Acta Derm Venereol (Stockh) 1993; 73: 88–91

Screening of Effects of Selenomethionine-enriched Yeast Supplementation on Various Immunological and Chemical Parameters of Skin and Blood in Psoriatic Patients

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Selenium (Se) is known to affect the immune system, and decreased Se-levels in blood of patients with moderate or severe psoriasis have been reported. In this study, the effect of Se-supplementation (400 μg/day for 6 weeks as Se-yeast, containing about 70% selenomethionine, SeMet) on skin and blood Se-content, on skin glutathione peroxidase activity and on various chemical and immunological parameters of blood and skin was investigated in 7 psoriatic patients. Before the SeMet-supplementation, serum and blood Se-levels were at the normal range, but they increased 42–45% during the Se-dosage, while zinc levels remained unchanged. Se-dependent glutathione peroxidase activity in both normal and lesional psoriatic skin remained unchanged during the trial, although a small net Se-uptake was detected. At the same time, a slight but statistically significant increase in the number of CD4+ T-cells was observed in the reticular dermis of the psoriatic lesions whereas the numbers of CD8+, CD11c+, and CD1+ cells were not significantly altered. Also, a relatively high number of patients (3 out of 7) showed a strongly reduced number of gamma/delta T-lymphocytes or increased CD8+ T-cells (2 patients) in peripheral blood. However, SeMet-supplementation was not related to these abnormalities or to the number of other peripheral blood immunocytes or to serum immunoglobulin levels. In addition, no marked effect on the clinical condition of the patients was observed. This pilot study suggests that SeMet may be able to modulate the immunological mechanism of psoriatic lesions by increasing the number of CD4+ T-cells. ***Key words: Psoriasis; T-lymphocytes.***

(Accepted November 25, 1992.)

Acta Derm Venereol (Stockh) 1993; 73: 88–91.

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Selenium (Se) is an essential nutrient for mammalian cells. Knowledge of the chemical form of Se present in food as well as of factors that can modify its bioavailability is still limited. Several chemical forms of Se (e.g. sodium selenate, sodium selenite, selenocystine, and selenomethionine, SeMet) have been used in supplement therapy (1). Biological methylation reactions are important regulators of metabolism, e.g. transcriptional activity of genes. Thus, methylation is of the utmost importance in mammalian cell differentiation. The methyl donor is S-adenosylmethionine (AdoMet), in which SeMet – as an analog of methionine – can replace this amino acid and form a Se-analog of AdoMet (2). Tracerstudies have indicated that SeMet is metabolized via the methionine metabolic pathways (3). Details of these metabolic processes are still poorly known. SeMet is effectively taken into several cultured cell lines, metabolized, and incorporated into proteins. So, it can affect various cellular functions, e.g. via changes in methylation (1).

Psoriasis is a common skin disease with unknown etiology. Decreased Se-levels in whole blood and plasma have been reported in patients with moderate and severe psoriasis (4–6). Se is essential for the activity of glutathione peroxidase (GSH-Px). Low GSH-Px-activities have been reported in several skin diseases such as atopic dermatitis, dermatitis herpetiformis, psoriasis (7) and severe acne (7, 8). Fairris et al. (6) have detected normal red cell GSH-Px-activities without changes of Se-content in red cells or skin during a 12-week SeMet-supplementation in psoriatic persons; however, platelet GSH-Px and Se as well as whole blood and serum Se-levels were significantly increased without any effect on the clinical status of the patients. Se enhances the phagocytotoxic activity of granulocytes (9) and cytotoxic T-cells (E. O. Kajander & A. Laatikainen, unpublished results), thus being a potent modulator of the immune system.

The purpose of this pilot study was to find out whether SeMet-yeast supplementation could influence the occurrence and distribution of immunocytes in lesional skin and peripheral blood of psoriatic patients. The sufficiency of the SeMet-dosage was confirmed by monitoring the blood and skin Se-levels as well as skin GSH-Px activity during the treatment.

MATERIALS AND METHODS

Chemicals

Reagents of analytical grade were from Sigma (St. Louis, MO) or Merck (Darmstadt, Germany). Se-yeast tablets (Selena®, obtained as a kind gift from Alko, Helsinki, Finland) contain about 70% of Se as SeMet (10).

Se-supplementation of psoriatic patients

Previously, the daily dosage of 600 μg Se-yeast for 3 months has been tested safe without any adverse effects (6). Seven psoriatic volunteers (age 21–52 years, 4 males and 3 females) were included in this study. The dermatological status of the patients included occasional to widely spread plaques. Neither PUVA baths nor etrerinate had been used during the last 2 years. Six patients had not applied corticosteroids or dithranol during the last month and the 7th patient (hydrocortisone cream) during the last 2 weeks before the study. The patients were administered SeMet-yeast tablets (8 tablets containing totally 400 μg Se) daily for 6 weeks. Upon entry to this study (end of April), the patients were examined and biopsied and blood samples were drawn, which was repeated at the end of the treatment period. The final

Table I. *Effect of SeMet-supplementation on serum, blood and skin Se-levels and on skin glutathione peroxidase (GSH-Px) activity*

	Before	After
Skin GSH-Px (mU/mg-protein)		
Lesion	33.1±8.3	26.0±14.0
Healthy-looking	63.7±46.8	48.5±28.3
(mU/mg-tissue)		
Lesion	0.95±0.40	0.79±0.46
Healthy-looking	0.95±0.87	0.71±0.38
Soluble protein (μg/mg-tissue)		
Lesion	28.7±8.7	28.8±6.6
Healthy-looking	16.5±8.1	15.7±6.2
Selenium in lesional skin		
pg/mg-protein	2670±1100*	4170±2820**
pg/mg-tissue	64±30*	90±43**
S-Se (μg/l)	151±35	214±31
(range)	(119–225)	(180–278)
B-Se (μg/l)	212±69	308±62
(range)	(175–366)	(248–440)
S-Zn (mg/l)	1.14±0.22	1.10±0.16
B-Zn (mg/l)	8.61±0.82	8.61±0.82

Values are mean ± S.D., $n = 7$, except $^{*}n = 4$, and $^{**}n = 3$

follow-up was performed 3 months after finishing the trial by clinical examination. During the study, no medications or other treatments were given. The study was approved by the Ethical Committee of the Kuopio University Hospital.

Skin samples

Skin biopsies from untreated sites without exposure to sunlight were taken before and at the end of the 6-week trial from the same psoriatic plaque and adjacent healthy-looking skin area; 4-mm punch biopsies were taken under local anesthesia (1% lidocaine with epinephrine) from lesional and non-lesional skin of 7 psoriatic patients. The non-lesional biopsy was taken at least 2 cm away from the plaque and served as a control.

Skin sample analysis

Biopsy specimens were divided into two halves. One half was ultrasonicated on icebath in 20 volumes of 25 mM imidazole-HCl, pH 7.4, for the assays of elementary Se and GSH-Px activity using 5 mM coumene hydroperoxide (11). The other half was used for histological analysis after embedding it in OCT (Miles Laboratories, Naperville, IL), followed by freezing and sectioning at 4 μm thickness on acid-washed and poly-L-lysine-coated slides. Serial sections were stained with monoclonal antibodies Leu-2A (CD8), Leu-3A+3B (CD4), Leu-M5 (CD11c), Leu-4 (CD3) (Leu-antibodies were from Becton-Dickinson, Mountain View, CA) and OKT-6 (CD1) (from Ortho Diagnostics, Raritan, NJ). Antibody binding was visualized with the avidin-biotin-peroxidase complex method (Vectastain mouse IgG ABC elite kit, from Vector Laboratories, Burlingame, CA) together with 0.05% 3,3′-diaminobenzidine tetrahydrochloride (Polysciences Inc., Warnington, PA) containing 0.04% nickel chloride and 0.03% hydrogen peroxide. The number of positive cells in the epidermis, papillary dermis and reticular dermis was estimated separately and scored. The thickness of the malpighian layer was measured across the thickest area of the epidermis.

Peripheral blood lymphocyte analysis

Lymphocyte phenotypes were analyzed from heparinized and separated peripheral blood mononuclear cells. The separation was performed by standard gradient centrifugation using Lymphoprep (Nycomed, Oslo, Norway). The cells were stained with monoclonal antibodies Leu-4 (CD3), Leu-2A (CD8), Leu-3 (CD4), HLA-DR, Leu-15 (CD11b), Leu-8, anti-T cell receptor (TCR) alpha/beta monoclonal antibody WT31 and anti-TCR gamma/delta monoclonal antibody according to the protocols provided by the manufacturers. All antibodies were purchased from Becton-Dickinson except gamma/delta TCR antibody that was from T Cell Sciences (Cambridge, MA). Four sets of doublestains were performed, and the samples were run in a FACScan flow cytometer (Becton-Dickinson). The results were analyzed using FACScan research software.

Assay methods

Serum immunoglobulins (Ig) G, A, M and E, and serum aspartate aminotransferase activity were analyzed by the routine methods at the Department of Clinical Chemistry of the Kuopio University Hospital (Kuopio, Finland). Protein assay was performed according to the method of Spector (12) using Coomassie brilliant blue G-250 (Serva, Heidelberg, Germany) with bovine serum albumin as the standard.

Statistical analysis

The statistical significance in immunohistochemical analysis was tested with the *t*-test (13).

RESULTS

During the 6-week SeMet-supplementation, 2 patients out of 7 experienced a slight and one patient a severe worsening of their disease, seen as appearance of new psoriatic plaques, but 2 patients reported some improvement in skin symptoms. However, no side effects were reported by patients. Also, serum aspartate aminotransferase levels remained at the normal range. After 3 months' follow-up, the overall clinical condition remained unchanged.

As expected, the SeMet-supplementation increased both blood and serum Se-levels by 42–45% while Zn-levels, measured as controls, showed no changes. In the psoriatic lesions, a slight elevation in skin Se-content was noticed, but no increase in Se-dependent GSH-Px-activity took place (Table I).

In the analysis of peripheral blood mononuclear cells, total T- and B-lymphocyte numbers were normal in all patients before and after the trial. Some abnormalities were, however, noticed in T-lymphocyte subsets. Two patients had a decreased ratio of CD4/CD8 T-lymphocytes due to elevated percentage of CD8+ T-lymphocytes (43% and 48%, compared with our reference values of 28±7%).

Interestingly, the same 3 patients who experienced a worsening of their disease also had constantly a low or a very low number of gamma/delta T-cells (≤1%) when compared to our normal reference material (6±3%). Since no generally accepted normal range exists for gamma/delta T-cells, no definite conclusions can be drawn from these findings at the moment. Our reference range for normal peripheral blood CD11b+ cells is 30±8%. Two patients with spreading skin lesions showed changes also in the number of CD11b+ cells during SeMet-supplementation. In one patient, these cells increased from 13% to 26%, while in the other the CD11b+ cells decreased from 30% to 8%. The effect of SeMet on the humoral immunity was studied by monitoring the serum im-

Table II. *Distribution and occurrence of Leu-2A, Leu-3A+3B, Leu-5M, Leu-4 and OKT-6-positive cells in the psoriatic lesions before and after the SeMet-supplementation*

The numbers of positively stained cells were roughly scored by pathologist: low (score 1), moderate (score 2), or high (score 3) (values in the table as mean score ± S.E.M., $n=7$). When alterations were observed (indicated as a–d in the table), positive cells per dermal capillaries were individually calculated and analyzed statistically; in the case of a, the difference was statistically significant (12.3±6.3 vs. 18.7±5.5, mean ± S.D., $p<0.05$; both values as positively stained cells per dermal capillary vessel), but in the case of b,c,d the difference was not significant (p-values <0.10, <0.50, <0.10, respectively).

Antibody		Epidermis	Papillary dermis	Reticular dermis
Leu-2A	Before	1.1±0.1	1.0±0.2	1.0±0.2
(CD8)	After	1.0±0.2	1.1±0.3	1.0±0.0
Leu-3A+3B	Before	1.1±0.1	1.9±0.1	1.6±0.2[a]
(CD4)	After	1.0±0.2	2.0±0.2	2.1±0.1[a]
Leu-5M	Before	1.0±0.1	1.4±0.2[b]	1.1±0.1[c]
(CD11c)	After	1.0±0.0	1.9±0.3[b]	1.7±0.2[c]
Leu-4	Before	1.0±0.2	1.4±0.2	1.6±0.1
(CD3)	After	1.1±0.1	1.4±0.2	1.7±0.2
OKT-6	Before	2.0±0.0	1.6±0.2	1.1±0.1[d]
(CD1)	After	1.7±0.2	1.3±0.2	1.6±0.2[d]

munoglobulin levels during the SeMet-supplementation, but no alterations were detected in serum IgG, A, M or E levels, all of which were at the normal range.

The mean thickness of the malpighian layer (in mm; values as mean ± S.D.) was slightly, but significantly ($p<0.05$), increased both in non-lesional skin (from 0.046±0.001 to 0.053±0.001) and lesional skin (from 0.355±0.057 to 0.416±0.072) after the SeMet-treatment. In lesional skin, thickening of the malpighian layer was associated with an increase in CD4+ cells in reticular dermis. The distribution of the immunocyte types tested is presented in Table II. No essential alterations in the distribution or occurrence of any immunocyte type were observed except the statistically significant increase in Leu-3A+3B (CD4)-positive cells (in 5 out of 7 patients, the remaining 2 without changes) in the reticular dermis of the psoriatic lesions (Table II).

DISCUSSION

Previous studies on the role of Se in biochemical methylation reactions (2) and in immune functions (9) could well suggest a role for Se in psoriasis, especially since reduced Se-levels in blood have been measured in psoriatic patients (4, 6). In this study, no marked change in the clinical condition of the psoriatic patients was observed following SeMet-supplementation, which parallels a previous report (6). One explanation could be that every patient had a normal Se-concentration in blood and serum alredy at the start, and thus, an increase in Se-levels had no effect.

An increase in platelet GSH-Px-activity during Se-supplementation has been reported both in psoriatic patients and in healthy Finnish men, whose Se-status is low (6, 14). In this study, we could not detect any increase in skin GSH-Px-activity after the 6-week SeMet-treatment, although a slight net Se-uptake into lesional skin was noticed. Possibly the lesional psoriatic skin and its GSH-Px-activity was saturated by Se due to sufficient supply already from normal diet. Fairris et al. (6) did not detect Se-incorporation into non-lesional psoriatic skin, although SeMet can replace methionine in proteins (1, 3). In the present study, Se-uptake was measured in lesional skin only. However, an earlier radioisotope study has shown that psoriatic patients are capable of assimilating SeMet from the gut and of normally incorporating SeMet into the body stores (15). Table I shows that quite different Se-levels were obtained, possibly depending on the reference parameter, because psoriatic and normal skin are very different. The total Se-concentrations in both skin types were about the same. Both low and normal Zn-levels in blood of psoriatic patients have been reported (16–18). The psoriatic patients in this study had normal Zn-concentrations in blood throughout the trial, in accordance with previous results (17, 18).

The biological role of Se seems to be related to the immune system (9, 19). In this study, a slight but statistically significant increase in the number of CD4+ T-cells was observed in the reticular dermis of the proriatic lesions after the SeMet-treatment. Also CD11c+ and CD1+ cells were increased in number, although the increase was not statistically significant. These alterations may be associated with the activation of psoriasis (20), which is supported by the simultaneous thickening of the malpighian layer.

Among the early events of developing psoriatic lesions is the non-specific accumulation of CD4+ T-lymphocytes and macrophages (20, 21). Therefore, a selective accumulation of CD8+ T-cells takes place into the young (3 days) psoriatic epidermis (22). However, in mature lesions, the CD4/CD8-ratio is reported to be increased in dermis but decreased in epidermis in comparison to peripheral blood (23). In an earlier study (24), it has been concluded that no gross imbalance between T-cell subpopulations exist in psoriatic lesions. There is a great variation in the distribution of CD4+, CD8+, CD1+ and HLA-DR+ cells in different types of psoriatic lesions (25), and accordingly, also the CD4/CD8-ratio depends on the type and phase of psoriasis (21).

In the present study, 2 patients out of 7 had a decreased CD4/CD8-ratio, whereas previously both a highly significant increase (26) as well as no change (27) in this ratio have been reported. Both the presence and lack of abnormalities in peripheral blood lymphocytes from psoriatic patients have been reported (26–30). Interestingly, low numbers of gamma/delta T-cells in peripheral blood were observed in the 3 psoriatic patients who also exhibited an active flare of psoriatic plaques. However, the relation of the observed alterations to Se is unlikely since the SeMet-supplementation had no effect on these changes. The physiological functions of gamma/delta T-cells are not know, but there are reports on increased numbers of these cells, e.g. in infectious diseases, autoimmune and immunodeficiency diseases (31). Predominantly, gamma/delta T-cells do not express CD4 or CD8 differentiation antigens on their cell surface (32). Variable results have also been reported on serum immunoglobulin levels in psoriatic patients. In pso-

riatic lesions, IgA, IgG, IgM, and complement C1q and C3 deposits have been demonstrated in epidermis (33). However, all immunoglobulin types (IgA, G, M, E) measured in this study settled at the normal reference range of the Kuopio University Hospital without any observable changes due to SeMet-treatment, which is in accordance with an earlier report (9).

This pilot study shows that the addition of SeMet in the diet of psoriatic patients with normal Se-levels results in increased blood Se-concentrations and incorporation of Se into the lesional skin. The additional supply of SeMet, however, was found to be ineffective in modulating the humoral and cellular immune system of blood. The slight but significant increase in CD4+ T-lymphocytes in the reticular dermis of the psoriatic lesions may suggest that Se is able to affect the immunologic processes of psoriatic lesions. To verify this clearly, psoriatic patients with low Se-status should be investigated. Regrettably, this is not possible in Finland, since generally used acricultural fertilizers are supplemented with Se and the Se-levels of the whole Finnish population are nowadays at normal range.

ACKNOWLEDGEMENTS

The authors wish to thank the Medical Council of the Academy of Finland, the Emil Aaltonen Foundation and the Juho Vainio Foundation for financial support. Ms. Ann-Mari Lappi, B. Med., Ms. Eija Kettunen, and Ms. Anne Koivisto are thanked for technical assistance.

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