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Randomized control trials

Supplementation of a dairy drink enriched with milk phospholipids in patients with atopic dermatitis – A double-blind, placebo-controlled, randomized, cross-over study

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SUMMARY

Background & aims: Reduced epidermal ceramide content may lead to an impaired skin barrier in atopic dermatitis. Plasma concentration of the ceramide precursor sphingomyelin increases after milk-fat consumption due to affected lipoprotein metabolism, although sphingomyelin, a main component of milk phospholipids, might also directly influence plasma sphingomyelin levels. The aim was to determine whether supplementation of a dairy drink with milk phospholipids improves skin parameters and influences plasma lipid profile.

Methods: In a double-blind cross-over study, 39 patients were randomized into 2 groups and daily received phospholipid milk (3 g phospholipids ≙ 0.75 g sphingomyelin) or normal whole milk as placebo control for 6 weeks. SCORAD indices, serum immune and plasma lipid parameters were determined.

Results: SCORAD indices did not differ between groups following control and phospholipid milk supplementation (control milk: 10.9 ± 5.9 vs. phospholipid milk: 11.7 ± 6.9, $P = 0.416$), but were significantly decreased compared to baseline (baseline: 15.6 ± 8.8, $P < 0.05$). Plasma sphingomyelin proportions were also similar after the treatments (control milk: 27.5 ± 2.3 vs. phospholipid milk: 27.4 ± 2.6% of total phospholipids, $P = 0.894$), but were significantly increased compared to baseline (20.7 ± 2.4% of total phospholipids, $P < 0.05$).

Conclusions: Supplementation of a dairy drink with milk phospholipids has no beneficial effect on skin parameters compared to consumption of whole milk in patients with atopic dermatitis. To elucidate an impact of the plasma sphingomyelin proportion on skin conditions, further studies are necessary.

Clinical trial ID: Registered under ClinicalTrials.gov. Identifier no. NCT01326520.

1. Introduction

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease with classical morphology and location and shows an age-dependent clinical manifestation.[1] Amongst other factors, a disturbance in the epidermal skin barrier and various immunological abnormalities play a central role in AD pathogenesis.[1,2] Serological and immune parameters such as soluble E-selectin (sE-selectin), macrophage-derived chemokine (MDC), IL-16 as well as total IgE have been reported to correlate with AD disease activity and scoring of atopic dermatitis (SCORAD) index, respectively. These correlations suggest that immunological parameters may be

Abbreviations: AD, atopic dermatitis; DLQ, dermatology life quality; fx5, food-allergen specific IgE against egg white, cow's milk, cod, wheat, peanut, and soya bean; hs-CRP, high-sensitivity C-reactive protein; MDC, macrophage-derived chemokine; PC, phosphatidyl choline; PE, phosphatidyl ethanolamine; PI, phosphatidyl inositol; PL, phospholipid; SCORAD, scoring of atopic dermatitis; sE-selectin, soluble E-selectin; SM, sphingomyelin; sx1, inhalant-allergen specific IgE against timothy, cultivated rye, common silver birch, mugwort, *Dermatophagoides pteronyssinus*, cat dander, dog dander and *Cladosporium herbarum*.

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involved in the pathogenesis of AD and their expression may strongly be associated with the clinical picture of AD.[3–5]

The epidermal barrier function is described as being predominantly localized in the *stratum corneum*, where ceramides, cholesterol and free fatty acids are the prevalent lipid classes.[6] On account of their amphiphilic structure, ceramides have been postulated as being essential for the formation and maintenance of the epidermal barrier function.[7] A reduced amount of ceramide was found in the epidermal *stratum corneum* in AD patients and can be explained by a diminished or deficient activity of the acid sphingomyelinase.[8,9] Sphingomyelin (SM) is one of the major metabolic precursors for formation of ceramides and its structure comprises antimicrobially active sphingosine as well as long-chain unsaturated fatty acids; both sphingosine and the fatty acids are of particular importance for an intact skin barrier.[10]

Nilsson and Duan[11] postulated that hypersphingomyelinemia occurs postprandial following milk-fat consumption and is strongly related to the production and clearance of apoB-containing lipoproteins. Bovine milk fat contains about 95% triglycerides and approximately 1% phospholipids (PLs), which are predominantly composed of phosphatidyl ethanolamine (PE, ≈ 35% of total PL), phosphatidyl choline (PC, ≈30% of total PL) and SM (≈20% of total PL).[12,13] Although the absorption rate of sphingolipids in humans is as yet unknown dietary supplementation of SM might also directly influence the plasma SM concentration. Furthermore, *in vivo* models of different animal species have shown that dietary supplemented PLs may affect cholesterol metabolism.[14–16] In particular SM deserves special attention because of its possible cholesterol-lowering effect.[17] Nevertheless, a high plasma concentration of SM was positively and independently correlated with an elevated risk of atherosclerosis,[18] but data describing the influence of dietary supplementation of milk PLs on plasma lipids *in vivo* are rare.[19,20]

To investigate the effect of milk PLs on AD skin parameters (primary outcome), immunological parameters, and the plasma lipid status (secondary outcomes), patients with mild to moderate AD enrolled in the study were given either milk enriched with milk PLs (3 g PL/d) or whole fat milk as placebo control milk in a double-blind, randomized, cross-over intervention study.

2. Materials and methods

2.1. Participants

The Ethics Commission of the University Hospital of the Friedrich Schiller University Jena declared no ethical concerns regarding the study. The study is registered at clinicaltrials.gov (NCT01326520). Inclusion criteria for the study were presence of mild to moderate AD in patients aged between 18 and 60 years. Exclusion criteria included an intolerance against milk proteins, an intake of systemic medication with corticosteroids or antihistamines, known or suggested atherosclerosis, hyperlipidemia, diabetes mellitus, angina pectoris, obesity, and pregnancy or lactation. The power analysis was based on the means and variances of SCORAD indices of a parallel-design study reported by Kimata.[21] Using these data and $n = 40$ subjects, the power of our study was estimated to be 89.5% (alpha = 0.05, beta = 0.105). Participants were recruited via placing advertisements in local newspapers, through flyers handed out in dermatology practices in Jena, and by direct provision of information to patients in the Department of Dermatology at the Jena University Hospital. Eligibility for the study was assessed by a telephone interview involving 58 interested persons. Of these, a total of 45 patients were included in the study. All participants were informed about the study conditions and written consent was given by participating subjects. A total of 6 patients withdrew during the course of the study (3 due to change of lifestyle, 1 because of an illness independent of the study, and 2 gave no reasons). Thus, 39 patients (14 men and 25 women; age: 25.4 ± 4.5 y) completed the study.

2.2. Study design

The study followed a double-blind, randomized (computer based, block, size: 3x12+1x10, 1:1), placebo-controlled 2 × 2 cross-over design and was conducted between March and October 2011 (Fig. 1). Patients were randomly assigned to daily consume either 250 mL PL milk ($n = 19$) or 250 mL control milk ($n = 20$) for 6 weeks. Patients who received PL milk as the first diet were given control milk as the second diet and *vice versa*. The diets were separated by a 4-week wash-out period. Before receiving the diets, a wash-in period of 2 weeks was included which involved patients consuming 250 mL normal whole milk daily.

Confirmation of AD diagnosis, clinical inquiries, clinical examinations, skin prick tests, blood withdrawals, and assessment of SCORAD indices took place at the Department of Dermatology, University Hospital, Friedrich Schiller University, Jena, Germany. Randomization of patients and provision of milk and questionnaires were realized by the Department of Nutritional Physiology, Friedrich Schiller University, Jena, Germany. Patients as well as the medical scientists involved in the study in the Department of Dermatology, University Hospital, Friedrich Schiller University, Jena, Germany were blinded.

2.3. Test products

The PL concentrate (Lipamin M20, charge: 110215/1, Uelzena eG, Uelzen, Germany) was prepared from butter serum and added to milk that had a fat content of 1.5% (Table 1). The total PL content of the concentrate was 31.2% (PC, 8.53%; SM, 7.85%; PE, 7.01%; phosphatidyl serine, 2.85%; phosphatidyl inositol (PI), 2.46%; other, 2.51%). The control milk which was also applied during the wash-in periods comprised commonly-available whole fat milk.

2.4. SCORAD index

The SCORAD index of all patients was recorded by the study nurse during each visit for the duration of the whole study and included a documentation of extent and intensity of skin lesions as well as of subjective symptoms. According to Oranje et al.,[22] a SCORAD index up to 25 points is assessed as mild dermatitis, from

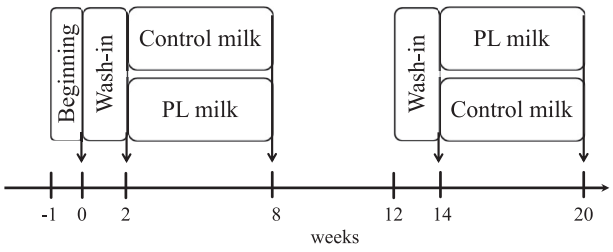

Fig. 1. Study design. Patients daily consumed 250 mL of normal whole milk during the wash-in periods and 250 mL of control milk (=normal whole milk) or PL milk during the test periods. Performances at **week 0** = **baseline**: clinical inquiry/examination, skin prick test, SCORAD, collection of blood samples, DLQ questionnaire, patient diary, 3-day dietary record; at **week 2 and 14**: SCORAD, collection of blood samples, DLQ questionnaire, patient diary, 3-day dietary record; at **week 8**: SCORAD, collection of blood samples, DLQ questionnaire, patient diary, 3-day dietary record, questionnaire about compatibility of milk consumption; at **week 20**: clinical inquiry/examination, skin prick test, SCORAD, collection of blood samples, DLQ questionnaire, patient diary, 3-day dietary record, questionnaire about compatibility of milk consumption. DLQ, dermatology life quality; PL, phospholipid; SCORAD, scoring of atopic dermatitis.