

# Diet and psoriasis: experimental data and clinical evidence

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## Summary

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Psoriasis is considered as a T-cell-mediated inflammatory skin disease which is characterized by hyperproliferation and poor differentiation of epidermal keratinocytes. While susceptibility to psoriasis is inherited, the disease is influenced by environmental factors such as infections and stress. Diet has been suggested to play a role in the aetiology and pathogenesis of psoriasis. Fasting periods, low-energy diets and vegetarian diets improved psoriasis symptoms in some studies, and diets rich in n-3 polyunsaturated fatty acids from fish oil also showed beneficial effects. All these diets modify the polyunsaturated fatty acid metabolism and influence the eicosanoid profile, so that inflammatory processes are suppressed. Some patients with psoriasis show an elevated sensitivity to gluten. In patients with IgA and/or IgG antigliadin antibodies the symptoms have been shown to improve on a gluten-free diet. The active form of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub>, exhibits antiproliferative and immunoregulatory effects via the vitamin D receptor, and thus is successfully used in the topical treatment of psoriasis. In this review, dietary factors which play a role in psoriasis are assessed and their potential benefit is evaluated. Furthermore, the risk of drug–nutrient interactions in psoriasis therapy is discussed.

Psoriasis is one of the most common chronic inflammatory skin disorders, affecting about 2% of the general population. Prevalence rates in Europe are quoted to be about 1–5%, whereas in the U.S.A. the prevalence is estimated to be about 4–6%. In contrast, far lower prevalence rates have been observed in East Africans, American blacks, Indians (0.7%), and among the Chinese population (0.4%).<sup>1</sup> While the causes of the disease are unknown, a genetic predisposition associated with environmental factors is assumed as a plausible aetiological explanation.<sup>2,3</sup> The significance of the genetic background becomes evident with a concordance of approximately 60% in monozygotic twins.<sup>4,5</sup> The disease has a strong association with HLA-C, with about two-thirds of patients carrying the HLA-Cw\*0602 allele compared with only 10–15% in the general population. Carriers of this allele have a higher psoriasis risk and the disease becomes manifest at an earlier age in these patients.<sup>6,7</sup> Psoriasis is considered as a T-cell-mediated inflammatory skin disease. T-helper (Th) 1 lymphocytes produce autoreactive interferon (IFN)- $\gamma$  and induce further cellular reactions, resulting in marked increases of keratinocyte proliferation, abnormal patterns of keratinocyte differentiation, concomitant inflammation, and dermal proliferation of small vessels.<sup>8</sup>

There are distinct clinical phenotypes of the disease, including chronic plaque lesions (psoriasis vulgaris of type I, early onset and type II, late onset), guttate psoriasis, psoriatic

erythroderma and drug-induced psoriasis as well as various forms of pustular psoriasis. At least 10% of patients develop arthritis. Apart from distinction of psoriasis types, the actual clinical status at the momentary stage of disease activity is an important factor determining the psoriatic phenotype.<sup>1,7</sup>

Psoriasis may substantially affect quality of life. Many different treatments are available which may allow short-term improvement and long-term control of the disease, but these measures do not lead to complete clearing of psoriasis.<sup>2,9</sup> The objective of this article is to assess dietary factors which play a role in psoriasis and to evaluate the extent of evidence for potential dietetic measures. Furthermore, the risk of drug–nutrient interactions in psoriasis therapy will be discussed.

## Energy intake and food selection

Studies have shown that symptoms of inflammatory diseases such as rheumatoid arthritis can be improved by fasting periods or low-energy diets.<sup>10,11</sup> The prevalence and severity of psoriasis have been reported to be lower in periods of insecure food supply. Therefore, the disease may also be improved by low-calorie diets. In mice, calorie restriction (by 33% of energy intake) for 4 weeks decreased the epidermal cell proliferation rate by 45%.<sup>12</sup> In a Croatian study in 82 patients with psoriasis vulgaris who received their usual topical therapy, 42 patients additionally received a low-energy diet whereas the

remaining 40 were supplied with regular hospital food. After 4 weeks patients on the low-energy diet showed significantly decreased clinical skin disorders in relation to the control group. The authors concluded that a low-energy diet could be an important adjuvant factor in the prevention and treatment of moderate nonpustular psoriasis.<sup>13</sup> In another study, 20 patients with arthritis and various skin diseases were studied during a 2-week period of modified fast followed by a 3-week period of vegetarian diet. During fasting, some patients with psoriasis experienced an improvement, which persisted during the vegetarian diet.<sup>14</sup> The direct cause of these positive effects is not sufficiently explained, and various mechanisms are discussed. The most important reason is probably the lack of arachidonic acid (AA) intake, resulting in lower leukotriene (LT) B<sub>4</sub> production (see 'Polyunsaturated fatty acids' and Fig. 1). During fasting, CD4+ T-cell activation is reduced and anti-inflammatory cytokines such as interleukin (IL)-4 increase.<sup>15</sup> Another reason may be a reduction of oxidative stress due to calorie restriction, because psoriasis appears to be associated with oxidative stress (see 'Oxidative stress and antioxidants').<sup>16,17</sup> A vegetarian diet may be beneficial because it is associated with a reduced AA intake. As psoriasis is positively connected with body mass index (BMI),<sup>18,19</sup> weight reduction is recommended for obese patients. Short-term fasting periods may improve severe symptoms and thus can be suggested for patients with a BMI in the upper range. There have been several observations indicating that alcohol consumption is highly prevalent in patients with psoriasis.<sup>20,21</sup> As alcohol stimulates the release of histamine, skin lesions can aggravate as a consequence.<sup>22</sup> Moreover, a high alcohol intake may be accompanied by an excessive intake of high-fat foods and saturated fats and a low intake of vegetables and fresh fruit.<sup>19,23</sup> Therefore, alcohol intake should be restricted in psoriasis.

## Polyunsaturated fatty acids

Two families of polyunsaturated fatty acids are distinguished depending on the location of the first double bond counted from the methyl end. The essential fatty acid linoleic acid

(C18:2n-6) belongs to the n-6 family. It is found in seeds, e.g. sunflower seeds, and can be converted to the more unsaturated derivative, AA (C20:4n-6). Food sources of AA are only animal-derived foods such as meat and egg yolk. The fatty acids  $\alpha$ -linolenic acid (C18:3n-3), eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) are the most abundant n-3 fatty acids in food.  $\alpha$ -Linolenic acid is found in linseed and walnut oil, whereas EPA and DHA are typical fish oil fatty acids, which are contained in oily fishes such as mackerel and herring. In addition to their roles in membrane phospholipids, polyunsaturated fatty acids are required for the formation of eicosanoids which are metabolic regulators, for example in immune, cardiovascular and regulatory systems.<sup>24</sup> Eicosanoid members include prostaglandins (PGs), thromboxanes, LTs, hydroxyl acids and lipoxins. For example, AA can be converted to PGE<sub>2</sub> and to LTB<sub>4</sub>, whereas eicosanoids derived from EPA are PGE<sub>3</sub> and LTB<sub>5</sub> (Fig. 1). The EPA-derived eicosanoids, PGE<sub>3</sub> and LTB<sub>5</sub>, possess less inflammatory action than do PGE<sub>2</sub> or LTB<sub>4</sub>, both formed from AA.<sup>24</sup> This is why eicosanoids derived from AA can exacerbate inflammatory processes and those derived from EPA exhibit anti-inflammatory properties.<sup>25</sup>

Animal studies indicate that fatty acids can modulate proinflammatory cytokine production and actions. N-6 polyunsaturated fatty acids such as AA may enhance IL-1 production and tissue responsiveness to cytokines, whereas n-3 polyunsaturated fatty acids such as EPA or DHA have the opposite effect. Among the underlying cellular mechanisms, the modification of the composition of membrane phospholipids by the different fatty acids predominates, resulting in changes of membrane fluidity, altering binding of cytokines to receptors and G protein activity. Several trials have demonstrated the anti-inflammatory effects in psoriasis of fish oils which are rich in n-3 polyunsaturated fatty acids.<sup>26</sup>

Overproduction of AA-derived eicosanoids has been implicated in many inflammatory and autoimmune disorders and also in psoriatic skin lesions. Elevated concentrations of AA and LTB<sub>4</sub> have been measured in the skin and erythrocyte membrane of patients with psoriasis.<sup>27,28</sup> Diets rich in n-3 fatty acids result in the substitution of AA by n-3 polyunsaturated

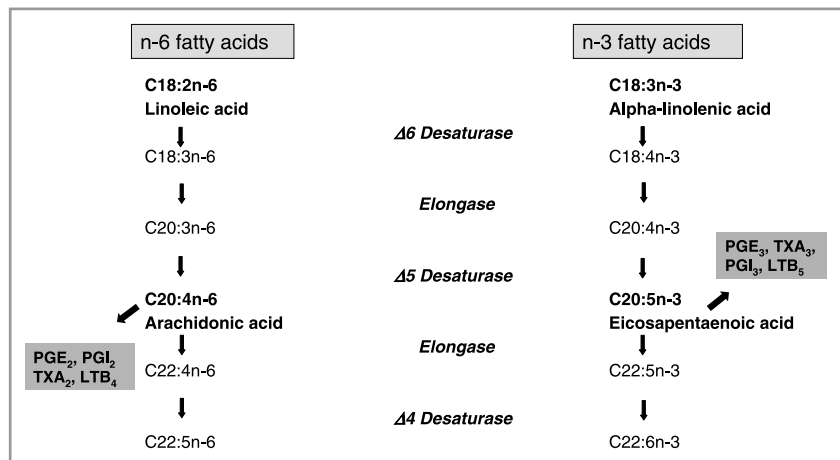


Fig 1. Metabolism of n-3 and n-6 fatty acids with eicosanoids.<sup>24</sup> PG, prostaglandin; TX, thromboxane; LT, leukotriene.

fatty acids in membrane phospholipids. As EPA can act as a competitive inhibitor of AA conversion to PGE<sub>2</sub> and LTB<sub>4</sub>, diets rich in EPA exhibit anti-inflammatory effects.<sup>29,30</sup> Low dietary AA intake which is typical for vegetarian diets can also reduce LTB<sub>4</sub> synthesis and may additionally improve inflammation. Although these mechanisms are well known, results of studies evaluating the effect of n-3 polyunsaturated fatty acids in the treatment of psoriasis are inconsistent and many of them were criticized because of shortcomings of study design.<sup>31</sup>

Several uncontrolled studies with fish or fish oil supplementation have been carried out. Most of them indicated a positive effect of n-3 fatty acids which may partly be due to the fact that the patients knew they were expected to have an improvement from the treatment. In one trial patients with psoriasis were advised to eat 170 g of white fish daily for a 4-week run-in period before being randomized either to continue with the white fish diet or to replace it by 170 g of oily fish daily for 6 weeks in a crossover design. Modest significant clinical improvement was observed after the oily fish diet only, whereas the white fish diet had no effect. At the same time, plasma EPA concentrations rose in the oily fish group. The authors concluded that the daily intake of oily fish such as mackerel, sardine, salmon, pilchard, kipper or herring, which are rich in n-3 fatty acids, might be a useful adjunct in the treatment of psoriasis.<sup>32</sup>

Four uncontrolled studies with EPA/DHA or fish oil supplementation with daily dosages between 2 and 12 g n-3 fatty acids reported beneficial effects of the intervention on psoriasis severity.<sup>28,33–35</sup> A positive effect of a combination of n-6 and n-3 fatty acids was observed in 17 patients with psoriasis after 4 months in another noncontrolled study.<sup>36</sup> In an open study testing the effects of fish oil supplementation in 26 patients with psoriasis, no clinically significant improvement could be shown in any of the patients with plaque-type psoriasis vulgaris. Only one patient with generalized pustular psoriasis showed marked improvement with the fish oil supplementation, accompanied by decreased LTB<sub>4</sub> levels.<sup>37</sup>

Results from randomized controlled trials are less positive. Among four studies, a benefit of oral n-3 fatty acid supplementation was reported in one study only,<sup>38</sup> whereas no beneficial effects compared with placebo were observed in the other three studies.<sup>39–41</sup> The positive result was described in a randomized placebo-controlled trial with patients with psoriasis receiving 3 g of oral n-3 fatty acid (predominantly EPA) from fish oil (10 g) daily. Within this treatment group a significant lessening of itching, erythema and scaling was observed after 8 weeks, with a trend towards an overall decrease in body surface area affected, whereas no change occurred in the olive oil (placebo) group.<sup>38</sup> In two randomized double-blind controlled studies, fish oil supplementation of 1.8 g EPA for 8 weeks<sup>39</sup> or 10 capsules of fish oil three times a day for 3 weeks<sup>37</sup> showed no benefit compared with olive oil supplementation. No benefit of fish oil supplementation compared with corn oil, which contains mainly n-6 fatty acids, was seen in a 4-month, double-blind, randomized

multicentre trial. One hundred and forty-five patients with moderate-to-severe psoriasis received either 5 g of EPA and DHA or an isoenergetic amount of corn oil in their diet. Although the ratio of AA and EPA in serum phospholipids decreased significantly in the fish oil group, the Psoriasis Area and Severity Index (PASI) score did not change significantly in either group. Scaling was reduced compared to baseline in both groups, but only a selected area of skin in the corn oil group showed a significant reduction in clinical signs. There was no significant difference in clinical manifestations between the groups. Clinical improvement was not correlated with an increase of n-3 fatty acid concentration in serum phospholipids among the patients in the fish oil group, whereas there was a significant correlation between clinical improvement and an increase in EPA and total n-3 fatty acids in the corn oil group.<sup>41</sup> The positive effect of corn oil rich in linoleic acid may be explained by the fact that LTB<sub>4</sub> production is suppressed at high intakes of linoleic acid.<sup>26</sup>

No effect on chronic stable plaque psoriasis was observed in a double-blind trial after the supplementation of a combination of n-3 fatty acid-rich marine oil with n-6 fatty acid-rich evening primrose oil in 37 patients with psoriasis.<sup>42</sup>

In contrast to the mostly negative results from oral supplementation studies with n-3 fatty acids, promising advances were made in parenteral application of n-3 fatty acids, indicating positive effects on acute inflammatory disorders.<sup>43</sup> In a 10-day trial, 20 patients hospitalized for acute guttate psoriasis with a minimum of 10% of body surface area involvement were randomly assigned to receive daily infusions with either a n-3 fatty acid-based lipid emulsion (EPA + DHA 4.2 g daily) or a conventional n-6 lipid emulsion (EPA + DHA < 0.1 g daily). The severity of disease, which was evaluated by daily scoring of erythema, infiltration and desquamation and by a subjective scoring of clinical manifestations, decreased markedly in all patients of the n-3 group, with significant improvements in all score systems ranging between 45% and 76% within 10 days. Only moderate improvement was observed in the n-6 group (16–25% score changes from baseline). Neutrophil EPA-derived 5-lipoxygenase product formation increased 10-fold in the n-3 group but not in the n-6 group.<sup>44</sup> The benefit of infusions with n-3 fatty acids (4.2 g of both EPA and DHA) has been confirmed in a double-blind, randomized, multicentre study with 83 patients hospitalized for chronic plaque-type psoriasis. After 14 days of intervention the total PASI score decreased significantly in both groups, the n-3 and the n-6 fatty acid control group, by 42% and 31%, respectively. A decrease in total PASI of at least 50% between the admission and the last value was stated in 37% of the patients receiving the n-3 emulsion and in 23% of the patients receiving n-6 fatty acid-based conventional emulsion. As an increase in neutrophil LTB<sub>5</sub> and platelet thromboxane B<sub>3</sub> generation occurred, the observed effects were probably related to changes in inflammatory eicosanoid generation.<sup>45</sup> The rapid effect of n-3 fatty acid supplementation in these studies indicates that intravenous supplementation may be more beneficial on inflammatory skin lesions than oral supplementation. In a

Cochrane review on base treatment of acute guttate psoriasis, the authors concluded that there is currently no firm evidence for intravenous n-3 fatty acids as a base treatment for acute guttate psoriasis.<sup>46</sup>

Some of the presented study results indicate modest improvements by additional n-6 fatty acids in psoriasis. Soyland *et al.*<sup>41</sup> found a moderate positive effect in the corn oil group and Mayer *et al.*<sup>43</sup> observed a moderate improvement after parenteral n-6 lipid emulsion. Kragballe,<sup>36</sup> who supplemented 17 patients with a combination of n-6 and n-3 fatty acids, found a positive but not significant effect. Modest improvements may result from a combined fatty acid therapy because patients with psoriasis have been shown to exhibit low concentrations of polyunsaturated fatty acids in membrane phospholipids. Patients with psoriatic arthritis exhibited a significant increase in saturated fatty acids and a significant decrease in n-6 polyunsaturated fatty acids in red blood cells compared with controls.<sup>47</sup> Furthermore, as already discussed, high doses of linoleic acid suppress LTB<sub>4</sub> production.<sup>26</sup>

## Gluten

In coeliac disease (CD), the ingestion of gluten-containing cereals results in small bowel mucosal inflammation and villous atrophy with crypt hyperplasia. The resulting malabsorption syndrome occurs in sensitive individuals upon the consumption of wheat, rye, barley, triticale, oats, spelt and kamut. The symptoms such as diarrhoea and abdominal distension normalize after the institution of a gluten-free diet. The toxic compounds are prolamins: gliadin in wheat gluten, secalins in rye, and hordeins in barley.<sup>48,49</sup> It is assumed that gluten-sensitive enteropathy commonly manifests with minimal or no gastrointestinal symptoms and that there is an association between latent gluten sensitivity and psoriasis.<sup>50-53</sup> In the case of 'silent' CD, antibody testing can be used to identify gluten-sensitive patients. Plasma cells produce IgA and IgG against various antigens including gliadin, transglutaminase, endomysin and reticulon. In diagnosing CD, IgG and IgA antigliadin antibodies (AGA) and serum antibodies against tissue transglutaminase have been shown to be useful.<sup>51</sup> Tissue transglutaminase seems to be the predominant autoantigen in both the intestine and the skin of patients with CD.<sup>54</sup> Some findings indicate an elevated incidence of psoriasis in patients with CD, but the data are inconsistent.<sup>54-56</sup> A case report of a patient with CD and psoriasis whose skin lesions improved shortly after starting a gluten-free diet seems to confirm the suggested association between CD and psoriasis.<sup>57</sup> On the other hand, a gluten-free diet may improve psoriasis severity even in patients with no CD but with IgA and/or IgG AGA.<sup>58</sup> AGA are more common in patients with psoriasis than in healthy persons. Measurement of IgA and IgG AGA by a microenzyme-linked immunosorbent assay method in 302 patients with psoriasis showed IgA AGA serum levels above the 90th percentile value of the reference group in 16% of the patients. Although the mean level of IgG AGA was not increased in the psoriasis group, there was a correlation between the values for IgA AGA and IgG AGA.<sup>50</sup>

Moreover, the presence of serum IgA AGA is often associated with duodenal inflammation.<sup>59</sup> Michaelsson *et al.*<sup>58</sup> evaluated the effect of a 3-month gluten-free diet in 33 AGA-positive and six AGA-negative patients with psoriasis. They used the PASI for assessment of disease severity. Thirty patients with AGA completed the gluten-free diet period and showed a highly significant decrease in mean PASI. No improvement was found in the AGA-negative patients. AGA values were reduced after the gluten-free diet in 82% of those patients who improved. After the gluten-free diet, patients consumed their ordinary diet for 3 months. During this period, the psoriasis deteriorated in 18 of the 30 patients with AGA who had completed the gluten-free period. As CD or latent gluten sensitivity was diagnosed in only 19 patients it can be concluded that patients with psoriasis with raised AGA may improve on a gluten-free diet even if small intestinal histology seems to be normal. The study has been criticized for some shortcomings of the design such as the small control group, no randomization and the possibility that the placebo effect might have played an important role in the positive results.<sup>56</sup> Should the findings of the study be true, patients with latent gluten sensitivity exhibited increased bowel permeability despite normal small intestinal histology. The increased intestinal permeability may allow the passage of small numbers of microbes which can act as superantigens and may induce the appearance or exacerbation of psoriasis in predisposed subjects which could be reversed by a gluten-free diet. Another explanation of the coincidence of CD and psoriasis may be the profile of released cytokines. In psoriasis the predominating Th1 cells mainly produce IFN- $\gamma$  and IL-2 (Fig. 2). T cells from patients with CD release a similar cytokine profile in response to a gluten challenge *in vitro*. Some case reports indicate that elevated serum levels of these cytokines may be sufficient to result in CD or psoriasis in predisposed individuals.<sup>56</sup>

Investigating the proliferating (Ki67) cells and tissue transglutaminase in involved skin of 28 AGA-positive patients with

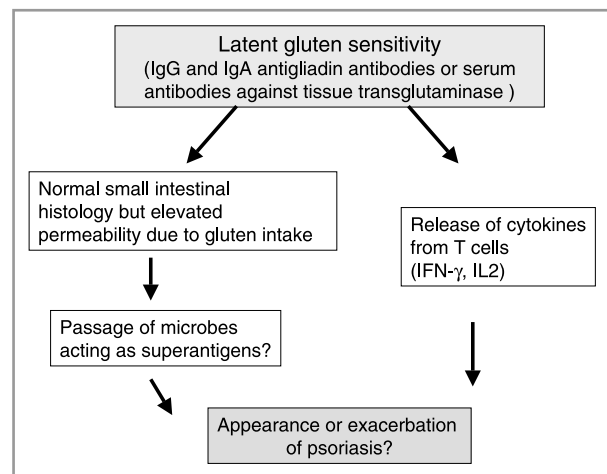


Fig 2. Potential effects of 'silent' coeliac disease. IFN, interferon; IL, interleukin.

psoriasis before and after 3 months of a gluten-free diet showed a significant decrease in proliferating cells after the diet even in patients without increased intraepithelial lymphocytes. After the gluten-free diet, tissue transglutaminase, which was highly overexpressed in the papillary endothelium of involved skin, decreased by 50%.<sup>60</sup>

### Oxidative stress and antioxidants

Oxidative stress and increased free radical generation have been linked to skin inflammation in psoriasis. Superoxide anion liberation was elevated in psoriatic dermal fibroblasts, which have been suggested to play a central role in the inflammatory mechanism of psoriasis.<sup>16</sup> Patients with psoriasis exhibit several markers of oxidative stress and show impaired antioxidant status: increased concentrations of malondialdehyde (MDA), a marker of lipid peroxidation, were measured in plasma and red blood cells, and decreased plasma levels of  $\beta$ -carotene and  $\alpha$ -tocopherol as well as decreased serum concentrations of selenium were found.<sup>16,47,61</sup> Results on the activity of antioxidant enzymes are inconsistent. In one study glutathione peroxidase activity was stimulated in both erythrocytes and platelets when compared with normal cells. At the same time the plasma selenium concentration was significantly reduced compared with the control group.<sup>27</sup> In another trial, activities of antioxidant enzymes such as catalase and glutathione peroxidase were reduced.<sup>16</sup> An increased production of MDA was consistently observed in psoriasis indicating advanced phospholipid peroxidation of the red blood cell membrane caused by a decrease of antioxidant resistance. This may explain the decreased membrane fluidity associated with the exacerbation of the disease.<sup>16</sup> Fish oil supplementation not only altered the lipid pattern of erythrocyte membranes but also led to a reduction of MDA in patients with psoriasis and therefore may reduce oxidative stress.<sup>27</sup> In an Italian case-control study with 316 patients with psoriasis and 366 controls, dietary intake was assessed by a semiquantitative food frequency questionnaire and data were adjusted for age, sex and BMI. Psoriasis risk (odds ratio) was significantly inversely related to the intake of carrots, tomatoes and fresh fruit as well as to the  $\beta$ -carotene intake. The intake of green vegetables showed an inverse association, with borderline statistical significance. The consumption of vegetables and fruits may be beneficial in psoriasis due to their high content of various antioxidants such as carotenoids, flavonoids and vitamin C.<sup>19</sup>

A sufficient status of antioxidants (e.g. vitamin C, vitamin E,  $\beta$ -carotene and selenium) may be helpful to prevent an imbalance of oxidative stress and antioxidant defence in psoriasis. While ascorbic acid acts as a water-soluble antioxidant,<sup>62</sup>  $\alpha$ -tocopherol is a chain-breaking antioxidant that prevents the propagation of lipid peroxidation.<sup>63</sup>  $\beta$ -Carotene displays antioxidant activity by scavenging free radicals and is a potent quencher of singlet oxygen.<sup>64</sup> Selenium is essential for the function of a number of selenoproteins such as glutathione peroxidases and thioredoxin reductase which take part in the antioxidant defence.<sup>65</sup> To date, only a few studies have

investigated the effect of antioxidant supplementation on psoriasis symptoms. In one supplementation trial, seven patients with psoriasis received selenium 400  $\mu$ g daily for 6 weeks as selenomethionine-enriched yeast.<sup>66</sup> Blood and serum selenium levels were normal at baseline. After supplementation there was a slight but significant increase only in the number of CD4+ T cells in the reticular dermis of the psoriatic lesions. Selenium supplementation had no marked effect on the clinical condition of the patients.<sup>66</sup> A previous study also showed no effect of daily supplementation of 600  $\mu$ g selenium-enriched yeast alone or together with 600 IU of vitamin E on the clinical symptoms of 69 patients with psoriasis. In this placebo-controlled study, blood, plasma and platelet selenium concentrations as well as platelet glutathione peroxidase activity and plasma vitamin E markedly increased in the supplemented group. However, the mean skin selenium concentration and red cell glutathione peroxidase activity remained unchanged.<sup>67</sup>

### Vitamin D<sub>3</sub> and analogues

Vitamin D is a prohormone which can be produced from 7-dehydrocholesterol by moderate exposure of skin to solar ultraviolet (UV) B rays. Its deficiency causes rickets, which arises from insufficient absorption of dietary calcium. A rich dietary source of vitamin D is cod liver oil. The biologically active form of vitamin D is produced by hepatic 25-hydroxylation, followed by  $1\alpha$ -hydroxylation, primarily in the kidney.<sup>68</sup> Beside its significance in calcium homeostasis and bone metabolism, the active form of vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>; calcitriol], exhibits effects via the vitamin D receptor (VDR) in more than 30 different tissues. One target tissue for 1,25(OH)<sub>2</sub>D<sub>3</sub> is the skin, as keratinocytes have a VDR. Human cultured keratinocytes exposed to calcitriol showed marked inhibition of growth and accelerated maturation. The effects on cell proliferation and differentiation via the VDR led to the concept of using 1,25(OH)<sub>2</sub>D<sub>3</sub> in psoriasis.<sup>69</sup> Calcitriol and its analogues exert antiproliferative and prodifferentiative as well as immunoregulatory activities. VDR ligands directly influence T-cell activation and modulate the phenotype and function of antigen-presenting cells and dendritic cells.<sup>70</sup> Meanwhile, vitamin D analogues including calcipotriene, 1,24-dihydroxyvitamin D<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub> are considered the first line of treatment for psoriasis.<sup>69,71</sup> They show the same efficacy as potent topical corticosteroids and are well tolerated even on a long-term basis.<sup>72</sup>

Insufficient vitamin D status is a widespread problem. Circulating 25-hydroxyvitamin D [25(OH)D] concentration is the best indicator to define vitamin D status. Observations that subjects with a constantly high UVB exposure living close to the Equator have mean 25(OH)D serum levels of 107 nmol L<sup>-1</sup> led to the assumption that levels above 100 nmol L<sup>-1</sup> can be regarded as adequate, where no disturbances in vitamin D-dependent body functions occur.<sup>73</sup> In Europe, prevalence of insufficient vitamin D status is high, as UVB radiation from sunlight is negligible from October to

April at the latitude of 52°N and from November to February at 42°N. In contrast, skin synthesis of vitamin D is possible throughout the year at 32°N or closer to the Equator.<sup>73</sup> Hypovitaminosis D is even more prevalent in older adults because of limited outdoor activities and decreased capacity of vitamin D synthesis of the skin compared with younger adults.<sup>74,75</sup> In an epidemiological survey of 11 European countries, vitamin D deficiency was found in 36% of elderly male and 47% of elderly female subjects.<sup>76</sup>

As insufficient vitamin D is a general problem, oral vitamin D supplementation may be considered in patients with psoriasis who do not use topical vitamin D analogues. In cases of topical treatment such supplementation must be avoided because of the risk of hypercalcaemia.

### Vitamin B<sub>12</sub>

Cobalamin (vitamin B<sub>12</sub>) participates as a coenzyme in two biochemical reactions in human metabolism. One reaction requiring methylcobalamin is the remethylation of homocysteine to methionine catalysed by methionine synthetase (see 'Nutritional status and nutrient–drug interactions'). Adenosylcobalamin is required as coenzyme for methylmalonyl-CoA mutase which catalyses the conversion of methylmalonyl-CoA to succinyl-CoA, a metabolite of the citric acid cycle. This is an important biochemical reaction in the degradation of odd-chain fatty acids and of branched-chain amino acids. Cobalamins are exclusively synthesized by bacteria. Rich sources of cobalamin are animal organ meats (especially liver and kidney), fish, egg and milk products.<sup>77</sup>

Vitamin B<sub>12</sub> may influence psoriasis due to its role in nucleic acid synthesis. *In vitro* studies also demonstrated immunomodulatory effects of vitamin B<sub>12</sub> on T lymphocytes and cytokines.<sup>78,79</sup> There were some studies in the 1950s reporting therapeutic efficacy after parenteral administration of vitamin B<sub>12</sub> in the treatment of psoriasis. However, these results could not be confirmed in other studies.<sup>80</sup>

The efficacy of topical vitamin B<sub>12</sub> treatment in plaque psoriasis has been investigated in one study using a vitamin B<sub>12</sub> cream containing avocado oil compared with calcipotriol treatment.<sup>81</sup> There was a more rapid development of beneficial effects with the use of calcipotriol, which was shown to be significantly superior to vitamin B<sub>12</sub> treatment after 8 weeks. However, no significant difference between both therapies was observed after 12 weeks of treatment. Furthermore, there was better tolerability of the vitamin B<sub>12</sub> cream in comparison with calcipotriol.<sup>81</sup> In this trial it cannot be excluded that components of the avocado oil such as unsaturated fatty acids may have contributed to the beneficial effects of the vitamin B<sub>12</sub> cream.

### Nutritional status and nutrient–drug interactions

Severe psoriasis has been associated with nutritional deficiencies because of an accelerated loss of nutrients from the

hyperproliferation and desquamation of the epidermal layer of skin. Furthermore, an elevated requirement of some nutrients such as antioxidants may occur. Among 50 hospitalized patients with psoriasis, 18% had decreased total protein, 16% had decreased serum albumin, 38% had elevated mean corpuscular volume and 39% had decreased haematocrit. These results support that patients with widespread psoriasis are at risk to develop nutritional abnormalities in protein and folate status.<sup>82</sup>

Beside the disease-related risk of poor nutritional status, patients with chronic diseases are often regular drug users. Therefore they are at particular risk for drug–nutrient interactions. In psoriasis, especially systemic therapy can be associated with alterations of the nutritional status. About 30% of patients with psoriasis have symptoms that are severe enough to require systemic therapy.<sup>83</sup> On the other hand, dietary factors can affect a drug's pharmacokinetics and pharmacodynamics. One systemic treatment in patients with psoriasis is the folic acid antagonist methotrexate which is used at low doses. It is hepatotoxic, leads to loss of appetite and its use is contraindicated in patients with poor nutritional status.<sup>84</sup> Patients with psoriasis who received low-dose methotrexate therapy (25 mg weekly) had significantly higher fasting plasma homocysteine and lower plasma folate levels than age-matched controls.<sup>85</sup> This finding is supported by studies in patients with rheumatoid arthritis on methotrexate therapy.<sup>86,87</sup> Homocysteine is derived from methionine and is used as a sensitive marker of folate status. Elevated homocysteine concentrations are associated with an elevated risk of atherosclerosis and may increase the risk of dementia.<sup>88–90</sup> Homocysteine can be degraded through two enzymatic pathways: the remethylation of homocysteine to methionine is catalysed by the methionine synthetase. In this reaction 5-methyl tetrahydrofolic acid is involved as a methyl group donor, while vitamin B<sub>12</sub> is the intermediate acceptor of the methyl group. In folate deficiency, plasma homocysteine rises. In the *trans*-sulphuration pathway, homocysteine forms cysteine, but this degradation pathway is not sufficient to normalize homocysteine concentrations in folate deficiency. Homocysteine can be used as a sensitive marker of folate status in patients with psoriasis receiving methotrexate. Folic acid supplements should be prescribed routinely to these patients. In order to reduce side-effects, 5 mg of folic acid two to five times weekly is commonly given to patients receiving methotrexate.<sup>91</sup>

Another systemic therapy in psoriasis is ciclosporin, an immunosuppressive agent. Owing to downregulation of the cytochrome P450 3A4 enzyme in the intestinal wall, the oral bioavailability of ciclosporin increases by more than 60% when taken with grapefruit juice. Patients should be advised to avoid the consumption of grapefruit juice when taking ciclosporin.<sup>92–94</sup>

Retinoids such as etretinate are synthetic analogues of retinoic acid (vitamin A). Systemic retinoids can induce symptoms of hypervitaminosis A including headache, weakness and anorexia. Patients taking retinoids should be advised to avoid food sources rich in vitamin A, particularly liver. Retinoids

can also induce hyperlipidaemia. Thus regular monitoring of this side-effect is necessary. Serum triglycerides can be significantly lowered by a diet low in saturated fatty acids and high in n-3 fatty acids from fish such as mackerel, sardine, salmon, herring or fish oil supplements.<sup>95</sup> Furthermore, alcohol intake and dietary monosaccharides should be reduced.<sup>96,97</sup>

Among the pro-oxidant 9-anthrones that are used in topical treatment of psoriasis, dithranol is the most common therapeutic agent. The therapeutic effect is based on the generation of reactive oxygen intermediates and anthrone radicals produced in the skin. As superoxide dismutase and  $\alpha$ -tocopherol acetate were effective in inhibiting cytokine elevation induced by dithranol, systemic antioxidant administration may reduce dithranol-associated side-effects.<sup>16</sup>

## Conclusions

The diet is one factor in the aetiology and pathogenesis of psoriasis. Vegetarian diets may be beneficial for all patients with psoriasis due to the low AA intake and the resulting reduced formation of inflammatory eicosanoids. Although the results of oral fish oil supplementation are inconsistent, patients can be recommended to include fish rich in n-3 polyunsaturated fatty acids in their diet. Moreover, in patients hospitalized for acute psoriasis parenteral n-3 polyunsaturated fatty acid infusions may be beneficial. Further investigations are needed to clarify the role of a gluten-free diet and underlying mechanisms on psoriasis in gluten sensitivity. A gluten-free diet may improve psoriasis severity in patients with IgA and/or IgG AGA. To date, apart from measurement of AGA or tissue transglutaminase, patients may be recommended to try whether a withdrawal of gluten for at least 3 months reduces the symptoms. Owing to its role in proliferation and maturation of keratinocytes, vitamin D has become an important therapeutic option in the treatment of psoriasis. As hypovitaminosis D is widespread, patients who do not use topical vitamin D analogues may benefit from vitamin D supplements. More well-designed trials are needed to confirm or reject the benefit of dietary manipulation in psoriasis. Drug-food interactions have to be considered in patients with psoriasis.

## References

- 1 Christophers E. Psoriasis—epidemiology and clinical spectrum. *Clin Exp Dermatol* 2001; **26**:314–20.
- 2 Naldi L, Svensson A, Diepgen T et al. Randomized clinical trials for psoriasis 1977–2000: the EDEN survey. *J Invest Dermatol* 2003; **120**:738–41.
- 3 Stern RS. Psoriasis. *Lancet* 1997; **350**:349–53.
- 4 Glaser R, Mrowietz U, Jenisch S et al. Simultaneous onset of psoriasis vulgaris in monozygotic twins. *Am J Clin Dermatol* 2001; **2**: 183–6.
- 5 Pisani M, Ruocco V. 'Twin' psoriasis in monozygotic twins. *Arch Dermatol* 1984; **120**:1418–19.
- 6 Capon F, Munro M, Barker J, Trembath R. Searching for the major histocompatibility complex psoriasis susceptibility gene. *J Invest Dermatol* 2002; **118**:745–51.
- 7 Gudjonsson JE, Johnston A, Sigmundsdottir H, Valdimarsson H. Immunopathogenic mechanisms in psoriasis. *Clin Exp Immunol* 2004; **135**:1–8.
- 8 Ghoreschi K, Mrowietz U, Röcken M. A molecule solves psoriasis? Systemic therapies for psoriasis inducing interleukin 4 and Th2 responses. *J Mol Med* 2003; **81**:471–80.
- 9 Al-Suwaidan SN, Feldman SR. Clearance is not a realistic expectation of psoriasis treatment. *J Am Acad Dermatol* 2000; **42**:796–802.
- 10 Palmblad J, Hafstrom I, Ringertz B. Antirheumatic effects of fasting. *Rheum Dis Clin North Am* 1991; **17**:351–62.
- 11 Muller H, de Toledo FW, Resch KL. Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. *Scand J Rheumatol* 2001; **30**:1–10.
- 12 Hsieh EA, Chai CM, De Lumen BO et al. Dynamics of keratinocytes in vivo using HO labeling: a sensitive marker of epidermal proliferation state. *J Invest Dermatol* 2004; **123**:530–6.
- 13 Rucevic I, Perl A, Barisic-Drusko V, Adam-Perl M. The role of the low energy diet in psoriasis vulgaris treatment. *Coll Antropol* 2003; **27** (Suppl. 1): 41–8.
- 14 Lithell H, Bruce A, Gustafsson IB et al. A fasting and vegetarian diet treatment trial on chronic inflammatory disorders. *Acta Derm Venereol (Stockh)* 1983; **63**:397–403.
- 15 Fraser DA, Thoen J, Reseland JE et al. Decreased CD4+ lymphocyte activation and increased interleukin-4 production in peripheral blood of rheumatoid arthritis patients after acute starvation. *Clin Rheumatol* 1999; **18**:394–401.
- 16 Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin disease. What's new. *J Eur Acad Dermatol Venereol* 2003; **17**: 663–9.
- 17 Rocha-Pereira P, Santos-Silva A, Rebelo I et al. Dislipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease. *Clin Chim Acta* 2001; **303**:33–9.
- 18 Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995; **32**:982–6.
- 19 Naldi L, Parazzini F, Peli L et al. Dietary factors and the risk of psoriasis. Results of an Italian case-control study. *Br J Dermatol* 1996; **134**:101–6.
- 20 Poikolainen K, Reunala T, Karvonen J. Smoking, alcohol and life events related to psoriasis among women. *Br J Dermatol* 1994; **130**:473–7.
- 21 Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. *Arch Dermatol* 1999; **135**:1490–3.
- 22 Smith KE, Fenske NA. Cutaneous manifestations of alcohol abuse. *J Am Acad Dermatol* 2000; **43**:1–16.
- 23 Zamboni S, Zanetti G, Grosso G et al. Dietary behaviour in psoriatic patients. *Acta Derm Venereol (Stockh)* 1989; **146** (Suppl.): 182–3.
- 24 Jones PJH, Papamandjaris AA. Lipids: cellular metabolism. In: *Present Knowledge in Nutrition* (Bowman BA, Russell RM, eds). Washington, DC: ILSI Press, 2001; 104–14.
- 25 Gil A. Polyunsaturated fatty acids and inflammatory diseases. *Biomed Pharmacother* 2002; **56**:388–96.
- 26 Grimble RF, Tappia PS. Modulation of pro-inflammatory cytokine biology by unsaturated fatty acids. *Z Ernahrungswiss* 1998; **37** (Suppl. 1): 57–65.
- 27 Corrocher R, Ferrari S, de Gironcoli M et al. Effect of fish oil supplementation on erythrocyte lipid pattern, malondialdehyde production and glutathione-peroxidase activity in psoriasis. *Clin Chim Acta* 1989; **179**:121–31.
- 28 Schena D, Chiericato GC, de Gironcoli M et al. Increased erythrocyte membrane arachidonate and platelet malondialdehyde (MDA) production in psoriasis: normalization after fish-oil. *Acta Derm Venereol (Stockh)* 1989; **146** (Suppl.): 42–4.

- 29 Grimminger F, Mayser P. Lipid mediators, free fatty acids and psoriasis. *Prostaglandins Leukot Essent Fatty Acids* 1995; **52**:1–15.
- 30 James MJ, Gibson RA, Cleland IG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000; **71**:S343–8.
- 31 Wilkinson DL. Do dietary supplements of fish oils improve psoriasis? *Cutis* 1990; **46**:334–6.
- 32 Collier PM, Ursell A, Zaremba K et al. Effect of regular consumption of oily fish compared with white fish on chronic plaque psoriasis. *Eur J Clin Nutr* 1993; **47**:251–4.
- 33 Lassus A, Dahlgren AL, Halpern MJ et al. Effects of dietary supplementation with polyunsaturated ethyl ester lipids (Angiosan) in patients with psoriasis and psoriatic arthritis. *J Int Med Res* 1990; **18**:68–73.
- 34 Kragballe K, Fogh K. A low-fat diet supplemented with dietary fish oil (Max-EPA) results in improvement of psoriasis and in formation of leukotriene B<sub>5</sub>. *Acta Derm Venereol (Stockh)* 1989; **69**:23–8.
- 35 Maurice PD, Allen BR, Barkley AS et al. The effects of dietary supplementation with fish oil in patients with psoriasis. *Br J Dermatol* 1987; **117**:599–606.
- 36 Kragballe K. Dietary supplementation with a combination of n-3 and n-6 fatty acids (super gamma-oil marine) improves psoriasis. *Acta Derm Venereol (Stockh)* 1989; **69**:265–8.
- 37 Kettler AH, Baughn RE, Orenge IF et al. The effect of dietary fish oil supplementation on psoriasis. Improvement in a patient with pustular psoriasis. *J Am Acad Dermatol* 1988; **18**:1267–73.
- 38 Bittiner SB, Tucker WF, Cartwright I, Bleehen SS. A double-blind, randomised, placebo-controlled trial of fish oil in psoriasis. *Lancet* 1988; **i**:378–80.
- 39 Bjorneboe A, Smith AK, Bjorneboe GE et al. Effect of dietary supplementation with n-3 fatty acids on clinical manifestations of psoriasis. *Br J Dermatol* 1988; **118**:77–83.
- 40 Gupta AK, Ellis CN, Goldfarb MT et al. The role of fish oil in psoriasis. A randomized, double-blind, placebo-controlled study to evaluate the effect of fish oil and topical corticosteroid therapy in psoriasis. *Int J Dermatol* 1990; **29**:591–5.
- 41 Soyland E, Funk J, Rajka G et al. Effect of dietary supplementation with very-long-chain n-3 fatty acids in patients with psoriasis. *N Engl J Med* 1993; **328**:1812–16.
- 42 Oliwiecki S, Burton JL. Evening primrose oil and marine oil in the treatment of psoriasis. *Clin Exp Dermatol* 1994; **19**:127–9.
- 43 Mayer K, Seeger W, Grimminger F. Clinical use of lipids to control inflammatory disease. *Curr Opin Clin Nutr Metab Care* 1998; **1**:179–84.
- 44 Grimminger F, Mayser P, Papavassilis C et al. A double-blind, randomized, placebo-controlled trial of n-3 fatty acid based lipid infusion in acute, extended guttate psoriasis. Rapid improvement of clinical manifestations and changes in neutrophil leukotriene profile. *Clin Invest* 1993; **71**:634–43.
- 45 Mayser P, Mrowietz U, Arenberger P et al. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, multicenter trial. *J Am Acad Dermatol* 1998; **38**:539–47.
- 46 Chalmers RJG, O'Sullivan T, Owen CM, Griffiths CEM. Interventions for guttate psoriasis (Cochrane Review). In: *The Cochrane Library, Issue 3*. Chichester: Wiley, 2004.
- 47 Azzini M, Girelli D, Olivieri O et al. Fatty acids and antioxidant micronutrients in psoriatic arthritis. *J Rheumatol* 1995; **22**:103–8.
- 48 Baum C, Moxon D, Scott M. Gastrointestinal disease. In: *Present Knowledge in Nutrition* (Bowman BA, Russell RM, eds). Washington, DC: ILSI Press, 2001; 472–82.
- 49 Connon JJ. Celiac disease. In: *Modern Nutrition in Health and Disease* (Shils ME, Olson JA, Shike M, Ross AC, eds), 9th edn. Baltimore: Williams & Wilkins, 1999; 1163–8.
- 50 Michaelsson G, Gerdén B, Ottosson M et al. Patients with psoriasis often have increased serum levels of IgA antibodies to gliadin. *Br J Dermatol* 1993; **129**:667–73.
- 51 Nelson DA. Gluten-sensitive enteropathy (celiac disease): more common than you think. *Am Fam Physician* 2002; **66**:2259–66.
- 52 Leffler D, Saha S, Farrell RJ. Celiac disease. *Am J Manag Care* 2003; **9**:825–31.
- 53 Duggan JM. Coeliac disease: the great imitator. *Med J Aust* 2004; **180**:524–6.
- 54 Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. *Am J Clin Dermatol* 2003; **4**:13–20.
- 55 Reunala T, Collin P. Diseases associated with dermatitis herpetiformis. *Br J Dermatol* 1997; **136**:315–18.
- 56 Chalmers RJG, Kirby B. Gluten and psoriasis. *Br J Dermatol* 2000; **142**:5–7.
- 57 Addolorato G, Parente A, de Lorenzi G et al. Rapid regression of psoriasis in a coeliac patient after gluten-free diet. A case report and review of the literature. *Digestion* 2003; **68**:9–12.
- 58 Michaelsson G, Gerdén B, Hagforsen E et al. Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. *Br J Dermatol* 2000; **142**:44–51.
- 59 Michaelsson G, Kraaz W, Gerdén B et al. Increased lymphocytic infiltration in duodenal mucosa from patients with psoriasis and serum IgA antibodies to gliadin. *Br J Dermatol* 1995; **133**:896–904.
- 60 Michaelsson G, Ahs S, Hammarstrom I et al. Gluten-free diet in psoriasis patients with antibodies to gliadin results in decreased expression of tissue transglutaminase and fewer Ki67+ cells in the dermis. *Acta Derm Venereol (Stockh)* 2003; **83**:425–9.
- 61 Serwin AB, Wasowicz W, Gromadzinska J, Chodyncka B. Selenium status in psoriasis and its relations to the duration and severity of the disease. *Nutrition* 2003; **19**:301–4.
- 62 Frei B. On the role of vitamin C and other antioxidants in atherogenesis and vascular dysfunction. *Proc Soc Exp Biol Med* 1999; **222**:196–204.
- 63 Kaul N, Devaraj S, Jialal I. Alpha-tocopherol and atherosclerosis. *Exp Biol Med (Maywood)* 2001; **226**:5–12.
- 64 Bendich A. From 1989 to 2001: what have we learned about the 'biological actions of beta-carotene'? *J Nutr* 2004; **134**:S225–30.
- 65 Burk RF, Levander OA. Selenium. In: *Modern Nutrition in Health and Disease* (Shils ME, Olson JA, Shike M, Ross AC, eds), 9th edn. Baltimore: Williams & Wilkins, 1999; 265–76.
- 66 Harvima RJ, Jagerroos H, Kajander EO et al. Screening of effects of selenomethionine-enriched yeast supplementation on various immunological and chemical parameters of skin and blood in psoriatic patients. *Acta Derm Venereol (Stockh)* 1993; **73**:88–91.
- 67 Fairris GM, Lloyd B, Hinks L et al. The effect of supplementation with selenium and vitamin E in psoriasis. *Ann Clin Biochem* 1989; **26**:83–8.
- 68 Lin R, White JH. The pleiotropic actions of vitamin D. *Bioessays* 2004; **26**:21–8.
- 69 Holick MF. Vitamin D: a millennium perspective. *J Cell Biochem* 2003; **88**:296–307.
- 70 Adorini L. Immunomodulatory effects of vitamin D receptor ligands in autoimmune diseases. *Int Immunopharmacol* 2002; **2**:1017–28.
- 71 Pinette KV, Yee YK, Amegadzie BY, Nagpal S. Vitamin D receptor as a drug discovery target. *Mini Rev Med Chem* 2003; **3**:193–204.
- 72 Fogh K, Kragballe K. New vitamin D analogs in psoriasis. *Curr Drug Targets Inflamm Allergy* 2004; **3**:199–204.
- 73 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; **89**:552–72.

- 74 Allain TJ, Dhesi J. Hypovitaminosis D in older adults. *Gerontology* 2003; **49**:273–8.
- 75 Latham NK, Anderson CS, Reid IR. Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review. *J Am Geriatr Soc* 2003; **51**:1219–26.
- 76 van der Wielen RP, Lowik MR, van den Berg H et al. Serum vitamin D concentrations among elderly people in Europe. *Lancet* 1995; **346**:207–10.
- 77 Wolters M, Ströhle A, Hahn A. Cobalamin: a critical vitamin in the elderly. *Prev Med* 2004; **39**:1256–66.
- 78 Sakane T, Takada S, Kotani H, Tsunematsu T. Effects of methyl-B<sub>12</sub> on the *in vitro* immune functions of human T lymphocytes. *J Clin Immunol* 1982; **2**:101–9.
- 79 Yamashiki M, Nishimura A, Koska Y. Effects of methylcobalamin (vitamin B<sub>12</sub>) on *in vitro* cytokine production of peripheral blood mononuclear cells. *J Clin Lab Immunol* 1992; **37**:173–82.
- 80 Baker H, Comaish JS. Is vitamin B<sub>12</sub> of value in psoriasis? *Br Med J* 1962; **ii**:1729–30.
- 81 Stücker M, Memmel U, Hoffmann M et al. Vitamin B<sub>12</sub> cream containing avocado oil in the therapy of plaque psoriasis. *Dermatology* 2001; **203**:141–7.
- 82 Prystowsky JH, Orologa A, Taylor S. Update on nutrition and psoriasis. *Int J Dermatol* 1993; **32**:582–6.
- 83 Peckham PE, Weinstein GD, McCullough JL. The treatment of severe psoriasis: a national survey. *Arch Dermatol* 1987; **123**:1303–7.
- 84 Lebwohl M. The role of salicylic acid in the treatment of psoriasis. *Int J Dermatol* 1999; **38**:16–24.
- 85 Refsum H, Helland S, Ueland PM. Fasting plasma homocysteine as a sensitive parameter of antifolate effect: a study of psoriasis patients receiving low-dose methotrexate treatment. *Clin Pharmacol Ther* 1989; **46**:510–20.
- 86 Haagsma CJ, Blom HJ, van Riel PL et al. Influence of sulphasalazine, methotrexate, and the combination of both on plasma homocysteine concentrations in patients with rheumatoid arthritis. *Ann Rheum Dis* 1999; **58**:79–84.
- 87 van Ede AE, Laan RF, Blom HJ et al. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2002; **41**:658–65.
- 88 Nygard O, Vollset SE, Refsum H et al. Total homocysteine and cardiovascular disease. *J Intern Med* 1999; **246**:425–54.
- 89 Stanger O, Herrmann W, Pietrzik K et al. Consensus paper on the rational clinical use of homocysteine, folic acid and B-vitamins in cardiovascular and thrombotic diseases: guidelines and recommendations. *Clin Chem Lab Med* 2003; **41**:1392–403.
- 90 Wolters M, Ströhle A, Hahn A. [Age-associated changes in the metabolism of vitamin B(12) and folic acid: prevalence, aetiopathogenesis and pathophysiological consequences]. *Z Gerontol Geriatr* 2004; **37**:109–35 (in German).
- 91 Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004; **43**:267–71.
- 92 Brown RO, Dickerson RN. Drug–nutrient interactions. *Am J Manag Care* 1999; **5**:345–55.
- 93 Dahan A, Altman H. Food–drug interaction: grapefruit juice augments drug bioavailability—mechanism, extent and relevance. *Eur J Clin Nutr* 2004; **58**:1–9.
- 94 Ducharme MP, Provenzano R, Dehoorne-Smith M, Edwards DJ. Trough concentrations of cyclosporine in blood following administration with grapefruit juice. *Br J Clin Pharmacol* 1993; **36**:457–9.
- 95 Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991; **54**:438–63.
- 96 Hellerstein MK. Carbohydrate-induced hypertriglyceridemia: modifying factors and implications for cardiovascular risk. *Curr Opin Lipidol* 2002; **13**:33–40.
- 97 Parks EJ, Parks EJ. Changes in fat synthesis influenced by dietary macronutrient content. *Proc Nutr Soc* 2002; **61**:281–6.