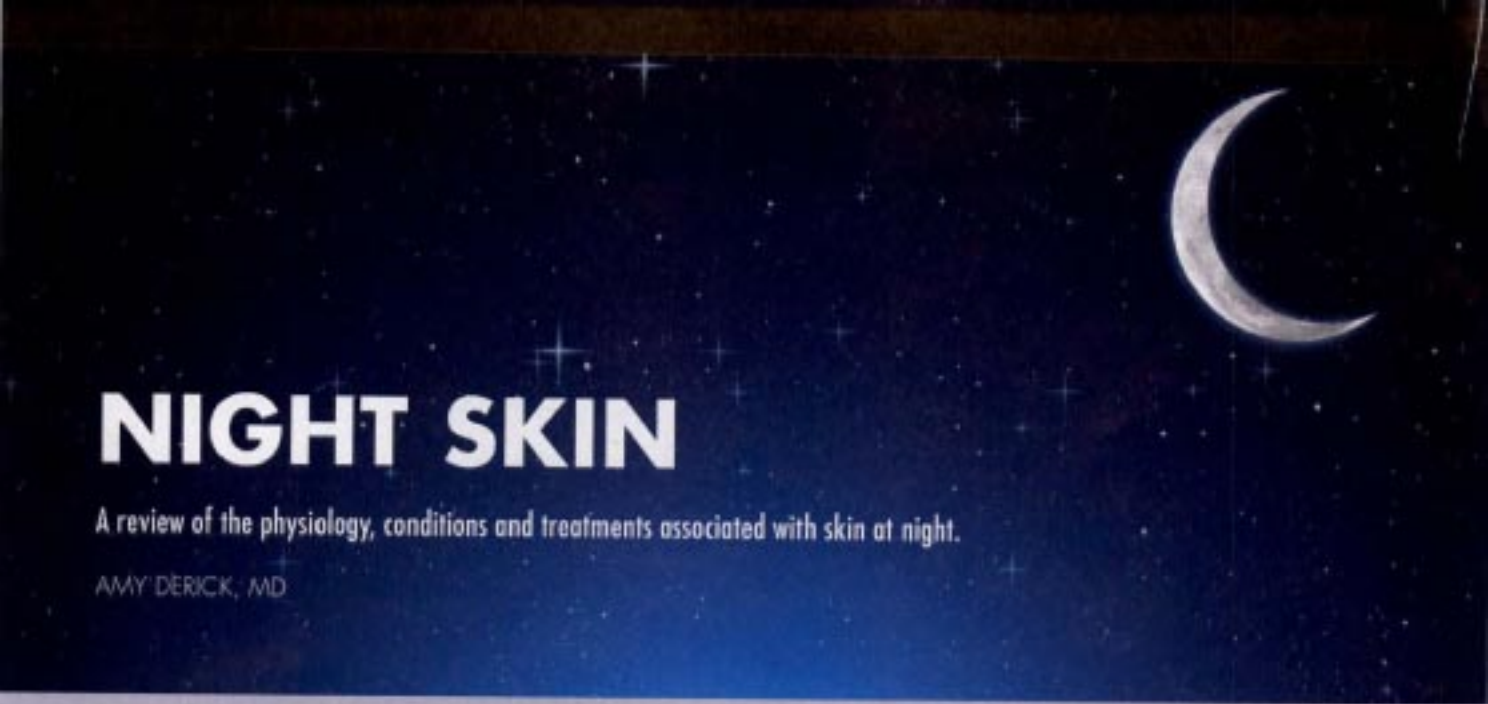

NIGHT SKIN

A review of the physiology, conditions and treatments associated with skin at night.

AMY DERICK, MD

The night is associated with unique skin physiologies, conditions and treatments. Although numerous related studies have been conducted, providers to date have not had a convenient, comprehensive reference. The purpose of this review is to compile research on topics related to night skin. Physiologies covered here include circadian rhythms, diurnal dermal fluid shift and skin repair. Conditions discussed include pillow creases, dark eye circles, chondrodermatitis nodularis helicis, hair breakage and night itching. In addition, the following treatments are addressed: retinoids, face washing, antiperspirants, pajama fabric choice, antioxidants, calcitriol and anthralin.

PHYSIOLOGY

Circadian Rhythms

The skin exhibits several differences in physiology from day to night. Some of these differences manifest in predictable circadian rhythms with peaks and troughs at consistent points throughout a 24-hour period.

One of the most researched circadian rhythms associated with the skin is ***sebum excretion***. Several independent studies have demonstrated a circadian rhythm of sebum excretion with a peak at midday.[1,2,3] Although an increase in sebum excretion has been correlated to an increase in skin temperature,[4] research has shown that the circadian rhythm of sebum excretion is independent of skin temperature.[1,2,5]

Transepidermal water loss (TEWL) is another phenomenon that exhibits circadian rhythmicity. TEWL is significant because it offers an in vivo indicator of skin barrier function.[6] The research yields inconsistent data on the precise placement of the circadian peak of TEWL. Some studies describe a peak in the afternoon,[7,8] and some place the peak in the evening or at night.[3,9,10] Although there seems to be some disagreement as to the timing of the circadian peaks and troughs, directionally the research indicates relatively high levels of TEWL toward the end of the day and relatively low levels of TEWL in the morning.

Skin temperature and skin pH have both displayed an observable circadian rhythm. One study places a peak for skin temperature in the evening and a trough in the morning. The same study observed maximal values for skin pH in the afternoon and minimal values in the evening.[3]

These studies indicate that skin excretes less sebum and loses more water at night than during the day. In addition, the skin is hotter and more acidic at night than in the daytime. The combination of these factors indicates that skin is likely to be drier and perhaps more vulnerable to irritation at night. Awareness of these natural fluctuations may aid patients and providers in developing an appropriate skin care routine.

Diurnal Dermal Fluid Shift

Research shows that the diurnal fluctuation of dermal fluid can impact the appearance and physiology of the skin. Evidence suggests that gravity, in combination with the difference in body position from day to night, may play a role in this demonstrated fluid shift. One study found that from the morning to the afternoon, the ***thickness of the skin*** significantly decreased on the face and arms, but significantly increased on the thighs and calves.[11] In parallel, the ***echogenicity*** significantly increased from the morning to the afternoon on the face and arms but decreased significantly on the thighs and calves. In addition, from morning to afternoon, the major parameters of ***skin elasticity*** increased significantly on the face and slightly on the arms but decreased significantly on the calves. The diurnal profiles of skin thickness and skin elasticity in the upper half of the body are the reverse of those in the lower half of the body. These findings suggest that shifts of dermal fluid from the face to the leg by gravity during the day cause the diurnal variation in skin thickness.[11]

Later research testing the aggravation of facial wrinkles over the course of the day confirmed the results of this skin thickness and elasticity study.[12] The second study showed that wrinkles on the forehead, in the corners of the eyes and in the nasolabial grooves were all more noticeable in the afternoon compared with the morning. ***Swelling***, which softens the appearance of wrinkles, tended to occur in the morning due to the effects of gravity during sleep. Furthermore, repeated

movements of the face due to changes of facial expression may gradually increase wrinkle formation and depth from the morning to the afternoon.[12]

In summary, as patients rest in a prone position during sleep, fluid accumulates in the upper regions of the body and face. Throughout the day, as patients spend more time upright, gravity pulls the fluid from the top half of the body to the bottom half. Thus in the morning the face contains more fluid and has thicker skin than at the end of the day. This leads to a decrease in the appearance of wrinkles in the morning but an increase in puffiness, especially around the eyes. Throughout the day, as fluid shifts to the lower half of the body, the eyes look more hollow, and wrinkles appear more defined. The combination of these factors may contribute to a tired appearance at the end of the day.

SKIN REPAIR AT NIGHT

The popular media often reports that skin repairs itself at night. While skin renewal is indeed an ongoing process, the question of whether or not renewal is more active during sleep is open to debate. There are many differences between skin during the day and skin at night. Some of these differences are physiological, some are environmental and some are behavioral. The question of whether or not the skin undergoes a special reparative process at night may ultimately be answered through an understanding of these physiological, environmental and behavioral differences.

Physiologic Differences

As described elsewhere in this review, there are relevant physiologic differences between skin at night and skin during the day. These differences seem to imply that the ***skin is potentially more vulnerable to irritation*** at night than during the day. Based on the reviewed research, there does not appear to be a compelling physiologic argument for specialized nocturnal skin repair.

Environmental and Behavioral Differences

The environmental and behavioral differences between skin during the day and at night are also significant. Perhaps most important is the ***absence of solar UV radiation*** at night. Additionally, such extraneous environmental stresses as pollution and extreme temperatures are less prevalent at night than during the day. Moreover, patients may wear makeup, drink alcohol, smoke tobacco or engage in other behaviors that cause stress to the skin while they are awake. The cumulative effect of these environmental and behavioral factors may damage the skin during the day. At night, while the patients sleep, their skin gets a reprieve from the trauma of the day.

Research designed to measure the ***impact of sleep deprivation*** on skin repair has yielded mixed results. One study noted a significant reduction in skin barrier function after sleep deprivation.[13] However, another more recent study concluded that REM sleep deprivation did not produce differences in the rate of healing.[14] Because of the inconsistency of the data, final judgment on this issue must be withheld until further research can be completed. Perhaps most presently compelling is the speculation that the ***relatively low extraneous stress*** on the skin at night gives the body's continuous repair processes a chance to catch up with the damage caused throughout the day.

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CONDITIONS

Sleep Lines

Sleep lines are creases in the skin that develop as a result of contact with a pillow during the night. This phenomenon was first described by Dr. Samuel Stegman in 1987. According to Dr. Stegman, these lines often manifest as waves across the forehead, oblique lines over the lateral orbicularis or lines on the sides of the nose and chin.[15] Later studies have confirmed these locations and have added that these creases also may be caused by underlying scar tissue.[16]

These primary, secondary, and even tertiary folds are superficial reflections of the subcutaneous attachments of the superficial muscular aponeurotic system (SMAS) at the glabella or at the condensation of the conjoining tendon of the temporalis muscle. These lines begin after the development of extrinsic and intrinsic aging, and they are augmented by sleeping patterns.[16]

Pillow creases can be diagnosed using a straightforward test. The physician must first ascertain the preferred sleeping position of the patient. Then he or she can simply apply pressure to the appropriate side of the patient's face with a pillow or hand. This pressure will mimic the effect of lying on a pillow at night. If the lines are in fact pillow creases, they should be accentuated by this familiar pressure.

Dr. Stegman believed that altering the patient's sleep patterns was important to successfully treating these lines. His experience suggested that after a few nights spent without the pillow pressing against the face, these creases became less evident. He further postulated that it would take 3 to 4 months for these lines to fade significantly.[15]

More recent research has had less luck with simple behavior modification. These studies have indicated that a detachment of the underlying SMAS ligaments is necessary to liberate these lines. These studies further note that pillow creases are improved with subcision and placing autologous fat into the pocket.[17] When this is combined with tightening from a CO_2 laser skin resurfacing, there appears to be overall improvement.[18] It is relevant to note that no treatment for these lines is likely to be permanent if the patient returns to the same pattern of sleeping habits that originally caused the creases.

Dark Eye Circles

A complaint commonly associated with lack of sleep is the formation of dark circles under the eyes. Dark circles under the eyes are defined as bilateral, round, homogeneous pigment macules on the infraorbital regions. Dark circles are caused

by ***multiple etiologic factors*** that include dermal melanin deposition, postinflammatory hyperpigmentation secondary to atopic or allergic contact dermatitis, periorbital edema, superficial location of vasculature, depression of the tear trough and shadowing due to skin laxity.[19]

Although patients anecdotally complain of dark circles under the eyes **(see Figure 1)**, true prevalence data is difficult to find. One study found that 9% of women under the age of 30 reported dissatisfaction with the darkness of the skin under the eyes.[20]

The appearance of dark circles under the eyes seems to be ***worsened by fatigue and lack of sleep***. This concept is demonstrated by the daily fluctuation of intensity of these dark circles. Because of this daily variability, dark circles have sometimes been described as a purely physiologic problem. Arguing against this idea is the fact that dark circles are more pronounced in certain ethnic groups and are also frequently seen in multiple members of the same family.[18]

A study designed to identify the genesis of eye circles concluded that this condition does not have a single anatomic basis. According to the research, the cumulative contribution score for each anatomic variable was as follows: cheek descent and hollow tear trough, 52%; prolapse of orbital fat, 48%; skin laxity and sun damage, 35%; eyelid fluid, 32%; orbicularis hyperactivity, 20%; and triangular cheek festoon, 13%.[21]

Prolapsed orbital fat and tear trough deformity both received the higher score and were more common in men. The average uniqueness score was 38%, with a range of 20% to 75%. No one category played a dominant role for most patients. Tear trough depression, skin laxity and triangular malar mound were significantly more common in patients older than 50 years.[21]

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Additionally, as discussed earlier, the ***diurnal shift of dermal fluid*** has an impact on the appearance of dark eye circles. As gravity drains the dermal fluid from the face throughout the day, the skin around the eyes thins, and vascularity becomes more apparent.[11] Skin laxity also increases, and by the evening the eyes present a more hollow, dark, and tired appearance.

Figure 1. A complaint commonly associated with lack of sleep is the formation of dark circles under the eyes.

Chondrodermatitis Nodularis Helicis

Chondrodermatitis nodularis helicis (CNH) is an inflammatory condition of the ear. **(See Figure 2.)** The associated lesions most commonly appear after 40 years of age, with 94% of cases presenting between 50 and 80 years of age. This condition affects both men and women, although men tend to have more lesions on the helix, and women the antihelix. This condition most commonly presents unilaterally, with bilateral lesions present in 6% to 10% of patients. Though uncommon, there have been reported cases of CNH in children.[22,23]

Although the etiology of CNH is not definitive, there are several ***predisposing factors*** including actinic damage, cold exposure, trauma, local ischemia and radiotherapy. One suggested pathogenesis is that these helical lesions start with perichondritis or folliculitis, secondarily extending to the skin.[24] On the other hand, antihelical lesions may begin with pressure-induced ischemia, involving the cartilage secondarily. These notions, however, are unverified to date.[23]

A variety of ***options*** have been suggested ***for treating CNH***. Patients have shown variable success with topical corticosteroid or topical antibiotic treatments. Another option is the use of a specially designed pillow that relieves pressure from the ear. Intralesional corticosteroid injections have also been successful, although in small series. Many surgical approaches have been suggested, including cryosurgery, electrodesiccation and curettage, full-thickness excision, CO_2 laser ablation and excision of skin with partial cartilage excision.[24]

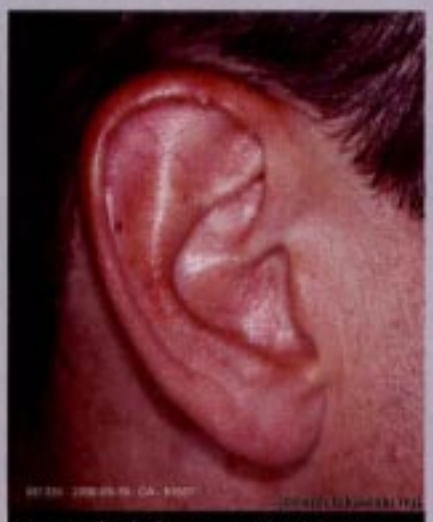

Figure 2. Chondrodermatitis nodularis helicis (CNH) is an inflammatory condition of the ear.

Although most providers seem to favor surgical treatment, some studies have shown superior results using non-surgical modalities. One study compared surgical excision to the use of a home-made pressure-relieving pillow. According to the research, 13 of the 15 patients (87%) treated non-surgically were healed at follow-up after 1 month of conservative treatment. In contrast, the recurrence rate of the surgically treated group was 14 of 41 (34%) patients.[25] This particular data set suggests a preliminary non-surgical approach. Attempting non-surgical therapy as a first defense seems unlikely to cause harm, and surgery will still remain as an alternative for resistant cases.

Hair Breakage

For some patients hair breakage during the night can present a frustrating problem. Although this specific issue has not been studied in detail, there is research on hair breakage in general. From this data, one can infer some behavioral modifications that may reduce hair breakage during the night.

Any behavior that applies physical stress to the hair at night should be avoided to minimize breakage. Any hair restraint (such as a clip or elastic band)

that pulls on the hair can increase the likelihood of breakage.

Furthermore, plasticization by water is demonstrated to lower hair-breaking load.[26] This implies that a patient is more likely to induce breakage by applying stress to wet hair as opposed to dry. Given this information, a provider can caution patients against detrimental behavior such as wearing a wet pony tail to bed.

These problems can be exacerbated by excessive tossing and turning at night. As a patient tosses from side to side on the pillow, hair can be pulled and broken. There is evidence that suggests disturbed and restless sleep is highly correlated to depression and anxiety.[27] Providers should not overlook this possibility when treating patients with unexplained nocturnal hair breakage.

Night Itching

For many patients itching is more pronounced during the night than during the day. There are a variety of potential mechanisms that could lead to this increase in pruritus, including the circadian rhythm of itch mediators and diurnal fluctuations in skin physiology such as temperature and barrier function.[28]

Night can be a particularly bothersome time for patients with inflammatory skin conditions. Up to 65% of patients who suffer from psoriasis,[29] atopic dermatitis[30] and chronic idiopathic urticaria[31] have reported a worsening of pruritus at night. Patients with cutaneous diseases such as lichen simplex chronicus[32] and scabies,[33] or patients with systemic diseases including chronic renal failure[34] and hematopoietic disorders,[35] have also reported an exacerbation of itch at night.

One plausible explanation for this increase in nighttime itch is the circadian rhythm related to TEWL, which has been shown to be at its highest at night and at its lowest during the morning.[8] High TEWL is traditionally correlated with low epidermal barrier repair function. This decreased repair functionality could facilitate the entry of irritants and itch-causing agents.[26]

Another reasonable explanation for an increase in nighttime pruritus is the circadian rhythm of skin temperature. Like TEWL, skin temperature has been shown to evidence a peak at night and a trough in the morning.[8] Because higher ambient temperature has been associated with aggravated itching,[29] it seems sensible to infer that higher skin temperature might share a similar correlation. Furthermore, it has been postulated that heat increases the itch sensation through its effect on nerve endings.[36]

An additional possible explanation for a surge in itching at night is the circadian rhythm involving the hypothalamus-pituitary axis. The levels of corticosteroids are at a trough in the evening, meaning the anti-inflammatory effects of this hormone are minimized during this time. This could diminish the body's ability to decrease inflammation effects of certain skin diseases.[28]

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Regarding the treatment of nocturnal pruritus, a physician has several options. Medications such as mirtazapine[37] and butorphanol[38] have both anti-pruritic and sedative effects. This combination of mechanisms could make these medications particularly useful in treating nighttime itch.

Although sedating antihistamines may have a role in treating nocturnal itch due to their soporific effects, there is little objective evidence that non-sedating antihistamines relive itch.[39,40,41] Although sleeping pills are sometimes prescribed in order to reduce nocturnal pruritus, there have been few studies investigating their efficacy. One study tested the effects of one of the most widely used benzodiazepines, namely nitrazepam, on nocturnal scratching.[42] Interestingly, while direct observation revealed no change in the total time spent scratching, patients taking nitrazepam reported improved sleep and decreased scratching.

Moisturizers and emollients may also prove critical to treating nighttime itch successfully. This idea partially stems from the observation that itch intensity in patients with atopic dermatitis is associated with TEWL, and TEWL increases at night. Moisturizers and emollients not only add moisture to the skin but also help prevent water evaporation by depositing a protective barrier. In addition, low pH moisturizers may be of further benefit through their ability to reduce the activity of tryptase, which is known to activate proteinase-activated receptor-2 (PAR-2) in skin nerve fibers.[43]

The topical calcineurin inhibitors tacrolimus and pimecrolimus could also be useful in treating nocturnal pruritus. Evidence suggests tacrolimus relieves the itch associated with atopic dermatitis, although it has no direct anti-pruritic action.[44] Furthermore, children with atopic dermatitis who were treated with pimecrolimus cream showed skin improvement that was correlated with improved sleep.[45]

TREATMENTS

Retinoids

A common component of a dermatologist-recommended skin care routine is the application of topical retinoids at night. It is commonly understood that bedtime application is preferable because tretinoin, all trans retinoic acid, is a light-sensitive molecule by nature of the array of conjugated double bonds.[46] A review of published research sheds light on the nature of this photo-instability and on new developments that may help to mitigate this limitation in the future.

In a study applying tretinoin to primate skin,[47] extensive conversion to 13-cis-retinoic acid (isotretinoin) was observed. While this data generated some interest regarding the role of isotretinoin in topical therapy of acne, in later controlled clinical studies the activity of isotretinoin was not superior to that of tretinoin.[46] It has been demonstrated that UV irradiation degraded up to 60% of tretinoin, isotretinoin and etretinate when applied topically ex vivo to monkey skin. In addition, the drugs and their breakdown products were measurable in both the epidermis and dermis.

Of relevant interest are recent in vitro light stability studies comparing a simple

gel and a microsphere-based formulation containing tretinoin. Under ambient (fluorescent) light, tretinoin decomposed in both cases. Importantly, however, the microsphere tretinoin preparation was found to be more stable in the presence of light than the classic gel.[48] Results of investigations revealed that after 24 hours of exposure to fluorescent light, 98% of the initial tretinoin in the tretinoin microsphere 0.1% formulation remained unchanged. When tretinoin gel microsphere 0.1% was combined with erythromycin-benzoyl peroxide topical gel and exposed to fluorescent light, 99% and 87% of the tretinoin was recovered after 4 and 24 hours, respectively, indicating only limited degradation.

In contrast, exposure of tretinoin gel 0.025% to 24 hours of fluorescent light resulted in up to 69% tretinoin degradation and up to 89% degradation when the gel was combined with the erythromycin-benzoyl peroxide topical gel. The data suggest that the tretinoin gel microshpere 0.1% formulation offers marked protection against tretinoin degradation, even in the presence of a strong oxidizing agent such as benzoyl peroxide.[48] These results have been confirmed by later studies.[49]

The delivery vehicle formulation also impacts the photostability of tretinoin. Investigation of the photodegradation of tretinoin in creams prepared with various oils revealed that tretinoin is far more stable in the cream formulations than in the respective oils alone. However, it was not clear whether this was due to the formulation or due to a different irradiation technique.[50]

Research suggests that the photosensitivity experienced by patients undergoing tretinoin therapy may be related to the process of chemical photodegradation.[51] Studies have demonstrated that the UVA component of light is a major contributor to the photodegradation of tretinoin and isotretinoin. In the future, the development of improved formulations and the use of effective UVA sunscreens may reduce the side effects of tretinoin therapy.[51]

Interestingly not all retinoids are as sensitive to light as tretinoin and isotretinoin. Adapalene has been shown to be stable for periods of up to 24 hours of light exposure, even in the presence of benzoyl peroxide.[52] In addition, a study of phototherapy for patients with psoriasis demonstrated that tazarotene remains chemically stable when exposed to both UVA and UVB light.[53] Providers might weigh the benefits of photostability along with other relevant factors such as tolerability and efficacy as they plan retinoid treatment regimens for their patients.

Calcitriol and Anthralin

Additional examples of photo instability are provided by the anti-psoriatic drugs calcitriol and anthralin. The photo sensitivity of these drugs is particularly relevant because many patients suffering from psoriasis may undergo light-based therapies. One study measured the effects of calcitriol exposure to the three forms of light that are used to treat patients suffering from psoriasis. The results of this study showed all three wavelengths caused calcitriol to degrade by over 90%. UVA irradiation resulted in degradation of more than 98%, broadband UVB irradiation resulted in degradation of 93%, and narrowband UVB reduced calcitriol to undetectable levels. The degradation was both extensive and rapid, with greater than 90% deterioration in a period of only 10 minutes.[54]

A study on anthralin reported the rate and extent of photo degradation in solution and in topical pharmaceutical vehicles. The researchers used a xenon lamp to produce artificial sunlight. The sensitivity of anthralin to light was strongly dependent on the nature of the solvent. Of interest from a therapeutic standpoint is that anthralin was highly sensitive to light in paraffin, a commonly used vehicle in therapeutic preparations.[55] Due to the instability of these topicals in light, calcitriol and anthralin may be better used at night on sun-exposed skin.

Face Washing

Face washing is a common element of many patients' nighttime skin-care rituals. Patients may ask their physicians what frequency of face washing is optimal. While there is no definitive answer, research suggests that face washing twice per day is useful for patients with acne.

In one study, acne patients were divided into groups of people who washed with a mild cleanser once, twice, or four times daily. Although the researchers observed no significant differences among the groups, at the end of the study, only the study group washing the face twice daily registered a statistically significant improvement in acne lesion count. The group washing only once per day actually experienced a worsening in its acne.[56] The data from this study suggests that a nighttime washing with a gentle cleanser should be advised in addition to at least one other washing during the day.

Antiperspirant

While many patients may consider the application of antiperspirant part of a morning routine, research suggests that night applications are more efficacious. In one study, 60 female subjects between the ages of 18 and 65 were divided into three groups. The first group applied antiperspirant in the morning only. The second group applied antiperspirant in the morning and evening. The third applied antiperspirant only in the evening. Each of the groups received treatment in only one axilla for 10 days, with the second untreated axilla serving as a control. Evaluations of percent sweat reduction after 3, 7 and 10 days of treatment showed that evening-only and twice-a-day application are significantly more effective than morning-only application.[57] Thus patients may benefit from twice-per-day application of commercial antiperspirants.

A second study compared the efficacy of newly available "prescription strength" over-the-counter anhydrous soft-solid antiperspirants to both prescription and traditional over-the-counter antiperspirants. This study demonstrated that a nighttime application regimen using "prescription

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strength" over-the-counter products provided statistically similar wetness protection to prescription aluminum chloride products and superior efficacy to commercial solid antiperspirant products.[58] Providers might consider a night or twice daily application of these new over-the-counter anhydrous soft-solid antiperspirants as a first line of defense for patients with severe axillary sweating.

Pajama Fabric Choice

Patients may be surprised to learn that the fabric they choose for their pajamas can influence the hydration level of their skin as measured by stratum corneum water content (SCWC). One study found that fabric material and subjective perception of coldness significantly predicted SCWC. Polyester fabric had a negative effect on SCWC compared with cotton, and subjective perception of coldness also had a negative effect on SCWC.[59] Other studies have confirmed these findings.[60] Thus for patients with concerns about dry skin at night, a cotton pajama fabric might be preferable to polyester.

Antioxidants

Antioxidants are a fashionable topic in both scientific journals and the popular media. The concept that antioxidants, either applied topically or ingested orally, can protect the body's cells against the damage from free radicals is attractive to researchers and consumers alike. However, for nighttime application of topical antioxidants, significant questions arise. The first question has to do with whether there is value in applying antioxidants after UV exposure. Other relevant questions relate to the quantity, type and concentration of antioxidants required for efficacy.

To answer the first question, it is relevant to discuss the nature of topical antioxidants in general. Importantly, research shows that topical application arms the skin with a reservoir of antioxidants that cannot be washed or rubbed off. This protection stays in the skin for several days after application.[61] Another study confirmed that application during a 4-day period provided progressive protection that yielded an antioxidant protection factor of four-fold.[62] It is this progressive protection, or reservoir concept, that makes nighttime application of topical antioxidants effective. A nighttime application could replace the antioxidants that were depleted during the current day and refill the reservoir for the following day.

The next question regards the specific nature of antioxidants that can effectively prevent free radical damage caused by solar radiation. One study found that topical vitamins C and E, as well as topical selenium, protect skin against sunburn, suntan and skin cancer. According to the research, these substances also reversed the mottled pigmentation and wrinkles of photoaging.[61] However, investigators found that only certain forms of these labile antioxidants were stable and active after percutaneous absorption. For effective topical applications, vitamin C must be non-esterified, acidic and optimally at 20% concentration; vitamin E must be the non-esterified isomer d-alpha-tocopherol at 2% to 5% concentration. Selenium is only percutaneously absorbed and active when applied topically as l-selenomethionine, optimally at 0.02% to 0.05%.[61]

Another study found that the combination of 15% L-ascorbic acid and 1% alpha-tocopherol provided significant protection against erythema and sunburn cell formation. The research confirmed that either L-ascorbic acid or 1% alpha-tocopherol alone was protective but concluded the combination was superior.[62]

A later study added that the incorporation of ferulic acid into a topical solution of 15% L-ascorbic acid and 1% alpha-tocopherol improved chemical stability of the vitamins (C+E) and doubled photoprotection to solar-stimulated irradiation of skin from four-fold to approximately eight-fold as measured by both erythema and sunburn cell formation.[62]

Using a proven antioxidant in a stable formulation, and in a concentration that has proven efficacy, could yield beneficial photo-protective results. Although night may offer relief from the stress of free radical-inducing UV radiation, night may also present an opportunity to replenish defensive antioxidant reserves. ■

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