



## Can poor sleep affect skin integrity?

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### SUMMARY

Modern society has reported a decline in sleep time in the recent decades. This reduction can increase the morbidity and mortality of several diseases and leads to an immunosuppressive state. The skin is the largest organ in the human body and collagen, its main component, has a key role in the structure and integrity of the organism. The entire sequence of events necessary during collagen formation can be affected by endogenous and exogenous factors. A variety of studies in the literature have shown that sleep plays a role in restoring immune system function and that changes in the immune response may affect collagen production. Several studies of prolonged sleep deprivation suggest a break in skin barrier function and mucous membranes. In fact, the reduction of sleep time affects the composition and integrity of various systems. Thus, we hypothesized that lack of sleep as well as other types of stress can impair skin integrity.

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### Introduction

Over the recent decades, sleep has received a great deal of attention. Long working hours and increased daily activities are just some of the reasons that lead to a reduction in sleep time. Stress is a factor inherent in the lack of sleep, and it is known that stressful situations can trigger changes in the immune system, mainly due to activation of the hypothalamic–pituitary–adrenal axis (HPA axis; [1]).

In the human body, the skin is the largest organ and plays a major role in maintaining homeostasis and protection. A large number of evidences relate stress to changes in the skin function, but there are no complete studies in the literature that relate sleep and skin integrity. The dermis is the major constituent of the skin and is composed primarily of elastin, collagen and glycosaminoglycans, which give the skin its elasticity and flexibility [2]. The collagen molecule has a key role in the structure and integrity of organisms, as it is responsible for providing strength, support and integrity to various tissues and organs. As the major structural component of the dermis, it functions to protect us from external agents such as ultraviolet radiation and bacterial invasion [3]. Studies on the molecular structure, biosynthesis, aggregation and quantity of collagen are very important in clarifying the links between embryological and pathological development and human diseases, wound healing and tissue regeneration.

The sequence of events necessary during collagen formation can be affected by both endogenous and exogenous factors. Enzymes,

oxygen, vitamin C, iron [4–7] and the immune system can also affect collagen production. There is evidence that the release of interleukin (IL)-1 increases the production of collagen type IV in mouse epithelial cells [8]. It stimulates the proliferation of fibroblasts, with increased production of collagenase, and it may even alter the production of collagen, depending on the type of lymphocyte stimulus used [9–11]. It is also worth mentioning that all of these immune parameters are modified by physiological stress, which activates the HPA axis [1]. Chronic stress can induce a state of immunosuppression [12].

In response to stress, corticotrophin-releasing factor (CRF, which regulates the HPA axis) initiates a cascade of events that culminate in the release of glucocorticoids (GC) release from the adrenal cortex. In chronic stress conditions, the HPA axis often exhibits an inadequate response to subsequent stressors. This augmented level of GC that occurs under chronic stress conditions has a strong immunomodulating effect that is mediated primarily by cytosolic GC receptors (see [13] for review). Excess of GC, whether endogenous or exogenous, has negative effects on nearly all tissues [14] and accelerates the aging process [15]. Several studies have linked the release of stress hormones such as GC to changes in skin integrity.

Studies investigating the relationship between stress and the immune system have shown that psychological stress increases various cutaneous dermatoses associated with abnormal skin barrier function (e.g., psoriasis and dermatitis) [16–21]. Recent studies in humans have shown that different types of stress affect epidermal barrier function [22,23]. In 2000, Denda and colleagues [24] have shown that damage to the epidermal barrier is due to the increase of GC, which inhibits the synthesis of lipids, resulting in a lower production and secretion of lamellar bodies. This

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phenomenon prevents the production of lamellar membranes in the stratum corneum of the epidermis, thus impairing skin integrity [25]. The immobilization stress was able to delay healing in mice [26], a process that is linked to decreased expression of pro-inflammatory cytokines (IL-1 $\alpha$  and IL-1 $\beta$ ) and growth factors [27,28], increasing susceptibility to infection by *Staphylococcus aureus* [29].

The literature documents a wide variety of negative effects of sleep deprivation (SD) and sleep restriction (SR) on the immune system and on psychomotor performance, cognitive function, mood, metabolism and behavior, after different periods of time [30–37]. Studies have shown that animals submitted to selective SD of paradoxical sleep for 96 h experienced a significant increase of prolactin, GC and catecholamines [38,39]. Because the SD methods by themselves are quite stressful, it is very difficult to determine whether the physiological changes observed are consequences of sleep loss, or are due to the stress induced by the method [40–43]. In fact, changes in HPA axis function occur, such as increases in the production of corticosterone and adrenocorticotropic hormone (ACTH) [38,39,44].

Several of the findings for chronic SD suggest a break in the skin barrier function and in mucous membranes. In humans, 42 h of total SD affected skin barrier homeostasis, increasing the levels of IL-1 $\beta$ , TNF- $\alpha$  (tumor necrosis factor) and NK (natural killer) cell activity [22]. Rats subjected to a prolonged period of selective or total SD developed ulcerative lesions on the legs and tail and a greater risk for bacterial invasion [45–49]. Experiments in mice revealed an increased production of collagen type IV epithelial cells when stimulated by IL-1 [8]. These cytokines also significantly increase the production of collagenase, which stimulates fibroblast proliferation [9,11] and may also increase or decrease the production of collagen depending on different stimuli on lymphocytes.

In 2004, Velazquez-Moctezuma and colleagues compared the effects of immobilization stress and selective SD for 24 and 240 h [50]. The results demonstrate that, despite the presence of intrinsic stressors, lack of sleep triggers a particular immune response, such as significantly increasing the number of *natural killer* cells (NK), and restraint stress causes only minor damage in the production of T and B cells, which is a rapidly reversible effect. A recent study from our laboratory showed that rats on the SR protocol for 21 days experienced more harm than did the rats on paradoxical SD for 96 h, because there was a significant decrease in the total number of leukocytes and lymphocytes and increased amounts of IgG [36], indicating that chronic sleep loss is more detrimental to the immune system and causes greater damage to the body.

Collectively, the data provided thus far have demonstrated that reduction of sleep time seems in many ways to affect the composition and integrity of various systems. The SD causes an increased production of glucocorticoids, which may alter the integrity of the lamellar bodies, thus impairing the integrity of the skin. In addition, the SD causes deregulation of the immune system, which consequently may also affect the integrity of collagen fibers.

In summary, we propose that sleep loss can lead to skin damage. This injury is mediated by deregulation of the HPA axis, which causes an elevation of the levels of GC. The augmented GC levels as well as SD alone have immunomodulating effects. There are much data suggesting that both factors (increased levels of IL-1 and GCs) are able to change the conformation of the collagen molecule and impair skin function. Thus, we hypothesize that lack of sleep can impair skin integrity. Evidence for this hypothesis is supported by several studies. Most convincingly, the intervention of SD in rats and humans has been shown to cause a break in skin barrier function and in mucous membranes.

There is little doubt about the importance of skin and collagen for homeostasis and protection of the body. Lack of sleep is inherent in modern society, and it is markedly important to verify

whether sleep loss can interfere with skin and its function, whether it exacerbates many skin diseases like psoriasis and dermatitis, and whether it alters the wound healing process. Thus, it has an important clinical application.

## Conflicts of interest

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