



EXTENDED REPORT

Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial

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Received 10 May 2011

Accepted 29 November 2011

ABSTRACT

Objectives Previous laboratory studies have identified two dairy fractions, glycomacropeptide (GMP) and G600 milk fat extract (G600), with anti-inflammatory effects in models of acute gout. The aim of this proof-of-concept clinical trial was to test the hypothesis that daily intake of skim milk powder (SMP) enriched with GMP and G600 can prevent gout flares.

Methods This was a 3-month randomised double-blind controlled trial of milk products for prevention of gout flares. One hundred and twenty patients with recurrent gout flares were randomised to one of three arms: lactose powder control, SMP control and SMP enriched with GMP and G600 (SMP/GMP/G600). The primary end point was change in the frequency of gout flares using a daily flare diary measured monthly for 3 months.

Results The frequency of gout flares reduced in all three groups over the 3-month study period compared with baseline. Over the 3-month study period there was a significantly greater reduction in gout flares in the SMP/GMP/G600 group (analysis of covariance $p_{\text{group}}=0.031$, Tukey post hoc test compared with lactose control, $p=0.044$). Following treatment with SMP/GMP/G600 over the 3-month period, greater improvements were also observed in pain and fractional excretion of uric acid, with trends to greater improvement in tender joint count. Similar adverse event rates and discontinuation rates were observed between the three groups.

Conclusions This is the first reported controlled trial of dietary intervention in patients with gout, and suggests that SMP enriched with GMP and G600 may reduce the frequency of gout flares.

Dietary modification is frequently recommended as a strategy for prevention and treatment of gout.¹ Longitudinal observational studies have shown a clear inverse relationship between low fat dairy intake and risk of developing gout.^{2,3} Several stages in gout pathogenesis may be influenced by dairy intake.⁴ Cross-sectional observational studies have shown that intake of low fat dairy is associated with lower serum urate concentrations.^{5,6} Short-term intervention studies have shown that intake of large amounts of milk proteins or skim milk has an acute urate lowering effect.^{7,8} In addition, certain dairy fractions, particularly glycomacropeptide

(GMP) and G600 milk fat extract (G600), have anti-inflammatory effects in experimental models of acute gout.⁹ GMP is the 64-amino acid carboxy-terminal fragment of κ -casein and G600 milkfat extract is a complex lipid fraction in which the phospholipids and gangliosides, particularly disialo ganglioside 3 (GD3), are enriched (see online supplement for further details). The aim of this proof-of-concept clinical trial was to determine whether daily intake of skim milk powder (SMP) enriched with GMP and G600 could reduce the frequency of gout flares.

METHODS

Study design

This was a 3-month randomised double-blind controlled trial of milk products in 120 patients with recurrent gout flares. The primary end point was change in the frequency of gout flares. The study was registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ACTRN12609000479202).

Patients

Patients were recruited from rheumatology clinics and by public advertisement in Auckland, New Zealand from July 2009 to June 2010 (final study visit October 2010). All patients were aged ≥ 18 years old, had a diagnosis of gout (according to the American College of Rheumatology diagnostic classification)¹⁰ and were experiencing frequent gout flares at the time of study enrolment (at least two flares in the preceding 4 months).¹¹ Exclusion criteria were lactose intolerance and severe renal impairment (estimated glomerular filtration rate (eGFR) <30 ml/min). One hundred and thirty-one patients were screened. Eleven patients did not meet the inclusion criteria and were not recruited into the study (three with eGFR <30 ml/min, two did not meet the diagnostic criteria for gout and six withdrew consent after screening; see figure 1 in online supplement). One hundred and twenty patients passed screening and were randomised into the study. Baseline dairy and calcium intake was assessed using a validated food frequency questionnaire¹² and is shown in table 1.

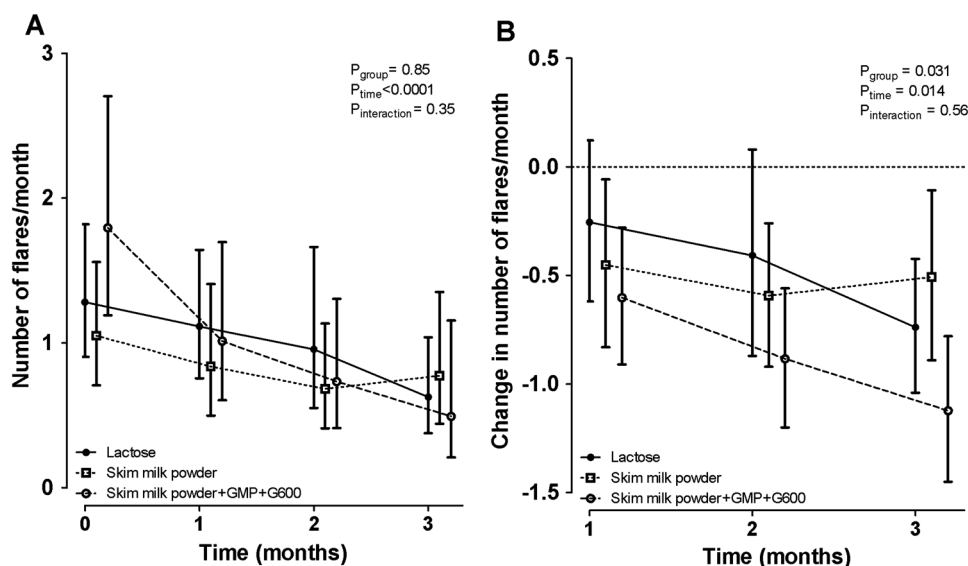


Figure 1 Primary end point: gout flares. (A) Total number of gout flares. (B) Change in number of flares from baseline. Data are presented as marginal means adjusted for baseline count (95% CI). GMP, glycomacropeptide; G600, G600 milk fat extract.

Table 1 Baseline clinical data

	Lactose (n=40)	SMP (n=40)	SMP/GMP/G600 (n=40)
Age, years, mean (SD)	57 (16)	56 (12)	56 (13)
Male, n (%)	37 (93%)	36 (90%)	35 (88%)
Caucasian ethnicity, n (%)	28 (70%)	28 (70%)	22 (55%)
Age of first episode, years, mean (SD)	42 (15)	39 (13)	43 (13)
Number of self-reported flares in preceding 4 months, mean (SD)	3.9 (2.7)	4.5 (2.3)	5.1 (9.6)
Allopurinol use, n (%)	21 (53%)	22 (55%)	22 (55%)
Colchicine use, n (%)	12 (30%)	7 (18%)	13 (33%)
Prednisone use, n (%)	4 (10%)	8 (20%)	4 (10%)
NSAID use, n (%)	11 (28%)	10 (25%)	11 (28%)
Diuretic use, n (%)	2 (5%)	1 (2.5%)	8 (20%)*
Number of gout flares in baseline month, mean (SD)	1.3 (1.5)	1.1 (1.4)	1.8 (2.4)
Tender joint count, mean (SD)	1.1 (1.7)	0.7 (1.0)	1.3 (1.7)
Swollen joint count, mean (SD)	0.7 (0.8)	0.8 (0.9)	1.1 (2.2)
Tophaceous gout, n (%)	8 (20%)	17 (43%)	10 (25%)
HAQ-II, mean (SD)	0.24 (0.44)	0.32 (0.39)	0.28 (0.41)
Patient global assessment, mean (SD)	1.8 (1.0)	2.0 (1.2)	2.0 (1.2)
Pain of self-reported flare in baseline month, mean (SD)	2.7 (1.6)	2.6 (1.7)	3.2 (2.1)
Serum urate, mmol/l, mean (SD)	0.44 (0.11)	0.41 (0.09)	0.42 (0.11)
Serum creatinine, μmol/l, mean (SD)	91 (18)	91 (19)	93 (20)
C reactive protein, mg/l, mean (SD)	4.7 (6.9)	3.6 (4.3)	7.5 (10.1)
Fractional excretion of uric acid, %, mean (SD)	4.7 (1.4)	4.8 (1.4)	4.5 (1.8)
Number of dairy servings/day, mean (SD)	2.5 (1.5)	2.2 (1.7)	2.7 (1.9)
Number of low fat dairy servings/day, mean (SD)	1.6 (1.5)	1.2 (1.1)	1.4 (1.4)
Total calcium intake/day, mg, mean (SD)	819 (471)	663 (362)	764 (351)

GMP, glycomacropeptide; G600, G600 milk fat extract; HAQ, health assessment questionnaire; NSAID, non-steroidal anti-inflammatory drug; SMP, skim milk powder.
*p<0.05 compared with SMP.

Protocol

Qualifying participants entered a 1-month run-in phase during which all completed a gout flare diary. Those returning a completed diary proceeded to randomisation. Patients were randomised to three separate treatment arms: lactose powder control, SMP control, and SMP enriched with GMP and G600 (1.5 g GMP protein (10% total protein) and 0.525 g G600 (3.5% of total protein weight)) (SMP/GMP/G600). Patients were randomised using a random block randomisation algorithm. Randomisation was performed prior to the commencement of the study by a study statistician and conveyed to a study coordinator who

applied printed labels to the study products. This individual had no direct contact with other study staff or with trial participants. Participants were allocated a study number according to the sequence of their enrollment. Participants and study staff were blinded to treatment allocation throughout the study. All visits took place at a single clinical research facility in a tertiary medical centre. Following randomisation, participants attended monthly study visits for 3 months. The protocol did not specify any other changes to gout management during the study, and gout flares occurring during the study were treated according to the discretion of the patient’s usual doctor.

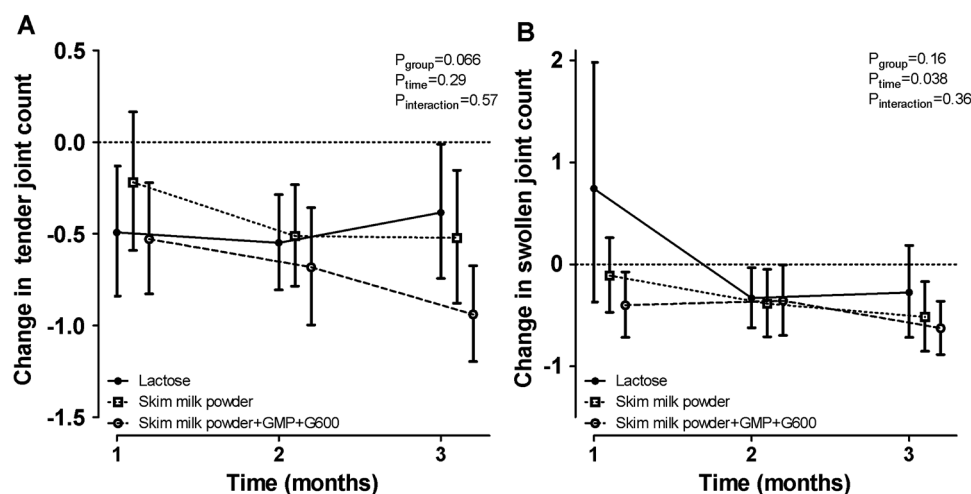


Figure 2 Secondary end point: joint counts. (A) Change in tender joint count from baseline. (B) Change in swollen joint count from baseline. Data are presented as marginal means adjusted for baseline count (95% CI). GMP, glycomacropeptide; G600, G600 milk fat extract.

Products

Each intervention was a cream-coloured powder administered daily as a 250 ml vanilla flavoured shake mixed in water by the patient using a wand blender. The amount of SMP used in the SMP formulations was adjusted to give a total protein content of 15 g. The lactose content of the lactose powder control was chosen to parallel the amount found in the SMP study products. Lactose, SMP and G600 milk fat extract were sourced from Fonterra Co-operative Group Ltd. GMP (Lacprodan CGMP-10) was a gift from Arla Foods Ingredients, Denmark. The products were dry-blended and packed into identical custom-made aluminium foil sachets. Products were stored at 4°C until completion of the trial. Full details of the products and quality testing are provided in the online supplement.

Measurements

Gout flares were recorded using a daily flare diary. Patients recorded the presence of a flare, the severity of pain using a 10-point Likert scale and the use of treatments for the gout flare. As identified in the recent European League Against Rheumatism/American College of Rheumatology funded validation study of gout flares, gout flare was defined as pain at rest >3 and patient self-reported flare.¹³ Baseline flare frequency was recorded as the number of gout flares recorded in the month prior to randomisation using the gout flare diary.

Assessments at the monthly study visits included measurement of tender (/68) and swollen (/66) joint counts, serum urate concentration, fractional excretion of uric acid, C reactive protein, patient global assessment of gout severity and health assessment questionnaire (HAQ-II).¹⁴ Enquiry regarding adverse events was made at each study visit.

Statistics

The primary end point was change in the frequency of gout flares using a daily flare diary, as defined by the recent European League Against Rheumatism/American College of Rheumatology gout flare definition study.¹³ Secondary end points were changes in swollen and tender joint counts, pain score, HAQ-II, patient global assessment, C reactive protein, serum urate concentration and fractional excretion of uric acid. The sample size of 120 patients was based on the primary end point using data from a previous open study of dietary intervention for management of gout flares.¹¹ Assuming a SD of 0.8, three groups of 40

were calculated to have at least 80% power at the 5% significance level in the Tukey–Kramer (pairwise) multiple comparison test at a 5% significance level to detect a difference of 1.02 gout flares per month (PASS 2002. NCSS and PASS; Number Cruncher Statistical Systems, Kaysville, Utah, USA). This total sample size of 120 included a provision for 20% non-differential loss to follow-up.

Data were analysed using procedures (MIXED, GENMOD, GLINMIX) of SAS V.9.2 (SAS Institute Inc). For dependent variables with low count frequency, a generalised linear mixed model analysis (assuming Poisson distribution) was performed to model the effect of treatment allocation and time and their interaction on the change in frequency of counts per month (flare frequency data and joint counts). The dependent variable was change from baseline, and baseline level was included as a covariate in the analysis. Normally distributed continuous end points were analysed using a mixed models analysis of covariance (ANCOVA) approach to repeated measures. For the change from baseline analysis, time zero was excluded. Significant main (treatment allocation and time) and their interaction effects were further investigated using the method of Tukey to preserve an overall 5% pairwise comparison. Marginal least squares means (adjusted for this covariate) are presented where indicated. All analysis was on an intention to treat basis. $p < 0.05$ was considered significant. All tests were two-tailed. Data analysis was completed by a biostatistician independent of the study sponsors.

RESULTS

Participants and study progress

Of the 120 patients enrolled in the study, two patients discontinued due to adverse events, eight were lost to follow-up and eight continued in the study without taking the milk products after experiencing an adverse event (intention to treat). One hundred and two patients completed the study as per protocol. The flow of patients through the study is shown in figure 1 in the online supplement. Baseline clinical data are shown in table 1. Patients were predominantly middle-aged Caucasian men. The three groups were well matched at baseline except for higher diuretic use in the SMP/GMP/G600 group. There were no significant differences between groups at baseline in flare frequency, pain scores or other measures of gout severity (table 1). There was no difference between the groups at baseline in the

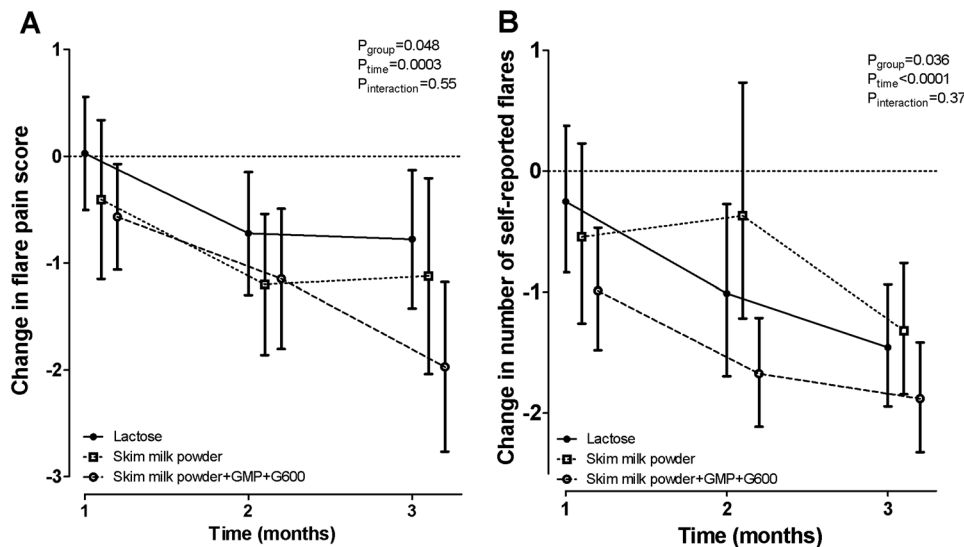


Figure 3 Secondary end point: patient-reported outcomes. (A) Change in pain of self-reported flares from baseline. Data are presented as mean (95% CI). (B) Change in number of self-reported gout flares from baseline. Data are presented as marginal means adjusted for baseline count (95% CI). GMP, glycomacropeptide; G600, G600 milk fat extract.

use of urate-lowering therapy or drugs to treat acute gout flares (table 1). Furthermore, the commencement or discontinuation rates of diuretics, allopurinol, colchicine, prednisone or non-steroidal anti-inflammatory drugs did not differ between groups throughout the follow-up period (data not shown). In the entire patient population, the median (range) intake of low fat dairy at baseline was 1.1 (0–6.1) servings/day. There was no difference in baseline calcium or dairy intake between the three groups.

Primary end point: gout flare frequency

The frequency of gout flares in the preceding month reduced in all three groups over the 3-month study period (figure 1). There was no difference between groups in the total number of gout flares over time (figure 1A). However, there was a significant difference between groups in the change in gout flares over the 3-month study period, with a significantly greater reduction in gout flares in the SMP/GMP/G600 group (ANCOVA $p_{\text{group}}=0.031$, Tukey post hoc test compared with lactose control $p=0.044$; figure 1B). There was no difference between the standard SMP group and the lactose group in the change in gout flares (Tukey post hoc test $p=0.81$) (figure 1B). There was no change in these results after adjusting for baseline dairy intake or diuretic use.

Secondary end points: joint counts

There was a trend to greater improvement in tender joint count with SMP/GMP/G600 compared with the other groups over the 3-month study period (ANCOVA $p_{\text{group}}=0.066$; figure 2A). There was no significant difference between groups in the change in swollen joint count (figure 2B).

Secondary end points: patient-reported outcomes

Improvements in patient global assessment of disease and HAQ scores were observed in all three groups over time. There was no significant difference between groups in the change in HAQ-II or patient global assessment (data not shown). However, the reduction in the mean pain scores during gout flares was greater in the patients treated with SMP/GMP/G600 over the 3-month study period (ANCOVA $p_{\text{group}}=0.048$, Tukey post hoc test vs lactose control $p=0.047$). There was no difference between the

standard SMP group and the lactose group in the change in flare pain scores (Tukey post hoc test $p=0.18$; figure 3A). Greater improvements were observed with SMP/GMP/G600 compared with the control groups in both components of the gout flare definition over the 3-month study period (for pain ANCOVA $p_{\text{group}}=0.048$ and for self-reported flares ANCOVA $p_{\text{group}}=0.036$; figure 3B).

Secondary end points: laboratory tests

There was no significant difference between groups in the change in C reactive protein (figure 4A) or serum urate (figure 4B). Treatment with SMP/GMP/G600 led to a significant increase in fractional excretion of uric acid compared with both lactose and standard SMP alone (ANCOVA $p_{\text{group}}=0.0002$, Tukey post hoc test lactose vs SMP/GMP/G600 $p=0.0002$, Tukey post hoc test standard SMP vs SMP/GMP/G600 $p=0.020$; figure 4C). There was no difference between the standard SMP group and the lactose group in the change in fractional excretion of uric acid (Tukey post hoc test $p=0.39$; figure 4C).

Adverse events

Similar adverse event rates and discontinuation rates were observed between the three groups (table 2). Overall, the most common single category of adverse events was gastrointestinal (diarrhoea, nausea and flatulence). There was no significant difference in gastrointestinal adverse events between the three groups. All serious adverse events related to hospital admissions; in the SMP group for gout flare, viral infection and prostate surgery and in the SMP/GMP/G600 group for gout flare and following an accidental fall. No serious adverse events were considered by the study investigators to be due to the study product. No deaths occurred during the study.

Intake of SMP/GMP/G600 for 3 months was not associated with changes in serum creatinine, waist circumference, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides. Weight increased by mean ($\pm 95\%$ CI) 0.43 (0.36) kg in the SMP/GMP/G600 group over the study period ($p=0.016$), but there was no difference between groups in the change of weight over time. Diastolic blood pressure reduced by mean ($\pm 95\%$ CI) 3.6 (1.8) mm Hg in

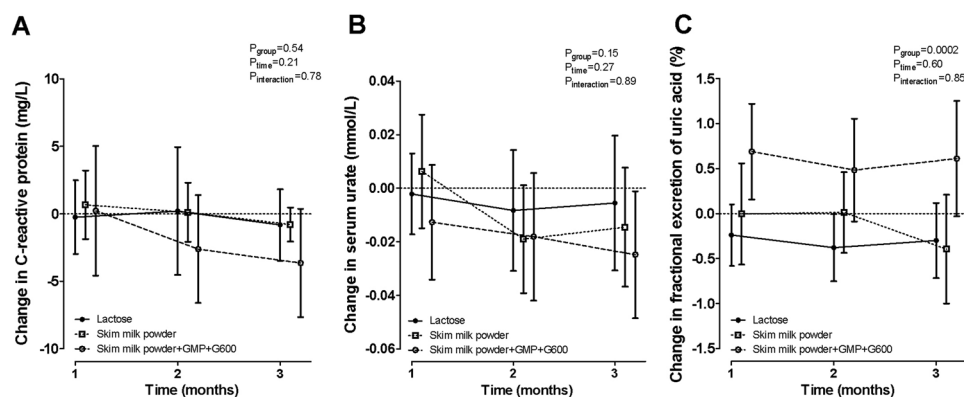


Figure 4 Secondary end point: laboratory tests. (A) Change in C reactive protein from baseline. (B) Change in serum urate from baseline. (C) Change in fractional excretion of uric acid from baseline. Data are presented as mean (95% CI). GMP, glycomacropeptide; G600, G600 milk fat extract.

Table 2 Adverse events

	Lactose (n=40)	SMP (n=40)	SMP/GMP/G600 (n=40)
Number of adverse events	19	20	19
Number (%) of patients with at least one adverse event	13 (33%)	15 (38%)	14 (35%)
Number (%) of patients with gastrointestinal adverse event*	5 (13%)	2 (5%)	7 (18%)
Number of serious adverse events	0	3	2
Number (%) of patients who discontinued study or stopped study medication	5 (13%)	6 (15%)	7 (18%)

*Gastrointestinal adverse events include nausea, flatulence or diarrhoea. GMP, glycomacropeptide; G600, G600 milk fat extract; SMP, skim milk powder.

the SMP/GMP/G600 group over the study period ($p=0.0002$), with a greater reduction in diastolic blood pressure in the SMP/GMP/G600 group compared with the lactose control (Tukey post hoc test, $p=0.001$).

DISCUSSION

This double-blind randomised controlled trial has suggested a significant benefit in the change in gout flares over time during treatment with SMP enriched with GMP and G600. In addition to showing improvements in the primary end point of gout flares, this analysis has shown greater improvements with SMP enriched with GMP and G600 in other clinically relevant end points (pain and fractional excretion of uric acid) and a trend to greater improvement in tender joint count. Products were generally well tolerated, although gastrointestinal adverse events such as flatulence, nausea and diarrhoea were reported in all groups. No adverse changes in renal function, lipid profile or blood pressure were observed during 3 months of SMP/GMP/G600.

In contrast to our previous study of SMP,⁸ we did not observe a urate-lowering or uricosuric effect of SMP alone in this study. It is likely that the acute urate-lowering effect of SMP is dose dependent, and our previous study tested much larger doses of SMP (a single dose of 80 g protein). Unlike lactose and standard SMP, daily intake of 15 g SMP enriched with GMP and G600 did have a uricosuric effect. It is unlikely that this is a non-specific effect due to a protein load as the standard SMP and SMP/GMP/G600 products had equivalent protein content. It seems unlikely that the uricosuric effect of SMP/GMP/G600 is the primary mechanism of flare reduction, given that only mild differences in serum urate were observed. Our previous analysis has shown that both GMP and G600 have significant anti-inflammatory effects in models of acute gout,⁹ and these agents may have reduced gout flares through inhibition of the inflammatory response to monosodium urate crystals present within the joint. A further possibility is that the SMP/GMP/G600 product has

analgesic effects which, in turn, led to improvements in both flare frequency and pain scores.

It is noteworthy that increased intake of standard SMP (equivalent increase of two servings of low fat dairy per day) did not have a significant effect on any of the end points studied. The dose used in this study is similar to that currently recommended for dietary management of gout.¹ These recommendations are primarily based on prospective cohort studies showing that intake of low fat dairy products is associated with reduced risk of incident gout and cross-sectional studies showing that dairy intake is associated with reduced serum urate concentrations in the general population.^{1,2,6} It is acknowledged that prospective cohort studies have advantages of long-term follow-up periods and the ability to assess the effects of whole food or food groups (as opposed to isolated nutrients). The opposing results highlight the need for further randomised controlled trials to support current dietary recommendations for gout management. Prior to the current study, no randomised controlled trials have addressed dietary interventions using relevant end points for patients with gout. The current study provides insights into the design for future clinical trials of dietary and other interventions to prevent gout flares. Of particular importance, all groups (including the control lactose group) had improvement in flare frequency and other end points over time. It is possible that at least some of this change represents regression to the mean since flare frequency at baseline was an inclusion criterion. This observation further highlights the importance of using adequate controls when including change in flare frequency as an outcome.¹¹ This is particularly important when recruiting patients with an episodic disease which has a high likelihood of spontaneous improvement.

A key inclusion criterion in the study was recurrent gout flares (at least two in the last 4 months). The patients in this study therefore had poorly controlled gout with high flare rates, inadequately controlled serum urate and relatively low use of allopurinol. The low use of allopurinol is consistent with our

previous study of patients with poorly controlled gout.¹⁵ In this population a reduction of one flare/month is likely to be clinically relevant. Whether clinically relevant benefits would be observed with SMP/GMP/G600 in patients established on effective urate-lowering therapy with fewer flares is uncertain; addressing this question is likely to require a much larger study.

This study has a number of potential limitations. It is a single-centre study in a location with a high prevalence of severe treatment-resistant gout.^{16 17} Although not statistically significant, the frequency of gout flares in the SMP/GMP/G600 group was slightly higher at baseline compared with the control groups. Importantly, baseline flare frequency was included as a covariate in the ANCOVA, with significant differences between groups identified in the change in gout flare frequency. The study used a single combination of GMP and G600. This combination was selected on the basis of laboratory data indicating that these two fractions individually inhibited the inflammatory response to monosodium urate crystals through different mechanisms.⁹ This study has not assessed the effects of GMP and G600 individually, and the relative effects of individual fractions or different combinations of these fractions are unknown. It is also uncertain whether the effects and safety profile observed with the SMP/GMP/G600 product would be sustained over longer time periods. However, this proof-of-concept study has demonstrated a difference between groups in the change in gout flare frequency and provides controlled data using validated end points. Future work will be directed at determining the effects of individual fractions and various combinations.

In summary, this is the first reported randomised controlled trial of dietary intervention in gout management, and suggests that daily intake of SMP enriched with GMP and G600 may reduce the frequency of gout flares. This study emphasises the importance of well-controlled intervention studies in patients with gout using validated outcome measures in order to guide dietary recommendations for this disease.

Contributors Nicola Dalbeth (the guarantor) accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish. Design of study protocol: ND, RA, GG, AH, BKS, AM, FM, IR, KP. Acquisition of study data: RA, AH, SW, KP. Data analysis: GG, BKS. Interpretation of data: ND, FM, IR, KP. Drafting of manuscript: all authors. Final approval of manuscript: all authors.

Funding Funding was provided by LactoPharma (a joint venture between Fonterra Ltd, Fonterra R&D Ltd and Auckland UniServices Ltd) and the New Zealand Government Foundation for Research Science and Technology.

Competing interests This work was funded by LactoPharma (a joint venture between Fonterra Ltd, Fonterra R&D Ltd and Auckland UniServices Ltd) and the New

Zealand Government Foundation for Research Science and Technology. BK-S, AM and KP are employees of Fonterra Co-operative Group Ltd. AM, ND and KP are named inventors on a patent application related to milk products and gout.

Patient consent Obtained.

Ethics approval The study was approved by the Northern Y regional ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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