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Mini Review

Biological Clocks: Is It Time for A Closer Watch on Skin Healing?

Joanne Lusher* and David Chapman Jones

Institute for Research in Healthcare Policy and Practice, University of the West of Scotland, UK

***Corresponding author:** Joanne Lusher, Institute for Research in Healthcare Policy and Practice, University of the West of Scotland, UK

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Introduction

Pain is a common consequence of skin healing that is caused by skin or nerve damage, infection and ischemia. Despite the fact that chronic wounds often require many years to heal, pain can be an understated symptom that is generally severe and persistent in wound healing. Indeed, pain management costs an estimated $635 Billion per year in the United States alone [1]. It is therefore imperative that we further examine the underlying causes of chronic wounds, and delayed wound healing, in an indirect attempt to reduce these overall costs of pain management. We propose that one way in which to address this is by taking a closer look at the impact that biological clocks have on skin healing. We appreciate that biological clocks play a vital role in mediating the function of organisms, tissues and cells. These cell autonomous circadian clocks are responsible for generating 24-hour day/night rhythms, governing cell division, DNA damage response, cell metabolism and tissue repair and regeneration. For example, in liver tissue, an organ with embyoinic regeneration (one of two, the other being tendon tissue), the expression of at least 10% of proteins is reported to be rhythmically regulated by clock genes. A functional clock ensures temporal segregation of different events to different parts of the 24-hour day, maintaining tissue homeostasis and promoting effective repair. Disruptions to clock rhythms (e.g. during ageing) are linked to increased risks of various human diseases that are linked to skin healing and other painful conditions. Whilst it is clear that skin also possess these peripheral clocks, the role which they play in mediating susceptibility to damage, via Ultraviolet Radiation [UVR] exposure, for example, or the efficacy of augmented repair strategies, such as day or night creams, remains unknown. Despite some risk factors for chronic wounds, such as age and sex, remain fixed [2] the majority include modifiable factors (e.g., diet and exercise). However, what science has yet to reveal is the complex pathways in which these factors interact to cause a more or less favourable outcome for patients [3].

Some individuals are genetically susceptible to non-healing or therapy-resistant wounds due to individual differences in their immunity and healing rate [4,5]. Furthermore, gene variants have been identified as having a protective mechanism over healing rate in a handful of modest studies [6,7] of, for instance, venous leg ulcer patients carrying the Leu34 and Leu564 alleles on the FX111 gene. A review of heredity factors in non-healing wounds [8] confirmed the lack of replication and small scale nature of existing studies, but summarised a selection of variants as potential risk factors for a type of chronic leg ulceration on; HFE [2] FGFR2; [9] TNFFA; [10] F5; [11] F2; [12] F13A; [13] ESRB; [14] IIFE; [2] and MMPI2 [15] genes. Finally, an additional 15 susceptibility genes for non-healing wounds have been revealed [16] and amongst them, variants on the S100 gene has shown promise. These insights warrant further investigation as evidence for a mode of inheritance is scant (Fowkes, 2001) and the pathogenesis of chronic wounds is still in its infancy [17]. Moreover, what is apparent is that the wound itself might not be directly heritable, but factors that influence experiences of pain [18], recovery and outcomes are.

We propose a novel approach would implicitly tackle the pain enigma that results from delayed skin healing and this would be to evaluate the extent that circadian clocks play on wound healing. This is an evolutionarily conserved system that allows life on earth to coordinate its physiology and behaviour to the day/night cycle. The core components of this molecular pacemaker responsible for driving the circadian rhythm in the mammalian central clock, the Supra-Chiasmatic Nuclei (SCN). This is identical in all peripheral clock tissues, including tissues of the musculoskeletal system [19]. Indeed, there is a large breadth of data that strongly suggest that disrupted circadian rhythms in peripheral tissues, as a result of sleep disorders, evening screen time, shift work and aging, can contribute to the development of painful conditions, including cancer and metabolic diseases [20]. Therefore, understanding how peripheral clocks are synchronized, and aligned, to the light–dark cycle is crucial for understanding the link between the circadian clock, health and painful diseases. The endogenous circadian rhythms of skeletal muscle [21], cartilage [22] tendon [23] and intervertebral disc [24] drive tissue-specific rhythmic

gene expression that regulates tissue homeostasis [25]. Research highlights how the tendon clock regulates the homeostasis of the collagen-rich extracellular matrix [26] The collagen fibrils in the extra cellular matrix enable the tendon to undergo repeated cycles of mechanical loading, and therefore, its maintenance has important consequences for biomechanics. It has previously been reported that arrhythmic mouse tendons with a mutation in clock or deletion of Bmal1 have premature aging phenotypes and aged wild-type tendons have a dampened circadian rhythm that is misaligned with the SCN [23]. Scheduled exercise can entrain the circadian rhythms of skeletal muscle and lung tissue clocks [27,28]. However, whether acute changes in the level of physical activity itself can explain clock gene changes, in humans, is yet to be divulged.

Findings from a recent systematic review concluded that exercise is a zeitgeber for the human circadian system, where multiple studies have demonstrated phase shifts in hormone secretion and body temperature cycles [29], the effect of exercise on individual peripheral clock rhythms has yet to be fully investigated yet begs clarity. Exercise can induce glucocorticoid release and generate heat in musculoskeletal tissues [30] and these effects are able to entrain peripheral clocks [22,28] Glucocorticoids can activate glucocorticoid response elements upstream of circadian gene promoters, including Per2 [31,32] Furthermore, the addition of dexamethasone can synchronize ex vivo tissues and cells in culture, including mouse tendons and primary mouse and human tendon cells, by driving period expression [33,34] Thus, reduced exercise-induced glucocorticoid release could potentially modulate the tendon circadian clock circuitry.

Overall, there remain lots of unknowns, however, research points to tendon repair occurring during moderate exercise in mice and humans and this shows promise for advances in research in painful conditions. This raises the interesting question about the importance of the time of day when people exercise and if exercising out-of-sync with the body clock disrupts tissue repair. We question whether the same hypothesis can be applied to skin healing and if so, what the optimal time for treatments should be. We know that dermal healing does not follow a linear trajectory so theoretically this could be linked with biological clocks. Our proposition is one that aims to characterise the influence of peripheral clocks on the physiology of skin; the morphology and cellular phenotype of skin; the extent of UVR-induced damage; and the efficacy of topical anti-ageing treatments. With the ultimate goal of optimising strategies for chronotherapy (timing the delivery of medication) for skin repair. It is now time to multiply the magnification of our microscopic lens as we intend this commentary to prompt some fresh thinking about the ways in which we can approach the burden of pain in skin healing by shifting our research focus to the role that biological clocks play in mediating the function of organisms, tissues and cells.

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