Disturbed Galactose Metabolism in Elderly and Diabetic Humans Is Associated with Cataract Formation[1]

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ABSTRACT Lactose consumption has been associated with a high incidence of cataract in northern Indian and southern Italian populations. Galactose absorbed after hydrolysis of lactose from milk in individuals with normal lactase activity is considered responsible. However, lactase-deficient subjects who often avoid drinking milk are able to digest lactose and absorb free galactose in fermented milk and yogurt. This study was conducted to evaluate the relationships between milk and yogurt consumption, galactose metabolism and cataract risk. Milk ingestion was dose-related with cataract risk in lactose digesters (particularly in diabetics) but not in lactose maldigesters. Conversely, yogurt intake had a protective dose-effect on cataract formation for the whole population. Maximal galactose concentrations after an oral galactose test increased exponentially with age. Red blood cell galactokinase activity was significantly lower in elderly subjects (>60 y) than in young individuals ($P < 0.05$), and galactose-1-phosphate uridyl-transferase activity was significantly lower in institutionalized subjects and in home-living elderly with cataract than in healthy elderly subjects ($P < 0.05$). We conclude that the cataractogenic action of milk lactose is dependent on the disturbance of galactose metabolism in elderly subjects and that yogurt is not cataractogenic, although the mechanism of the protective effect of yogurt remains unknown. J. Nutr. 123: 1370–1376, 1993.

INDEXING KEY WORDS:

• *galactose* • *lactase activity*
• *humans* • *aging* • *cataracts*

Infants fed only milk have high intestinal β-galactosidase and hepatic galactokinase activities, allowing optimal utilization of lactose and galactose. These activities slowly decrease during the first years of life (Shin-Buehring et al. 1977a), particularly the intestinal lactase activity, which drastically decreases in most non-Indo-European populations (Witte et al. 1990). In Indo-European populations, which are lactose-digesters for the most part, milk ingestion (Bhatnagar et al. 1989, Simonelli et al. 1989) and a marginal decrease in galactose-1-phosphate uridyltransferase (GPUT) activity (Beutler et al. 1973, Skalka and Prchal 1980) have been associated with cataract formation. Early cataract formation is known to occur in congenital galactosemia (Kinoshita 1965), for which a galactose-free diet is the only therapy. High galactose diets induce lens opacification in animals at a rate that is proportional to the plasma galactose concentration and the lens aldose reductase activity (Birlouez-Aragon et al. 1989, Van Heyningen 1959). The mechanism of galactose-dependent cataract formation is very similar to that of diabetes-related cataract formation. Sugars could have a direct toxic action in the lens by inducing protein glycation (nonenzymatic glycosylation) (Perry et al. 1987) and free radical damage (Thoralley et al. 1984).

Yogurt is considered as an autodigestive source of lactose (Dewit et al. 1988) and contains free galactose (5 g/100 g). Yogurt consumption should therefore be associated with a higher risk of cataract formation than milk, regardless of the lactase activity of the population.

We therefore conducted a retrospective case-control study on 240 elderly subjects from the Paris area to detect any association between milk and yogurt consumption and cataract. We also analyzed the galactose metabolism in two groups of institu-

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TABLE 1

Percentage of lactose consumers and digesters in diabetic and nondiabetic subjects with cataract and in age-and sex-matched controls

	Nondiabetic subjects				Diabetic subjects (58–78 y)	
	Under 75 y		Over 75 y			
	Control (n = 51)	Cataract (n = 43)	Control (n = 28)	Cataract (n = 67)	Control (n = 41)	Cataract (n = 32)
Age,[1] y	67.0 ± 4.1	65.1 ± 7.1	81.9 ± 4.1	80.9 ± 4.6	65.5 ± 7.1	71.3 ± 7.6
Lactose digesters,[2] %	53.0	76.7*	60.7	55.4	71.4	65.6
Lactose consumers,[3] %	51.2	53.5	46.7	54.8	71.4†	86.9†

[1]Values are means ± SD.

[2]Lactose digesters were determined by breath hydrogen of $<10^{-5}$ mol/L after ingestion of 18 g of lactose following a 12-h fast. *$P < 0.05$, chi-square test between control and cataract subjects; Odds ratio = 2.3.

[3]Subjects were considered to be lactose consumers when they ingested >10 g of lactose per day (equivalent to 200 mL of milk). Lactose consumption was evaluated by a retrospective questionnaire, taking into account milk (50 g/L lactose) and yogurt (45 g/kg lactose + 5 g/kg galactose) intake. †$P < 0.05$, chi-square test between diabetic and nondiabetic subjects.

tionalized and home-living elderly subjects and in young subjects by oral galactose tests. Red blood cell galactokinase and GPUT activities were measured.

MATERIAL AND METHODS

The experimental research was approved by the Ethics Committee of St Louis Hospital, Paris, and written consent was obtained from the subjects in the study. All biochemicals used were purchased from Sigma (Paris, France) and were of the highest purity available. Radioactive galactose was obtained from CEA (Saclay, France).

Case-control study. Three groups of subjects selected from patients at three Paris hospitals (St Louis, La Pitié and Cochin) were questioned regarding milk intake and were analyzed for their ability to digest lactose (**Table 1**): 94 nondiabetic subjects under 75 y (63–72 y) (Group 1), 95 nondiabetic subjects over 75 y (78–86 y) (Group 2), and 73 diabetic (all types) subjects (58–78 y) (Group 3). Each group contained two subgroups with the same mean age and sex ratio (60%) women); one subgroup included patients hospitalized for cataract removal (advanced idiopathic cataract); the other included patients hospitalized for general medical problems and having visual acuity better than 16/20. Lactose digestion was measured by the hydrogen breath test (Dewit et al. 1988) in fasting patients fed 18 g of lactose. Breath H_2 levels of >10 μL/L (Stimotron hydrogen test apparatus) over 3 consecutive hours indicated lactose maldigestion. The milk drinking habits were recorded as numbers of 100-mL units per day or per week, and frequency of use in meal preparation. Yogurt consumption was analyzed as the number of 125-g units per day or week. Lactose consumption was evaluated by taking in account milk (50 g/L lactose) and yogurt (45 g/kg lactose + 5 g/kg galactose) intake.

Oral galactose tests. The tests were conducted on four groups of subjects: 15 young (23 ± 3 y) healthy volunteers from our Institute; 25 home-living elderly subjects divided in two age groups, septuagenarians (70 ± 6 y) and octogenarians (82 ± 3 y), half of them having a cataract associated with visual acuity lower than 8/20 (St Louis Hospital, Paris); and 19 institutionalized nonagenarian (90 ± 4 y) subjects (Broca Hospital, Paris) in poor general health, with most of them having a cataract. Each fasting subject ingested 0.5 g galactose/kg body wt. Capillary blood samples (50 μL) were taken before and 40 min (mean peak time) after galactose ingestion. For a subgroup of subjects, blood was drawn at 20, 40, 60, 90 and 120 min. The samples were centrifuged and plasma galactose measured by a fluorimetric method (Orfanos et al. 1977), in which galactose is transformed by the specific action of galactose dehydrogenase to galactonolactone with the production of fluorescent NADH (sensitivity 5 μmol/L). A control sample was prepared by adding to the plasma the reaction mixture without the enzyme.

Red blood cell enzyme activity. The RBC were washed three times with saline phosphate buffer (pH 8) and suspended in an equal volume of 1 mmol/L dithiothreitol. The galactokinase activity was measured isotopically according to the method of Shin-Buehring et al. (1977b). Phosphorylated [^{14}C]galactose was separated from the ^{14}C substrate by ion-exchange chromatography as described by Ng et al. (1965) [activity expressed as nmol product/(min·g hemoglobin)]. The hemoglobin content of washed erythrocytes suspended in 1 volume of dithiothreitol was measured by the Drabkin method (Sigma kit, cat. no. 525-2; Drabkin 1935). The GPUT activity was measured fluorimetrically at 37°C

TABLE 2

Percentage of subjects with cataract as a function of daily milk consumption

	Milk consumption (mL/d)			Odds ratio[1]	
	0–100	100–200	200–400	>100 mL	>200 mL
		%			
Nondiabetic lactose digesters	36.1	65.7	75.0	2.7 [1.2–5.9]	4.0 [1.3–12.7]
Diabetic lactose digesters	15.8	42.8	76.0	7.2 [1.4–38]	3.94 [2.1–7.4]
Lactose maldigesters[2]	56.5	52.4	34.5	1.1 NS	0.57 [0.44–1.08]

[1]Odds ratios give the relative risk of cataract, with the confidence interval in brackets, for milk consumption >100 mL/d for lactose digesters and >200 mL/d for lactose maldigesters.
[2]Diabetic and nondiabetic lactose maldigesters are considered together. NS = not significant.

(Beutler and Mitchell 1968) by quantifying the production of NADPH during the transferase plus epimerase steps in the presence of excess galactose-1-phosphate substrate [1 unit = 2 nmol NADPH formed/(min·g hemoglobin)]. The standard curves were calculated by increasing the NADPH concentration in the RBC hemolysates, to take into account the eventual hemoglobin interference.

Statistical analysis. The relative risk of cataract formation associated with lactase activity or milk and yogurt intake was evaluated by the Odds ratios (OR) and their confidence intervals (Morris 1988). Correlations were calculated using Lotus 123 software. Chi-square test was used for comparing percentages of subjects according to various dietary habits and Student's *t* test for comparing mean values. Values in the text are means ± SD. Differences were considered significant when $P < 0.05$.

RESULTS

Epidemiological study. Most of the subjects (53 to 77%) in the study were able to digest lactose. There was no correlation between the percentage of lactose digesters and age. The median lactose intake was 10 g/d for the nondiabetic groups. A significantly higher percentage of subjects in the diabetic group than in the nondiabetic population consumed >10 g lactose/d (Table 1).

The milk-drinking habits of the cataract and control populations were compared separately in the groups of lactose digesters and maldigesters. **Table 2** shows an increase in the percentage of lactose digesters with cataract with increasing daily milk intake. The relative risks were 2.7 and 4.0 ($P < 0.05$) for the nondiabetic subjects and 7.2 and 3.9 ($P < 0.05$) for the diabetic persons consuming >100 mL or >200 mL of milk daily, respectively. No difference was found in the percentage of subjects with cataract between persons with low (0–100 mL/d) and median (100–200 mL/d) milk consumption in the population with lactose malabsorption (Odds ratio 1.1, not significant), but there were significantly fewer subjects with cataract when the consumption rose above 200 mL of milk per day (OR = 0.57, $P < 0.05$) (Table 2).

The yogurt consumption habits of each group were compared and the Odds ratios calculated for a mean consumption of 125 g yogurt/d (the median consumption level). The OR for all groups were similar (0.3 to 0.6; $P < 0.05$). The relationship between yogurt consumption and cataract risk was therefore analyzed for the whole group. The percentage of subjects with cataract decreased significantly with daily yogurt consumption: 59.7, 57.7, 43.3 and 31.4% for yogurt intake of 0, <125 g, 125–250 g and >250 g per day, respectively.

Because milk and yogurt, the two main dairy products consumed in our populations, had opposite effects on the risk of cataract formation, the relative consumption of both products was analyzed. The distribution of the control and cataract populations according to the relative yogurt and milk consumption was significantly different ($P < 0.001$; chi-square test; **Table 3**): twice as many subjects with cataract consumed >100 mL of milk and <125 g of yogurt per day, compared with the controls.

Metabolic study. The galactose tolerance curves as a function of age for a subgroup of subjects are shown in **Figure 1**. The time corresponding to maximal concentrations was 40 min for all subjects older than 80 y, 30 min for the young subjects, and between 30 and 40 min for septuagenarians. Therefore, concentrations at fasting baseline were calculated for all subjects, and the galactose peaks (evaluated by the concentrations at 40 min after galactose ingestion for elderly subjects above 79 y, and at 30 min for the septuagenarians and young subjects) were calculated without consideration of the presence of cataract. Galactose utilization varied among the different age groups in four ways:

TABLE 3

Distribution of the population with cataract and of the age- and sex-matched control population according to relative milk and yogurt intake[1]

Population	Group 1	Group 2	Group 3	Group 4
		%		
Control	18.8	37.5	25.0	18.8
Cataract	9.3***	31.4	22.1	37.1***

[1]Group 1 consumed >125 g yogurt and <100 mL milk per day. Group 2 consumed >125 g yogurt and >100 mL per day. Group 3 consumed <125 g yogurt and <100 mL milk per day. Group 4 consumed <125 g yogurt and >100 mL milk per day. ***$P < 0.001$ between cataract and control groups by chi-square test.

1) The mean of the maximum plasma galactose concentration was much higher in the nonagenarian and octogenarian subjects (6.54 ± 3.55 and 5.18 ± 1.97 mmol/L, respectively) than in the young subjects (1.08 ± 0.21 mmol/L) and septuagenarian subjects (2.49 ± 1.61 mmol/L). The differences were significant between septuagenarians and octogenarians ($P < 0.05$, Student's t test) or nonagenarians ($P < 0.01$) but not between octogenarians and nonagenarians.

2) The variability was much higher in the nonagerian group than in octogenarian or septuagenarian groups, and was particularly low in the young group.

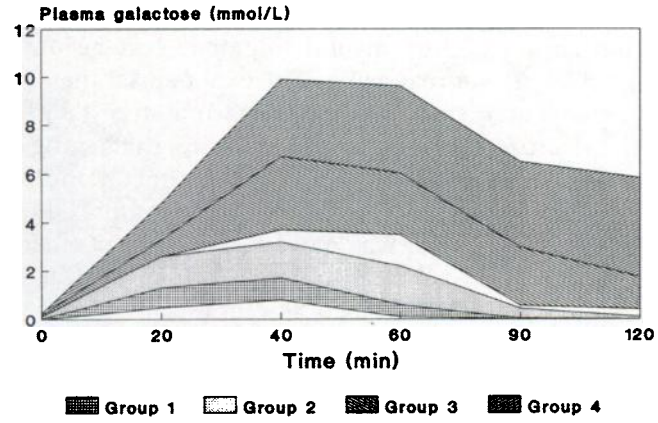

FIGURE 1 Plasma galactose concentration curves in various age-group subjects after oral galactose (0.5 g/kg galactose in 100 mL of water). Group 1: young and healthy subjects (age 23 ± 3 y, $n = 15$); Group 2: septuagenarian home-living subjects (68 ± 6 y, $n = 8$); Group 3: octogenarian home-living subjects (80 ± 2 y, $n = 11$); Group 4: nonagenarian institutionalized subjects (88 ± 3 y, $n = 12$); Subjects with and without cataract are considered together. For each group, areas are drawn from the mean plasma concentration plus the SD. Area 1 partially overlaps area 2, and area 3 partially overlaps area 4.

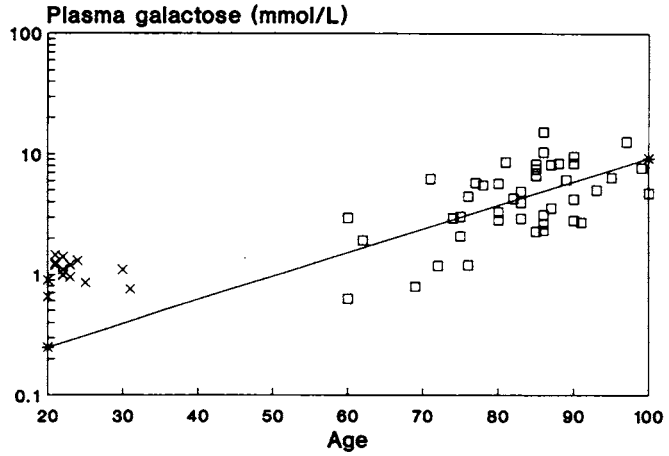

FIGURE 2 Regression line between the logarithm of maximal plasma galactose concentration after oral ingestion of 0.5 g/kg galactose and age over 60 y. Correlation $r = 0.57$, $n = 44$, $P < 0.005$. Maximal plasma concentrations observed in young healthy subjects (x) are shown for comparison with the regression line.

3) The plasma galactose concentrations were still >0.6 mmol/L at 120 min in octogenarians and nonagenarians; by this time concentrations had returned to fasting levels in young and septuagenarian subjects.

4) Mean fasting galactose concentrations were significantly higher in nonagenarians and in octogenarians (0.19 ± 0.07 mmol/L) than in young subjects (0.03 ± 0.04 mmol/L) and in septuagenarians (0.08 ± 0.06 mmol/L).

An exponential relationship was found between the subject's age and the plasma galactose peak in the elderly group ($r = 0.57$, $n = 44$; $P < 0.005$; **Fig. 2**). Plasma galactose concentrations in young healthy subjects were slightly above the regression line.

The home-living elderly subjects (septuagenarians plus octogenarians) with cataract had a significantly higher maximal plasma galactose concentration than those without cataract (5.58 ± 1.35 instead of 3.96 ± 0.96 mmol/L).

Red blood cell galactokinase activity was very low in all elderly subjects compared with young subjects ($P < 0.05$): 24.4 ± 5.9 nmol/(min·g hemoglobin) ($n = 18$) in nonagenarians and 20.5 ± 4.2 nmol/(min·g hemoglobin) in septuagenarians and octogenarians (with or without cataract, $n = 10$; Birlouez-Aragon et al. 1990) instead of 37.6 ± 4.5 nmol/(min·g hemoglobin) ($n = 16$) in young subjects (Birlouez-Aragon et al. 1990). Red blood cell GPUT activity was significantly lower in nonagenarians [356.2 ± 68.5 nmol/(min·g hemoglobin, $n = 18$], and in the group of home-living elderly subjects with cataract [344.6 ± 54.3 nmol/(min·g hemoglobin), $n = 5$; Birlouez-Aragon et al. 1990] than in home-living elderly individuals without cataract [457.8 ± 51.6 nmol/(min·g hemoglobin), $n = 5$; Birlouez-Aragon et al. 1990].

DISCUSSION

The incidence of age-related cataracts increases as the life expectancy becomes longer in developing countries (Harding 1991). The mechanism by which the lens becomes opaque is still unknown, but is undoubtedly due to the age-dependent changes that affect several tissues, particularly those with noninsulin-dependent glucose transport, such as the lens, nervous system, kidney and arterial vessels (Furth 1988). This has led to the theory that sugars play a key role in aging, in the same way that hyperglycemia could be the responsible factor for the long-term pathologies associated with diabetes (Monnier 1988). The polyol pathway now seems to be less important than the toxic effects associated with protein glycation and oxidative stress (Cheng and Gonzalez 1986, Hotherstall et al. 1988, Thoralley et al. 1984). Glycation is a non-enzymatic, poorly controlled reaction that seems to increase with the concentration of circulating blood sugar (mainly with diabetes) and with aging (due to decreasing homeostasis). The two main toxic effects of glycation are to increase the oxidative stress leading to protein oxidation and lipid peroxidation (Hunt et al. 1990) and to alter protein structure and function, particularly by inducing protein cross-linking (Perry et al. 1987). Cataract can be produced in vitro by high sugar concentration and inhibited by many glycation inhibitors (Ajiboye and Harding 1989) and antioxidants (Creighton and Trevithick 1979).

However, glucose is not the only sugar involved. Galactose, fructose and phosphorylated sugars are much more reactive in terms of glycation and autoxidation (Walton et al. 1988). Although their circulating concentrations are normally low, certain conditions can lead to higher levels, with possible deleterious effects. Dietary galactose, for example, is highly cataractogenic in subjects with a metabolic genetic defect such as galactosemia (Beutler et al. 1973, Skalka and Prchal 1980) or in animals when it is consumed in large amounts (Birlouez-Aragon et al. 1989). Furthermore, epidemiological studies have associated galactose absorption and low GPUT with a higher incidence of cataract (Bhatnagar et al. 1989, Rinaldi et al. 1984, Simonelli et al. 1989, Simoons 1982). A preliminary study (Birlouez-Aragon et al. 1990) confirmed these results: lactose ingestion (>10 g/d) and ability to digest lactose were found to be two risk factors of senile cataract. Furthermore, in lactose digesters, milk ingestion was calculated to increase by 2.7 and 6.3 the risk of senile and diabetes-related cataracts, respectively (Birlouez-Aragon and Stevenin 1990). We demonstrate here, for a larger population, a dose-dependent effect of milk ingestion on cataract incidence in lactose digesters, who actually absorb galactose. Conversely, lactose maldigesters consuming high quantities of milk (>200 mL/d) are at less risk. Two explanations could be advanced for this protective effect: *1)* the colonic fermentation of lactose could modify the availability of galactose liberated by the residual lactase, or *2)* the high riboflavin content of milk could optimize the cellular riboflavin status, which has been reported to be protective (Bhat 1974). Interestingly, milk ingestion seems to have a greater cataractogenic effect in diabetic lactose digesters who also drink significantly more milk than do the nondiabetics. This suggests that galactose absorption could be cataractogenic, and this may explain the greater risk of cataract found in diabetic subjects.

These results, which confirm that lactose digesters are at greater risk of cataract than lactose maldigesters, raise two points. First, plasma galactose concentration remains low in lactose digesters after milk ingestion (150–220 μmol/L) (Bas et al. 1990) because of the limiting lactase step and the highly efficient hepatic galactose metabolism in healthy subjects. Second, in our study, the total lactose ingestions of the lactose-digesting and maldigesting groups were comparable, confirming that milk consumption habits predominantly depend on socioeconomic and geographical factors (Scrimshaw and Murray 1988). In lactose maldigesters, it has been shown that yogurt (an autodigesting source of lactose) when chronically consumed allows hydrolysis of lactose not only in yogurt but also in milk (Dewit et al. 1988). Therefore, yogurt consumption should increase galactose absorption in lactose maldigesters and thus lead to a relative risk of cataract in lactose maldigesters such as in lactose digesters, which is opposite of what was shown in the preliminary results of our study (Birlouez-Aragon and Stevenin 1990).

This study shows that a subject's galactose utilization capacity after an oral tolerance test becomes impaired with normal aging. The exponential increase in the maximal galactose concentration after 0.5 g/kg oral galactose with age could indicate that aging is directly associated with the decreased metabolic capacity and lower RBC galactokinase and/or GPUT activities. The defect was most marked in the elderly institutionalized subjects, but the influence of aging or related pathologies, such as chronic infection, remains unclear. In a previous study (Birlouez-Aragon et al. 1990), diabetic subjects were shown to have higher plasma galactose concentrations than nondiabetic subjects after 0.5 g/kg galactose ingestion, but not lower RBC galactokinase and GPUT activities. The relationship between insulin and galactose utilization is still unclear, but insulin could activate cell galactose uptake (Levine et al. 1950, and our unpublished data). We have shown here again that elderly subjects with cataract metabolize oral galactose more slowly than do elderly subjects without cataract, confirming the results of Simonelli et al. (1989). Galactokinase was found to be significantly lower [at the

limit of the lower normal range, 20–40 nmol/[min·g hemoglobin)] in all elderly subjects than in young persons without any difference between controls and subjects with cataracts (Birlouez-Aragon et al. 1990). However, GPUT activity was found to be significantly lower in elderly home-living or institutionalized subjects with cataract (most institutionalized subjects had cataract) than in elderly home-living persons without cataract (Birlouez-Aragon et al. 1990). The GPUT activities in the subjects with cataract were at the low end of the normal range [350–450 nmol/(min·g hemoglobin)]. Thus, the marginal decrease in galactokinase and sometimes in GPUT, together with a lower glucose peripheral utilization in diabetic persons and elderly subjects (Silverstone et al. 1957), could induce a sufficient increase in the circulating galactose concentration to allow substantial lens glycation and oxidation. If this is the case, other tissues, such as the nervous system and arterial vessels, could also be damaged.

We have confirmed here the protective effect of yogurt on cataract formation already observed for a smaller population (Birlouez-Aragon and Stevenin 1990). We furthermore demonstrated a dose-related action on cataract in all subjects with or without lactase activity, diabetic or not and regardless of age. The specificity of the relationship between yogurt intake and cataract prevention needs to be confirmed by further epidemiological studies, and the protective factor elucidated. Two hypotheses may be put forward: the presence of free galactose in yogurt could have an activating action on intestinal galactokinase activity (Bas et al. 1991), and the possible activation of insulin secretion after yogurt ingestion compared with milk ingestion could increase the rate of galactose and glucose utilization (Dewit et al. 1988). The protective action of yogurt could explain why lactose ingestion in alactasic populations chronically ingesting yogurt is not cataractogenic.

This study indicates that milk is not an ideal food for elderly persons and diabetic subjects able to substantially digest lactose. Milk and dairy foods can, however, provide a variety of nutrients such as protein, calcium and riboflavin, which are important for elderly persons. We suggest that lactose-free milk might optimize the nutritional quality of this food. If the protective action of yogurt on cataract formation is confirmed, its consumption should be encouraged, as a good source of calcium for lactose digesters or maldigesters.

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