

REVIEW ARTICLE

Nicotinamide and the skin

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ABSTRACT

Nicotinamide, an amide form of vitamin B₃, boosts cellular energy and regulates poly-ADP-ribose-polymerase 1, an enzyme with important roles in DNA repair and the expression of inflammatory cytokines. Nicotinamide shows promise for the treatment of a wide range of dermatological conditions, including autoimmune blistering disorders, acne, rosacea, ageing skin and atopic dermatitis. In particular, recent studies have also shown it to be a potential agent for reducing actinic keratoses and preventing skin cancers.

Key words: nicotinamide, skin cancer, skin disease.

INTRODUCTION

Nicotinamide (niacinamide) is an amide form of vitamin B₃. Other forms of vitamin B₃ include niacin (nicotinic acid) (Fig. 1), more complex amides and a variety of esters, such as inositol hexanicotinate. Vitamin B₃ is an essential water-soluble vitamin that is not stored in the body. It is maintained by the dietary intake of vitamin B₃ and tryptophan. Tryptophan is an essential amino acid that is found in most forms of protein and constitutes approximately 1% of total dietary protein. While it can be converted to niacin in the liver, its conversion is relatively inefficient; approximately 60 mg of tryptophan is required to produce 1 mg of niacin. Vitamin B₃, mainly in the form of niacin or nicotinamide, is found in a wide variety of food including chicken, pork, beef, fish, legumes, nuts, grain products, mushrooms, yeast extracts and coffee (Table 1).¹ The recommended daily

intake of vitamin B₃ in niacin equivalent is 16 mg for men, 14 mg for women, 18 mg for pregnant women and 17 mg for lactating women.² A diet that is deficient in vitamin B₃ leads to pellagra, a disease characterised by the four Ds of diarrhoea, dermatitis, dementia and death.³ As a result of improved diet and the addition of vitamin B₃ to food in developed countries, pellagra is now rare and is generally limited to individuals suffering from malabsorption syndromes, psychiatric illnesses or alcohol dependence. However, in parts of Africa and Asia pellagra is still endemic due to malnutrition and the reliance on staple foods that lack vitamin B₃, such as maize and durra.⁴ In Australia, nicotinamide is available without prescription as 500 mg tablets. It is also present in smaller quantities (usually ~30 mg) in most multivitamin preparations.

Nicotinamide and nicotinic acid have essentially the same vitamin actions. However, nicotinic acid has lipid-lowering effects and causes vasodilation, which nicotinamide does not. Thus, nicotinic acid is used clinically as an adjunct therapy for elevated blood lipids.⁵ However, when high doses of nicotinic acid are given, its vasodilatory effect may cause flushing, itching, hypotension and headaches.⁶ The safety of high-dose nicotinamide has been reviewed by Knip and colleagues who concluded, based on 19 previous studies, that ‘nicotinamide has been used at pharmacological doses (of up to 3 g/day) in many people over many years with a low incidence of side effects and toxicity’.⁷ Reported side effects associated with nicotinamide are rare, but include flushing, facial erythema, urticaria, sore mouth, dull headache, heartburn, nausea, gastrointestinal symptoms, an inability to focus the eyes, dry hair and fatigue.⁷ There has been a single case report of severe but reversible

Abbreviations:

AD	atopic dermatitis
AK	actinic keratosis
ATP	adenosine triphosphate
BCC	basal cell carcinoma
cAMP	cyclic adenosine monophosphate
NAD	nicotinamide adenine dinucleotide
NMSC	non-melanoma skin cancers
PARP-1	poly-ADP-ribose polymerase 1
PDE	phosphodiesterase
SCC	squamous cell carcinoma
TEWL	transepidermal water loss

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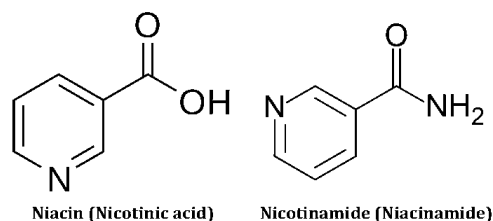


Figure 1 Chemical structures of the two main forms of vitamin B5.

Table 1 Vitamin B5 in selected foods

Food (100 g)	Niacin equivalent (mg)
Meat	
Chicken breast, grilled	11.52
Lamb, cooked	9.41
Bacon, grilled	8.52
Beef, cooked	3.51
Seafood	
Tuna, grilled	18.91
Salmon, grilled	7.72
King prawns, cooked	5.13
Barramundi, steamed	3.81
Fruit	
Bananas	0.60
Apples	0.13
Vegetables	
Mushrooms	3.72
New potatoes, baked	2.62
Carrots	0.90
Brown onions	0.71
Cos lettuce	0.47
Tomatoes	0.17
Nuts and seeds	
Peanuts, roasted	22.71
Sunflower seeds	18.98
Almonds	7.74
Walnuts	5.04
Macadamia nuts	3.27
Legumes	
Soya beans, boiled	4.25
Lentils, boiled	1.55
Bread and rice	
Wholemeal bread	7.56
White bread	6.52
Brown rice, boiled	2.35
White rice, boiled	0.56
Dairy and eggs	
Cheddar cheese	5.10
Mozzarella cheese	4.96
Eggs, boiled	2.71
Full cream milk	1.02
Skim milk	0.85
Beverages	
Espresso coffee	5.23
Ale	0.51
Red wine	0.43
Yeast	
Vegemite	150.17

hepatotoxicity in a patient taking an extremely high dose of nicotinamide (9 g/day).⁸ When the intake of nicotinamide is excessively high a small amount can be converted by gut bacteria to nicotinic acid in rodents; however, this back-conversion has not been demonstrated in humans.⁹

CELLULAR EFFECTS

Nicotinamide is the precursor of nicotinamide adenine dinucleotide (NAD), a key coenzyme in the production of adenosine triphosphate (ATP). ATP is the so-called cellular energy currency that transports chemical energy within cells. Therefore, nicotinamide supplementation boosts cellular energy and may enhance energy-dependent cellular processes such as DNA repair.¹⁰ Nicotinamide is also the sole substrate and an inhibitor of the nuclear enzyme poly-ADP-ribose polymerase 1 (PARP-1), which is activated by UV radiation.¹¹ PARP-1 has several important cellular properties, such as DNA repair and genomic stability, as well as the regulation of some transcription factors, particularly with relation to the expression of inflammatory cytokines, chemokines, adhesion molecules and inflammatory mediators.¹² When PARP-1 is overexpressed, however, NAD may be over-consumed, leading to cellular dysfunction or necrosis.¹² Having adequate cellular energy and properly functioning PARP-1 is important for a number of skin conditions, for which nicotinamide may have beneficial effects.¹³

AUTOIMMUNE BLISTERING DISORDERS OF THE SKIN

Autoimmune blistering disorders of the skin are characterised by autoantibodies directed against desmosomal structural proteins (e.g. pemphigus), hemidesmosomal structural proteins (e.g. pemphigoid and epidermolysis bullosa acquisita), epidermal/tissue transglutaminases (e.g. dermatitis herpetiformis) or basement membrane components (e.g. immunoglobulin A bullous dermatosis). The use of nicotinamide for autoimmune blistering disorders of the skin has been studied most frequently for bullous pemphigoid, with most promising results. Although there has been only one case report¹⁴ suggesting that nicotinamide monotherapy may be effective against bullous pemphigoid, a number of case reports have suggested that nicotinamide in combination with tetracycline may be an effective treatment for this condition.¹⁵⁻¹⁷

Furthermore, a randomised, open-label clinical trial compared nicotinamide 500 mg thrice daily plus tetracycline 500 mg four times a day to prednisone 40 to 80 mg a day in 18 patients with bullous pemphigoid.¹⁸ Five of the 12 patients in the nicotinamide and tetracycline group had complete responses, compared with one of the six patients in the prednisone group. The results suggest that nicotinamide and tetracycline therapy may have an efficacy comparable to prednisolone in selected patients. Furthermore, the nicotinamide and tetracycline group suffered fewer adverse effects, such as hypertension, erosive gastritis and serious infections, including one death due to sepsis, which occurred in the prednisone group.

A number of other cases have been reported where nicotinamide has been used in combination with tetracycline antibiotics with successful results for other autoimmune blistering disorders including pemphigus, cicatricial pemphigoid, lichen planus pemphigoides, dermatitis herpetiformis and immunoglobulin A bullous dermatosis.¹⁹ A double-blinded, controlled trial randomised 60 skin lesions in eight pemphigus vulgaris patients to either nicotinamide 4% gel or placebo gel for 30 days and found the mean epithelialisation index for the skin lesions that received nicotinamide to be significantly higher (26 *vs* -5.8, $P < 0.001$).²⁰ The exact mechanism of nicotinamide's actions in autoimmune blistering disorders is unclear. However, nicotinamide has known anti-inflammatory properties, with the inhibition of proinflammatory cytokines such as interleukin 1 beta, interleukin 6, interleukin 8 and tumour necrosis factor.²¹

ACNE AND ROSACEA

A double-blinded, controlled trial randomised 160 patients with moderate and predominantly inflammatory acne to receive 4% nicotinamide gel or 4% erythromycin gel, a standard acne therapy, twice daily for 8 weeks. By the end of 8 weeks the two groups had experienced a similar regression of inflammatory lesions. However, the group treated with 4% nicotinamide gel had significantly greater improvement in seborrhoea scores.²² Another double-blinded, controlled trial randomised 76 patients with moderate inflammatory acne to receive 4% nicotinamide gel or 1% clindamycin gel, another standard acne therapy, twice daily for 8 weeks. By the end of 8 weeks both treatments had produced similar improvements (a 60% reduction in papules and pustules with nicotinamide *vs* a 43% reduction with clindamycin, $P = 0.17$; and 52% reduction in acne severity with nicotinamide *vs* 38% reduction with clindamycin, $P = 0.16$), suggesting that 4% nicotinamide gel is likely to have comparable efficacy to 1% clindamycin gel.²³

Excess sebum production is implicated as a factor for the pathogenesis of comedones and inflammatory lesions in acne. A double-blinded, placebo-controlled, randomised trial with 130 patients found that a 2% nicotinamide moisturiser significantly reduced sebum excretion rates when compared to a placebo moisturiser.²⁴ The overgrowth of *Propionibacterium acnes* and the subsequent activation of interleukin 8 is another factor implicated in acne pathogenesis.^{25,26} An *in vitro* study has demonstrated that nicotinamide significantly decreased interleukin 8 secretion in a *P. acnes* keratinocyte model of inflammation, suggesting another possible mechanism of action in the application of nicotinamide for acne.²⁷ Acne is associated with impaired skin barrier function, as demonstrated by increased transepidermal water loss (TEWL).²⁸ Nicotinamide has been shown to decrease TEWL, thus improving the skin barrier, which is another potentially beneficial effect for patients with acne.²⁹⁻³¹

An open-label, multicentre prospective cohort study (no control group) assessed the effectiveness of oral Nicomide (Avion Pharmaceuticals, Atlanta, GA USA) (nicotinamide

750 mg, zinc 25 mg, copper 1.5 mg and folic acid 500 µg) for the treatment of acne and rosacea. Nicomide was given to 198 patients with acne or rosacea for 8 weeks and a significant improvement in the patients' self-evaluation of their condition was found ($P < 0.0001$).³² At the time of writing this review, no controlled studies of Nicomide are known and the official prescribing information on Nicomide notes that the drug has not been approved by the US Food and Drug Administration. Furthermore, an investigator-blinded observational study of 50 patients with rosacea found that a nicotinamide-containing moisturiser improved the signs and symptoms of rosacea over the 4-week study period, compared to no treatment as the control.³³ Impaired skin barrier function is also implicated in the pathogenesis of rosacea.^{34,35} As indicated, nicotinamide improves the skin barrier function; thus it may be of benefit for rosacea.²⁹⁻³¹

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a common dermatological condition with a variety of functional abnormalities. Skin affected by AD appears dry clinically and has a decreased level of ceramide.³⁶ Ceramide is a stratum corneum lipid and is essential for a healthy stratum corneum layer, which provides most of the skin's barrier function. Several studies have shown that skin affected by AD has an impaired skin barrier function, as demonstrated by its reduced TEWL.³⁷⁻³⁹ Nicotinamide has been shown to increase the biosynthesis of ceramide and other stratum corneum lipids²⁹ and decrease TEWL.²⁹⁻³¹

Aquaporin 3 is a gene that encodes water-permeable channels. The upregulation of aquaporin 3 has been found to be associated with AD, which leads to water loss through the skin.⁴⁰ Nicotinamide has been shown to prevent the upregulation of aquaporin 3, thereby decreasing water permeability and water loss.⁴¹ AD is an inflammatory skin condition and nicotinamide is known to have anti-inflammatory properties by inhibiting PARP-1 and the associated expression of inflammatory cytokines, chemokines, adhesion molecules and inflammatory mediators.¹² Increased cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) has been shown to contribute to many changes associated with AD, such as increased histamine and immunoglobulin E.⁴² Nicotinamide has been shown to inhibit cAMP PDE and stabilise mast cells, thereby reversing some of the changes associated with AD.⁴² Clinically, a study compared nicotinamide cream to white petrolatum on 28 patients with AD and found that nicotinamide cream decreased TEWL significantly more than white petrolatum.⁴³

AGEING SKIN

A double-blinded, split-face, randomised controlled trial applied 5% nicotinamide cream or vehicle to the face of 50 Caucasian women for 12 weeks. The study found significant improvements in skin appearance, including reductions in fine lines and wrinkles, hyperpigmented spots, red blotchiness and skin sallowness, as well as improved

elasticity.⁴⁴ Another double-blinded, split-face, randomised controlled trial applied a cosmetic containing 4% nicotinamide cream or vehicle control cosmetic to the face of 30 Japanese women for 8 weeks.⁴⁵ Significant improvements in wrinkle grades ($P < 0.001$) and skin roughness ($P < 0.05$), compared to the control, were found. Nicotinamide has been demonstrated to inhibit melanosome transfer from melanocytes to keratinocytes and promote skin lightening *in vivo*.⁴⁶ A double-blinded, randomised controlled trial with 202 patients found that a topical formulation containing 2% N-acetyl glucosamine and 4% nicotinamide significantly reduced the detectable area of facial spots and the appearance of pigmentation compared to vehicle formulation ($P < 0.05$).⁴⁷ These findings suggest that nicotinamide may be an effective agent for reducing signs of ageing.

OTHER DERMATOLOGICAL CONDITIONS

Nicotinamide, by inhibiting PARP-1, exerts anti-inflammatory properties. In addition to the dermatological conditions mentioned previously, there have been anecdotal reports of the use of oral nicotinamide for other inflammatory dermatological conditions, including polymorphous light eruption, necrobiosis lipoidica, granuloma annulare and erythema elevatum diutinum.¹⁹ The improvement of dry skin has also been demonstrated with use of nicotinamide-containing moisturisers.⁴⁸

PHOTOCARCINOGENESIS

Around 90% of non-melanoma skin cancers (NMSC) and 65% of melanomas can be attributed to exposure to UV radiation.⁴⁹ Both UVA (320–400 nm) and UVB (290–320 nm) radiation have been shown to cause skin cancer.⁵⁰ UV radiation causes skin cancer via two main pathways: DNA damage and UV-induced immunosuppression.⁵¹

Exposure to even low doses of UV radiation causes glycolytic blockade, the inhibition of enzymes involved in energy production and the depletion of human keratinocytes of ATP.⁵² As DNA repair is a highly energy-dependent process, this UV-induced energy depletion is thought to hinder efficient DNA repair and increase the risk of genetic mutations. Nicotinamide has been shown to unblock glycolysis and replenish ATP in UV-irradiated cultured human keratinocytes.¹⁰ Nicotinamide also regulates PARP-1, an important DNA repair enzyme that is activated by UV radiation.¹¹ Studies using cultured human keratinocytes and *ex vivo* human skin have shown nicotinamide to enhance DNA repair.⁵³ Nicotinamide increased both the proportion of cells undergoing excision repair and the repair rate in cultured human keratinocytes. In both cultured human keratinocytes and *ex vivo* human skin, nicotinamide reduced the formation of cyclobutane pyrimidine dimers, which are photo lesions generated mainly after UVB exposure; and also 8-oxo-7,8-dihydro-2'-deoxyguanosine, which are oxidative DNA lesions primarily induced by UVA.

Animal studies have shown that nicotinamide prevents the immune-suppressive effects of UV radiation in mice when given topically⁵⁴ or orally.⁵⁵ Clinical studies have confirmed these animal findings and have shown that nicotinamide prevents UV-induced immunosuppression when administered orally at daily doses of 500 mg or 1500 mg and topically at 5% concentration.^{56,57} The immune suppressive effects of both UVB (300 nm) and long-wave UVA (385 nm) were similarly reduced by nicotinamide.⁵⁸

Actinic keratoses (AK) are extremely common and over 40% of Australian adults have at least one lesion.⁵⁹ It is estimated that 0.6% of AK progress to squamous cell carcinoma at 1 year and 3% at 4 years.⁶⁰ A phase 2 double-blinded controlled trial randomised 34 otherwise healthy patients to receive oral nicotinamide 500 mg or matched placebo twice daily for 4 months.⁶¹ In the nicotinamide group, a 35% reduction in total AK relative to the placebo group was found at 4 months ($P = 0.0006$).

Another phase 2 double-blinded controlled trial randomised 41 patients to receive nicotinamide 500 mg or matched placebo once daily for 4 months.⁶¹ In the nicotinamide group a 29% reduction in AK relative to the placebo group was found at 4 months ($P = 0.005$). In these two studies nicotinamide was found to be effective in reducing AK regardless of whether a patient had many AK at baseline or only a few. Another double-blinded randomised controlled trial looked at the effect of topical nicotinamide on AK.⁶² In all, 30 patients were randomised to receive 1% topical nicotinamide or vehicle twice daily for 6 months. At 3 months the nicotinamide group had a 22% reduction in AK ($P = 0.04$), compared to a 10% reduction in AK for the placebo group ($P = 0.3$). However, at 6 months this difference was not maintained (25% reduction for the nicotinamide group and 22% reduction for the placebo group). It is unclear why the reduction was not maintained. It may be due to a lack of statistical power with the small sample size of 30. Another potential explanation is that topical nicotinamide accelerates the resolution phase of those AK that may occur once UV immune suppression is reversed (as observed in seasonal fluctuations in AK numbers). Some commercially available sunscreens in Australia now contain nicotinamide as one of their ingredients.⁶⁵

NMSC, primarily basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) are the most common cancers in Australia.⁶⁴ In UV-irradiated mice, topical nicotinamide significantly reduced the incidence of skin cancer from 75 to 43% ($P = 0.016$).⁵⁴ Another murine study has shown that dietary supplementation with 0.1, 0.5 or 1.0% niacin reduces the incidence of skin cancer from 68 to 60, 48 ($P = 0.038$) and 28% ($P = 0.026$), respectively, showing a dose-dependent response.⁵⁵ An analysis of the pooled results from two phase 2 AK clinical trials involving 74 healthy patients showed that nicotinamide significantly reduced the number of new NMSC. In the 37 placebo patients, 20 new NMSC (12 BCC and eight SCC) were found compared to only four new NMSC (two BCC and two SCC) in the 37 nicotinamide patients, over the two 4-month study periods (relative rate = 0.24, $P = 0.010$).⁶¹ These studies,

however, did not list a new NMSC as a primary end-point but rather were designed to assess AK counts with and without nicotinamide. Currently, a phase 3 double-blinded randomised controlled trial (Oral nicotinamide to reduce actinic cancer) is being conducted at Royal Prince Alfred and Westmead Hospitals in Sydney. A total of 586 high-risk patients have been randomised 1:1 to nicotinamide 500 mg or matched placebo twice daily for 12 months, with the primary outcome being the number of new NMSC by study completion.

TOPICAL AND ORAL NICOTINAMIDE THERAPY IN THE CLINIC

Oral vitamin B3 is available over the counter in Australia and online from other countries as both nicotinic acid, which is also known as niacin, and as nicotinamide (also known as niacinamide). However, the labelling of the bottles by manufacturers can be confusing. Some bottles have been labelled as vitamin B3, with the actual form, whether nicotinic acid or nicotinamide, visible only in small print. There may also be a misunderstanding that nicotinamide and nicotinic acid are the same medication at the point of sale. A case has been reported where a patient developed flushing as a result of her pharmacist inadvertently substituting nicotinic acid for nicotinamide.⁶⁵ Therefore, it is prudent to highlight these points to patients to ensure that they take the correct medication.

The use of oral nicotinamide in clinical practice has remained minimal. Despite the combination of nicotinamide and tetracycline having been shown to be beneficial for bullous pemphigoid, we know of no studies that compared the combination with tetracycline alone. In practice, dermatologists have found that tetracycline or doxycycline as the sole systemic agent will clear some cases of bullous pemphigoid and have accordingly omitted nicotinamide. The clinical role of nicotinamide in treating other autoimmune blistering disorders and other dermatological conditions is even less clear. Studies of topical nicotinamide have suggested it has anti-inflammatory, anti-ageing, anti-carcinogenic and moisturising properties. Consequently, it is likely that more applications will be found for topical nicotinamide.

CONCLUSION

Nicotinamide is widely available and inexpensive, with an excellent and established safety profile. It is already used clinically for some dermatological conditions, such as bullous pemphigoid, and shows promise for a number of other inflammatory conditions. Recent research findings suggest that nicotinamide may be a potential chemopreventive agent against skin cancer. There is also considerable evidence to suggest the benefit of nicotinamide against ageing changes. Some commercially available sunscreen formulations have already included nicotinamide. A phase 3 clinical trial is currently underway to evaluate oral

nicotinamide's efficacy in reducing basal cell and squamous cell carcinomas.

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