Oligomeric but not monomeric silica prevents aluminum absorption in humans[1–3]

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ABSTRACT

Background: Soluble silica, a ubiquitous component of the diet, may be the natural ligand for dietary aluminum and may prevent its accumulation and toxicity in animals. However, previous studies on the inhibition of aluminum absorption and toxicity by soluble silica have produced conflicting results. We recently identified a soluble silica polymer, oligomeric silica, that has a much higher affinity for aluminum than does monomeric silica and that may be involved in the sequestration of aluminum.

Objective: By using ^{26}Al as a tracer, we investigated the effects of oligomeric and monomeric silica on the bioavailability of aluminum (study 1) and compared the availability of silicon from oligomeric and monomeric silica in the human gastrointestinal tract (study 2).

Design: In study 1, three healthy volunteers each ingested aluminum alone (control), aluminum with oligomeric silica (17 mg), and aluminum with monomeric silica (17 mg). In study 2, five healthy volunteers ingested both the oligomeric and monomeric forms of silica (34 mg). Serum and urine samples were analyzed for aluminum and silicon.

Results: Oligomeric silica reduced the availability of aluminum by 67% (P = 0.01) compared with the control, whereas monomeric silica had no effect (P = 0.40). Monomeric silica was readily taken up from the gastrointestinal tract and then excreted in urine (53%), whereas oligomeric silica was not detectably absorbed or excreted.

Conclusions: The oligomeric, high-aluminum-affinity form of soluble silica reduces aluminum availability from the human gastrointestinal tract. Its potential role in the amelioration of aluminum toxicity in other biological systems requires attention. *Am J Clin Nutr* 2000;71:944–9.

KEY WORDS Oligomeric silica, monomeric silica, orthosilicic acid, silicon, silicic acid, silica, aluminum, absorption, bioavailability, gastrointestinal uptake, accelerator mass spectrometry

INTRODUCTION

Soluble silica (silicic acid) is ubiquitous in the diet [20–50 mg Si/d (1)] and natural waters [0.8–44 mg Si/L (2)] and, unlike crystalline silica (quartz), it has no associated toxicity. Indeed, in veterinary and laboratory animals, silicon is important in the synthesis of collagen and bone (3–5). The few supplementation studies in humans have also shown associated increases in trabecular bone volume (6) and bone mineral density (7). Silica deprivation experiments in the 1970s in growing chicks (8) and rats (9) suggested that silica is essential for normal growth and development, although this remains to be confirmed. Birchall (10) suggested that soluble silica is essential to living organisms because it binds endogenous aluminum and thereby prevents its toxicity. Although some experiments clearly showed that soluble silica reduced aluminum bioavailability, toxicity, or both (11–16), others failed to show any such effects (16–18).

However, studies have focused on monomeric silica [$Si(OH)_4$], also termed orthosilicic acid, but this form has a low affinity for Al^{3+} (log K_{eff} = 4.7 ± 0.05, where K_{eff} is the effective stability constant, at pH 7.2) (19) and recent data suggest that for efficient binding of aluminum and silica, at least one needs to be polymeric. Duan and Gregory (20) showed an interaction between monomeric silica and polyhydroxy aluminum, whereas we showed the marked interaction between oligomeric silica, a polymer of Si(OH)4, and monomeric aluminum (log Ke_{ff} = 11.70 ± 0.30 at pH 7.2) (21).

Oligomeric silica is formed as a metastable intermediate in the progressive polymerization of silicic acid in neutral solutions at concentrations >2 mmol/L and, when diluted (<2 mmol/L), is transiently stable (<1–50 d) depending on the aluminum concentration (21). Thus, the weathering and dissolution of solid-phase silica and certain pore waters are probable environmental sources of oligomeric silica (2, 22). Oligomeric silica has yet to

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be fully characterized, but studies so far suggest that it is colloidal with a mean particle diameter of <20 nm (R Jugdaohsingh, RPH Thompson, and JJ Powell, unpublished observations, 1998) and that it forms a high-affinity complex with aluminum with a molar ratio of 35 silicon:1 aluminum (21).

In this article we report the effects of monomeric and oligomeric silica, given in amounts typical of human diets, on the bioavailability of aluminum in healthy subjects (study 1). Absorption of aluminum into serum and its excretion in urine were monitored by using the ^{26}Al tracer isotope, allowing for investigation of typical dietary amounts (5 mg/d) of aluminum (23). We also looked separately at the bioavailability of the 2 different forms of silica when ingested in the absence of aluminum (study 2). This work aimed to clarify the conflicting results in the literature on the amelioration of aluminum availability by soluble silica (11–18).

SUBJECTS AND METHODS

Subjects

For both studies 1 and 2, healthy volunteers with normal creatinine clearance (112–119 mL/min) were recruited from the Gastrointestinal Laboratory (St Thomas' Hospital). The subjects in study 1 were 3 men with a mean (±SD) age of 29 ± 4 y, weight of 76.9 ± 11.2 kg, height of 177 ± 10 cm, and body mass index (BMI, in kg/m^2) of 24.4 ± 2.2. In study 2, the subjects were 3 men and 2 women with a mean (±SD) age of 28 ± 3 y, weight of 66.4 ± 12.6 kg, height of 170 ± 11 cm, and BMI of 22.8 ± 2.4. The subjects had not taken ^{26}Al tracer isotope previously.

Approval of the study was obtained from St Thomas' Hospital Local Research Ethics Committee. The dose of ^{26}Al tracer isotope was approved by the Administration of Radioactive Substances Advisory Committee support unit of the Department of Health, United Kingdom. Details of the study and potential risks associated with the ^{26}Al radioisotope were explained to the volunteers, all of whom signed consent forms before the study began.

Dietary restrictions

Throughout the study periods, subjects ingested an unrestricted diet except that they avoided foods high in silicon and aluminum and foods that might affect aluminum uptake and excretion. The latter included foods containing aluminum chelators, such as polyphenols and citric acid, and those that cause diuresis, such as tea, coffee, and alcohol. Subjects consumed 2–2.5 L fluid daily and recorded their diet during the study periods. Before ingestion of the solution, the subjects fasted overnight from 2200 and continued to fast the next day until 5 h after ingesting the test solution at ≈1400.

Aluminum radioisotope

The ^{26}Al radioisotope has a half-life of 730 000 y and decays with emission of positrons and gamma radiation. The 3 men in study 1 each ingested 453 ± 12 ng (323.6 ± 8.6 Bq) ^{26}Al on 3 occasions. This was a small amount of radiation with an effective dose equivalent to the whole body of 1.94 ± 0.05 μSv per dose (equivalent to one-fiftieth of a single, modern chest X-ray).

Materials

The water was ultrapure (18 MΩ/cm) from an Elga water purifier (Elga, High Wycombe, United Kingdom). Silica was prepared in water from a stock basic (4.87 mol NaOH/L) concentrated sodium silicate solution (7 mol Si/L; Aldrich Chemical Co, Gillingham, United Kingdom). ^{26}Al (10 MBq/L in 1 mol HCl/L) was supplied by the Los Alamos National Laboratory, Isotope and Nuclear Chemistry Division, University of California. We prepared a stock aluminum tracer solution containing 4.47 μg ^{26}Al and 1.35 mg ^{27}Al in 1 mol HCl/L. We used citric acid monohydrate (crystalline, extra pure; Merck Ltd, Lutterworth, United Kingdom) prepared in ultrapure water. Polypropylene plastic ware (Merck Ltd, Aldrich Chemical Co, and Elkay Laboratory Products Ltd, Basingstoke, United Kingdom), acid-washed (10% nitric acid by vol) for 24 h and rinsed with ultrapure water, was used throughout. Clean-air facilities (class J clean-air room and class C laminar-air-flow workstation) were used when appropriate to avoid contamination of samples with silicon and aluminum.

Silica preparation

We prepared oligomeric silica, fresh on each occasion, at 42 mmol Si/L by dilution of the stock sodium silicate solution and neutralization to pH 7.2 with HCl. This 42-mmol/L solution was incubated at room temperature for 24 h before dilution (1–2 mmol Si/L) to prepare the doses. Monomeric silica was prepared either by incubation (>7 d) at room temperature (23°C) of the 2-mmol/L oligomeric solution to allow its depolymerization (study 2) or by direct dilution of the stock sodium silicate solution (to 1 mmol/L) followed by incubation (>7 d) at room temperature (study 1).

Study design

Study 1: ingestion of aluminum in the presence and absence of silica

This study was conducted in 3 male volunteers over 8 wk. Each subject ingested 3 different aluminum solutions: aluminum citrate with oligomeric silica (week 1), aluminum citrate with monomeric silica (week 5), and aluminum citrate alone (week 8). On day 1 of each study week, each subject collected his urine in a single container for 24 h; this was the predose urine. On day 2 at 0930, after fasting overnight, subjects ingested 621 mL of the dose solution (pH 7.2) containing aluminum citrate [137 μg ^{27}Al (8.1 μmol/L) plus 453 ± 12 ng ^{26}Al with 80.8 μmol citrate/L] that had been incubated, with or without silica (1 mmol Si/L), for 48 h. All postdose urine was collected for a total of 72 h (in 3 × 4 h, then 1 × 12 h, and then 2 × 24 h collections). Blood samples (10 mL) were also collected via an all-plastic intravenous cannula (Medicut, 1.3 mm outer diameter × 45 mm; Sherwood Medical, Tullamore, Ireland) inserted into a forearm vein; we collected 1 predose sample and additional samples at intervals during the 72-h postdose period. Isotopic abundance ratios of ^{26}Al to ^{27}Al were measured in urine, serum, and dose samples by using accelerator mass spectrometry (Australian National University, Canberra) as described previously (18, 24). Total silicon was measured in solutions by inductively coupled plasma optical emission spectrometry (ICPOES) as reported previously (25, 26). The percentage of monomeric silica in aliquots of the solutions was determined at the time of each ingestion, as described previously (21), by reaction with molybdic acid (27). In addition, amounts of ultrafilterable silicon and aluminum were determined in aliquots by using filter units (5000 nominal molecular weight, Biomax Ultrafree-15; Millipore, Watford, United Kingdom). Filtrates were analyzed for silicon and aluminum by ICPOES. ^{26}Al that was adherent to emptied dose containers was measured in

thorough acid rinses (1% nitric acid by vol) by accelerator mass spectrometry.

Study 2: ingestion of silica in the absence of aluminum

This study was conducted in 5 volunteers (3 men and 2 women) over 3 wk. Silica solutions (2 mmol Si/L) were ingested by subjects to facilitate the detection of urinary silica excretion above baseline. In week 1, each subject ingested 600 mL of 1.5 L of their oligomeric silica solution (2 mmol Si/L, pH 7.2). In week 3, after natural depolymerization of the silica solutions over time, an additional 600-mL dose was ingested by each volunteer. In both study weeks, day 1 was used as a run-in period when dietary restrictions (*see* above) were observed. On day 2, two predose urine collections, each of which lasted 8 h (0–8 h and 16–24 h), were performed. After ingestion of silica on day 3, postdose urine was collected for four 8-h periods (total of 32 h). In 2 volunteers, 1 predose and postdose blood samples (5 mL) were also collected via an intravenous all-plastic cannula at various intervals over 24 h. Urine, serum, and aliquots of the silica solutions were analyzed for total silicon by using ICPOES as described previously. Monomeric silica in the dose solutions was determined at the time of ingestion, as described above, by ultrafiltration and reaction with molybdic acid.

Statistical analysis

The results are expressed as means ± SDs. In study 1, we tested the hypothesis that soluble silica reduces the gastrointestinal availability of aluminum; comparisons were made by using paired, one-tailed Student's *t* tests. Because 2 forms of silica were investigated, a Bonferroni correction for multiplicity of testing was applied to the *P* values and significance was defined as $P < 0.025$ (0.05/2). Correlations between urinary and serum concentrations of aluminum were assessed by using Pearson's product-moment correlation coefficients, with significance defined as $P < 0.05$. In study 2, we investigated which of the 2 forms of silica was bioavailable from the gastrointestinal tract; comparison was by paired, one-tailed Student's *t* test and significance was defined as $P < 0.05$.

RESULTS

Study 1: ingestion of aluminum in the presence and absence of silica

Each subject ($n = 3$) ingested 3 aluminum-containing solutions at 3–4-wk intervals (during weeks 1, 5, and 8). During

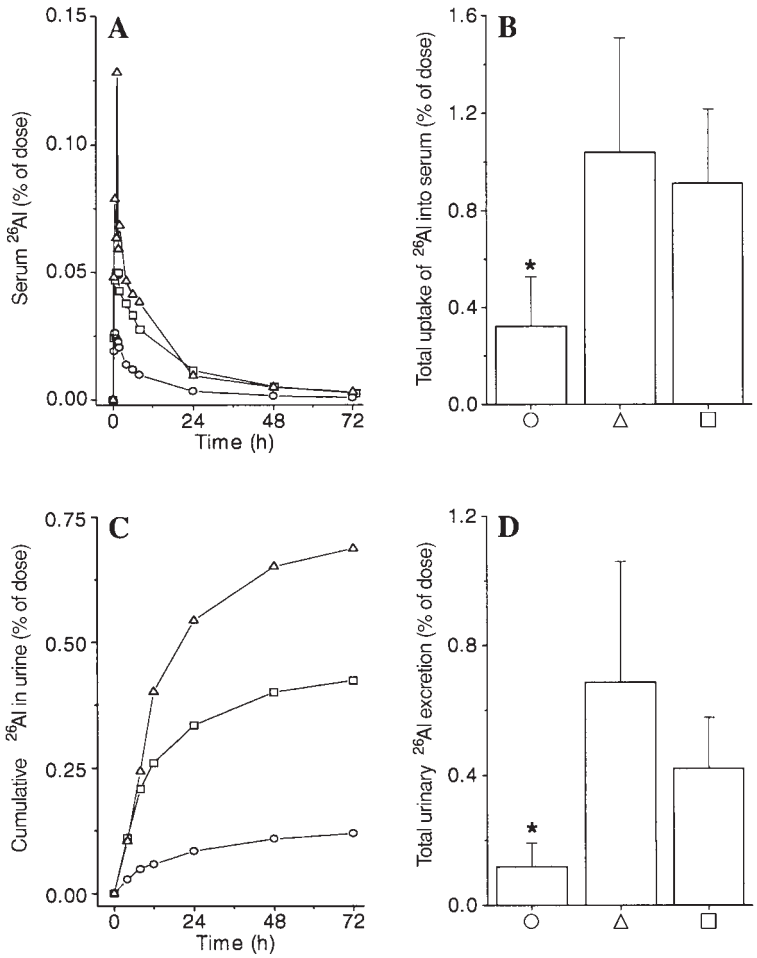

FIGURE 1. Study 1: the effect of silica on the bioavailability of aluminum after ingestion of ^{26}Al-labeled aluminum citrate with oligomeric silica (○), ^{26}Al-labeled aluminum citrate with monomeric silica (△), and ^{26}Al-labeled aluminum citrate alone (control; □); $n = 3$ (A and C). B: Mean (± SD) total uptake of ^{26}Al into serum over 72 h derived from the area under the serum curve. *Significantly different from control, $P = 0.01$ (paired, one-tailed *t* test). D: Mean (± SD) total excretion of ^{26}Al in urine over 72 h. *Significantly different from control, $P = 0.02$ (paired, one-tailed *t* test).

week 1, aluminum (5 μmol) citrate (50 μmol) was ingested in a solution of oligomeric silica (583 μmol Si). In vitro experiments showed that, in this solution, silicon and aluminum were 36% and 6.4% ultrafilterable (ie, <5000 molecular weight), respectively, and silicon was 51% reactive with molybdic acid (ie, 51% of silica was in the monomeric form). During week 5, aluminum (5 μmol) citrate (50 μmol) was ingested in a solution of monomeric silica (603 μmol Si). In vitro studies showed that silicon and aluminum were 95% and 83% ultrafilterable, respectively, and silicon was 99% reactive with molybdic acid. During week 8, aluminum (5 μmol) citrate (50 μmol) was ingested alone in ultrapure water and the aluminum was 87% ultrafilterable in this solution. After the solutions were ingested, we performed vigorous acid rinses and analysis by accelerator mass spectrometry that confirmed that negligible quantities of aluminum remained adherent to the empty containers (0.064 ± 0.032% of the ingested dose; $n = 9$).

In all cases, ingestion of the solutions increased the concentrations of aluminum in serum over the 72-h study period (**Figure 1**A), although oligomeric silica significantly reduced the appearance of aluminum in serum by 67 ± 13% ($n = 3$, $P = 0.01$) compared with the control solution of aluminum without silica (Figure 1B). In contrast, aluminum with monomeric silica did not differ significantly from the control. Results in urine (Figure 1C) mirrored those in serum (Figure 1A); urinary aluminum excretion was reduced by 72 ± 12% compared with the control ($n = 3$, $P = 0.02$) when aluminum was ingested with oligomeric silica but did not differ significantly from the control when aluminum was ingested with monomeric silica (Figure 1D). The area under the curve of aluminum in serum (0–72 h) was significantly correlated with aluminum excreted in urine over the same period ($r = 0.86$, $P < 0.01$; $n = 9$), which suggests that the absorption-excretion profiles of aluminum were similar for the 3 solutions.

Study 2: ingestion of silica in the absence of aluminum

In a second, separate study, the availability of oligomeric and monomeric silica from the gastrointestinal tract was investigated in the absence of aluminum. Oligomeric silica was prepared (day 0) at a concentration of 2 mmol/L. The depolymerization of this oligomeric silica solution was confirmed between days 0 and 14 by using both reaction with molybdic acid and ultrafiltration (**Figure 2**). On each occasion (day 0 and day 14), 600 mL of solution (1.2 mmol Si) was ingested by each healthy volunteer ($n = 5$). In marked contrast with the bioavailability of monomeric silica on day 14, the bioavailability of oligomeric silica on day 0 was poor (**Figure 3**). Analysis of urine showed significantly increased excretion of silicon between 0 and 8 h postdose ($P < 0.001$) after ingestion of monomeric silica (53.2 ± 8.5% of dose solution, $n = 5$), but only a marginal increase after ingestion of oligomeric silica (Figure 3B). This marginal increase in urinary excretion of silicon after ingestion of oligomeric silica may represent contamination of the solution with monomeric silica (Figure 2). In 2 of the volunteers, sequential blood samples were also obtained and they confirmed that the availability of silicon from the monomeric silica solution (day 14) was >20% of the ingested dose, greatly exceeding its availability from oligomeric silica (day 0), which was not detectable (Figure 3A).

Oligomeric silica is predominately negatively charged and therefore interaction with mucus and coelimination in feces, as happens with dietary cations, is unlikely. The large size of the oligomeric silica species, which was not ultrafilterable (Figure 2) and had a mean diameter of <20 nm by particle light scattering (R Jugdaohsingh, RPH Thompson, and JJ Powell, unpublished observations, 1998), probably precludes significant passive absorption (28). However, the low availability of silicon from oligomeric silica also suggests that even during transit through the gastrointestinal tract, the species was not greatly broken down or absorbed.

DISCUSSION

Our previous studies showed that oligomeric silica has a high affinity for aluminum and that 280 μmol Si/L chelates 8 μmol Al/L (21). Hence ≈8 μmol Al/L was used in this study with a concentration of silicon (≈1000 μmol/L) that ensured excess aluminum-binding capacity. Before ingestion, all solutions were incubated for 48 h to ensure that binding was complete between silica and aluminum and also to allow silica not bound to aluminum to depolymerize fully (21). Citrate was used as the

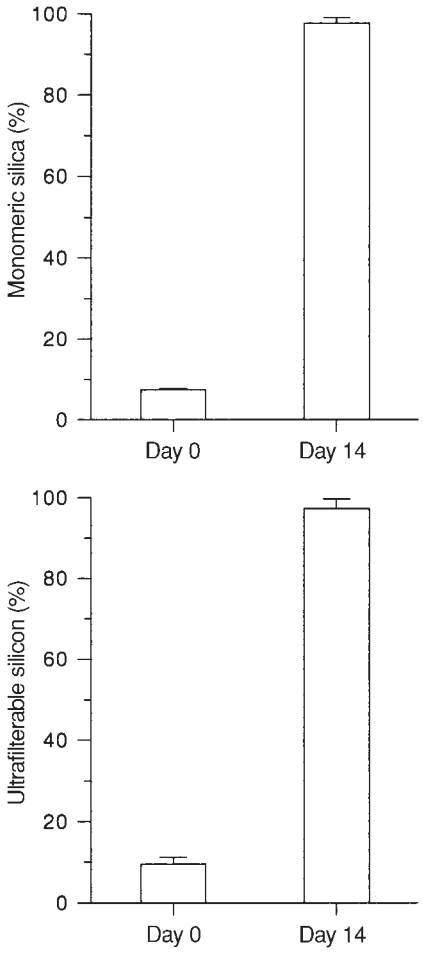

FIGURE 2. Study 2: mean (± SD) silica speciation in 2-mmol/L solutions over time ($n = 5$). Silica was prepared in oligomeric form on day 0; at this time, only a small percentage of contaminant monomeric silica [$Si(OH)_4$] was measured by reaction with molybdic acid and a low proportion of monomeric silica contamination was confirmed in this solution by ultrafiltration (<5000 molecular weight). In contrast, by day 14 silica was >98% depolymerized to monomeric silica and a similarly high percentage was ultrafilterable.

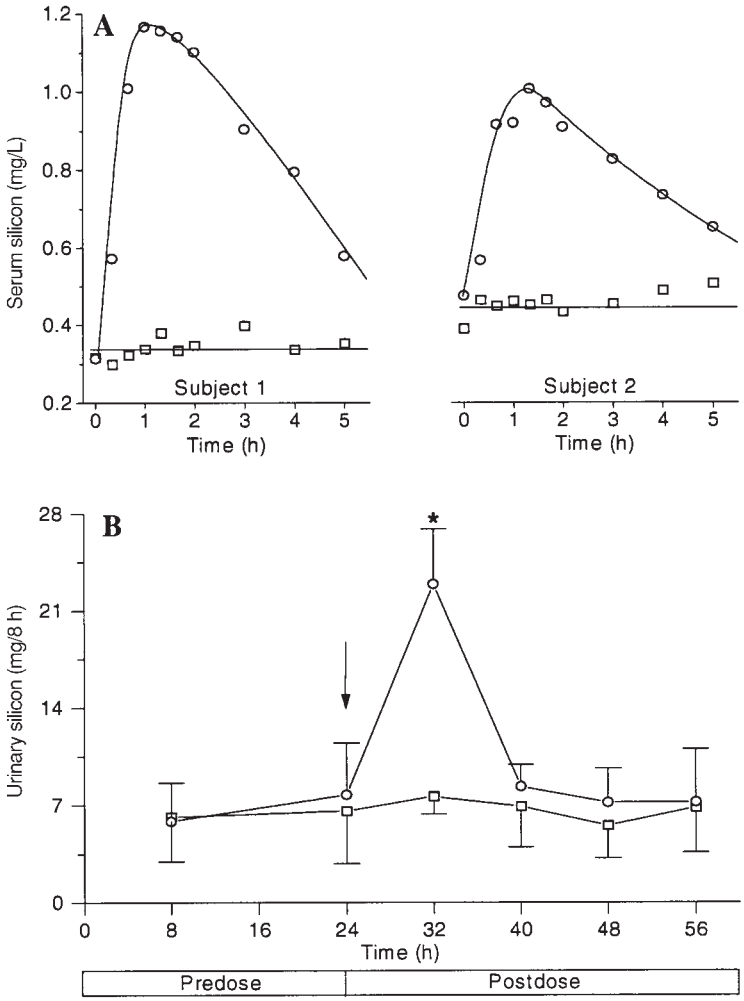

FIGURE 3. Study 2: availability of silicon from 2-mmol/L solution over time. Silica was prepared in oligomeric form. After its ingestion (time 0 in A and indicated by arrow in B), there was no significant increase in serum silicon concentration (A; □) or mean (± SD; n = 5) excretion in urine (B; □). In contrast, with the same solution on day 14 when silica was > 98% monomeric, there was a marked increase in serum silicon concentration (A; ○) and excretion into urine (B; ○). *Urinary excretion of silicon was significantly greater 0–8 h postdose with monomeric than with oligomeric silica, $P < 0.001$ (paired one-tailed t test).

aluminum counter ion because it maintains aluminum in a monomeric form in aqueous solution, it prevents adhesion of Al^{3+} to the dosing containers, and silica has been shown to affect aluminum availability even in the presence of citrate (12, 14). The concentrations of aluminum and silicon used in this study fall within the broad dietary ranges for these elements. Nonetheless, the results have wide application because oligomeric silica binds to aluminum rapidly in many different forms and under a range of experimental conditions (21; R Jugdaohsingh, RPH Thompson, and JJ Powell, unpublished observations, 1999).

Oligomeric silica reduced both the serum concentrations and urinary excretion of aluminum. Indeed, urinary and serum aluminum concentrations were correlated, suggesting similar absorption-excretion profiles. Because there are no other routes of aluminum excretion (29), this is consistent with reduced aluminum absorption. Thus, our data suggest that the strong interaction observed in vitro (21) between oligomeric silica and aluminum is maintained in the human gastrointestinal tract, leading to a marked reduction in the absorption of aluminum. The large colloidal size of the oligomeric silica species virtually precludes passive diffusion of the silica-aluminum complex (28). This is unlike the situation with monomeric silica, which is easily absorbed and has a low affinity for aluminum (19, 21) and no effect on the gastrointestinal absorption of aluminum.

Clearly, research on environmental or biological systems that aims to show interactions between soluble silica and aluminum now must distinguish carefully between these different forms of silica. Indeed, traces of oligomeric silica in solution will profoundly affect the availability of aluminum and would readily account for discrepancies in results published regarding the amelioration of aluminum absorption and toxicity by silica (11–18). In studies in which concentrated silica is added to aluminum-containing solutions before dilution (13, 14), the formation of oligomeric silica–aluminum complexes with associated aluminum-ameliorating effects is likely. In contrast, in studies in which concentrated silica solutions are diluted before addition to aluminum (17, 18), the formation of monomeric silica without effects on aluminum binding or amelioration is likely.

However, in any study in which the soluble silica concentration of freshly prepared solutions approaches or is >2 mmol/L at or near neutral pH (11, 15, 16), the formation of oligomeric silica is likely and amelioration of aluminum effects should be observed.

This work also raises questions about biologically relevant forms of dietary silica. Previous investigations (17, 18, 30) focused on absorbable monomeric silica, whereas the more common, poorly absorbed fraction of polymeric and oligomeric dietary silica may be of greater importance in preventing the uptake of aluminum. To determine whether oligomeric silica is absorbed at all will require further studies with silicon-based radioisotopes (31). Indeed, colloidal species of this size are normally absorbed passively at 1–5% of the ingested dose (32). Alternatively, if after absorption silica concentrates at its biological site of action, then the in situ formation of oligomeric silica could occur, leading to local sequestration of Al^{3+} ions. For example, in one study it was suggested that silica concentrates in the renal tubule allowing interaction with, and facilitated excretion of, aluminum (30). In the current study, ingestion of monomeric silica increased urinary aluminum excretion compared with ingestion of aluminum alone in 2 of the 3 subjects, but this effect was not significant and will need to be addressed in a separate study.

Finally, the current findings do not exclude a role for monomeric silica in other aspects of cellular or structural biology. However, monomeric silica itself is unlikely to contribute to the natural sequestration of toxic and ubiquitous Al^{3+} ions.

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