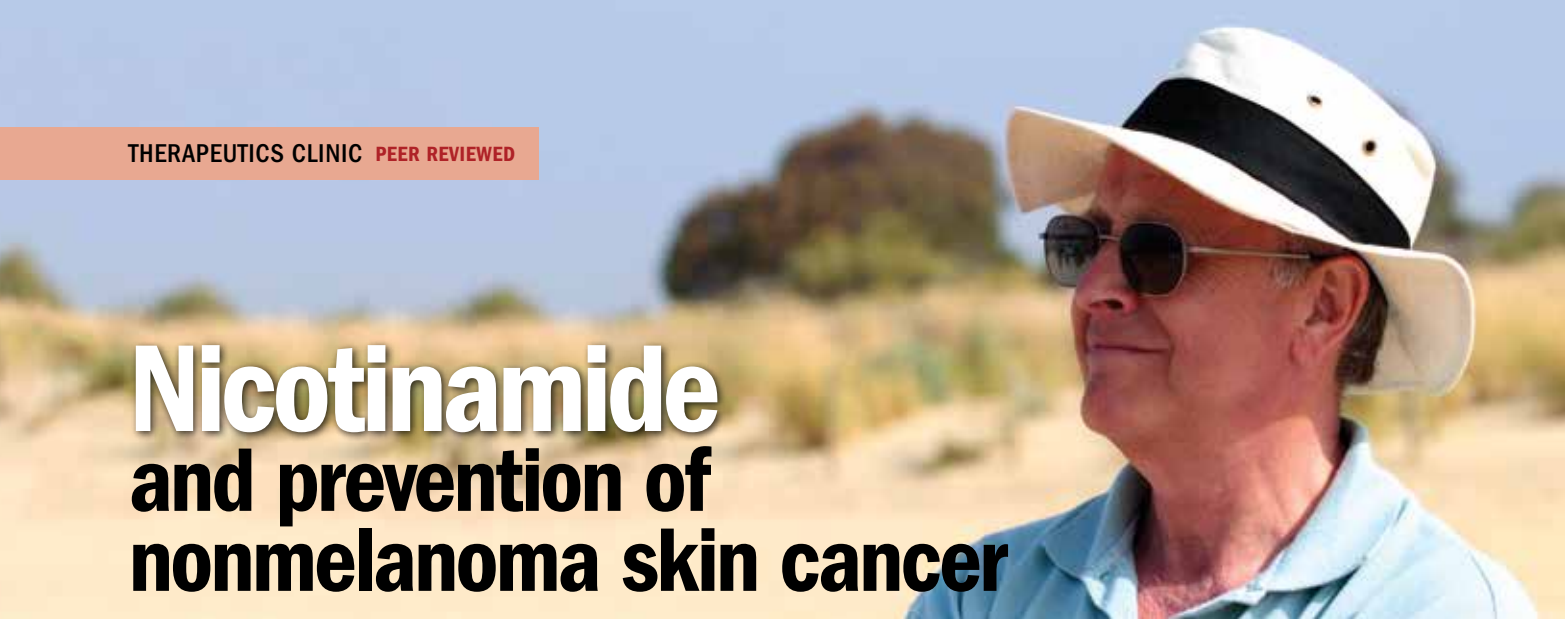

Nicotinamide and prevention of nonmelanoma skin cancer

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Evidence suggests that nicotinamide supplements can reduce the development of nonmelanoma skin cancer in high-risk patients. It may be a useful adjunct to sun protection for nonmelanoma skin cancer prevention in patients at high risk.

The water-soluble B-group vitamin nicotinamide is central to the function of some of the most important regulatory enzymes involved in DNA repair following exposure to ultraviolet (UV) radiation. Recent trials strongly suggest that nicotinamide supplementation protects against some of the damaging effects of UV exposure.[1,2]

What is nicotinamide?

Nicotinamide is the amide form of vitamin B3 (niacin). It is naturally present in trace amounts in foods such as yeast, meat, fish, nuts, legumes and cremini mushrooms. It is also produced in the body indirectly from tryptophan and directly from niacin. Nicotinamide is readily available in Australia as an inexpensive over-the-counter vitamin supplement.

Nicotinamide has been investigated over the past 50 years for a wide range of therapeutic applications.[3] Current clinical uses of nicotinamide include treatment of autoimmune bullous diseases such as bullous pemphigoid and topical treatment of acne and facial melasma, where it inhibits melanosome transfer.

Role of nicotinamide in skin cancer prevention

UV radiation causes skin cancer via two main mechanisms: DNA damage and UV-induced immunosuppression.[4,5] In Australia, up to 99% of nonmelanoma skin cancers (NMSCs), mainly basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), can be attributed to UV radiation exposure.[6] UV radiation has a direct damaging effect on DNA.[7] To avoid the risk of genetic mutations, damaged DNA is repaired when possible. When DNA repair is not possible then the cancer-prone cell is cleared by apoptosis. Immune surveillance detects and clears damaged cells that may lead to NMSC. UV-induced immunosuppression increases the risk of damaged cells developing into skin cancer.[4]

Nicotinamide is central to many cellular oxidation–reduction (redox) and non-redox reactions.[2] It is a precursor of the coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate, which function to accept or donate electrons, respectively, in many redox reactions, including catabolism of carbohydrates, fats and proteins and biosynthesis of macromolecules. Apart from its essential role in cellular metabolism and synthesis, nicotinamide is also the sole substrate and an inhibitor of the nuclear enzyme poly-ADP-ribose polymerase 1 (PARP-1). This enzyme is important in DNA repair, stress responses, cell signalling, transcription, regulation, apoptosis, chromatin structure, cell differentiation and the inflammatory response.[8,9] UV damage to DNA leads to PARP activation. Correctly functioning PARP-1 along with sirtuin proteins increases cell resistance to genotoxic insult, which otherwise can lead to mutagenesis and skin cancer formation.[10] Thus, theoretically nicotinamide should be able to aid in skin cancer prevention.

Evidence on nicotinamide and skin cancer

Studies have shown that nicotinamide reduces UV-induced immunosuppression at oral doses of 500 to 1500 mg per day.[11,12] In addition, recent Australian trials have shown that nicotinamide supplementation can reduce numbers of actinic keratoses and the development of NMSC.[1,2]

Actinic keratoses strongly predict a risk of NMSC. Two phase 2 double-blind randomised controlled trials involving 74 people in Sydney found that oral nicotinamide reduced actinic keratoses in patients with sun-damaged skin.[2] At the end of the four-month trials, the number of actinic keratoses was 29% lower among those who received nicotinamide 500 mg once daily and 35% lower among those who received nicotinamide 500 mg twice daily than among those who received placebo. The odds of developing at least one skin cancer were significantly lower with nicotinamide

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treatment, as was the rate of new skin cancers.

More recently, a double-blind randomised controlled trial investigated the effects of oral nicotinamide (500 mg twice daily for 12 months) on the development of new NMSCs in 386 patients in Sydney aged over 18 years who had been diagnosed with at least two NMSCs in the previous five years.[1] Patients diagnosed with invasive melanoma in the previous five years were excluded from the study. Participants had a mean age of 66 years (range 30 to 91 years), and 63% were men. At enrolment, they had been diagnosed with a mean of eight NMSCs in the previous five years (range 0 to 61) and had a mean of 47 actinic keratoses (range 0 to 214). Almost half had used sunscreen in the previous week.

The study found that after 12 months of therapy, the rate of new NMSCs was 23% lower in the nicotinamide group compared with the placebo group (mean of 1.8 *vs* 2.4 NMSCs per person). The rate of new BCCs was reduced by 20% ($p = 0.12$), and the rate of new SCCs was reduced by 30% ($p = 0.05$). The number of actinic keratoses was 13% lower at 12 months ($p = 0.001$). There were no significant differences between placebo and nicotinamide in the number or types of adverse events. There was no evidence of continuing benefit after nicotinamide was discontinued. The authors concluded that oral nicotinamide is safe and effective in reducing the rates of NMSCs and actinic keratoses in high-risk patients.[1]

Tolerability

Nicotinamide has been used at pharmacological doses up to 3 g per day for more than 50 years.[3] Repeated studies have demonstrated its tolerability, with a reported low incidence of side effects. Nausea and gastrointestinal side effects have been reported at doses higher than 3 g per day.[13] At very high doses, reversible hepatotoxicity has been reported in animals and humans.[3] Unlike nicotinic acid and niacin, nicotinamide is not a vasodilator, and therefore flushing is unlikely to occur.

How does nicotinamide fit into NMSC prevention strategies?

Oral nicotinamide supplementation can be proposed as an adjunct to other skin cancer prevention measures in patients who have current evidence of sun damage, either previous NMSC or actinic keratoses. There is no evidence of benefit for patients without a significant history of skin cancer. Chemoprevention with nicotinamide does not reduce the need for ongoing sun protection, sunscreen use and skin surveillance for high-risk patients.

Nicotinamide supplementation to prevent skin cancer should not be recommended for children as there is no evidence of its effectiveness in this age group. There is also a risk that its use might encourage sun overexposure in the belief they are protected. This is the same rationale underlying the limitation on sunscreen labelling to a maximum sun protection factor of 'SPF 50+'.

Other agents currently prescribed for skin cancer prevention include oral retinoids such as acitretin, used especially in patients who have undergone transplantation. However, the effectiveness of this expensive agent tends to wane over time, and its long-term use is associated with significant side effects.

Further studies on nicotinamide are needed, especially to ensure that the reductions in NMSC continue with long-term treatment. Investigation of any effect on melanoma incidence would be a priority for the Australian population.

Conclusion

Recent evidence suggests that nicotinamide at a dose of 500 mg twice daily reduces NMSC incidence by up to 23% in patients with previous NMSC. Nicotinamide appears to have a good safety profile with minimal side effects. It seems reasonable to recommend nicotinamide for motivated patients at high-risk of NMSC as an adjunct to ongoing sun protection, sunscreen use and regular skin checks. There is no evidence of benefit for patients without a significant history of skin cancer and no evidence to recommend this treatment in children. MT

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