. Behaviour of laminin 1 and type IV collagen in uninvolved psoriatic skin. Immunohistochemical study using confocal laser scanning microscopy. Arch Dermatol Res 1996;288:527–31.

44. Vaccaro M, Magaudda L, Cutroneo G, Trimarchi F, Barbuzza O, Guarneri F, et al. Changes in the distribution of laminin alpha 1 chain in psoriatic skin: immunohistochemical study using confocal laser scanning microscopy. Br J Dermatol 2002;146:392–8.

45. McFadden JP, Powles A, Kimber I, Fry L. Psoriasis and basement-membrane laminin. Br J Dermatol 2013;169:718–9.

46. McFadden JP, Kimber I. A review on the potential role of basement membrane laminin in the pathogenesis of psoriasis. Scand J Immunol 2016;83:3–9.

47. Gál B, Dulic S, Kiss M, Groma G, Kovács L, Kemény L, et al. Increased circulating anti-α6-integrin autoantibodies in psoriasis and psoriatic arthritis but not in rheumatoid arthritis. J Dermatol 2017;44:370–4.

48. Iorio V, Troughton LD, Hamill KJ. Laminins: roles and utility in wound repair. Adv Wound Care (New Rochelle) 2015;4:250–63.

49. Morhenn VB, Nelson TE, Gruol DL. The rate of wound healing is increased in psoriasis. J Dermatol Sci 2013;72:87–92.

50. Bergboer JG, Tjabringa GS, Kamsteeg M, van Vlijmen-Willems IM, Rodijk-Olthuis D, Jansen PA, et al. Psoriasis risk genes of the late cornified envelope-3 group are distinctly expressed compared with genes of other LCE groups. Am J Pathol 2011;178:1470–7.

51. Cooper L, Johnson C, Burslem F, Martin P. Wound healing and inflammation genes revealed by array analysis of 'macrophageless' PU.1 null mice. Genome Biol 2005;6:R5.

52. Chandra A, Ray A, Senapati S, Chatterjee R. Genetic and epigenetic basis of psoriasis pathogenesis. Mol Immunol 2015;64:313–23.

53. Eckert RL, Broome AM, Ruse M, Robinson N, Ryan D, Lee K. S100 proteins in the epidermis. J Invest Dermatol 2004;123:23–33.

54. Stuart PE, Nair RP, Ellinghaus E, Ding J, Tejasvi T, Gudjonsson JE, et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. Nat Genet 2010;42:1000–4.

55. Zenz R, Eferl R, Kenner L, Florin L, Hummerich L, Mehic D, et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins [published erratum appears in Nature 2006;440:708]. Nature 2005;437:369–75.

56. Jeong SH, Kim HJ, Jang Y, Ryu WI, Lee H, Kim JH, et al. Egr-1 is a key regulator of IL-17A-induced psoriasin upregulation in psoriasis. Exp Dermatol 2014;23:890–5.

57. Osterland CK, Wilkinson RD, St Louis EA. Expression of c-myc protein in skin and synovium in psoriasis and psoriatic arthritis. Clin Exp Rheumatol 1990;8:145–50.

58. Zhu W, Li J, Su J, Li J, Li J, Deng B, et al. FOS-like antigen 1 is highly expressed in human psoriasis tissues and promotes the growth of HaCaT cells in vitro. Mol Med Rep 2014;10:2489–94.

59. Haase I, Hobbs RM, Romero MR, Broad S, Watt FM. A role for mitogen-activated protein kinase activation by integrins in the pathogenesis of psoriasis. J Clin Invest 2001;108:527–36.

60. Gazel A, Banno T, Walsh R, Blumenberg M. Inhibition of JNK promotes differentiation of epidermal keratinocytes. J Biol Chem 2006;281:20530–41.

61. Costanza G, Doldo E, Ferlosio A, Tarquini C, Passeri D, Cascella R, et al. Expression and potential role of cellular retinol binding protein I in psoriasis. Oncotarget 2018;9:36736–49.

62. Mommers JM, van Rossum MM, van Erp PE, van De Kerkhof PC. Changes in keratin 6 and keratin 10 (co-)expression in lesional and symptomless skin of spreading psoriasis. Dermatology 2000;201:15–20.

63. Zhang C, Xiao C, Dang E, Cao J, Zhu Z, Fu M, et al. CD100-plexin-B2 promotes the inflammation in psoriasis by activating NF-κB and the inflammasome in keratinocytes. J Invest Dermatol 2018;138:375–383.

64. Buommino E, Tufano MA, Balato N, Canozo N, Donnarumma M, Gallo L, et al. Osteopontin: a new emerging role in psoriasis. Arch Dermatol Res 2009;301:397–404.

65. Schönefuss A, Wendt W, Schattling B, Schulten R, Hoffmann K, Stuecker M, et al. Upregulation of cathepsin S in psoriatic keratinocytes. Exp Dermatol 2010;19:e80–8.

66. Gordon K, Kochkodan JJ, Blatt H, Lin SY, Kaplan N, Johnston A, et al. Alteration of the EphA2/Ephrin-A signaling axis in psoriatic epidermis. J Invest Dermatol 2013;133:712–22.

67. Ferrari SM, Ruffilli I, Colaci M, Antonelli A, Ferri C, Fallahi P. CXCL10 in psoriasis. Adv Med Sci 2015;60:349–54.

68. Gillitzer R, Wolff K, Tong D, Müller C, Yoshimura T, Hartmann AA, et al. MCP-1 mRNA expression in basal keratinocytes of psoriatic lesions. J Invest Dermatol 1993;101:127–31.

69. Brunner PM, Glitzner E, Reininger B, Klein I, Stary G, Mildner M, et al. CCL7 contributes to the TNF-α-dependent inflammation of lesional psoriatic skin. Exp Dermatol 2015;24:522–8.

70. Langkilde A, Olsen LC, Sætrom P, Drabløs F, Besenbacher S, Raaby L, et al. Pathway analysis of skin from psoriasis patients after adalimumab treatment reveals new early events in the anti-inflammatory mechanism of anti-TNF-α. PLoS One 2016;11:e0167437.

71. Thélu J, Rossio P, Favier B. Notch signalling is linked to epidermal cell differentiation level in basal cell carcinoma, psoriasis and wound healing. BMC Dermatol 2002;2:7.

72. Basset-Séguin N, Escot C, Molès JP, Blanchard JM, Kerai C, Guilhou JJ. C-fos and c-jun proto-oncogene expression is decreased in psoriasis: an in situ quantitative analysis. J Invest Dermatol 1991;97:672–8.

73. Kjellerup RB, Johansen C, Kragballe K, Iversen L. The expression of dual-specificity phosphatase 1 mRNA is downregulated in lesional psoriatic skin. Br J Dermatol 2013;168:339–45.

74. Kane D, Roth J, Frosch M, Vogl T, Bresnihan B, FitzGerald O. Increased perivascular synovial membrane expression of myeloid-related proteins in psoriatic arthritis. Arthritis Rheum 2003;48:1676–85.

75. Romana-Souza B, Santos JS, Monte-Alto-Costa A. β-1 and β-2, but not α-1 and α-2, adrenoreceptor blockade delays delays rat cutaneous wound healing. Wound Repair Regen 2009;17:230–9.

76. Romana-Souza B, Nascimento AP, Monte-Alto-Costa A. Propranolol improves cutaneous wound healing in streptozotocin-induced diabetic rats. Eur J Pharmacol 2009;611:77–84.

77. Khosneviszadeh M, Ashkani-Esfahani S, Namazi MR, Noorafshan A, Geramizadeh B, Miri R. Topical simvastatin enhances tissue regeneration in full thickness skin wounds in rat models. Iran J Pharm Res 2014;13:263–9.

78. Cheon SS, Wei Q, Gurung A, Youn A, Bright T, Poon R, et al. β-catenin regulates wound size and mediates the effect of TGF-β in cutaneous healing. FASEB J 2006;20:692–701.

79. Gurung A, Uddin F, Hill RP, Ferguson PC, Alman BA. β-catenin is a mediator of the response of fibroblasts to irradiation. Am J Pathol 2009;174:248–55.

80. Chen Y, Whetstone HC, Lin AC, Nadesan P, Wei Q, Poon R, et al. β-catenin signaling plays a disparate role in different phases of fracture repair: implications for therapy to improve bone healing. Plos Med 2007;4:e249.

81. Dobrev H. In vivo study of skin mechanical properties in psoriasis vulgaris. Acta Derm Venereol 2000;80:263–6.

82. Reischl J, Schwenke S, Beekman JM, Mrowietz U, Stürzebecher S, Heubach JF. Increased expression of Wnt5a in psoriatic plaques. J Invest Dermatol 2007;127:163–9.

83. Kim JE, Bang SH, Choi JH, Kim CD, Won CH, Lee MW, et al. Interaction of Wnt5a with Notch1 is critical for the pathogenesis of psoriasis. Ann Dermatol 2016;28:45–54.

84. Gudjonsson JE, Johnston A, Stoll SW, Riblett M, Xing X, Kochkodan JJ, et al. Evidence for altered Wnt signaling in psoriatic skin. J Invest Dermatol 2010;130:1849–59.

85. Miyoshi H, Stappenbeck TS. Counteracting stem cell expansion during wound repair: distinct roles of non-canonical Wnt and TGF-β. Cell Cycle 2013;12:387–8.

86. Nickoloff BJ, Naidu J. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. J Am Acad Dermatol 1994;30:535–46.

87. Gerdes S, Laudes M, Neumann K, Baurecht H, Mrowietz U. Wnt5a: a potential factor linking psoriasis to metabolic complications. Exp Dermatol 2014;23:438–40.

88. Whyte JL, Smith AA, Helms JA. Wnt signaling and injury repair. Cold Spring Harb Perspect Biol 2012;4:a008078.

89. Gustafson B, Smith U. Cytokines promote Wnt signaling and inflammation and impair the normal differentiation and lipid accumulation in 3T3-L1 preadipocytes. J Biol Chem 2006;281:9507–16.

90. Xie W, Zhou L, Li S, Hui T, Chen D. Wnt/β-catenin signaling plays a key role in the development of spondyloarthritis. Ann N Y Acad Sci 2016;1364:25–31.

91. Li X, Wang J, Zhan Z, Li S, Zheng Z, Wang T, et al. Inflammation intensity-dependent expression of osteoinductive Wnt proteins is critical for ectopic new bone formation in ankylosing spondylitis. Arthritis Rheumatol 2018;70:1056–70.

92. Sieper J, Appel H, Braun J, Rudwaleit M. Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 2008;58:649–56.

93. Jadon DR, Sengupta R, Nightingale A, Lu H, Dunphy J, Green A, et al. Serum bone-turnover biomarkers are associated with the occurrence of peripheral and axial arthritis in psoriatic disease: a prospective cross-sectional comparative study. Arthritis Res Ther 2017;19:210.

94. Daoussiss D, Liossis SN, Solomou EE, Tsanaktsi A, Bounia K, Karampetsou M, et al. Evidence that Dkk-1 is dysfunctional in ankylosing spondylitis. Arthritis Rheum 2010;62:150–8.

95. Briolay A, Lencel P, Bessueille L, Caverzasio J, Buchet R, Magne D. Autocrine stimulation of osteoblast activity by Wnt5a in response to TNF-α in human mesenchymal stem cells. Biochem Biophys Res Commun 2013;430:1072–77.

96. Bougault C, Briolay A, Boutet MA, Pilet P, Delplace S, Le Goff B, et al. Wnt5a is expressed in spondyloarthritis and exerts opposite effects on enthesis and bone in murine organ and cell cultures. Transl Res 2015;166:627–38.

97. Yang Y, Topol L, Lee H, Wu J. Wnt5a and Wnt5b exhibit distinct activities in coordinating chondrocyte proliferation and differentiation. Development 2003;130:1003–15.

98. Seifert O, Söderman J, Skarstedt M, Dienus O, Matussek A. Increased expression of the Wnt signalling inhibitor Dkk-1 in non-lesional skin and peripheral blood mononuclear cells of patients with plaque psoriasis. Acta Derm Venereol 2015;95:407–10.

99. Van Amerongen R, Fuerer C, Mizutani M, Nusse R. Wnt5a can both activate and repress Wnt/β-catenin signaling during mouse embryonic development. Dev Biol 2012;369:101–14.

100. Zhu X, Wu Y, Huang S, Chen Y, Tao Y, Wang Y, et al. Overexpression of Wnt5a in mouse epidermis causes no psoriasis phenotype but an impairment of hair follicle anagen development. Exp Dermatol 2014;23:926–8.

101. Van den Bosch MH, Blom AB, Sloetjes AW, Koenders MI, van de Loo FA, van den Berg WB, et al. Induction of canonical Wnt signaling by synovial overexpression of selected Wnts leads to protease activity and early osteoarthritis-like cartilage damage. Am J Pathol 2015;185:1970–80.

102. Fathke C, Wilson L, Shah K, Kim B, Hocking A, Moon R, et al. Wnt signaling induces epithelial differentiation during cutaneous wound healing. BMC Cell Biol 2006;7:4.

103. Igota S, Tosa M, Murakami M, Egawa S, Shimizu H, Hyakusoku H, et al. Identification and characterization of Wnt signaling pathway in keloid pathogenesis. Int J Med Sci 2013;10:344–54.

104. Haudenschild AK, Hsieh AH, Kapila S, Lotz JC. Pressure and distortion regulate human mesenchymal stem cell gene expression. Ann Biomed Eng 2009;37:492–502.

105. Brunt LH, Begg K, Kague E, Cross S, Hammond CL. Wnt signalling controls the response to mechanical loading during zebrafish joint development. Development 2017;144:2798–2809.

106. Arnsdorf EJ, Tummala P, Jacobs CR. Non-canonical Wnt signaling and N-cadherin related beta-catenin signaling play a role in mechanically induced osteogenic cell fate. PLoS One 2009;4:e5388.

107. Liang X, Huang X, Zhou Y, Jin R, Li Q. Mechanical stretching promotes skin tissue regeneration via enhancing mesenchymal stem cell homing and transdifferentiation. Stem Cells Transl Med 2016;5:960–9.

108. Rosenberger C, Solovan C, Rosenberger AD, Jinping L, Treudler R, Frei U, et al. Upregulation of hypoxia-inducible factors in normal and psoriatic skin. J Invest Dermatol 2007;127:2445–52.

109. Quan C, Cho MK, Shao Y, Mianecki LE, Liao E, Perry D, et al. Dermal fibroblast expression of stromal cell-derived factor-1 (SDF-1) promotes epidermal keratinocyte proliferation in normal and diseased skin. Protein Cell 2015;6:890–903.

110. Vasku V, Bienertova Vasku J, Slonková V, Kanková K, Vasku A. Matrix metalloproteinase-2 promoter variability in psoriasis. Arch Dermatol Res 2009;301:467–73.

111. Gu J, Märker-Hermann E, Baeten D, Tsai WC, Gladman D, Xiong M, et al. A 588-gene microarray analysis of the peripheral blood mononuclear cells of spondyloarthropathy patients. Rheumatology (Oxford) 2002;41:759–66.

112. Alves de Medeiros AK, Speeckaert R, Desmet E, Van Gele M, De Schepper S, Lambert J. JAK3 as an emerging target for topical treatment of inflammatory skin diseases. PLoS One 2016;11:e0164080.

113. Bai J, Liu Z, Xu Z, Ke F, Zhang L, Zhu H, et al. Epigenetic downregulation of SFRP4 contributes to epidermal hyperplasia in psoriasis. J Immunol 2015;194:4185–98.

114. Yang G, Im HJ, Wang JH. Repetitive mechanical stretching modulates IL-1β induced COX-2, MMP-1 expression, and PGE2 production in human patellar tendon fibroblasts. Gene 2005;363:166–72.

115. Rui YF, Lui PP, Ni M, Chan LS, Lee YW, Chan KM. Mechanical loading increased BMP-2 expression which promoted osteogenic differentiation of tendon-derived stem cells. J Orthop Res 2011;29:390–6.

116. Hsieh JL, Jou IM, Wu CL, Wu PT, Shiau AL, Chong HE, et al. Estrogen and mechanical loading-related regulation of estrogen receptor-β and apoptosis in tendinopathy. PLoS One 2018;13:e0204603.

117. Skutek M, van Griensven M, Zeichen J, Brauer N, Bosch U. Cyclic mechanical stretching enhances secretion of Interleukin 6 in human tendon fibroblasts. Knee Surg Sports Traumatol Arthrosc 2001;9:322–6.

118. Langberg H, Olesen JL, Gemmer C, Kjaer M. Substantial elevation of interleukin-6 concentration in peritendinous tissue, in contrast to muscle, following prolonged exercise in humans. J Physiol 2002;542:985–90.

119. Archambault J, Tsuzaki M, Herzog W, Banes AJ. Stretch and interleukin-1β induce matrix metalloproteinases in rabbit tendon cells in vitro. J Orthop Res 2002;20:36–9.

120. Arnoczky SP, Tian T, Lavagnino M, Gardner K, Schuler P, Morse P. Activation of stress-activated protein kinases (SAPK) in tendon cells following cyclic strain: the effects of strain frequency, strain magnitude, and cytosolic calcium. J Orthop Res 2002;20:947–52.

121. MacKenna DA, Dolfi F, Vuori K, Ruoslahti E. Extracellular signal-regulated kinase and c-Jun NH2-terminal kinase activation by mechanical stretch is integrin-dependent and matrix-specific in rat cardiac fibroblasts. J Clin Invest 1998;101:301–10.

122. Skutek M, van Griensven M, Zeichen J, Brauer N, Bosch U. Cyclic mechanical stretching of human patellar tendon fibroblasts: activation of JNK and modulation of apoptosis. Knee Surg Sports Traumatol Arthrosc 2003;11:122–9.

123. Burström L, Nilsson T, Wahlström J. Whole-body vibration and the risk of low back pain and sciatica: a systematic review and meta-analysis. Int Arch Occup Environ Health 2015;88:403–18.

124. Ward MM, Reveille JD, Learch TJ, Davis JC Jr, Weisman MH. Occupational physical activities and long-term functional and radiographic outcomes in patients with ankylosing spondylitis. Arthritis Rheum 2008;59:822–32.

125. Wehland M, Aleshcheva G, Schulz H, Saar K, Hübner N, Hemmersbach R, et al. Differential gene expression of human chondrocytes cultured under short-term altered gravity conditions during parabolic flight maneuvers. Cell Commun Signal 2015;13:18.

126. Zeeman ME, Kartha S, Jaumard NV, Baig HA, Stablow AM, Lee J, et al. Whole-body vibration at thoracic resonance induces sustained pain and widespread cervical neuroinflammation in the rat. Clin Orthop Relat Res 2015;473:2936–47.

127. Zeeman ME, Kartha S, Winkelstein BA. Whole-body vibration induces pain and lumbar spinal inflammation responses in the rat that vary with the vibration profile. J Orthop Res 2016;34:1439–46.

128. Yin H, Berdel HO, Moore D, Davis F, Liu J, Mozaffari M, et al. Whole body vibration therapy: a novel potential treatment for type 2 diabetes mellitus. Springerplus 2015;4:578.

129. Przepiera-Będzak H, Fischer K, Brzosko M. Serum VEGF, EGF, basic FGF, and acidic FGF levels and their association with disease activity and extra-articular symptoms in ankylosing spondylitis. Pol Arch Med Wewn 2016;126:290–2.

130. Przepiera-Będzak H, Fischer K, Brzosko M. Serum levels of angiogenic cytokines in psoriatic arthritis and SAPHO syndrome. Pol Arch Med Wewn 2013;123:297–302.

131. Przepiera-Będzak H, Fischer K, Brzosko M. Serum interleukin-18, fetuin-A, soluble intercellular adhesion molecule-1, and endothelin-1 in ankylosing spondylitis, psoriatic arthritis, and SAPHO syndrome. Int J Mol Sci 2016;17. pii: E1255.

132. Butt C, Lim S, Greenwood C, Rahman P. VEGF, FGF1, FGF2 and EGF gene polymorphisms and psoriatic arthritis. BMC Musculoskelet Disord 2007;8:1.

133. Appel H, Wu P, Scheer R, Kedor C, Sawitzki B, Thiel A, et al. Synovial and peripheral blood CD4+FoxP3+ T cells in spondyloarthritis. J Rheumatol 2011;38:2445–51.

134. Rothschild BM, Woods RJ. Erosive arthritis and spondyloarthropathy in Old World primates. Am J Phys Anthropol 1992;88:389–400.

135. Swezey RL, Cox C, Gonzales B. Ankylosing spondylitis in nonhuman primates: the drill and the siamang. Semin Arthritis Rheum 1991;21:170–4.

136. Andonian BJ, Masi AT, Aldag JC, Barry AJ, Coates BA, Emrich K, et al. Greater resting lumbar extensor myofascial stiffness in younger ankylosing spondylitis patients than age-comparable healthy volunteers quantified by myotonometry. Arch Phys Med Rehabil 2015;96:2041–7.

137. Wu Q, Inman RD, Davis KD. Neuropathic pain in ankylosing spondylitis: a psychophysics and brain imaging study. Arthritis Rheum 2013;65:1494–503.

138. Pompeu JE, Romano RS, Pompeu SM, Lima SM. Static and dynamic balance in subjects with ankylosing spondylitis: literature review. Rev Bras Reumatol 2012;52:409–16.

139. Li C, Wei X, Zou Q, Zhang Y, Yin X, Zhao J, et al. Cerebral functional deficits in patients with ankylosing spondylitis- an fMRI study. Brain Imaging Behav 2017;11:936–42.

140. Demontis A, Trainito S, Del Felice A, Masiero S. Favorable effect of rehabilitation on balance in ankylosing spondylitis: a quasi-randomized controlled clinical trial. Rheumatol Int 2016;36:333–9.

141. Erbek SS, Erbek HS, Yilmaz S, Topal O, Yucel E, Ozluoglu LN. Cochleovestibular dysfunction in ankylosing spondylitis. Audiol Neurootol 2006;11:294–300.

142. Amor-Dorado JC, Barreira-Fernandez MP, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Diaz de Teran T, et al. Audiovestibular manifestations in patients with ankylosing spondylitis. Medicine (Baltimore) 2011;90:99–109.