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Effect of xylitol gum on the level of oral mutans streptococci of preschoolers: block-randomised trial

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Objectives: To assess the influence of xylitol chewing gum consumption on mutans streptococci level of 3–4 years old Japanese preschoolers. **Methods:** 248 participants were examined regarding caries-related factors at baseline and were followed up at 6, 9, and 12 months after the baseline: assessors were blinded, subjects were open labelled and blocked parallel randomised; 142 were selected to use xylitol gum for 3 months (from months 6 to 9) and 106 were controls. **Results:** 161 participants were analysed (xylitol $n = 76$, control $n = 85$). Nineteen caries-related variables, including xylitol gum consumption, were analysed for any association with the main outcome, plaque mutans streptococci scores development within the intervention period, by logistic regression. Six showed statistically significant associations by univariate analysis ($P < 0.05$). However, only xylitol gum consumption remained a significant negative association ($P < 0.05$) by multiple analyses. Interestingly, over 10% xylitol group children experienced diarrhoea, which was larger than previous investigations. **Conclusion:** Xylitol gum is effective in avoiding increased plaque mutans streptococci in young children.

Key words: *Xylitol gum, mutans streptococci, caries*

The prevalence of tooth decay has decreased in industrialised countries[1], including Japan[2]. However, the prevalence of dental caries in the deciduous dentition in Japan has remained high, according to the latest Japanese national oral health survey in 2005[3], which reported that only 38.1% of 5–6-year-olds were caries-free. Japan is still in the process of reducing decay in the deciduous dentition.

Mutans streptococci (MS) is an important factor associated with the prevalence and incidence of caries[4,5]. An epidemiological incidence study clarified the tight relationship between caries development and MS scores in plaque and saliva in Japanese preschool children[6]. Increased fluoride use seems to have contributed to a reduction in caries prevalence in many industrialised countries; however, access to fluoride is limited in Japan[7] and the recent decrease in children's decay in Japan has been accompanied by reduced MS infection in the deciduous dentition[8].

Several studies have analysed the influence of xylitol on the prevention of dental caries[9–12], on the control of risk factors for caries, including mutans streptococci infection[13–17], and on the maternal transmission of mutans streptococci[18,19]. Thus, xylitol gum consumption may be effective in decreasing decay in deciduous teeth in Japan. Few studies have examined the influence of xylitol gum consumption on the control of risk factors, including mutans streptococci infection, in preschoolers (e.g., 5-year-olds[15]). Although the minimum intervention to achieve some effectiveness is useful from a public health viewpoint, most of the xylitol intervention periods were over 6 months[9–19]. Moreover, to our knowledge, no previous report has addressed its effects in young Japanese children with deciduous teeth.

In this study, to assess the effects of short period xylitol gum consumption on Japanese preschool children's mutans streptococci levels, we investigated the multifactorial aetiology of plaque mutans streptococci score development within a 3-month period of xylitol gum consumption in preschool children, from 3 to 4-years. At the same time, we also confirmed if there were any side effects within the xylitol gum consumption period.

MATERIALS AND METHODS

Participants and interventions

We assessed 432 children ranging in age from 3 to 4-years at baseline, who attended five preschools in Tokyo, Japan, a non-fluoridated area (*Figure 1*). The preschools were within just 2 km of one another, so their socio-economic backgrounds are almost the same. Two preschools were excluded; one refused to participate (n = 114) because of a lack of understanding of the importance of the study by the staffs, and the other was eliminated from the other food consumption group (n = 70). Therefore, we examined the children (n = 248) of three preschools.

This study was approved by the ethics committee of Nihon University School of Dentistry (trial registration number was UMIN000003112 and full trial protocol: http://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000003777&type=summary&language=E). The parents of all the children were asked to complete a questionnaire and to allow us to examine the children's teeth and to take microbiological samples.

At baseline, 142 participants who attended two preschools were in the xylitol group, and 106 who attended one preschool were in the control group. We just selected randomly one of three preschools as a control group by a block randomisation procedure, at that time; the three preschool sizes were unknown to the investigators. Children in both groups did not have any special oral hygiene instructions or professional tooth cleanings.

The xylitol chewing gum used in this study was 100% xylitol pellet-shaped gum, containing 1.33 g xylitol/-pellet (prepared by Lotte Co. Ltd., Tokyo, Japan). Subjects in the xylitol gum group were instructed to chew one gum pellet for 5 minutes, 4 times/day (after breakfast, lunch, snacks, and dinner) for 3 months (from 6 to 9 months after baseline). Children in the control group were untreated during the same period. In this study, the trial design was parallel and the interventions were open (subjects were open labelled), but clinical examiners, sample collectors and sample assessors were blinded regarding the interventions.

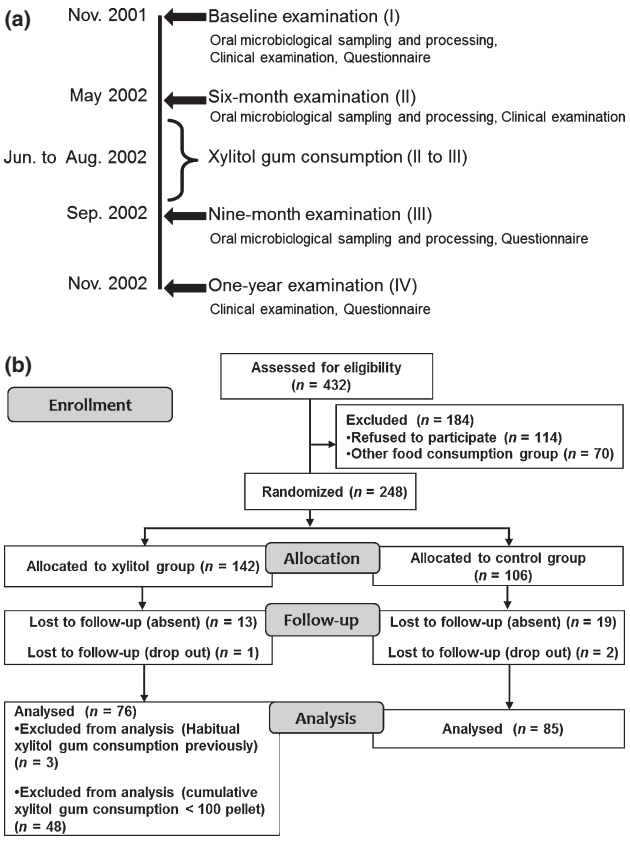

Figure 1. Study design (a) and trial flow diagram (b) during the 1-year study.

Sample size

Based on the colonisation rate described in a previous study[14], 31 participants per group were needed to achieve a power of 95% to detect a difference of plaque mutans streptococci scores (two-tailed, $\alpha = 0.05$)[20]. After adjustment for dropouts (30%), data for 41 participants per group were judged as necessary.

Objectives and outcomes

To assess the influence of 3 months of xylitol gum consumption on the level of oral mutans streptococci of young children, plaque MS level development within the intervention period was the primary outcome in this study and was measured by oral microbiological sampling and processing. Additionally, caries-related background factors that influenced the outcomes were also examined by questionnaire and clinical examination. There were no changes in trial outcomes once the trial had commenced.

Oral microbiological sampling and processing

At baseline, 6 and 9 months, the Dentocult SM® Strip mutans and Site Strip (Orion Diagnostica, Espoo, Finland) were used to evaluate the MS levels in unstimulated saliva and plaque collected from eight specified interdental spaces, as previously described[21]. The plaque MS level in this study was defined as the mean of MS scores at eight specified interdental spaces.

Questionnaire

At baseline, the parents of all children were asked to complete a questionnaire related to caries. The each

questionnaire and related categorisations were as follows:

- Habitual consumption of sweet snacks (yes/no)
- Fluoride topical application usage (yes/no)
- Habitual use of sweet drinks (yes/no)
- Fluoride toothpaste usage (yes/no)
- Brushing frequency/day (<3 times/3 ≤ times)
- Parental teeth-cleaning habits (yes/no)
- Frequent snacks (yes/no)
- Frequent xylitol gum consumption (yes/no).

At the 9 months and 1-year follow-up examinations, occurrences of diarrhoea within the xylitol gum consumption period and information on the total amount of xylitol gum consumed (estimated from the number of xylitol gum consumption days/week and the number of xylitol gum consumption times/day before and during the summer vacation period) were recorded.

Clinical examination

Caries prevalence was examined and calibrated by two experienced examiners (Cohen's kappa = 0.88) on three occasions, 6 months apart, between November 2001 and November 2002. Caries per tooth surface was diagnosed visually without radiographs[22]. Only manifest lesions accompanied by enamel loss or cavities involving the dentine of primary teeth were considered.

The labial, buccal, and lingual tooth surfaces were inspected visually for the presence of dental plaque, without using a disclosing solution. Children with visible plaque on one or more tooth surfaces were categorised as positive (visible plaque)[23].

Statistical analyses

Data were analysed using the JMP® 7.02 software package (SAS Institute, Cary, NC, USA). Differences in variables between groups were examined using the chi-squared test and the Wilcoxon test. Paired differences within the same group between examination times were examined using the Wilcoxon test for paired samples, and mean difference within the paired samples between two groups was assessed using MANOVA. Single and multiple logistic regression analyses were used to define predictors of the development of plaque MS scores. A *P*-value <0.05 was considered as statistically significant.

RESULTS

Trial profile

The anticipated trial of this study started from September 2001. Within the month, the number of participants was greater than expected (41 participants per each group) (*Figure 1*). At baseline, 142 participants were in the xylitol group, and 106 in the control group. From 248 subjects at the baseline, 36 children were lost because they left the schools or did not attend the examination. Three xylitol gum-group children were eliminated because of previous frequent xylitol gum consumption. Additionally, 48 children who consumed fewer than 100 pieces of cumulative xylitol gum within 3 months (months 6–9) were eliminated from the analysis (*Figure 1*), thus xylitol gum-group children were analysed as the subjects who consumed at least one gum per day within a three month period. Primary reasons for dropout from the xylitol group were diarrhoea and possibly lack of understanding of the importance of continued gum consumption. The percentage of dropouts was 46% (66/142) in the xylitol group and 20% (21/106) in the control group. The mean frequency and dose of xylitol consumption were 2.5 times/day (range, 1.1–4.7) and 3.33 g/day, respectively, during the 3-month xylitol gum consumption period. At the conclusion of the study the groups consisted of 161 subjects (76/xylitol, 85/control), and the 161 children were analysed (mean age = 4.1 years at baseline; 85 males and 76 females) for the data analysis.

Baseline and 6 months characteristics

No important difference was found between the follow-up and dropout groups (*Table 1*). Except salivary MS score >0, no other difference was found between the xylitol and the control groups at baseline (*Table 1*).

Table 1 Baseline characteristics of the total 248 subjects (a) and 161 subjects followed up (b)

(a)

	Follow-up (*n* = 161)	Dropout (*n* = 87)	*P*
Age (4 years old), *n* (%)	111 (68.9)	61 (70.1)	0.85*
Male, *n* (%)	85 (52.8)	52 (59.8)	0.29*
dfs index, mean (SE)	3.4 (0.5)	3.7 (0.7)	0.54†
Individual Plaque MS score‡, mean (SE)	0.6 (0.1)	0.6 (0.1)	0.64†
Salivary MS score > 0, number (%)	55 (34.2)	33 (37.9)	0.55*

(b)

	Xylitol (*n* = 76)	Control (*n* = 85)	*P*
Age (4 years old), *n* (%)	50 (65.8)	61 (71.8)	0.41*
Male, *n* (%)	41 (54.0)	44 (51.8)	0.78*
dfs index, mean (SE)	2.5 (0.8)	4.2 (0.7)	0.07†
Individual Plaque MS score‡, mean (SE)	0.5 (0.1)	0.7 (0.1)	0.14†
Salivary MS score > 0, number (%)	19 (25.0)	36 (42.4)	0.02*

*Statistical evaluation using the chi-square test.
†Statistical evaluation using the Wilcoxon test.
‡Mean per person of Dentcult SM site strip scores from eight specified inter dental spaces: 54/55, 52/53, 51/61, 62/63, 64/65, 74/75, 71/81, and 84/85.

Moreover, no significant difference was found between the groups in the results from the questionnaire at baseline. A difference in salivary MS score >0 was found between the groups at baseline (25.0 *vs*. 42.4%; $P = 0.02$), which was not found at the 6-month follow-up (32.9 *vs*. 44.7%; $P = 0.13$).

New caries lesions were detected in 70 children at 6 months. The caries prevalence in the 161 children increased from 42.2% (68/161) at baseline to 52.2% (84/161) at the 6-month follow-up. The mean ± SE dfs (caries experienced surfaces) in the subjects was 3.4 ± 0.5 (ds, 1.7 ± 0.4; fs, 1.6 ± 0.3) at baseline, and 4.9 ± 0.6 (ds, 2.3 ± 0.4; fs, 2.6 ± 0.4) at the 6-month follow-up. At the 6-month follow-up, no significant difference between the groups was found in oral hygiene (visible plaque), caries prevalence, dfs, individual plaque MS score, salivary MS score development (baseline to 6 months), and plaque MS score development (baseline to 6 months).

Effects of xylitol gum on caries and plaque MS score developments

To assess the influence of xylitol gum on caries development, the Wilcoxon test for paired samples was performed (*Table 2*). No significant difference in number of carious lesions was found between the first 6 months (baseline to 6 months) and the second 6 months (6 months to 1 year) in either the xylitol gum ($P = 0.71$) or control groups ($P = 0.41$). Using MANOVA, no significant mean difference within pairs (first 6 months *vs*. second 6 months) or between the groups (xylitol gum *vs*. control groups) was found ($P = 0.49$). Regarding the influence of the 3-month xylitol gum consumption on plaque MS score development, the Wilcoxon test for paired samples revealed no significant difference between the first six months and the following 3 months in the xylitol gum group ($P = 0.74$); however, a significant difference was found between the two in the control group ($P < 0.01$). Using MANOVA, a significant mean difference within pairs (the first 6 months and the following 3 months) between the groups (xylitol gum and control groups) was observed ($P < 0.01$).

Table 2 Effect of 3-month xylitol gum consumption on caries development (a) and plaque MS score development (b)

(a)

Group	Caries development		*P*	
	Baseline to 6 months (I* to II†)	6 months to 1 year (II to IV‡)		
Xylitol gum ($n = 76$)	1.7 (0.3)§	1.6 (0.3)	0.71¶	
Control ($n = 85$)	1.6 (0.3)	1.8 (0.3)	0.41¶	0.49**

(b)

Group	Plaque MS score development		*P*	
	Baseline to 6 months (I to II)	6 to 9 months (II to III††)		
Xylitol gum ($n = 76$)	0.0 (0.1)‡‡	−0.1 (0.1)	0.74¶	
Control ($n = 85$)	−0.2 (0.1)	0.2 (0.1)	<0.01¶	<0.01**

*I, Examination at baseline.
†II, Examination at 6 months after the baseline survey.
‡IV, Examination at 1 year after the baseline survey.
§Development of dfs index, mean (SE).
¶Statistical analysis using the Wilcoxon (matched pairs) test.
**Mean difference within pairs between two groups using MANOVA.
††III, Examination at 9 months after the baseline survey.
‡‡Development of individual plaque MS score, mean (SE).

Single and multiple logistic analyses

To clarify the indicators that influenced plaque MS score development within the 3 months (from months 6 to 9), the dichotomised risk indicators were further analysed using logistic regression. A univariate analysis examined the ability of each of 19 variables to predict plaque MS score development during the xylitol gum-consumption period (months 6 to 9). Six variables showed statistically significant associations including xylitol gum consumption (xylitol gum consumption, no [control group]: OR, 0.45; 95% CI, 0.23–0.91) (*Table 3*). The following variables did not show any significant association with plaque MS score development ($P < 0.10$): age, gender, frequent snacks, habitual use of sweet drinks, brushing frequency <3 times/day, parents' teeth-cleaning habits, non-use of fluoride toothpaste, non-use of fluoride topical application, habitual consumption of sweet snacks, visible plaque (6 months), salivary MS score > 0 (6 months), salivary MS score development (baseline to 6 months), and plaque MS score development (baseline to 6 months). In the multivariate analysis, only xylitol consumption remained as a significant negative association in the final model ($P < 0.05$; *Table 3*).

Side effect

The percentage of children who experienced diarrhoea within the xylitol-consuming period (3 months, from 6 to 9 months after baseline) was 11% (8/76) in the xylitol-consuming children. Interestingly, 24% (11/45) of children, who did not consume gum well (their cumulative gum consumption was fewer than 100 pieces in three months), experienced diarrhoea, which proportion was larger than well-consumed children (11%).

Table 3 Univariate (a) and multiple (b) logistic regression analysis of caries-related factors for an association with plaque MS score development during xylitol gum consumption in the period (from II* to III†) in 3- to 4-year-old children (n = 161)

(a)

Variables	Category	Number of subjects	Development of plaque MS score from II to III			
			n (%)‡	OR	95% CI	P
Plaque MS score at II	0	79	18 (23)	1.00		
	>0	82	32 (39)	2.17	1.09–4.32	0.03
Salivary MS score at I§	0	106	27 (25)	1.00		
	>0	55	23 (42)	2.10	1.05–4.20	0.03
Caries experience at I	No	93	22 (24)	1.00		
	Yes	68	28 (41)	2.26	1.14–4.46	0.02
Caries experience at II	No	77	17 (22)	1.00		
	Yes	84	33 (39)	2.28	1.14–4.57	0.02
Caries development from I to II	No	91	22 (24)	1.00		
	Yes	70	28 (40)	2.09	1.06–4.12	0.03
Xylitol gum consumption	No	85	33 (39)	1.00		
	Yes	76	17 (22)	0.45	0.23–0.91	0.02

(b)

Variables	B	SE	OR	95% CI for OR	P
Plaque MS score at II: >0	0.25	0.23	1.66	0.67–4.10	0.27
Salivary MS score at I: >0	0.04	0.23	1.08	0.43–2.66	0.87
Caries experience at I: Yes	0.19	0.26	1.47	0.52–4.19	0.46
Caries experience at II: Yes	−0.00	0.40	1.00	0.20–4.75	1.00
Caries development from I to II: Yes	0.12	0.32	1.27	0.37–4.79	0.71
Xylitol gum consumption: Yes	−0.37	0.19	0.48	0.23–0.99	<0.05
Constant	0.84	0.21			<0.01

*II, Examination at 6 months after the baseline survey.
†III, Examination at 9 months after the baseline survey.
‡number (%).
§I, Examination at baseline.

DISCUSSION

This study investigated the effects of xylitol gum consumption on oral health at the youngest age studied, to our knowledge. In Japan it had not been permitted to use xylitol as a sugar substitute for food until 1997. When this study started in 2001, xylitol gum itself was not as popular within Japanese market as it is currently.

In the multivariate analysis, only xylitol consumption remained a significant negative association in the final model ($P < 0.05$). Xylitol gum consumption was significantly associated with reduced plaque MS, even after adjustment for different potential confounders like the oral hygiene variable (visible plaque) and dietary habits (habitual consumption of sweet snacks, habitual use of sweet drinks, frequent snacks) (data not shown). Certainly each of the other caries related factors including salivary MS level, plaque MS level, caries prevalence and caries development before the intervention had a significant association in the univariate model in this study. This result indicated that three months of xylitol gum consumption clearly reduced the amount of MS infection in Japanese preschool children (3–4-years-old), although each of the other caries related factors before the intervention still had an influence on the amount of MS infection in this study.

In order to observe how caries related factors including MS level changed without intervention, we started the intervention after 6 months. From the results in *Table 2*, no significant influence of 3-month xylitol gum consumption on caries development in the second 6 months (6 months to 1 year) was found. However, a significant mean difference within pairs (the first 6 months and the following 3 months) between the groups (xylitol gum and control groups) on plaque MS score development was observed ($P < 0.01$; MANOVA). This difference came from the significant difference between the first 6 months and the following 3 months in the control group ($P < 0.01$) and the absence of such a difference in the xylitol gum group ($P = 0.74$). Young children's eating and drinking habits are typically restricted when they go to preschool, but they are relatively free during the holidays[24]. Therefore, the most problematic period for controlling caries in young children is the summer holidays in Japan. This could be a reason for the significant difference in the control group. Although, the xylitol gum consumption period included

1.5 months of the summer holiday, the xylitol gum consumption itself may have reduced the likelihood of any increase in plaque MS score development during that time.

The culture and dental public health services in Japan differ from those in countries where other studies have been conducted[15–17], for example, access to fluoride is limited in Japan, and fluoride toothpaste is the only available source of fluoride[7]; the percentage of fluoride toothpaste users was 61% in this study (data not shown). Although most of the toothpastes included fluoride, toothpaste usage within young children was not so popular in Japan. Therefore, a report for fluoride toothpaste usage of infants and school children in Japan in 2003[25] mentioned 63% (894/1,410) of young children aged 3 and 4 years were fluoride toothpaste users. However, the results in these Japanese preschool children were consistent with previous studies in other countries. Moreover, the effects of xylitol gum on reducing plaque MS score development within 3 months (from 6 to 9 months) were clear, not only in the univariate model but also in the multivariate model. However, because of the short study period and the relatively small number of subjects, no significant difference was evident between the two groups in terms of caries development.

Although the amount of xylitol consumed was relatively small and the intervention period was short at three months, the percentage of children who experienced diarrhoea was 11% (8/76) in xylitol-consuming children. That in eliminated xylitol-group children (fewer than 100 pieces cumulative gum consumption in three months), was a larger proportion, 24% (11/45), than the former one. These results are quite different from a previous study in Japanese adult subjects in which no participants interrupted the study because of any side-effects of the xylitol chewing gum[19]. In other countries, most previous studies in children[10,15] and in adult[18] reported no adverse side effects but a few studies reported experiences of diarrhoea after xylitol consumption in children (2/157)[26] and adults (3/5)[27]. The reason for this side effect could be explained from the young age of the participants in this study and the original food culture in Japan. The tolerance for amounts of xylitol in those children would be expected to increase[28].

This study had several limitations. Firstly it did not use a control gum, which might have affected blinding and had an effect on salivary stimulation in the control children. However, the impact of chewing on plaque MS levels would be expected to be negligible. In previous studies, chewing a gum base 3–5 times a day[29] or sugar-free gum sweetened with sorbitol/maltitol[30] did not decrease MS levels. Second, the study was a blocked randomised trial. However, the preschools were within 2 km of one another and they have almost the same socio-economical and sociodemographical background.

Xylitol gum consumption over a 3-month period is effective in avoiding increased plaque mutans streptococci in 3–4-year-old children. Interestingly, over 10% of xylitol group children experienced diarrhoea, which was a much larger proportion than in previous investigations.

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