Scientific Studies
SiliciuMax® Pó

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Biodisponibilidade

Biodisponibilidade nutricional comparativa do silício estabilizado em maltodextrina (SiliciuMax® Pó)

Introdução

A biodisponibilidade do silício (Si) à partir da suplementação de ácido ortossilícico estabilizado em maltodextrina (SiliciuMax® Pó - Silicium España) foi avaliada por Boqué e Arola (2015) no centro de pesquisa CTNS (Centre Tecnològic de Nutricioò I Salut) da Universitat Rovira i Virgili na cidade espanhola de Reus, situada na província de Tarragona na comunidade autônoma da Catalunha.

Metodologia

O estudo foi randomizado, cruzado, controlado e conduzido com 3 grupos de voluntários humanos sadios em situação pós-prandial. A dose empregada de diferentes suplementos de silica no tratamento foi equivalente a 21,6 mg de silício organico, incluindo o ácido ortossilícico estabilizado em maltodextrina (SiliciuMax® Pó).

A biodisponibilidade de diferentes suplementos de silício foi avaliada através da varíavel principal relacionada à excreção urinária de silício. De acordo com Pruksa e colaboradores (2014), o silício excretado na urina é uma medida totalmente confiável e fornece uma ideia correta da biodisponibilidade e absorção do silício após a sobrecarga do mesmo.

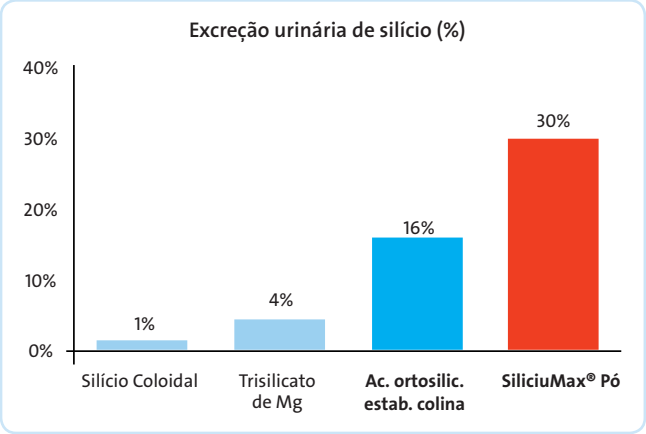
Posteriormente a realização desse estudo, os resultados foram comparados com os dados publicados no estudo de Spripanyakorn e colaboradores no qual a biodisponibilidade de várias fontes suplementares de silício também foram avaliadas em humanos (2009).

Resultados

Os resultados do estudo mostraram que a biodisponibilidade do ácido ortossilícico estabilizado em maltodextrina (SiliciuMax® Pó), determinada pela excreção urinária total determinada através da análise da coleta da urina em 2 períodos concluiu que a excreção urinária de silício no período compreendido entre 3 e 6 horas após a ingestão do ácido ortossilícico estabilizado em maltodextrina (SiliciuMax® Pó) na dose equivalente a 21,6mg silício elementar foi aproximadamente de 30% dessa dose ingerida (ver tabela I). A excreção urinária de silício provê uma ideia da cinética de absorção do silício à partir da suplementação. Os efeitos adversos relacionados com a suplementação foram classificados como mínimos e a aderência dos pacientes durante a avaliação foi de 100% .

Tabela I. Excreção urinária de Si (% da dose)

Adaptado à partir dos dados obtidos por Sripanyakorn e colaboradores (2009) e do estudo de Boqué e Arola (2015).



Nutritional bioavailability study comparative of three silica rich food complements, Centre Tecnològic de Nutricioò I Salut, 2015 October

Discussão e conclusão

A análise da quantidade total de silício excretada na urina dos indivíduos sadios que participaram do estudo reflete a absorção desse elemento à partir da ingestão de suplementos de silício e os níveis obtidos permaneceram acima dos valores basais. A porcentagem de absorção de silício à partir do consumo de alimentos convencionais é baixa e o níveis de absorção são muito inferiores aos obtidos nesse estudo.

Segundo Pruksa e colaboradores (2014) o silício excretado na urina é uma medida confiável e acurada da absorção de sílica após uma sobrecarga desse elemento. Além disso, de acordo com esses mesmos pesquisadores, a coleta de urina durante o período coberto nesse estudo (0-6horas) é suficiente para estimar acuradamente a absorção/biodisponibilidade do silício à partir de alimentos ou suplementos (PRUKSA et al., 2014). A confiabilidade dos dados obtidos é reforçada pelos dados apresentados por Reffit (1999) onde a concentração de silício no sangue (AUC) foi significativamente correlacionada com os níveis de silício excretados na urina. A quantificação de silício no sangue é complexa e devida aos seus níveis serem constantes, mas muito baixos. Isso ocorre devido o silício, uma vez ingerido e absorvido no intestino, ser rapidamente distribuído para os tecidos sem se ligar a nenhuma proteína ou ser rapidamente excretado na urina (SRIPANYAKORN, 2005). Nesse contexto, a função renal parece ser um fator determinante na concentração de silício no plasma sanguíneo. A prova disso é a observação em indivíduos saudáveis de um clearance renal do silício plasmático (quantidade de silício filtrado pelos rins e que aparece na urina) de 70-80%, com uma excreção diária total de cerca de 20mg (dose do estudo). Portanto, de acordo com o encontrado em várias pesquisas, a excreção urinária de silício é um bom indicador da ingestão de silício (REFFITT,1999; WIDNER, 1998; PRUKSA, 2014).

No estudo de Sripanyakorn e colaboradores (2009) publicado no British Journal of Nutrition, foi analisado a biodisponibilidade do silício presente em diferentes alimentos e suplementos. A absorção do silício à partir do ácido ortossilícico estabilizado em colina, trissilicato de magnésio e sílica coloidal foram baixas, respectivamente de 16%, 4% e 1% (SRIPANYAKORN et al., 2009). Os resultados desse estudo confirma a tese que a absorção de silício correlaciona-se de forma inversamente proporcional ao grau de polimerização desse mineral. Portanto, a absorção de silício depende não somente se a fonte de silício é orgânica ou inorgânica, mas também se sua forma é monomérica ou polimérica. Formas poliméricas como a sílica coloidal (dióxido de silício coloidal) apresentam uma menor biodisponibilidade. No estudo realizado por Boqué e Arola (2015) a taxa de absorção de silício encontrada para o silício estabilizado em maltodextrina (SiliciuMax® Pó) foi de 30%. Entretanto, o estudo foi conduzido pela fração de apenas 6 horas e embora seja esse o período quando ocorre o pico de excreção urinária do silício, a remoção pela urina do silício ingerido continuará até cerca de 12 horas após a ingestão. Portanto, é possível que os níveis de silício obtidos para o silício estabilizado com maltodextrina sejam ainda um pouco maiores caso a avaliação se prolongue por até 12horas.

A alta hidrossolubilidade do silício estabilizado em maltodextrina (SiliciuMax® Pó) também pode explicar sua boa biodisponibilidade oral, visto que a mesma pode ser limitada pela baixa solubilidade do ingrediente ativo no fluido gastrintestinal (AMIDON et al., 2005). Portanto, é também esperado que a biodisponilidade do silício estabilizado em maltodextrina seja maior que outras formas menos solúveis tal como silício estabilizado em moléculas de natureza proteica.

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The comparative absorption of silicon from different foods and food supplements

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Dietary Si (orthosilicic acid; OSA) appears important in connective tissue health, and although the sources and intakes of Si are well established, its absorption is not. Si absorption was measured from eight high-Si-containing sources: alcohol-free beer; OSA solution (positive control); bananas; green beans; supplemental choline-stabilised OSA (ChOSA); supplemental monomethyl silanetriol (MMST); supplemental colloidal silica (CS); magnesium trisilicate British Pharmacopoeia antacid (MTBP). Two of the supplements and the antacid were pre-selected following an *in vitro* dissolution assay. Fasting, healthy subjects (CS, n 3; others, $n \geq 5$) each ingested two of the sources separated by a 1-week wash-out period. Blood and urine were collected and measured for total Si concentrations by inductively coupled plasma optical emission spectrometry. Absorption, based on urinary Si excretion, was highest for MMST and alcohol-free beer (64 % of dose), followed by green beans (44 %), OSA (43 %), ChOSA (17 %), bananas and MTBP (4 %) and CS (1 %). Peak serum concentrations occurred by 0.5 h for MMST and green beans, 1.5 h for OSA and alcohol-free beer, 2 h for ChOSA and CS, and 4 h for MTBP. Area under the serum curves correlated positively with urinary Si output (r 0·82; $P<0·0001$). Absorption of Si from supplements and antacids was consistent with their known chemical speciation and kinetics of dissolution under simulated gastrointestinal conditions. Monomeric silicates were readily absorbed, while particulate silicates were decreasingly well absorbed with increasing polymerisation. The present results highlight the need to allow for relative absorption of Si from different foods or supplements in subsequent epidemiological and intervention studies.

Dietary silicon: Silicon supplements: Absorption: Gastrointestinal dissolution

It is well reported that Si plays a role in optimal connective tissue formation, especially for skin and bone health[1–3]. One important driver for this association has been epidemiological studies showing relationships between dietary Si intakes and bone mineral density: originally reported in a US cohort[4], the positive association between dietary Si intake and bone mineral density has now been repeated in a UK cohort[5]. Nonetheless, this relationship is based upon Si intake[6] rather than Si availability (absorption) from the diet[4] and there is evidence that Si absorption from different foods varies (Jugdaohsingh *et al.*[7] and Table 1). With sufficient information a correction for different dietary Si availabilities could be considered in epidemiological studies.

Bananas have a high Si content (about 5·5 mg/100 g), but preliminary evidence suggests that Si absorption is negligible (about 2 %) compared, for example, with green beans, which are high in absorbable Si (about 2·5 mg Si/100 g and about 50 % absorbed)[7]. In addition, supplemental Si is used widely and likely to vary in intestinal availability (<1 to 50 %) depending on its chemical form[8,9]. Supplemental Si is generally purposeful (self-administered), but may also be inadvertent, such as through the long-term ingestion of silicate-containing antacids[10,11]. In our experience different countries tend to favour very different forms of Si supplements and these may be expected to have different absorption profiles; for example, organic Si, typically monomethyl silanetriol (MMST), is commonly used in France, whereas colloidal mineral Si appears to be more common in Germany, and choline-stabilised orthosilicic acid (ChOSA) in Belgium[8]. The chemistries of these differ in that MMST is not only organic but also monomeric, while the other silicates show varying degrees of polymerisation, which may explain the differential absorption that experiments in rats and preliminary experiments in human subjects have suggested[7,12,13]. Indeed, collation of findings from several papers suggests all of the above, but none of this work has been undertaken in one study – i.e. a side-by-side comparison study. Thus the purpose of the present study was to include the ingestible sources of high Si content in one study and determine their relative/comparative absorption. This may not only better inform dietary

Abbreviations: BP, British Pharmacopoeia; ChOSA, choline-stabilised orthosilicic acid; ICPOES, inductively coupled plasma optical emission spectrometry; MMST, monomethyl silanetriol; SGIF, simulated gastrointestinal fluid; UHP, ultra-high purity.

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Table 1. Silicon content of foods and its availability

(Mean values and ranges and mean values with their standard errors)

Food groups	Si content (mg/100 g)*			Si content per portion*		Estimated absorption (% ingested dose)†	
	Number of samples	Mean	Range	Si (mg/portion)	Mean portion size	Mean	SE
Cereals, grains and products							
Breakfast cereals	16	7·79	1·34–23·4	2·92	37·5 g	43·6	5·6
Breads and flour	15	2·87	0·34–6·17	1·45	50·5 g	25·7	7·6
Biscuits	5	1·56	1·05–2·44	0·406	26 g		
Rice	8	1·54	0·88–3·76	1·85	120 g	52·6	6·6
Pasta	7	1·11	0·62–1·84	2·55	230 g	58·3	
Fruits							
Raw and canned	33	1·34	0·1–4·77	1·35	101 g	13·7	7·4
Dried	3	10·54	6·09–16·61	3·51	33·3 g	16·6	3·8
Vegetables	49	1·79	0·1–8·73	1·25	70 g	26·3	12·3
Legumes	11	1·46	0·38–4·42	0·759	52 g		
Nuts and seeds	4	0·78	0·28–1·99	0·174	22·3 g		
Milk and milk products	3 + TDS	0·31	0·07–0·47	0·288	93 g		
Meat and meat products	TDS		0·1–1·89	0·125–2·36	125 g		
Beverages (non-alcoholic)							
Tap water	11	0·37	0·10–0·61	0·740	200 g	49·3‡	5·4
Mineral and spring waters	14	0·55	0·24–1·46	1·82	330 g	52·1	1·9
Tea and coffee§	6	0·51	0·24–0·86	1·33	260 g		
Fruit juices§	11	0·38	0·05–1·5	0·866	228 g		
Fizzy and carbonated drinks§	6	0·15	0·11–0·19	0·507	338 g		
Milk-based drinks§	6	1·3	0·2–3·96	3·38	260 g		
Beverages (alcoholic)							
Beers	76	1·92	0·9–3·94	6·37 11·0	Can or bottle 1 pint (568 ml)	55‖	9·7
Wines§	3	1·35	0·68–2·31	1·69	125 g		
Port and sherries§	2		1·24–1·26	0·62–0·63	50 g		
Liquor and spirits§	1	0·13	0·06–0·20	0·052	40 g		

TDS, sample from the UK Food Standards Agency Total Diet Study[22].

* Si content of foods is from Powell *et al.* [6].

† Percentage estimated absorption of Si is from Jugdaohsingh *et al.* [7], where urinary Si excretion (0–6 h) was used as a surrogate marker for absorbed Si. Data are from three subjects (two males and one female) each ingesting between two and five different foods in the appropriate food group except for pasta and raisins. Only one sort of pasta was ingested by two subjects and one type of raisin by three subjects.

‡ Data are from Reffitt *et al.* [14]; eight subjects (six males and two females). Urine collection was 0–8 h in five subjects and 0–4 h in three subjects.

§ Although not investigated, the availability of Si in these beverages is likely to be similar to drinking water and beer (about 50 %).

‖ Data are from Sripanyakorn *et al.* [15]; nine subjects (five males and four females). Urine collection was 0–6 h.

Si databases for use in epidemiological studies, so that they can be refined to take account of intestinal availability, but is also relevant to recent Food and Drug Administration and European Union efforts to use micronutrient absorption from supplements as one indication of their quality.

Here we used an *in vitro* screening assay and then followed with an *in vivo* absorption protocol based upon previous work that used urinary Si as a proxy for Si absorption[14].

Materials and methods

Materials

Water was ultra-high purity (UHP; 18 MΩ/cm) from an Elga water purifier (Elga Ltd, High Wycombe, Bucks, UK). Horsetail capsules were purchased from Good 'n' Natural Manufacturing Corporation (Bohemia, NY, USA). High-strength silica complex tablets (referred to as 'silica complex' in the following text) were from Holland and Barrett (Nuneaton, Warwicks, UK). ChOSA was obtained from BioMinerals NV (Destelgergen, Belgium). Magnesium trisilicate mixture British Pharmacopoeia (BP) (referred to as magnesium trisilicate BP in the text) was from Lloyds Pharmacy Ltd (Coventry, Warwicks, UK). Colloidal silica was from Saguna GmbH (Bielefeld, Germany). MMST was obtained from LLR-G5 Ltd (Castlebar, Co. Mayo, Republic of Ireland). Alcohol-free beer (Clausthaler Premium Classic) was bottled by Surfax Ltd (Sawbridgeworth, Herts, UK). Bananas and sliced frozen green beans were purchased from local Sainsbury's and Safeway supermarkets in London, UK, respectively. Sodium silicate (14 % NaOH and 27 % SiO_2 (7 mol Si/l)) and hydrochloric acid (HCl, 5 mol/l) were purchased from Aldrich Chemical Co. (Gillingham, Dorset, UK). Concentrated (35 %, w/v) HCl was AnalaR grade, from Merck Ltd (Lutterworth, Leics, UK). Nitric acid (65 % (w/v) HNO_3) was high purity from Fluka Ltd (Gillingham, UK). NaCl (>99·5 %) was from Sigma Chemical Co. (Poole, Dorset, UK). Ammonium molybdate ($(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$; AnalaR grade), $NaHCO_3$ (AnalaR) and sulfuric acid (0·5 M-H_2SO_4, AnalaR, volumetric standard) were from BDH Ltd (Poole, Dorset, UK). Pepsin powder was from Fluka Chemicals (Gillingham, Dorset, UK). Ultrafree-4 centrifugal filter units (5000 nominal molecular-weight cut-off) were from Millipore UK Ltd (Watford, Herts, UK).

These were cleaned before use by centrifugation at 3000 rpm with 3 × 4 ml UHP water for 10 min to remove the glycerine preservative on the membrane. Polypropylene transport tubes, pre-washed with UHP water and air-dried (in a class J clean room) before use for blood sample collection were from Sarstedt Ltd (Leicester, Leics, UK). Polypropylene Mauser bottles (2·5 litres) for urine collection were from Aldrich Chemical Co. These were cleaned with 10 % (v/v) HNO_3 (AnalaR; BDH Ltd) for 24 h then thoroughly rinsed with UHP water, air dried in a class J clean air room, and pre-weighed before use. These containers were used throughout the study to avoid Si contamination. All intravenous cannulae (1·2 × 45 mm) were from Johnson & Johnson Medical (Pomezia, Italy). Syringes were from Terumo Europe N.V. (Leuven, Belgium). Pasteur pipettes (3·5 ml), used for sample transfer, were from Greiner Bio-One Limited (Stonehouse, Glos, UK).

Preparation of test solutions, foods and silicon supplement

UHP water (0·66 litres) containing orthosilicic acid (21·4 (SE 0·5) mg Si) was prepared by diluting 371 μl of concentrated basic sodium silicate into 2·1 litres UHP water to a concentration of 32·5 (SE 0·8) mg Si/l and then neutralised with 5 M-HCl to pH 7·0[15]. The Si concentration was determined by inductively coupled plasma optical emission spectrometry (ICPOES). The solution was prepared at least 24 h before ingestion unless otherwise stated. ChOSA was prepared by adding 1 ml of the product (20 mg Si/ml) to 199 ml UHP water and then immediately ingested. Sliced frozen green beans were cooked in an 800 W microwave oven without water for 7 min before ingestion. Alcohol-free beer, bananas (ripe and peeled), magnesium trisilicate BP, colloidal silica and MMST were ingested without any further preparation or dilution.

Dissolution study

To identify potentially bioavailable sources of Si for further human intervention studies, the dissolution of several 'over-the-counter' Si-containing products was first studied. These were horsetail capsules, high-strength silica complex tablets, ChOSA (viscous liquid or suspension), magnesium trisilicate BP (suspension) and colloidal silica (suspension). Half of each tablet or capsule, or 0·25 ml liquid or suspension, was weighed in a 10 ml polypropylene tube, mixed thoroughly with 5 ml simulated gastrointestinal fluid (SGIF), and then pre-heated to 37°C in a water-bath. SGIF (pH 1·25) was prepared according to the British Pharmacopoeia[16]. Briefly, 2 g NaCl were dissolved in 80 ml 1 M-HCl and 920 ml UHP water and, just before use, 3·2 g pepsin powder was added. The Si-containing products, mixed with 5 ml pre-warmed (to 37°C) SGIF, were placed in pre-washed dialysis bags (12 500 nominal molecular-weight cut-off), which were then placed in a 50 ml tube containing 30 ml pre-warmed (to 37°C) SGIF (pH 1·25). After 2 h, the SGIF mixture in the surrounding solution was pH adjusted to 7·0 (i.e. intestinal conditions) with 1 M-$NaHCO_3$; the pH within the dialysis bag was not adjusted. The SGIF surrounding the dialysis bag was sampled (0·5 ml) into a 10 ml polypropylene tube at time intervals (0 min, 15 min, 1 h, 2 h, 4 h, 6 h and 24 h) and diluted with 2·5 ml 0·7 % HNO_3 with or without prior ultrafiltration before elemental analysis by ICPOES[15].

Absorption study

Subjects. Healthy volunteers (aged 19–40 years; sixteen males and sixteen females) with normal serum creatinine levels were recruited by circular email from King's College London. Ethical approval was obtained from King's College London Local Research Ethics Committee. Subjects who had been taking Si supplements and/or medicines containing Si were excluded. Subjects with a history of chronic illness were also excluded, as were pregnant and lactating women. Before the study, the volunteers signed a consent form immediately following oral and written explanation of the study details. Age, sex, height, weight, BMI and serum creatinine were recorded for each subject. Subjects fasted overnight from 22.00 hours and remained fasted until 14.30 hours the following day (end of the study period), except for the ingestion of the test solutions or meals and the UHP water that were supplied at 08.30 hours and 11.30 hours, respectively. Subjects were asked to avoid high-Si-containing foods 24 h before the start of the study; these were beer, breakfast cereals, rice and certain vegetables and fruit, particularly bananas and green beans.

Sample size. Urinary excretion of Si, used as a surrogate marker of bioavailable Si[7,14], was used to estimate the sample size required for the present study. From a previous study, a standard deviation (σ) of 9·4 % was estimated for the percentage excretion of urinary Si[15]. We recognise from our previous studies that baseline serum Si levels and Si absorption can vary quite substantially between subjects; so, to keep subject numbers manageable, quite large differences in Si absorption and excretion are required between test substances. Thus a potential difference of 20 % for excretion of urinary Si between subjects after ingestion of the test substances was assumed with 90 % power at a significance level of 95 %. Five completed subjects were estimated to be the minimum required for each test.

Study design. Due to the practicalities of organising one large study, four separate studies were conducted to investigate bioavailability of Si from the eight different sources. The exact subject numbers for each study depended on the number of volunteers available at the times of investigation, although a minimum of five, as noted above, was used except in one instance. In study 4, we initially intended to investigate absorption of Si from MMST only, but then decided to also assess absorption from colloidal silica, so that three products could be compared for simulated gastrointestinal digestion *in vitro v.* absorption *in vivo*. Three of the fourteen volunteers agreed to undertake this additional test. In each study (except study 4), subjects ingested two test foods or products in a randomised order on two separate weeks to allow for 1-week washout between tests. However, in study 4, eleven of the fourteen subjects undertook just one absorption test.

In study 1, subjects (three males and two females) ingested 660 ml alcohol-free beer containing 22·9 mg Si or the same volume of a solution of orthosilicic acid containing 21·5 mg Si as a positive control[7,15]. In study 2, subjects (three males and two females) ingested 250 g peeled bananas (13·6 mg Si) or cooked green beans (6·1 mg Si). In study 3, subjects (four males and four females) ingested 200 ml UHP water supplemented with 20 mg Si from ChOSA (20 mg Si/ml)

or 12·4 ml magnesium trisilicate BP containing 200 mg Si followed by 187·6 ml UHP water. In study 4, subjects (six males and eight females) ingested 60 ml MMST containing 6·9 mg Si or, in a small subset of subjects (*n* 3), ingested 60 ml colloidal silica containing 780 mg Si. The doses ingested for the latter four tests were the maximum doses recommended by the manufacturers, because, despite large differences in dose between the test substances, we anticipated that this would be counter-balanced by their differing degrees of absorption. In addition, we wished to ensure that detectable absorption was seen for all test substances and, as there is no evidence for saturation of the absorption pathway (here or published elsewhere), we chose the highest doses.

For all four studies, on day 1 (week 1), at 08.30 hours fasted subjects emptied their bladder and thereafter collected urine for 3 h (i.e. between 08.30 and 11.30 hours) in a pre-cleaned, pre-weighed container to determine their baseline Si excretion. Subjects ingested 0·6 litres UHP water over this period and returned to their normal eating habits thereafter, but avoided foods and drinks high in Si as mentioned previously, and then fasted again after 22.00 hours.

On day 2 (week 1) at 08.30 hours, the same fasted subjects emptied their bladder and an intravenous cannula was inserted into a forearm vein. Two 5–10 ml blood samples were collected for baseline Si measurements. Subjects then ingested one of the test solutions, products or meals as mentioned above. Further blood samples (5–10 ml) were collected at 30 min intervals for the first 2 h and then at 1 h intervals for the remaining 4 h. Subjects also collected urine in two 3 h collections (i.e. 08.30–11.30 hours and 11.30–14.30 hours) in two separate pre-cleaned, pre-weighed containers. Subjects ingested 0·5–0·7 litres UHP water over each 3 h period (08.30–11.30 hours and 11.30–14.30 hours).

On week 2, the same fasted subjects repeated the procedure described above, but ingested the alternative solution, food or product for their group (i.e. orthosilicic acid on week 2 if subjects had alcohol-free beer on week 1 and vice versa; bananas on week 2 if subjects had cooked green beans on week 1 and vice versa; ChOSA on week 2 if subjects had magnesium trisilicate BP on week 1 and vice versa; colloidal silica on week 2 if subjects had MMST on week 1 and vice versa).

Collection of serum. Blood samples were collected from the cannula in the forearm vein into a clean 10 ml polypropylene tube and left to stand for at least 1 h to clot. The clotted blood samples were then centrifuged at 3000 rpm (IEC6000B; Thermo Scientific, Dunstable, Beds, UK) for 10 min at 4°C. Sera were separated into 10 ml polypropylene transport tubes and stored at −20°C until elemental analysis. Blood samples were processed in a class C laminar clean-air cabinet to avoid Si contamination from ubiquitous airborne dust.

Collection of urine. Urine collections were weighed and then a 10–100 ml homogeneous sample was sampled into a polypropylene bottle and diluted with an equal volume of 0·7 % (v/v) HNO_3 to reduce any precipitation of minerals during storage at 4°C until elemental analysis[17].

Elemental analysis

Analysis for total Si was by ICPOES (JY 24; Horiba Jobin Yvon SAS, Longjumeau, France) with a V-groove nebuliser and Scott-type double-pass spray chamber at 251·611 nm. Analysis was by peak profile with a window size of 0·1 nm with fifty-four increments per profile. Integration times were 0·5 s and 0·3 s per increment for serum and urine, respectively[15]. Sample flow rate was 1 ml/min.

Before analysis, serum samples were diluted 1 + 4 with 0·25–0·7 % (v/v) HNO_3. Diluted urine samples were incubated in their closed containers at 40°C overnight to re-dissolve any urinary precipitates and then allowed to cool to room temperature before analysis[17]. Sample-based standard solutions were used (i.e. pooled diluted serum or pooled diluted urines spiked with Si from a standard inductively coupled plasma solution).

All samples were analysed at least in duplicate. The detection limit for the measurement of Si was 5 μg/l in aqueous 0·7 % (v/v) HNO_3. Since serum and urine samples were diluted 1 + 4 and 1 + 1, respectively, detection limits for Si in the original undiluted samples were 25 and 10 μg/l, respectively (there was no difference in sensitivity between diluted acid and diluted samples). There are no standard reference materials for Si in biological samples, but recovery was assessed by spiking sera and urine samples with known concentrations of Si and then preparing and analysing them as above. Recoveries were 100·2 (SE 9·5) % for serum samples (thirty-three different spiked samples, assessed in duplicate) and 99·5 (SE 2·3) % for urine (eighteen different spiked samples, assessed in duplicate). Precision was calculated by analysing prepared standards on four different occasions. Three standards were prepared in serum, containing 110 parts per billion (ppb), 270 ppb and 534 ppb Si, and the precisions were 101 (SE 16), 99·8 (SE 1) and 101 (SE 5) %, respectively. Similarly, three standards were prepared in urine, containing 1·0 parts per million (ppm), 9·95 ppm and 20·4 ppm Si, and the precisions were 97·2 (SE 6), 98·3 (SE 3·2) and 100·4 (SE 0·8) %, respectively.

As serum and urine samples were diluted with 0·25–0·7 % (v/v) nitric acid, contamination of Si in the acid was also determined by preparing and analysing the acid samples (or blank) identically as per serum and urine samples. Although minor, this contaminant Si was subtracted from the samples.

Statistical analysis

All the data are presented as mean values with their standard errors unless otherwise specified. Repeated-measures ANOVA was used to compare the increase above baseline in serum and urinary Si following ingestion of the test foods or products and also for the assessment of the efficiency of dissolution with simulated digestion in the *in vitro* screening assay. ANOVA was used to compare differences in baseline serum and urinary Si and characteristics of subjects among the groups. Statistical analyses were two sided and a P value $\leq 0{\cdot}05$ was defined as significant. SPSS software (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Dissolution study

Among the products tested under simulated gastrointestinal conditions, ChOSA had the greatest dissolution, followed by

magnesium trisilicate BP, colloidal silica, and horsetail, respectively (all $P<0{\cdot}001$ by repeated-measures ANOVA; Fig. 1). These were soluble only under simulated intestinal conditions of the assay (i.e. pH 7, 2–22 h) and not under gastric conditions (pH 1·25) for the short period of exposure (2 h; Fig. 1). Silica complex did not dissolve (Fig. 1). The three most soluble products, namely ChOSA, magnesium trisilicate BP and colloidal silica were then further studied in the *in vivo* absorption study.

Absorption study

Subject characteristics are given in Table 2. All subjects had normal serum creatinine concentrations, confirming that they had normal renal function.

Serum silicon

The mean baseline (fasting) serum Si concentration was 113·9 (SE 11·8) μg/l (range 38·5–326·7 μg/l) (Fig. 2) and, as expected, this increased significantly following the ingestion of a solution containing orthosilicic acid ($P<0{\cdot}0001$) and following the ingestion of alcohol-free beer ($P<0{\cdot}0001$) with peak concentrations observed about 1.5 h following ingestion (Fig. 2(a)). Serum levels had almost returned to baseline by the end of the study period (i.e. at 6 h) in both groups. A significant increase in serum Si concentration was also observed following the ingestion of green beans ($P=0{\cdot}04$) but, interestingly, not with bananas (250 g) ($P=0{\cdot}43$) despite their high Si content (Fig. 2(b)). Additionally, serum Si increased significantly following the ingestion of colloidal silica (780 mg Si; $P<0{\cdot}001$), magnesium trisilicate BP (200 mg Si; $P<0{\cdot}0001$), ChOSA (20 mg Si; $P<0{\cdot}0001$) and MMST (6·9 mg Si; $P<0{\cdot}0001$) (Figs. 2(c) and (d)). Peak serum Si concentrations were observed 2 h following the ingestion of ChOSA and colloidal silica and at 4 h for magnesium trisilicate BP, but earlier at about 30 min for MMST and green beans. Notably, after the ingestion of magnesium trisilicate BP and colloidal silica the serum Si concentrations were still markedly elevated above baseline at the end of study period (i.e. at 6 h).

Urinary silicon

The mean baseline fasting urinary Si excretion was 0·745 (SE 0·053) mg per 3 h (range 0·236–1·589 mg per 3 h) (Fig. 3). A significant increase in urinary Si over a 6 h period (collected as 2 × 3 h periods) was observed following the ingestion of orthosilicic acid ($P<0{\cdot}0001$; Fig. 3(a)), alcohol-free beer ($P<0{\cdot}001$; Fig. 3(b)) and green beans ($P=0{\cdot}04$; Fig. 3(c)), but not after the ingestion of bananas ($P=0{\cdot}13$; Fig. 3(d)). Similarly, an increase in urinary Si was also observed following the ingestion of colloidal silica ($P=0{\cdot}03$; Fig. 3(e)), magnesium trisilicate BP ($P<0{\cdot}001$; Fig. 3(f)), ChOSA ($P<0{\cdot}001$; Fig. 3(g)) and MMST ($P<0{\cdot}001$; Fig. 3(h)). Following the ingestion of magnesium trisilicate BP, urinary Si was greatest in the second 3 h collection period, whilst for all foods and food supplements urinary Si excretion was greatest in the first 3 h collection period.

After correcting for differences in ingested Si dose from the different Si-containing sources, the percentage of the dose excreted in urine over the 6 h period was highest from MMST (64·0 (SE 5·3) %; range 30·4–105 %) and alcohol-free beer (60·1 (SE 0·8) %; range 57·2–62·0 %), followed by green beans (43·6 (SE 14·9) %; range: 22·1–102 %), orthosilicic acid (43·1 (SE 3·6) %; range 30·0–50·5 %) and ChOSA (16·5 (SE 6·7) %; range 8·57–27·9 %) (Fig. 4). Bananas (3·9 (SE 2·0) %; range 0·05–11·7 %), magnesium trisilicate BP (3·7 (SE 0·6) %; range 1·46–7·23 %) and colloidal silica (1·2 (SE 0·4) %; range 0·96–1·62 %) provided very low increases in urinary Si (Fig. 4). Although the latter group only included

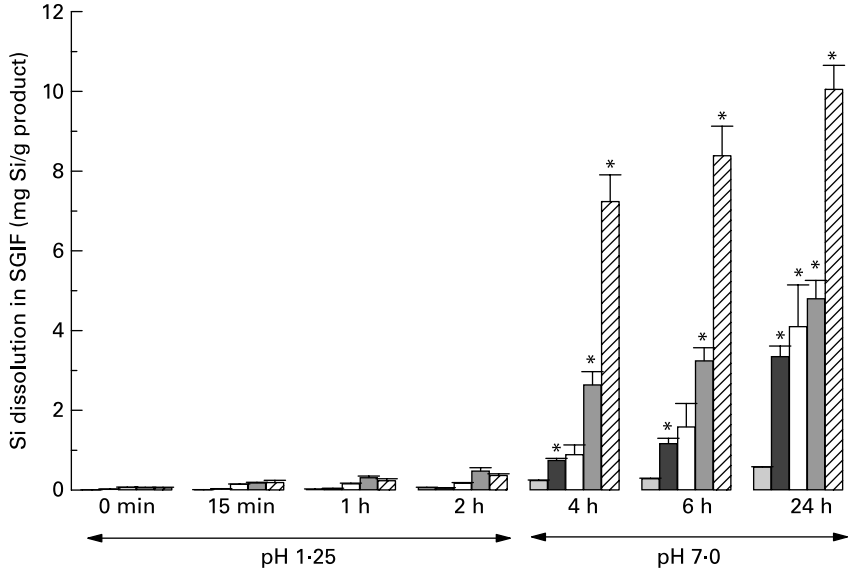

Fig. 1. Dissolution (mg Si/g product) of Si from different Si-containing products and supplements under simulated gastrointestinal (SGI) conditions at timed intervals following neutralisation of SGI fluid (SGIF) from gastric to intestinal pH. (□), Silica complex; (■), horsetail; (□), colloidal silica; (▨), magnesium trisilicate British Pharmacopoeia; (▨), choline-stabilised orthosilicic acid (BioSil; BioMinerals NV, Destelgergen, Belgium). Results are means of three samples, with standard errors represented by vertical bars. *Mean value was significantly different from that at baseline (i.e. 0 min) ($P<0{\cdot}01$; repeated-measures ANOVA).

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Table 2. Characteristics of subjects

(Mean values with their standard errors and ranges)

	Study 1: OSA and alcohol-free beer			Study 2: green beans and bananas*			Study 3: ChOSA and magnesium trisilicate BP			Study 4: MMST and colloidal silica†		
	Mean	SE	Range	Mean	SE	Range	Mean	SE	Range	Mean	SE	Range
Subjects (*n*)												
Males		3			3			4			6	
Females		2			2			4			8	
Age (years)	26·7	2·5	22·0–36·0	23·4	1·0	22·0–27·0	27·3	2·0	19·0–38·0	28·2	1·8	21·0–38·1
Weight (kg)	61·1	4·5	48·0–71·0	73·5	4·9	60·5–90·9	61·6	3·3	50·0–79·6	59·5	2·9	41·0–81·0
Height (cm)	164·0	2·4	158–168	169·0	1·6	167–175	164·3	1·8	156–170	166·1	2·2	154–179
BMI (kg/m^2)	22·8	1·1	19·4–25·0	25·6	1·3	21·7–29·7	22·8	1·1	19·8–30·1	21·4	0·7	17·3–26·2
Serum creatinine (μmol/l)‡	72·4	5·0	57–67	72·8	7·1	56–88	76·8	4·5	54–98	71·8	4·5	65–86

OSA, orthosilicic acid; ChOSA, choline-stabilised orthosilicic acid (BioSil; BioMinerals NV, Destelgergen, Belgium); BP, British Pharmacopoeia; MMST, monomethyl silanetriol (LLR-G5 Ltd, Castlebar, Co. Mayo, Republic of Ireland).

* Bananas were ripe and peeled. Greens beans were cooked.

† As explained in the Materials and methods section, only three of the fourteen subjects in this group undertook the ingestion test with colloidal silica.

‡ Normal creatinine levels: 80–122 μmol/l for males; 65–101 μmol/l for females.

three subjects, the consistently low percentage absorption indicates that the results are robust.

Percentage increase in urinary Si following the ingestion of these Si-containing sources over the 6 h study period correlated positively with the increase in serum Si over the same period (i.e. area under the curve 0–6 h) (r 0·82, $P<0·0001$; Fig. 5).

Discussion

First, concentrating on the Si sources of known speciation (i.e. fluids and food supplements), our data confirm what has been suggested previously, namely that the degree of polymerisation of Si (i.e. as silicate) is inversely proportional to its intestinal absorption[1,12–14]. In other words, monomeric silica ($Si(OH)_4$, orthosilicic acid, soluble silica), which is a small, neutrally charged molecule, is readily absorbed in the gastrointestinal tract, while larger, charged polymers and colloidal species need to be broken down to the soluble monomer in the gastrointestinal lumen before absorption[13,14]. The rate (kinetics) of dissociation or dissolution of the polymers or colloids will depend upon the degree of polymerisation[12,18].

The solubility limit of silica is about 2–3 mM at intestinal, peri-neutral pH[18]. Drinking water and other beverages, including beer, have total Si concentrations lower than 2 mM and, thus, predominantly contain the soluble monomeric species giving high gastrointestinal absorption[15]. At higher Si concentrations (>2–3 mM), as is present in most supplements, larger and less absorbable polymers or colloids of silica are present. The exception is MMST, which is presented as a silica supplement in solution, and where a methyl group replaces one hydroxyl group of orthosilicic acid, which raises the solubility limit of Si and maintains it in a small, monomeric and well-absorbed[19] form. ChOSA, also presented in solution, albeit highly concentrated, is polymerised, although extensive polymerisation and aggregation of silica particles are prevented by the presence of a high concentration of choline in the supplement. This we confirmed with ultra-filtration of the supplement (which is a viscous fluid) without dilution, finding negligible Si that was ultra-filterable (less than nominal 3000 kDa), but upon dilution to 1 + 155 with pH 7 buffer, 58 % of the Si was then ultra-filterable (data not shown). Thus, the choline protects the silica from extensive polymerisation and precipitation by maintaining it in aqueous suspension, so that upon further dilution before ingestion it will start to depolymerise to form orthosilicic acid. Clearly this is not as efficient as starting with monomeric silicate, but goes some way to achieving de-polymerisation and bioavailable $Si(OH)_4$ (i.e. 17 % absorbed from ChOSA *v.* 45–65 % from the other sources). In contrast, 'colloidal silica', which is in fact precipitated and completely polymerised silica, showed very low absorption (less than 2 %), presumably because it is so aggregated and the rate of hydrolysis in the gastrointestinal lumen is slow compared with the window of opportunity for absorption in the small bowel. It is well recognised that silica is more soluble under near-neutral conditions (intestinal conditions) compared with mildly acidic conditions (i.e. gastric conditions)[18] and, as shown in Fig. 1, the release of Si from colloidal silica by 4 h of simulated digestion was still low compared with that of ChOSA, for example.

The above findings are therefore important for two reasons. First, they inform on the mechanisms of Si absorption and the requirements for luminal processing and chemical speciation, while second, in further epidemiological studies (for example, Jugdaohsingh *et al.* [4] and Macdonald *et al.* [5]) and intervention studies[20] adjustments could be made for the different forms of supplemental Si that have been ingested. It is also interesting to note that a number of misnomers occur with these commercial supplements. For example, what is referred to by the manufacturers as 'colloidal silica' is really particulate silica, while choline-stabilised 'orthosilicic acid' is choline-stabilised colloidal or nanoparticulate silica.

The results with magnesium trisilicate BP are more difficult to interpret. First, this is an antacid and so buffers the gastric environment. Second, there was a very long absorption profile for Si from magnesium trisilicate BP and, hence, urinary Si excretion, which is used as a proxy for absorption, was not near completion by 6 h. It is likely that the gastric buffering and the slow absorption are related. Although as noted above, silicate requires less acid conditions for its dissolution, the initial disaggregation of solid-phase materials (i.e. magnesium trisilicate) may well require acid digestion

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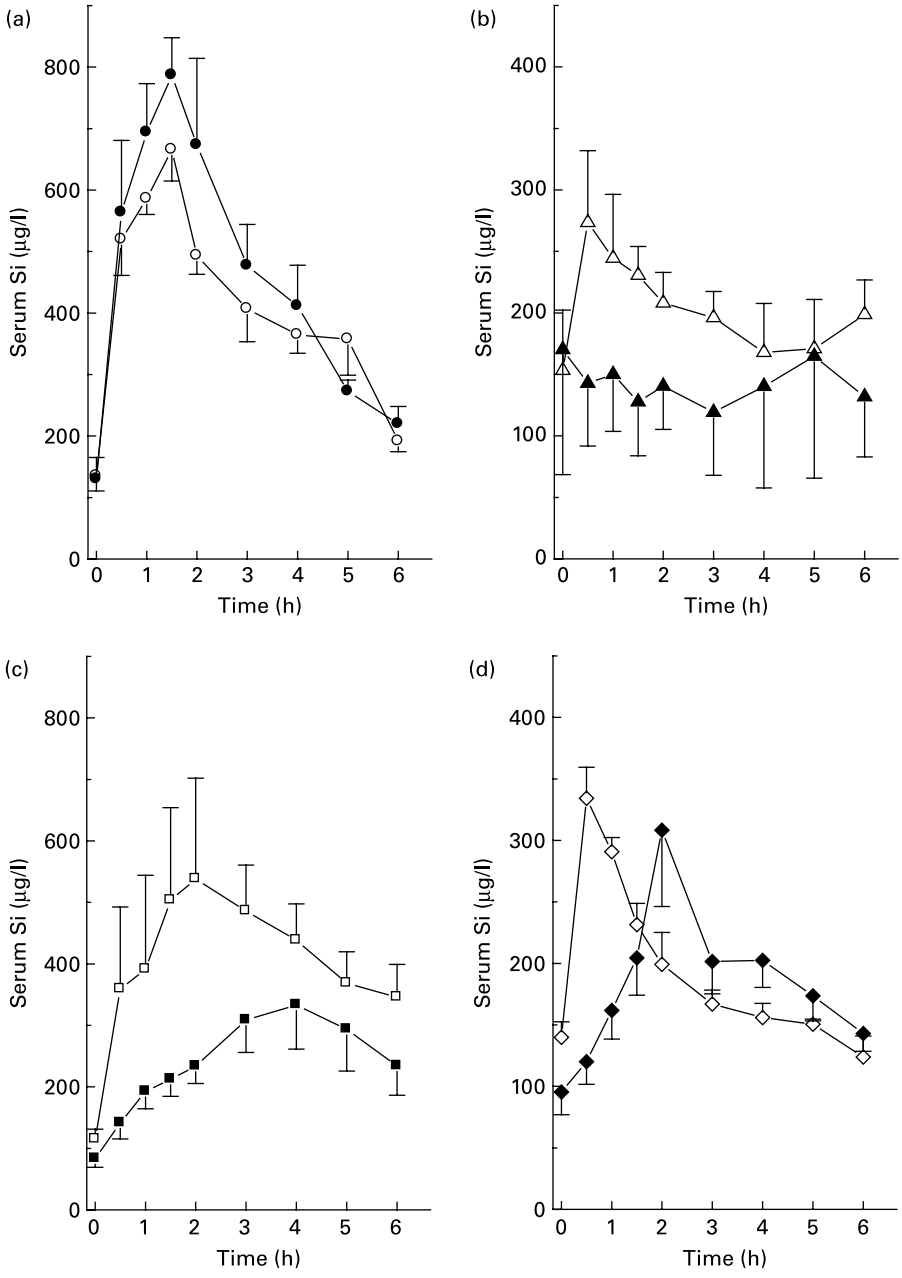

Fig. 2. Serum Si (μg/l) over the 6 h period following the ingestion of: (a) an orthosilicic acid (OSA) solution containing 21·4 mg Si (–○–; *n* 5) and alcohol-free beer containing 22·9 mg Si (–●–; *n* 5); (b) cooked green beans containing 6·1 mg Si (–△–; *n* 5) and ripe, peeled bananas containing 13·6 mg Si (–▲–; *n* 5); (c) colloidal silica containing 780 mg Si (–□–; *n* 3) and magnesium trisilicate British Pharmacopoeia (BP) containing 200 mg Si (–■–; *n* 8); (d) choline-stabilised orthosilicic acid (ChOSA) containing 20 mg Si (–◆–; *n* 8) and monomethyl silanetriol (MMST) containing 6·9 mg Si (–◇–; *n* 14). Results are means, with standard errors represented by vertical bars. To allow for optimal clarity of figures with respect to graphical overlap, each of (c) and (d) show one set of data from study 3 and from study 4; i.e. magnesium trisilicate BP (shown in (c)) was ingested in study 3 with ChOSA (shown in (d)), while colloidal silica (shown in (c)) was ingested in study 4 with MMST (shown in (d)). Si-containing supplements and products were ingested at the maximum dose recommended. The increase in serum Si following the ingestion of alcohol-free beer, OSA, magnesium trisilicate BP, ChOSA and MMST was statistically significant (all $P<0·0001$), as it was for colloidal silica ($P<0·001$) and green beans ($P=0·04$), but not for bananas ($P=0·43$).

and presumably with buffering this is slow. Hence, the opportunity for subsequent silicate dissolution is similarly slow and relatively short-lived. However, based upon our findings in the present study with another form of polymerised and aggregated Si, namely colloidal silica, it is likely that the percentage absorption from antacids is also of small magnitude. Nonetheless, antacids are sometimes taken in extremely high doses for long periods of time and, indeed, the appearance of Si-containing kidney stones is well reported in high-dose, long-term antacid users[11,21]. This may be rare, but illustrates that even if percentage absorption is low, Si uptake can be excessive if the dosing is high enough and prolonged.

Our observations on the absorption of Si from solid foods are also interesting. Si occurs in the plant-based aspect of the diet and is referred to as phytolithic silica. As preliminary evidence has suggested, this phytolithic silica is not a single

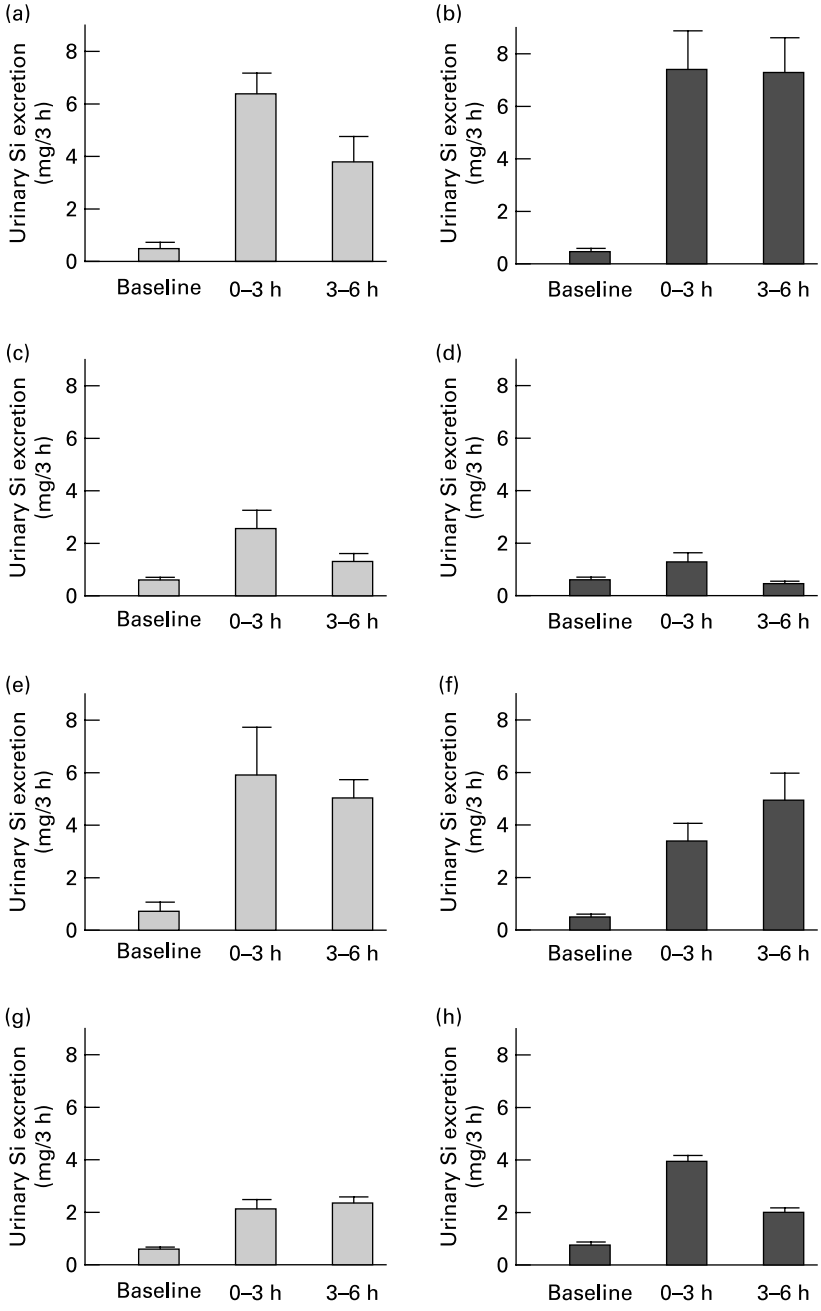

Fig. 3. Urinary Si excretion (mg/3 h) over the 6 period following the ingestion of: (a) an orthosilicic acid (OSA) solution containing 21·4 mg Si (*n* 5); (b) alcohol-free beer containing 22·9 mg Si (*n* 5); (c) cooked green beans containing 6·1 mg Si (*n* 5); (d) ripe, peeled bananas containing 13·6 mg Si (*n* 5); (e) colloidal silica containing 780 mg Si (*n* 3); (f) magnesium trisilicate British Pharmacopoeia (BP) containing 200 mg Si (*n* 8); (g) choline-stabilised orthosilicic acid (ChOSA) containing 20 mg Si (*n* 8); (h) monomethyl silanetriol (MMST) containing 6·9 mg Si (*n* 14). Results are means, with standard errors represented by vertical bars (*n* 5–14, see Table 1). Si-containing supplements and products were ingested at the maximum dose recommended. The increase in urinary Si excretion (0–6 h) was statistically significant following the ingestion of OSA ($P<0·0001$), alcohol-free beer ($P<0·001$), green beans ($P=0·04$), magnesium trisilicate BP ($P<0·001$), ChOSA ($P<0·001$), MMST ($P<0·001$) and colloidal silica ($P=0·03$), but not following the ingestion of bananas ($P=0·13$).

entity (i.e. a single Si species), but may mirror the complex situation with supplements described above (i.e. a mixture of different species). The absorption of Si from bananas was very poor, as previously reported by us[7], and so it is likely that this is a well-polymerised form of Si that cannot be efficiently hydrolysed in the gut. In contrast, Si is well absorbed from green beans, again, confirming our previous report[7], and this therefore must be in a much more labile form that is easily dissolved in the gastrointestinal tract. Thus, in epidemiological studies it will be important to dissect out which Si-containing foods behave like bananas and which like green beans, so that a weighting can be applied for bioavailability. It may well be that bananas are the exception for high-Si-containing foods because in a small study all

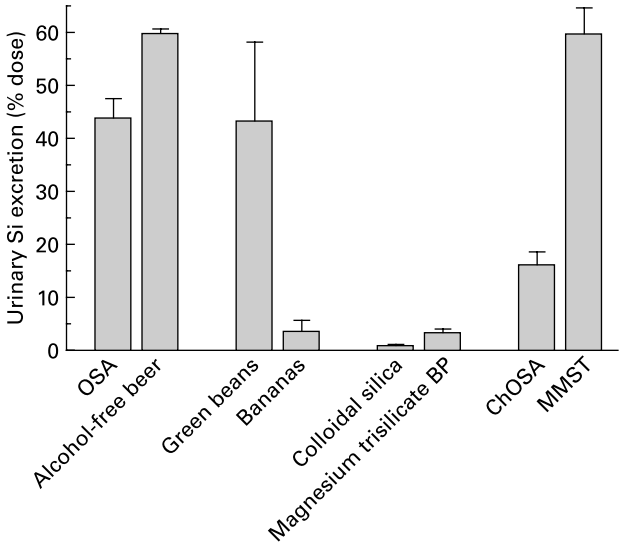

Fig. 4. Percentage increase in excretion of urinary Si over the 6 h period following the ingestion of: an orthosilicic acid (OSA) solution containing 21·4 mg Si (*n* 5); alcohol-free beer containing 22·9 mg Si (*n* 5); cooked green beans containing 6·1 mg Si (*n* 5); ripe, peeled bananas containing 13·6 mg Si (*n* 5); colloidal silica containing 780 mg Si (*n* 3); magnesium trisilicate British Pharmacopoeia (BP) containing 200 mg Si (*n* 8); choline-stabilised orthosilicic acid (ChOSA) containing 20 mg Si (*n* 8); monomethyl silanetriol (MMST) containing 6·9 mg Si (*n* 14). Results are means, with standard errors represented by vertical bars. Si-containing supplements and products were ingested at the maximum dose recommended.

other high-Si-containing foods behaved like green beans in providing on average about 40 % absorbable Si[7]. Nonetheless, further work could confirm this.

The kinetics of Si absorption were also studied. In the main, kinetics were in keeping with total absorption such that those foods requiring hydrolysis in the gut before absorption were slow to reach peak serum Si levels (i.e. magnesium trisilicate BP, colloidal silica and ChOSA) compared with monomeric forms of Si. Interestingly, Si from MMST was very rapidly absorbed and presumably is related to the organic moiety, which may allow rapid penetration of the intestinal mucosa by the molecule. The observation that Si from green beans is rapidly absorbed is also of interest; the chemical speciation of Si in this food should be undertaken.

The final aspect of the work shown here is that *in vitro* dissolution probably provides a good guide to the relative absorption for Si *in vivo*. It does not provide absolute absorption, as it cannot completely model or mimic *in vivo* conditions. Further work should confirm this, but if this were the case, then provision of a database for dietary Si levels and how they relate to Si absorption could well be achieved by modelling *in vitro* data with limited supporting *in vivo* data.

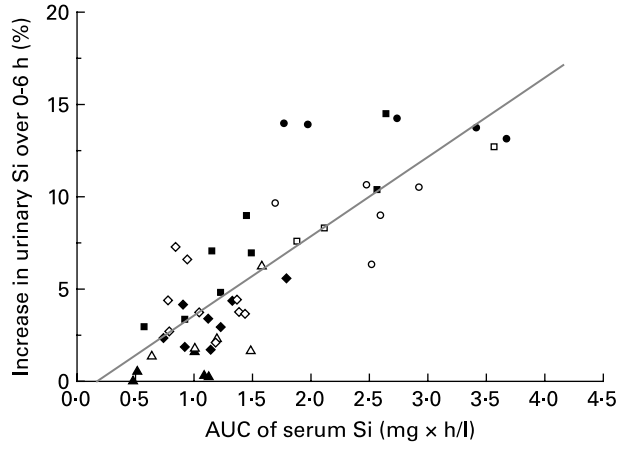

Fig. 5. Correlation (*r* 0·82, $P<0·0001$; *n* 48) between area under the curve (AUC; 0–6 h) of serum Si (mg × h/l) and the increase in urinary Si excretion following the ingestion of the different Si sources over the 6 h study period: orthosilicic acid (○; *n* 5); alcohol-free beer (●; *n* 5); cooked green beans (△; *n* 5); ripe, peeled bananas (▲; *n* 5); colloidal silica (□; *n* 3); magnesium trisilicate British Pharmacopoeia (■; *n* 8); monomethyl silanetriol (◇; *n* 9); choline-stabilised orthosilicic acid (◆; *n* 8).

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J. J. P. has consulted on several Si supplements. All other authors have no conflict of interest.

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Silicon balance in human volunteers; a pilot study to establish the variance in silicon excretion versus intake

Supannee Pruksa[1], Atitaya Siripinyanond[2], Jonathan J Powell[3] and Ravin Jugdaohsingh[3*]

Abstract

Background: Accumulating evidence suggests a role for silicon in optimal connective tissue health. Further proof of its importance/essentiality may be provided by studies involving imposed depletion followed by ^{29}Si challenge to estimate metabolic balance. Prior to conducting these expensive studies, we first established the variance of estimating normal Si excretion *versus* intake using a single oral dose of typical dietary Si, orthosilicic acid.

Methods: Healthy volunteers were recruited from Loei Rajabhat University, separated into two matched groups (three males and three females/group) and maintained on a standardized diet for the three study days. One group ingested 500 ml water containing orthosilicic acid (28.9 mg Si) and the other group received 500 ml water alone, all on a fasted stomach. Blood samples and total urine and faeces were collected over the 48 h post-dose period and 24 h before-hand (baseline) and analysed for silicon by inductively coupled plasma optical emission spectrometry.

Results: Serum Si analysis confirmed the ready absorption of silicon from the orthosilicic acid solution. Mean total urinary and faecal Si excretions over the 24 h post-dose period accounted for 57 ± 9.5% and 39 ± 9.4% of the ingested dose, respectively. Thus in total 96.3 ± 5.8% of the ingested dose was recovered in faecal plus urinary excretions over the 24 h post-dose period.

Conclusions: We report that in healthy subjects (presumably in Si balance), the ingestion of a soluble dose of dietary Si results in the same quantity (within analytical error) being excreted within 24 h. It is currently not known if this all originated from the dose solution or if there was some exchange with the body Si pool but, given the low variance in these silicon balance data, isotopic studies are now merited.

Keywords: Silicon, Orthosilicic acid, Absorption, Balance studies, Urine, Faeces

Background

Silicon is a critical element in the biology and/or survival of a number of lower life forms, including diatoms, certain sponges and many plants [1-4]. In humans and other mammals its role (if any) is less well defined despite being a common dietary trace element (20–50 mg/day is ingested by adults in western populations [5-8]). Indeed, the environmental ubiquity and limited (bio) chemistry of silicon have led to claims that its ingestion, ready absorption and excretion by mammals are all simply inevitable consequences of oral exposure to a small soluble molecule (orthosilicic acid, $Si(OH)_4$) that 'washes through' the system and has no biological function [9,10]. Against this, evidence is accumulating to suggest that, in mammals, silicon plays an important role in optimal connective tissue health [11-14]. Its exact role/function remains unestablished, but there is evidence to suggest it's involved in the synthesis and/or stabilisation of extracellular matrix components, namely collagen, and in the proliferation of connective tissue cells [9,14]. There is also evidence to suggest that silicon is carefully conserved when dietary deficiency is imposed [15,16]. To translate these findings to humans, and provide more evidence for its essentiality, balance studies using Si isotope(s) following a low silicon diet may demonstrate (i) retention of silicon following ingestion

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and (ii) whether ingested and absorbed silicon displaces some endogenous silicon or is simply washed through.

Despite the simple form of balance studies, where quantitative faecal and urinary excretion of a substance (and/or metabolites) are compared to the amount of substance ingested, they are fraught with difficulties [17]. Faecal collection and analysis is especially demanding: gastrointestinal transit times vary between individuals and temporary mucosal retention of a substance may also occur, adding further variability. Volunteers must provide complete collections and analysis of different fractions and sample types causes inevitable compound error.

For silicon, a basic human balance study, no matter how precise or accurate, would tell us little about the homeostasis of the element. If silicic acid is not utilised/metabolised, but is washed through the system, then a perfect study would recover 100% of the ingested dose. On the other hand, if it were utilised and/or metabolised, a 100% recovery would *still* be expected assuming that volunteers are themselves in balance (i.e. not deficient). Nonetheless, the value of such a study would be to determine what sort of variance one might expect in balance if this were to be attempted in subsequent isotope and/or depletion studies (i.e. are these expensive and time consuming studies worth doing?). It would also have the added value of confirming whether urinary silicon, which is typically used to estimate silicon absorption in humans, is a valid measure for this purpose.

Here we sought to determine the balance in excretion of silicon (faecal and urinary) *versus* intake, using a single oral dose of silicic acid (28.9 mg Si) in human volunteers on a standardized diet.

Subjects and methods

Subjects

Fourteen healthy volunteers (seven males and seven females, aged 18–23 years old) were recruited by advertisement on notice boards at Loei Rajabhat University, Thailand. Two subjects (one male and one female) were excluded due to fainting during blood collection at the screening stage. The remaining 12 subjects were self-reportedly healthy with normal renal function, as assessed by serum creatinine, and were not taking Si supplements and/or medicines containing Si and were not pregnant or lactating. The 12 subjects were divided into two groups of six, matched for age, body mass index (BMI) and male to female ratio. One group ingested 500 mL UHP water (Control group) and the other group 500 ml of the Si supplement solution (28.9 mg Si; Si-supplemented group). Anthropogenic data (age, height, weight, BMI and serum creatinine) were collected for each participant and there was no significant difference in subject characteristics between the two groups (Table 1). The study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the Loei Rajabhat University Local Research Ethics Committee. All participants gave signed written consent following oral and written explanation of the study details.

Table 1 Characteristics of the study volunteers

Characteristics	Control group (3 M & 3 F)		Si-supplemented group (3 M & 3 F)	
	Mean ± SD	Range	Mean ± SD	Range
Age (y)	21.2 ± 1.9	(18.1–23.1)	21.0 ± 1.3	(19.0–22.0)
Weight (kg)	55.1 ± 7.3	(45.2–65.4)	56.4 ± 6.6	(50.0–66.8)
Height (cm)	163 ± 10	(155–176)	165 ± 8	(157–176)
BMI (kg/m^2)	20.6 ± 1.7	(18.1–22.7)	20.8 ± 2.5	(18.2–25.0)
Serum creatinine[1] (mg/dL)	0.92 ± 0.15	(0.80–1.10)	0.88 ± 0.15	(0.80–1.10)
Baseline 24 h Si excretion:				
Urine (mg/24 h)	12.48 ± 2.26	(9.72–15.31)	12.93 ± 2.85	(9.11–16.34)
Faeces (mg/24 h)	9.50 ± 1.41	(7.99–11.48)	9.35 ± 2.01	(6.68–11.47)

[1]Normal creatinine levels: male 0.9-1.3, female 0.6-1.1 mg/dL.

Materials

Glassware was avoided throughout the study to prevent Si contamination. Ultra high purity (UHP) water was from a water purifier (Labscan Asia Co Limited, Bangkok, Thailand). The stock basic sodium silicate solution was from Lakehead University, Canada (Professor Stephen Kinrade). The stock silicon ICP standard solution (1,000 mg/L Si) was from Merck Ltd (Poole, UK). Nitric acid (65% (w/v) HNO_3) and hydrochloric acid (37%) were high purity from RCI Labscan Limited (Bangkok, Thailand). Polypropylene tubes (15 and 50 mL) were from Elkay Laboratory Products UK Ltd (Basingstoke, UK). Polypropylene bottles (30 and 2,000 mL) were from VWR International (Poole, UK). All intravenous catheters (1.2 × 45 mm) and plastic syringes were from Nipro Ltd (Pranakhonsriayuthaya, Thailand). Pasteur pipettes (3.5 mL), used for sample transfer, were from Greiner Bio-One Limited (Stonehouse, UK). Pipette tips (100–1,000 μL) were from Hycon (Biomed C. Ltd., Bangkok, Thailand).

Preparation of Si supplement

The Si supplement (orthosilicic acid solution, OSA) was prepared fresh, just prior to ingestion, by dilution of the stock basic sodium silicate solution (1.58 mol Si/L or 45.72 g Si/L) into UHP water and pH neutralization to 7.2 with HCl. The Si concentration in the test solution (2.06 mmol/L or 57.78 mg/L) was confirmed by inductively coupled plasma – optical emission spectrometry (ICP-OES; Perkin Optima, model 2100 DV).

Study design

Twenty four hours prior to ingestion of the test solutions (study day 0), all subjects collected 24 h urines (as two 12 h collections) and faeces (one 24 h collection) for baseline Si measurements. All subjects fasted overnight from 22.00 h and reported, still fasted, to Loei Rajabhat University the following morning (study day 1) at 08.00 h where they emptied their bladder and bowel into containers (part of 24 h baseline collections) and had an intravenous catheter inserted into a forearm vein. Two 10 mL blood samples were collected into polypropylene tubes for baseline Si measurements. Subjects were given 500 mL of the test solution (Si supplement or water) and asked to consume it as quickly as possible, i.e. within 10–15 min. Thereafter, further blood samples (10 mL) were collected at 30 min intervals for the first 2 h, 1 h intervals for next 4 h and finally at 9, 12, 24 and 48 h post-ingestion (the latter two were collected at 08.00 h on study days 2 and 3). Subjects also collected their urine as four 3 h collections (i.e. 08.00-11.00 h, 11.00-14.00 h, 14.00-17.00 h and 17.00-20.00 h) plus three 12 h collections (i.e. 20.00 h study day 1 to 08.00 h study day 2, 08.00 h study day 2 to 20.00 h study day 2, 20.00 h study day 2 to 08.00 h study day 3) in separate pre-weighed, pre-cleaned plastic containers. Additionally, subjects also collected all their faeces over the 48 h post-dose period as two 24 h collections (08.00 h study day 1 to 08.00 h study day 2, 08.00 h study day 2 to 08.00 h study day 3) in containers provided. A summary of the study design is shown in Figure 1.

Standardized meals

All 12 participants received the same meals, and the same amount of each meal, for breakfast, lunch and dinner during the study/sample collection periods: namely, study day 0 (baseline collection), study day 1 and study day 2. Males and females received the same amount of each meal and therefore their silicon intakes were identical. The contribution of Si from the three meals was estimated from reference food Si values [5,18] or from direct analysis (i.e. drinking water) and was, on average, 24 mg Si/day over the study period (Table 2). Meals were eaten as follows: breakfast at 08.00 h for study day 0 and study day 2, and at 12.30 h for study day 1 as subjects remained fasted until then; lunch at 12.30 h for study day 0 and study day 2, and at 16.30 h on study day 1; dinner at 18.30 h for study day 0 and study day 2, and at 20.30 h on study day 1. The total intake of Si from the meals on study day 1 was 23.86 mg. All subjects ate at the same times.

Sample preparations

Serum samples Blood samples were collected in 15 mL polypropylene tubes and left to stand for at least 1 h at room temperature to clot. The clotted blood samples were then centrifuged (Hettich Zentrifugen, Tuttlingen, Germany) at 3,000 rpm for 10 min at room temperature. The separated serum fractions were collected into new 15 mL polypropylene transport tubes and stored at −20°C until elemental analysis. Prior to analysis, the serum samples were thawed at room temperature (23°C) and then diluted 1 + 4 with 0.25% (v/v) high purity HNO_3.

Urine samples Urine collections were weighed and volumes calculated assuming a density of 1. After thorough mixing, a 10 mL homogenous sample was collected into a 30 mL polypropylene bottle and diluted with equi-volume 0.7% (v/v) high purity HNO_3 (i.e. 1 + 1 dilution) to reduce any precipitation during storage [19]. The diluted samples were stored at 4°C until elemental analysis. Prior to analysis, the diluted samples were incubated overnight in their closed containers at 40°C in an oven to dissolve any precipitates that may have formed during storage [19]. Samples were cooled to room temperature prior to total elemental analysis for Si.

Faecal samples Faecal collections were weighed and after thorough manual mixing with a disposable wooden spatula,

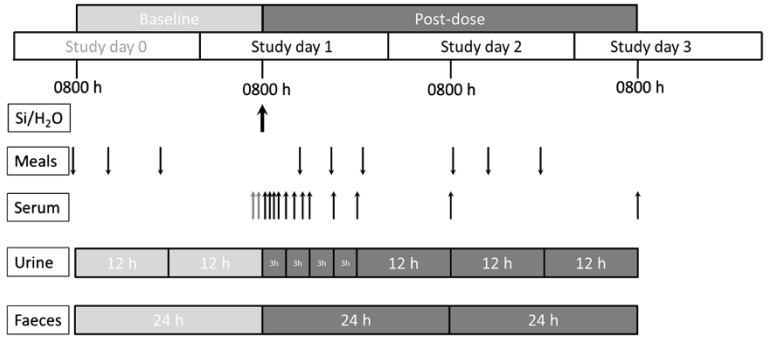

Figure 1 Study design. Summary of the timing of ingestion of the test solutions (Si-supplement or ultra-high purity water; Si/H_2O shown by *thick black arrow*) and standardised meals (*down arrows*), and the collection of serum (*thin up arrows*), urine and faecal samples (collection periods indicated). Pre-dose (baseline; *light grey*) and post-dose (*dark grey*) collections are indicated.

Table 2 Estimated silicon content[1] of the meals (mg Si/meal) provided to all participants during the study period

Meals	Components	Day 0[3] (mg Si)	Day 1 (mg Si)	Day 2 (mg Si)
Breakfast	Egg fried rice with pork/chicken, orange juice, drinking water[2]	6.78	7.70	7.34
Lunch	Rice with chicken, drinking water[2], yogurt, sponge cake	7.59	7.33	9.01
Dinner	Rice with stir-fried pork/chicken with kale, melon, drinking water[2]	9.93	7.43	7.97
	Total Si intake per day	24.29	23.86	23.91

[1]Calculated from reference food Si values (5, 18).
[2]Produced from tap water by reverse osmosis (Si concentration = 0.67 mg Si/L as analysed here by ICP-OES).
[3]Day 0 = pre-dose, baseline collection period, conducted 24 h prior to ingestion of the test solutions on day 1.

a homogenous sample (from each collection) was collected into a 50 mL polypropylene bottle and stored at −20°C. Prior to analysis, approximately 0.25-0.5 g of the faecal samples was digested with an equi-volume (5 mL) of concentrated (65% (w/v)) HNO_3 and hydrogen peroxide (30-40%) at room temperature for 24 h. These were incubated at 40°C until total digestion was obtained. Sample (acid) blanks were similarly prepared. An aliquot (1 mL) of the digested samples and sample blanks were diluted with 5 mL UHP water prior to total element analysis for Si.

Total elemental analysis

Total elemental analysis for Si was carried out (at 251.611 nm) by ICP-OES; Perkin Elmer Optima model 2100 DV, equipped with a Cross flow nebuliser and Cyclonic spray chamber. Nebulizer flow rate was 0.8 L/min. Peak area was 7.7 points and integration times were 20 seconds/analysis/element. Sample flow rate was 2 mL/min. Matrix matched standards, sample blanks, diluents and quality control samples were run alongside the samples.

Serum, urine and faecal samples The diluted serum, urine, and faecal samples from the same subject were analyzed together in the same batch. Sample-based standards were prepared in the pooled diluted sera, baseline urine, or baseline faecal samples using the 1,000 mg/L Si ICP standard solution.

Test solutions The Si supplement solution, UHP water and drinking water (part of standardized meals) were also analyzed for Si by ICP-OES using appropriate standards.

Sample diluents As the serum and urine samples were diluted with 0.25-0.7% HNO_3, Si content of the acid diluents was also measured by ICP-OES. Although minor, this contaminant Si was subtracted from each of the sample data.

Statistical analysis

Sample size (power) calculation was based on the available data on urinary Si excretion [20]. No previous data exist for faecal Si excretion. A relative standard deviation (σ) of 9.4% [20] was estimated for the variance in urinary Si and a potential difference of 20% for the excretion of urinary Si between the Si supplement and water test solutions was assumed, with 90% power at a 5% significance level. Sample size formula for the difference of two independent means was used for the calculation and six completed subjects were the minimum required for each test solution.

Area under the curve (AUC) of serum Si was calculated using the linear trapezoidal rule [21]. Due to a small number of subjects in each group, differences in serum AUC, and in urinary and faecal excretions of Si, between the two groups (Si vs. control), were analysed non-parametrically using the Mann–Whitney Rank test. Statistical analyses were two sided and a P value ≤ 0.05 was considered significant. SPSS for Windows version 13.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

Results

Gender specific analysis showed no significant difference in silicon absorption, excretion (urinary and fecal) and balance between male and female subjects and so the combined (pooled) dataset is shown for clarity and because of the small number of subjects.

Serum Si absorption

Mean baseline serum Si concentrations were similar in the control and the Si-supplemented groups (114 ± 17 μg/L (range 85 – 130 μg/L) vs. 112 ± 26 μg/L (range 83 – 148 μg/L)) and remained close to baseline in the control group following ingestion of UHP water (Figure 2A). In contrast, and as expected, serum Si concentrations increased markedly above baseline following ingestion of the orthosilicic acid solution (28.9 mg Si in UHP water) in the Si-supplemented group, with peak Si concentration (206 ± 48 μg/L; range: 133 – 250 μg/L) observed 1 to 2 hours post-ingestion (Figure 2A). Thereafter, serum Si concentrations began to drop rapidly back towards baseline concentrations. However, the ingestion of meals at 4.5 h and 8.5 h post-dose maintained serum Si concentrations above baseline in the Si-supplemented group and increased Si concentration above baseline in the control group, until 12 h post-dose. Area under the curve (AUC) of serum Si over the 24 h period was not significantly different between the two test solutions. However, AUC for the

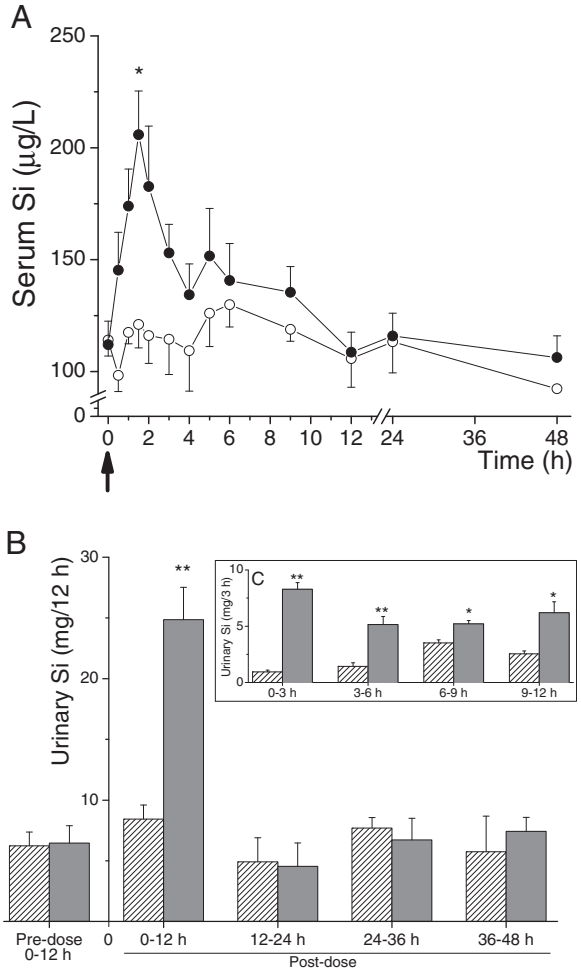

Figure 2 Serum Si absorption and urinary Si excretion following ingestion of the test solutions. (A) Serum silicon absorption. Serum Si following ingestion of UHP water alone (○—○; Control group) or following ingestion of UHP water containing 28.9 mg Si as orthosilicic acid (●—● Si-supplemented group). Data are means ± SE of 6 subjects per group. The large arrow below the x-axis indicates the time of ingestion of the test solutions (i.e. t = 0). *P = 0.009 (Mann–Whitney Rank test). **(B and C)** Urinary silicon excretion. Urinary excretion of Si following ingestion of UHP water alone (*stripped bars*; Control group) and UHP water containing 28.9 mg Si as orthosilicic acid (*grey bars*; Si-supplemented group). **(B)** Silicon levels in the 12-h urine collections over the 48 h study period. **(C)** The *insert* shows more detailed analysis of Si output over the first 12 h following ingestion of the test solutions. Data are means ± SD of 6 subjects per group. *P = 0.009, **P = 0.002 (Mann–Whitney Rank test).

period prior to breakfast, i.e. 0–4 h post-dose, was significantly higher following ingestion of orthosilicic acid solution, compared to UHP water alone (648 ± 137 mg h/L (range 459 – 819 mg h/L) vs. 453 ± 104 mg h/L (range 319 – 630 mg h/L); P = 0.04).

Urinary Si excretion

Mean total baseline 24 h urinary Si excretion was 12.48 ± 2.26 (range 9.72 – 15.31) and 12.93 ± 2.85 (range 9.11 – 16.34) mg, respectively, in the control and Si-supplemented groups and did not change markedly in the control group following ingestion of UHP water (13.34 ± 2.48 mg; range 11.36 – 18.21 mg). In contrast, in the Si-supplemented group, ingestion of the orthosilicic acid solution (28.9 mg Si in UHP water) led to a marked increase in urinary excretion of Si in the 0–12 h post-dose collection (P = 0.002; Figure 2B). A more detailed analysis of the 0–12 h collection in the Si-supplemented group showed that the peak increase in Si output was at 0–3 h post-dose (Figure 2C). Again, the ingestion of meals at 4.5 h and 8.5 h post-dose maintained urinary Si output above baseline in the 6–9 h and 9–12 h post-dose collections, as clearly mirrored in the control group (Figure 1C). Urinary Si output in the remaining collections (12–24 h, 24–36 h and 36–48 h), were comparable to baseline levels and similar between the two groups.

The increase in urinary Si output in the Si-supplemented group over the 24 h post-dose period following ingestion

of the orthosilicic acid solution (i.e. over and above baseline urinary Si excretion) was 16.5 ± 2.7 mg (range 14.4 – 20.5 mg) and this accounted for 57.0 ± 9.5% (range 49.8 – 71.0%) of the supplemental Si dose (28.9 mg) ingested.

Faecal Si excretion

Mean total baseline 24 h faecal excretion of Si was 9.5 ± 1.4 (range 8.0 – 11.5) and 9.4 ± 2.0 (range 6.7 – 11.5) mg, respectively, in the control and Si-supplemented groups (Figure 3) and did not change markedly in the control group following ingestion of UHP water. However, the ingestion of the orthosilicic acid solution led to a significant increase in faecal Si content in the 24 h post-dose collection compared to baseline ($P = 0.002$; Figure 3). This increase in faecal Si excretion in the Si-supplemented group, by + 11.4 ± 2.7 mg (range + 7.6 – 14.9 mg) over 0–24 h period, accounted for 39.3 ± 9.4% (range: 26.4 – 51.6%) of the ingested supplemental Si dose (28.9 mg).

Silicon balance

In the Control group urinary and faecal Si excretion over the 24 h post-dose period accounted for 99.6 ± 8.1% (range 90.6 – 112.9%) of the total Si intake over that period, whilst in the Si-supplemented group average recovery from urine and faeces was slightly less at 94.8 ± 9.4% (range 83.3 – 105.6%; Table 3). Of the supplemental Si dose ingested (28.89 mg), 27.83 ± 1.67 (range 25.6 – 29.5) mg (or 96.3 ± 5.8%; range 88.5 – 102.2%) was recovered from urinary and faecal excretion over the 24 h post-dose period in the Si-supplemented group.

Discussion

The present study investigated the balance in excretion of silicon *versus* its intake, using a single dose of typical dietary silicon (28.9 mg) in healthy human volunteers on a standardized diet. Our results show that, within error, all (96 ± 6%) of the ingested dose was excreted in urine and faeces over the 24 h post-dose period. Whether it is, fully, the same Si being excreted that is being absorbed will need to be addressed with a different study design. However, to get within 5% of intake with variance of ~ 6% is better than may have been expected, especially with the complexities of faecal and urine collection and analysis [17,22]. Typical recovery from such studies, even with radiolabelled compounds, can be 80% or less, much less than from animal studies [23,24]. The high renal clearance of Si and the lack of interaction with serum proteins probably aids recovery [25,26].

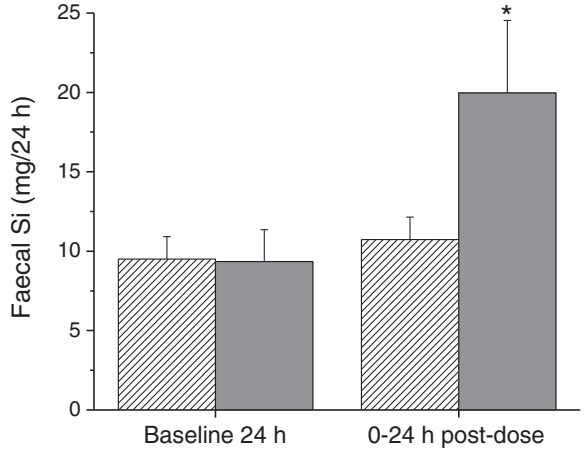

Figure 3 Faecal silicon excretion. Mean (± SD) faecal excretion of Si following ingestion of UHP water (*stripped bars*) and UHP water containing 28.9 mg Si (*grey bars*) in six subjects. *$P = 0.002$ (Mann–Whitney Rank test).

As mentioned previously, 100% recovery is expected if (a) Si metabolism is regulated but the subjects are in Si balance (i.e. are Si replete) or (b) if Si has no active biological function and thus Si metabolism is not regulated at all. This study cannot prove which is true but we believe that the former is more likely based on previous murine data where urinary Si output was found to be conserved in Si-deprived animals to maintain tissue Si levels [15]. To now show this in humans we will need to repeat the study with subjects who are in negative Si balance (i.e. Si deplete at the start of the supplementation period by prior dietary Si deprivation for a week or so). Supplementation with the Si dose should then result in less Si being excreted, as more is retained to replenish the depleted body Si pool, compared to a Si-replete group.

Secondly, from this current work, we cannot be certain that the Si excreted in urine and faeces all originated from the ingested Si dose and that there was not some exchange with the body Si pool- as for example occurs with dietary phosphate [27]. This can only be answered with an isotope label study, where isotopic Si is used for the dose solution to discriminate it from Si of the body pool and from dietary sources (i.e. the meals ingested). However this is also not straight forward. ^{31}Si and ^{32}Si are both radioactive and would result in exposure to radiation (beta decay) with short (t½ = 157 min) or long (t½ = 153 years) half-lives, respectively. Using a stable isotope such as ^{29}Si would avoid radioactive exposure but it has a high natural abundance (ca. 5% of all endogenous $Si(OH)_4$). Hence, a relatively accurate balance, as now proven is possible in this study, will be key to the success of the follow on stable isotope work. Moreover, with recent developments in inductively coupled plasma – mass spectrometry methods, to measure ^{28}Si and ^{29}Si in biological samples [28], we are confident that it will now be possible to discriminate the source of excreted Si (i.e. all 'washed through' following ingestion or some from the body pool following exchange with absorbed silicon). Both this question and that of Si retention following oral Si challenge to Si-depleted volunteers are big questions in

Table 3 Silicon intake, excretion, and balance over 24 h period (study day 1)

	Control group (n = 6)		Si-supplemented group (n = 6)	
	Mean ± SD	Range	Mean ± SD	Range
Silicon intake				
Si supplement (mg)	-		28.89	
Dietary Si intake (mg)	23.86		23.86	
Total Si intake (mg/24 h)	23.86		52.75	
Silicon excretion				
Urinary Si (mg/24 h)	13.34 ± 2.48	(11.36–18.21)	29.41 ± 3.55	(25.44–35.78)
Faecal Si (mg/24 h)	10.74 ± 1.41	(8.74–12.02)	19.96 ± 4.58	(14.31–25.53)
Total excretion (mg/24 h)	23.77 ± 1.94	(21.62–26.95)	50.02 ± 4.98	(43.93–55.68)
Silicon balance (mg)	0.09 ± 1.94	(−3.09–2.24)	2.73 ± 4.98	(−2.93–8.82)

human Si metabolism and this study proves that they may now be answered with carefully designed isotopic balance studies in Si replete and deplete individuals. In the work presented herein subjects were carefully matched to reduce variability between the two groups, however a cross-over design is undoubtedly more robust to really minimise inter-individual variation in silicon handling [29,30]. Thus, although more burdensome to the subjects, for the future work a cross-over study design will be seriously considered.

Finally, measurement of faecal Si excretion for the first time in a human study, as we report here, allowed the absolute absorption of Si from the orthosilicic acid dose solution to be estimated which, at 61 ± 9% of the ingested dose, is similar to the estimate from total urinary Si output over the 24 h collection period (57 ± 10%). These estimates are comparable with previous data (absorption being stated as ~ 50–60% of the ingested dose) from shorter urine collections, 0–6 or 0–8 h post-dose [20,25,29-34]. Hence, we can conclude that (a) urinary silicon does measure silicon absorption following oral Si challenge and (b) in general 0–6 or 0–8 h urinary collections are adequate to estimate absorption/bioavailability of Si from readily absorbed dietary sources, supplements and test solutions (Si materials requiring prolonged digestion prior to absorption may differ in this respect as previously noted [30].

Conclusions

In conclusion the present study reports that urinary and faecal Si excretion can be measured with high precision (with inter-subject variance ~ 6%) and that in normal healthy subjects who are presumed to be in Si balance, ingestion of a soluble dose of Si results in an equivalent quantity being excreted within 24 h. We confirm that urinary silicon may be used as an accurate measure of silicon absorption, assuming robust study design. This work also provides clear evidence that a proper isotope-based balance study can now be undertaken in silicon replete and depleted volunteers to inform on homeostasis of silicon and thus provide strong evidence (or not) for beneficial utilisation of the element by humans.

Abbreviations

AUC: Area under the (serum) curve; HCl: Hydrochloric acid; HNO_3: Nitric acid; ICP-OES: Inductively coupled plasma-optical emission spectrometry; OSA: Orthosilicic acid; SD: Standard deviation; Si: Silicon; Si(OH): Orthosilicic acid; UHP: Ultra-high purity.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

The authors' contributions were as follows: SSP, AS and RJ designed the research; SS conducted the research; RJ and AS had study oversight; SSP and RJ analysed the data; SSP, JJP and RJ wrote the paper & had primary responsibility for final content. All authors read and approved the final manuscript.

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Papel Nutricional e Benefícios para a Saúde

Dietary silicon intake and absorption[1–3]

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ABSTRACT

Background: Increasing evidence suggests that silicon is important in bone formation. The main source of silicon for humans is the diet, but the bioavailability of silicon from solid foods is not well understood.

Objective: We estimated the dietary intake of silicon by adults, separately for men and women and for different age groups. Foods that were major contributors to silicon intake were identified. We then estimated the gastrointestinal uptake of silicon from major food sources and studied how uptake correlated with the silicon contents of the foods.

Design: Silicon intakes were determined in cohorts from the original Framingham Study and the Framingham Offspring Study by using a 126-item food-frequency questionnaire. Gastrointestinal uptake of silicon from foods was estimated in 3–8 healthy subjects by using urinary silicon excretion as a surrogate measure of silicon uptake.

Results: Mean silicon intakes in men (30 and 33 mg/d in the original Framingham and Framingham Offspring cohorts, respectively) were significantly higher than those in women (24 and 25 mg/d in the 2 cohorts, respectively; $P = 0.0001$). Silicon intake decreased with age ($P < 0.001$, adjusted for sex). The major food sources were beer and bananas in men and bananas and string beans in women. Silicon was readily available from foods; a mean of 41% of the ingested silicon was excreted in urine. The silicon content of the foods consumed was significantly correlated with urinary silicon excretion ($P = 0.019$).

Conclusions: Solid foods are a major source of available silicon. The association between dietary silicon intake and bone health should now be investigated. *Am J Clin Nutr* 2002;75:887–93.

KEY WORDS Silicon, orthosilicic acid, phytolithic silica, silicon intake, gastrointestinal absorption, bioavailability, cohort study, diet, nutrition, bone formation

INTRODUCTION

Evidence that silicon plays a major role in bone formation has been accumulating recently, yet the bioavailability of silicon from the diet is unclear. Indeed, it is assumed that silicon, as orthosilicic acid [$Si(OH)_4$], is available only from fluids (such as drinking water and beer) but not from foods, in which it exists as polymeric or phytolithic silica (1–5). However, because fluids account for only 20–30% of total silicon intake (6–8), and because silica in solid foods could be hydrolyzed to orthosilicic acid in the gastrointestinal tract (9,10), studies should be done to determine whether silicon may be available from foods. This issue has special importance for epidemiologic studies that aim to correlate silicon intake with bone health.

Studies of silicon deprivation in growing animals conducted in the early 1970s showed reduced growth and marked defects of bone and connective tissue (11, 12). In addition, silicon supplementation of postmenopausal women with osteoporosis not only inhibits bone resorption but also increases trabecular bone volume (13) and bone mineral density (14). These results are supported by the ovariectomized rat model of postmenopausal osteoporosis (15, 16), in which oral silicon completely abrogates the loss of bone mass. We showed in osteoblast cell lines and human bone marrow stromal cells in vitro that physiologic concentrations of orthosilicic acid increase the synthesis of bone markers including type I collagen, the major organic component of bone matrix (DM Reffitt, N Ogston, R Jugdaohsingh, et al, unpublished observations, 2001). Orthosilicic acid may also be involved in the mineralization of bone matrix (17, 18).

Several reports about the silicon content of foods have been published (6–8). However, no data are available on the bioavailability of silicon from solid foods. Bioavailability data are available only for dietary fluids (5, 9, 19, 20). The bioavailability of silicon from phytolithic silica in plant-based foods is thought to be low. It is believed that much, if not all, of this silicon is excreted in the feces (1, 3–5, 21). This assumption has not, however, been confirmed.

The kidney is the major route of excretion of absorbed silicon, which is highly filtered and only slightly reabsorbed by the tubules (9). Thus, urinary silicon is a good proxy for absorption (9)

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TABLE 1
Characteristics of the study population

	Framingham Offspring cohort[1]: age groups (y)					Original Framingham cohort[2]: age groups (y)		
	26–39	40–49	50–59	60–69	70–83	67–69	70–79	80–95
Sample size								
Men	94	403	529	458	121	25	273	76
Women	96	508	602	493	114	50	429	123
Weight (kg)								
Men	86.7 ± 14.7[3]	86.9 ± 13.7	88.9 ± 15.1	84.7 ± 12.2	81.9 ± 14.8	86.5 ± 14.2	79.0 ± 12.5	74.2 ± 10.7
Women	68.3 ± 14.9	69.6 ± 16.0	70.1 ± 13.8	68.8 ± 14.5	68.4 ± 12.9	67.5 ± 11.5	64.6 ± 13.0	61.0 ± 10.7
Height (cm)								
Men	177.3 ± 6.9	176.6 ± 6.0	176.0 ± 6.4	173.7 ± 6.3	172.2 ± 6.3	173.9 ± 6.2	170.7 ± 6.9	168.6 ± 6.8
Women	164.7 ± 6.1	163.5 ± 5.9	161.8 ± 5.5	159.7 ± 5.6	157.1 ± 5.7	159.0 ± 6.8	156.8 ± 6.2	154.1 ± 6.9
BMI (kg/m^2)								
Men	27.6 ± 4.4	27.8 ± 4.1	28.7 ± 4.5	28.0 ± 3.6	27.5 ± 3.8	28.5 ± 4.7	27.1 ± 4.0	26.1 ± 3.5
Women	25.2 ± 5.5	26.0 ± 5.8	26.8 ± 5.2	27.0 ± 5.5	27.7 ± 5.3	26.7 ± 4.3	26.3 ± 5.2	25.7 ± 4.3

[1] Minimum and maximum ages were 30 and 83 y for men and 26 and 81 y for women, respectively.
[2] Minimum and maximum ages were 68 and 95 y for men and 67 and 93 y for women, respectively.
[3] $\bar{x}$ ± SD.

and was used in the present study as a surrogate measure of silicon uptake from the gastrointestinal tract. The aims of this study were to determine *1*) the intake and gastrointestinal uptake of dietary silicon in adults and *2*) whether the silicon content of foods can be used as a marker for its uptake.

SUBJECTS AND METHODS

Framingham Study cohorts

The subjects in the study of silicon intake were members of the Framingham Study cohorts. The population-based original Framingham Heart Study cohort was established in 1948 to examine risk factors for heart disease. This cohort included 5209 men and women, most of whom were white (22–24). The subjects, who were aged 28–62 y at study entry, are seen biennially for a physical examination and a battery of questionnaires and tests. Since the study began 50 y ago, nearly two-thirds of the subjects have died. The surviving, now elderly, cohort subjects are still representative of the general Framingham population in terms of age and sex distribution. At biennial examination 20 (1988–1989), 976 cohort members (602 women and 374 men) completed a semi-quantitative food-frequency questionnaire.

The Framingham Offspring Study cohort members are the children (and their spouses) of the original Framingham Heart Study cohort. The Framingham Offspring Study began with 5135 participants in 1971, and subjects are examined every 4 y. There were 3799 participants in the fifth examination cycle, from 1991–1995. Food-frequency questionnaires were available for 3418 subjects (1813 women and 1605 men) and the results were included in this analysis.

To determine silicon intakes separately for men and women and for different ages, subjects in both cohorts were separated by sex into 10-y age groups (**Table 1**). The protocol for this study was approved by the Institutional Review Board for Human Research at Boston University.

Experimental subjects

Healthy subjects with normal renal function (defined as normal plasma creatinine concentrations) were recruited from the Gastrointestinal Laboratory at St Thomas' Hospital and the Department of Nutrition and Dietetics at King's College London. Study 1 was conducted with 8 subjects (4 men and 4 women). Their mean (±SD) values for age and body mass index (BMI, in kg/m^2) were 29.5 ± 7.4 y and 23.1 ± 2.2, respectively. In study 2, the subjects were 2 men and 1 woman (mean age: 27.7 ± 5.5 y; mean BMI: 22.2 ± 2.2).

Ethical approval for these studies was obtained from King's College London Local Research Ethics Committee. The details of both studies and their potential risks were explained to the subjects, each of whom signed a consent form before the study began.

Study design and methods

Silicon intake in the Framingham Study cohorts

Usual dietary intakes of subjects in the Framingham cohorts were assessed with a semi-quantitative, 126-item food-frequency questionnaire (25, 26). This questionnaire has been validated for many nutrients and in several populations (25–27). Before the examination, these questionnaires were mailed to the subjects, who were asked to complete them and bring them to their appointments. Completed questionnaires were excluded, as previously reported (28), if calculated energy intakes were <2.51 or >16.74–17.57 MJ/d or if >12 food items were left blank. A total of 976 questionnaires from the original Framingham cohort and 3418 questionnaires from the Framingham Offspring cohort were analyzed for silicon intake. Processing of the questionnaires to calculate food intake amounts and energy intakes was carried out at Harvard University in Boston.

Silicon values per 100 g (as consumed) of each food item in the food-frequency questionnaire were first obtained from the collated data of Pennington (6). Silicon contents of composite foods were then calculated from the individual components of these foods. If values for reported silicon contents of foods varied between laboratories, additional analyses were performed independently by the authors at King's College London. With the exceptions of liquor and orange juice, our data correlated highly ($r = 0.82$; $n = 28$) with values reported by Pennington (6). Therefore, in almost all instances we used the Pennington values in the database, but we used our own values for orange juice (0.01 ± 0.01 mg Si/100 g;

range: 0.0004–0.25 mg/100 g) and liquor (0.13 ± 0.04 mg Si/100 g; range: 0.06–0.21 mg/100 g).

The data were entered into a data management program (SAS, version 8.1; SAS Institute Inc, Cary, NC) at the Dietary Assessment Research Program at Tufts University in Boston. Data were corrected for the weight of each food item as reported by each individual subject. Because the data were presented as dry weight, silicon contents of brown rice, white rice, and pasta were corrected by 0.30, 0.39, and 0.30, respectively, on the basis of US Department of Agriculture published factors for converting between cooked and raw forms of these foods (29). The silicon values for all the food items were then summed to obtain total silicon intake per subject. We then divided the silicon intake for each food item by the total silicon intake per subject to obtain the proportional ranking of food sources.

Silicon uptake in the experimental subjects

Two studies were undertaken in the experimental subjects. First, we investigated whether silicon was available from a meal of silicon-rich foods that did not include silicon-containing fluids (study 1). Second, we investigated the gastrointestinal uptake of silicon from the major food sources of silicon in the Framingham cohorts (study 2).

In both studies, subjects fasted overnight from 2200 onward. They continued to fast until 6 h after ingestion of the test meal (≈1500). Throughout this study period, subjects ingested ultra-high purity (UHP) water (0.166 L/h) with negligible silicon content (26 μg/L). No other foods or drinks were permitted during the study period.

The UHP water (18 MΩ/cm) was from an Elga (High Wycombe, United Kingdom) water purifier. Blood samples were collected into 10-mL polypropylene transport tubes (Medfor Products, Farnborough, United Kingdom). Urine was collected in preweighed, 2.5-L polypropylene Mauser bottles (Aldrich Chemical Co, Gillingham, United Kingdom). These bottles had been rinsed thoroughly with UHP water and air-dried in a clean-air room. Clean-air facilities (class J clean-air room and class C laminar air-flow workstation) were used throughout to avoid contamination of the samples with silicon.

Foods were purchased from supermarkets and local shops in London. The corn flakes and museli used were Kellogg's Corn Flakes and Kellogg's All-Bran Plus, respectively (Kellogg Marketing and Sales Co Ltd, Manchester, United Kingdom). The wheat biscuits were Weetabix (Weetabix Ltd, Kettering, United Kingdom). The white rice was Uncle Ben's Long Grain Rice (packed in Belgium for Pedigree Master Foods, Master Foods Ltd, Dublin). The raisins were Safeway Homebaker California Seedless Raisins (produced in California for Safeway, Hayes, United Kingdom). The mineral waters were Evian and Volvic (Danone Group, London). All the other foods used were the shops' own brands.

Study 1. Study 1 was conducted over 2 d. Subjects fasted overnight and then at 0900 on day 1 emptied their bladders and thereafter collected urine for 3 h in a single container (predose urine sample). During this time period, they ingested only 0.5 L UHP water. At the end of this period, the subjects returned to their normal eating habits. Subjects fasted again overnight from day 1 to day 2. At 0900 on day 2, each subject had an all-plastic intravenous cannula (Venflon, 1.2 mm × 45 mm; Infusion Therapy AB, Helsingborg, Sweden) inserted into a forearm vein. Subjects then emptied their bladders, and two 5-mL blood samples were collected 10 min apart for baseline silicon measurements. The blood was collected into polypropylene transport tubes without anticoagulant. Each subject then ingested a meal of 100 g white rice (microwave cooked), 150 g green beans (microwave cooked), and 100 g raisins. The total silicon content of this meal was 13.15 mg. A 5-mL blood sample was collected immediately after consumption of the meal (t = 1 min) and additional 5-mL samples were obtained at 20-min intervals for 2 h and then at 60-min intervals for another 4 h (total of 6 h).

Two urine collections were completed after consumption of the meal, from 0 to 3 h and from 3 to 6 h. Thus, each collection lasted for a total of 3 h. Each subject ingested 0.5 L UHP water during each 3-h urine collection. At the end of the 6-h period, each subject ate a low-silicon lunch consisting of 100 g potato waffle (grilled) and 200 g peeled orange. The meal supplied a total of 1.09 mg Si. A final 3-h urine collection (from 6 to 9 h) was then completed, and again each subject ingested 0.5 L UHP water during this period. Samples of the ingested meals were retained for total silicon analyses (*see* Sample analyses, below).

Study 2. Study 2 was conducted over 25 d. Throughout this time period, subjects fasted overnight. On days 1 and 2 at 0900, subjects emptied their bladders and then ingested 0.5 L UHP water. An additional 0.5 L UHP water was consumed from 3 to 6 h by each subject. Subjects collected their urine for 6 h in a single container on both days, which were considered baseline days 1 and 2. Thereafter, on days 3–25, the single-item meals listed in **Table 2** (B1–H2) were ingested at 0900 and 6-h urine collections were then completed. Again, 1 L UHP water was ingested during each 6-h period. Samples of the meals were retained for total silicon analyses.

Sample analyses

Blood and urine samples were processed and analyzed for total silicon by inductively coupled plasma optical emission spectroscopy (Jobin-Yvon JY24; Instrument SA, Longjumeau, France) at a wavelength of 251.611 nm as described previously (9). Samples of the meals were also analyzed for total silicon content by inductively coupled plasma optical emission spectroscopy at 251.611 nm. Food and beverage samples were analyzed in 3 different ways, depending on the specific food: *1*) without pretreatment (used for UHP water and mineral waters), *2*) after dilution (used for milk, orange juice, and liquor), and *3*) after microwave-assisted acid digestion (used for solid foods). The silicon contents of foods were determined for their edible portions.

Statistical analysis

The results are expressed as means ± SDs unless otherwise stated. We compared the silicon intakes of men and women by using a two-sample t test and we analyzed for a correlation between silicon intake and age by using linear regression analysis. Both of these analyses were done with SAS for WINDOWS, version 8.1 (SAS Institute Inc), and for both, $P < 0.05$ was considered statistically significant.

In the silicon uptake studies, comparisons to baseline were made by using paired, one-tailed Student's t tests in MICROSOFT EXCEL 97 SR-1 (Microsoft, Redmond, WA). Because 3 postdose urine collections were compared with baseline silicon excretion in study 1, and 22 foods were compared with UHP water (the control) in study 2, a Bonferroni correction for multiplicity of testing was applied to the P values. Thus, significance was set at $P < 0.017$ (0.05/3) in study 1 and $P < 0.0023$ (0.05/22) in study 2. We used Pearson's product-moment correlation coefficients to analyze

TABLE 2
Meals, portion sizes, and silicon intakes in study 2[1]

Meal and food source	Portion ingested	Silicon intake
		mg
Baseline		
A1: UHP water[2]	1 L	0.03
Cereals[3]		
B1: corn flakes[4]	100 g	2.42
B2: wheat biscuits[5]	100 g	2.78
B3: high-bran cereal[6]	100 g	10.17
Breads		
C1: white	200 g	3.38
C2: whole-meal	200 g	4.50
C3: granary	200 g	8.94
C4: croissants	100 g	1.67
Rice and pasta[7]		
D1: white rice[8]	200 g	2.48
D2: brown rice (with husks)	200 g	4.14
D3: pasta (frusili)	250 g	1.50
Vegetables		
E1: potato waffles (grilled)	200 g	0.90
E2: new potato (with skin)[9]	200 g	0.58
E3: carrot (raw, peeled)	200 g	4.58
E4: lettuce, iceberg (raw)	250 g	1.03
E5: green beans (cooked)[9]	250 g	6.10
Fruit		
F1: banana (yellow, peeled)	250 g	13.60
F2: orange (peeled)	210 g	0.67
F3: strawberries	200 g	0.24
F4: raisins (California seedless)	100 g	8.25
Milk		
G1: Cold semi-skimmed	0.4 L	0.21
Mineral waters		
H1: mineral water[10]	0.5 L	3.44
H2: mineral water (high-silicon)[11]	0.5 L	7.23

[1] Each meal included only the food source listed, without any additional components, although 1 L ultra-high purity (UHP) water was also consumed by each subject over the 6-h urine collection period for meals B1–H2.
[2] 1 L UHP water was consumed as 0.5 L at $t = 0$ h with an additional 0.5 L from 3 to 6 h.
[3] Ingested with 0.4 L cold semi-skimmed milk.
[4] Kellogg's Corn Flakes; Kellogg Marketing and Sales Co Ltd, Manchester, United Kingdom.
[5] Weetabix; Weetabix Ltd, Kettering, United Kingdom.
[6] Kellogg's All-Bran Plus; Kellogg Marketing and Sales Co Ltd.
[7] Cooked by boiling in tap water.
[8] Uncle Ben's Long Grain Rice; Pedigree Master Foods, Master Foods Ltd, Dublin.
[9] Cooked in a microwave.
[10] Evian; Danone Group, London.
[11] Volvic; Danone Group.

for a correlation between silicon intake and urinary silicon excretion; $P < 0.05$ was considered significant.

RESULTS

Silicon intake in the Framingham Study cohorts

Total daily dietary intakes of silicon in the 2 Framingham Study cohorts are shown in **Figure 1**. At all ages, intakes were significantly greater in men than in women. The mean intakes for men and women, respectively, were 33.1 ± 19.4 and 25.0 ± 11.4 mg/d in the Framingham Offspring cohort and 29.6 ± 14.8 and 24.2 ± 9.5 mg/d in the original Framingham cohort. Silicon intakes decreased significantly with age in the Framingham Offspring cohort ($P < 0.001$, adjusted for sex); on average, intakes were 0.1 mg lower for every additional year of age. The major dietary contributors to total silicon intakes are shown in **Table 3**.

Silicon uptake in the experimental subjects

In study 1, the mean baseline serum silicon concentration was 7.5 ± 3.1 μmol/L (range: 2.5–12.2 μmol/L; $n = 8$). A full set of blood samples was obtained from 7 of the 8 subjects. For these subjects, the peak increase over baseline was measured in the serum 100–120 min after ingestion of the silicon-rich meal (**Figure 2**A). The mean increase above baseline in the area under the curve from 0–6 h after the meal was 32.9 ± 7.9 μmol·h. This accounted for 7.0 ± 1.7% of the total silicon ingested; we used mean estimated plasma volumes of 2.13 L for women and 2.46 L for men (30).

Urinary excretion of silicon also increased significantly above baseline after ingestion of the meal (Figure 2B). The silicon excreted during the first 6 h (corrected for baseline silicon excretion) accounted for a mean of 38.2 ± 10.9% of intake. Only a small percentage of the ingested silicon (4.7 ± 3.7% of intake, baseline corrected) was present in the 6–9-h urine collection. It is likely that much of this amount came from ingesting the low-silicon lunch, which supplied 1.09 mg Si. Therefore, in study 2, urine was only collected from 0 to 6 h after the meals.

Urinary silicon excretion during the 6 h after subjects consumed different foods (study 2) is shown in **Figure 3**. Marked increases above baseline in the excretion of silicon were measured for cereals, whole-meal bread, granary bread, rice, pasta, green beans, raisins, and mineral waters. The results showed that little silicon was available from bananas, despite their high silicon content (5.44 mg/100 g edible portion). Overall, a positive

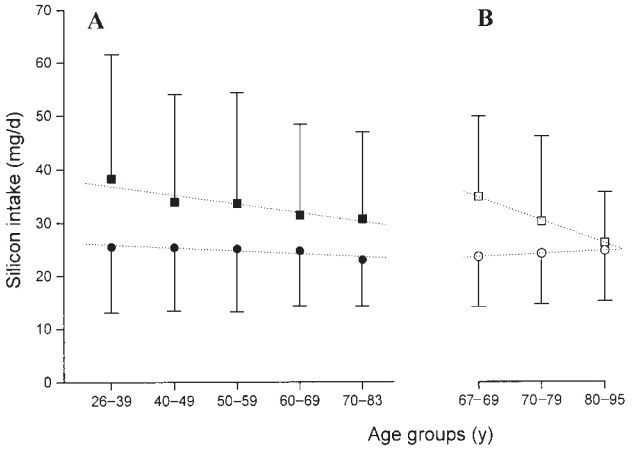

FIGURE 1. Mean (±SD) total dietary silicon intakes in men (■, □) and women (●, ○) in the Framingham Offspring cohort (A) and the original Framingham cohort (B). Silicon intakes were significantly higher in men than in women in both cohorts ($P = 0.0001$; two-sample t test). Sample sizes were as follows for men and women, respectively: in the Framingham Offspring cohort, 94 and 96 for 26–39 y, 403 and 508 for 40–49 y, 529 and 602 for 50–59 y, 458 and 493 for 60–69 y, and 121 and 114 for 70–83 y; in the original Framingham cohort, 25 and 50 for 67–69 y, 273 and 429 for 70–79 y, and 76 and 123 for 80–95 y.

TABLE 3
Major (top 10) food sources that contributed to total silicon intakes in the study population[1]

	Men		Women	
Ranking	Food source	Contribution	Food source	Contribution
		%		%
Framingham Offspring cohort[2]				
1	Beer	17.6 ± 23.7	Bananas	10.5 ± 10.1
2	Bananas	9.1 ±10.2	String beans	4.6 ± 4.5
3	White bread	4.6 ± 6.0	White bread	4.6 ± 6.2
4	Cold cereal	4.5 ± 6.3	Cold cereal	4.4 ± 5.8
5	Coffee	3.5 ± 3.7	Dark bread	3.7 ± 5.0
6	Beans and lentils	3.3 ± 4.0	Beans and lentils	3.7 ± 4.6
7	Pizza	3.2 ± 3.5	Coffee	3.5 ± 3.9
8	Dark bread	3.1 ± 4.7	Muffins and bagels	3.5 ± 4.1
9	String beans	3.0 ± 3.1	Beer	3.3 ± 10.0
10	Muffins and bagels	2.7 ± 3.5	Cooked oatmeal	3.3 ± 6.6
Original Framingham cohort[3]				
1	Bananas	13.4 ± 13.1	Bananas	13.9 ± 12.2
2	Beer	10.6 ± 19.6	String beans	5.4 ± 4.9
3	White bread	5.4 ± 7.3	Cooked oatmeal	5.3 ± 9.2
4	Cold cereal	5.0 ± 5.9	Cold cereal	5.3 ± 6.5
5	Cooked oatmeal	4.3 ± 7.5	Dark bread	5.3 ± 6.7
6	String beans	4.1 ± 4.4	White bread	4.7 ± 6.8
7	Beans and lentils	3.6 ± 4.4	Potatoes	3.8 ± 3.3
8	Potatoes	3.2 ± 2.9	Beans and lentils	3.0 ± 4.1
9	Dark bread	3.2 ± 4.4	Muffins and bagels	2.3 ± 3.5
10	Muffins and bagels	2.5 ± 4.5	Coffee	2.2 ± 3.0

[1] $\bar{x}$ ± SD.
[2] Total percentage contribution of the foods listed: 54.6% and 45.1% for men and women, respectively.
[3] Total percentage contribution of the foods listed: 55.3% and 51.2% for men and women, respectively.

correlation between silicon intake and excretion in urine (a surrogate measure for uptake) was observed (**Figure 4**).

DISCUSSION

Total dietary intakes of silicon in the 2 Framingham cohorts were between 13 and 62 mg/d, similar to the previously reported values of 20–50 mg/d from Western diets (6–8, 21, 31). Silicon intakes in the present study were also ≥2-fold higher than typical Western intakes of iron and zinc, 2 other elements of physiologic importance. Thus, the diet is a major source of silicon for humans, with higher intakes obtained from diets rich in grains, cereal products, and plant-based foods than from dairy and animal products (6–8). Asians and Indians have much higher silicon intakes than do Western populations (32, 33) as a result of their higher intakes of plant-based foods (32, 34), and it is interesting that in these communities there is a lower incidence of hip fracture than in the West (35).

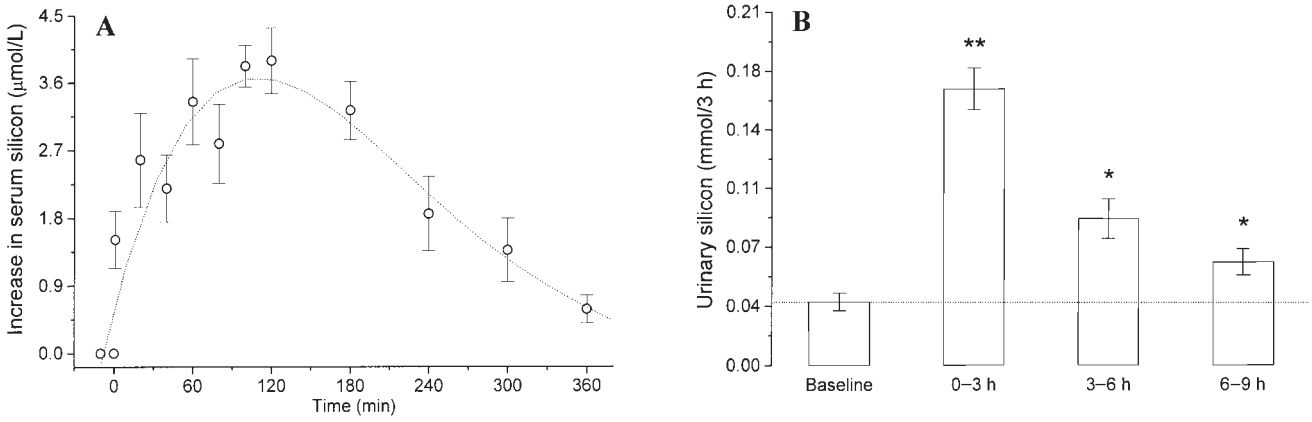

FIGURE 2. Mean (±SE) increase in serum silicon concentration (A; $n = 7$) and mean (±SE) excretion of silicon in urine (B; $n = 8$) for the experimental subjects in study 1 after ingestion of the test meal (total silicon intake: 13.15 mg). The first 2 values in A are the baseline serum concentrations in 2 predose blood collections; the mean of these values was used to calculate the subsequent increase in serum silicon. The dotted line in B represents the mean baseline excretion of silicon in urine. At 6 h postdose, subjects ingested a low-silicon lunch (total silicon intake: 1.09 mg). *,**Significantly higher than baseline urinary silicon excretion (paired, one-tailed t test with Bonferroni correction for multiple comparisons): $^{*}P < 0.01$, $^{**}P < 0.001$.

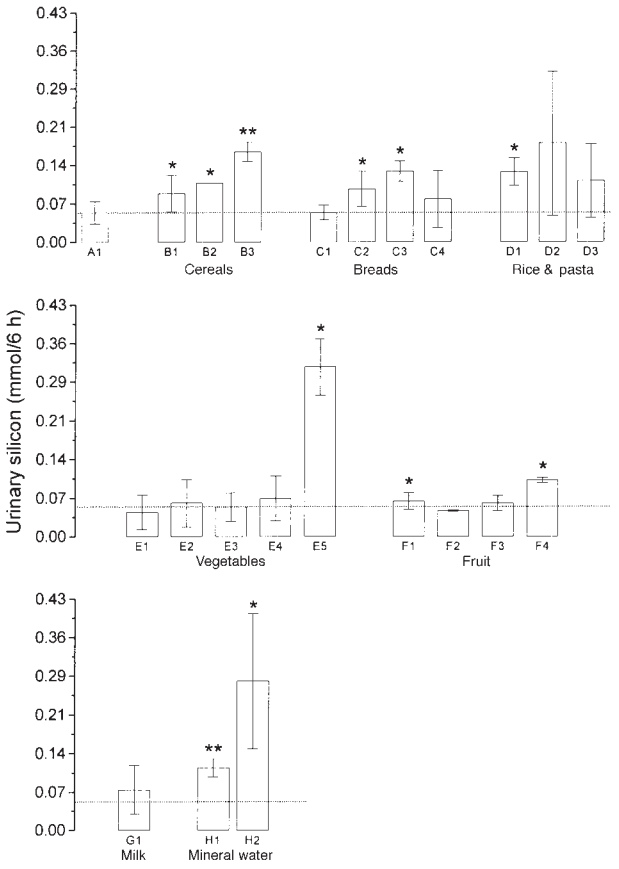

FIGURE 3. Mean (±SD) excretion of silicon in 6-h urine collections after ingestion of single-item meals by experimental subjects in study 2 (n = 3 for all bars except n = 2 for B2). The dotted lines represent the mean baseline urinary silicon excretion (also shown by the bar labeled A1) after ingestion of ultra-high purity water. Baseline excretion for each subject was calculated from 2 separate 6-h urine collections. *,**Significantly higher than baseline urinary silicon excretion: $^{*}P \leq 0.05$ (paired, one-tailed t test), $^{**}P \leq 0.0023$ (paired, one-tailed t test with Bonferroni correction for multiple comparisons).

In the present study, silicon intakes were 20–33% higher in men than in women, and silicon intakes decreased in both sexes with increasing age. In a younger population (25–30 y), Pennington (6) calculated that women's intakes (18.9 mg/d) were one-half those of men (40.1 mg/d). The primary reason for this difference was higher beer consumption by the young men, which accounted for 45% of their total silicon intake. In the present study, beer was also the highest contributor to total silicon intake in men (Table 3). A previous study showed that silicon in beer is readily bioavailable because it is solubilized during the mashing process of beer making (5). However, no previous study investigated silicon bioavailability from other major food sources such as bananas, grains and grain products (eg, bread, cold cereal, and oatmeal), and string beans (Table 3). Coffee was a source of dietary silicon because of its drinking water content, and pizza was also a source because of its bread base. Surprisingly, rice and pasta, which contain large amounts of silicon (6), were not among the major contributors to silicon intake in the 2 cohorts (mean contributions: 2.6–3.2% from brown rice and 2.4–3.1% from pasta in the Framingham Offspring cohort). This indicates that intakes of rice and pasta were low in our population.

Once we had confirmed that silicon is readily available from meals, as shown by its rapid absorption and rapid excretion in the urine (Figure 2), we then investigated absorption from some individual foods. Overall, a mean of 40.9 ± 36.3% of ingested silicon was excreted over a 6-h period in the urine, again confirming that food-based, phytolithic silica is digested and absorbed from the gastrointestinal tract. Silicon in grains and grain products (rice, breakfast cereals, breads, and pasta) was readily absorbed, as indicated by the mean urinary excretion of 49 ± 34% of intake (range: 10–100%). However, except for green beans and raisins, the silicon in vegetables and fruit was less readily absorbed, as indicated by the mean urinary excretion of 21 ± 29% of intake (range: 0–40%). Surprisingly, silicon uptake was low (2.1 ± 1.2% of intake) from bananas, which are high in silicon (5.4 mg Si/100 g edible portion) and were one of the highest contributors to silicon intake in the Framingham cohorts. This suggests either that silicon is mainly present in an unavailable form in bananas or that this silicon is absorbed late from the gastrointestinal tract (after 6 h). In general, however, silicon was readily available from foods and in many cases, it showed absorption similar to that of silicon from fluids. For instance, urinary silicon excretion (as an indicator of absorption) was 41–86% from corn flakes, white rice, and brown rice and was 50–86% from mineral waters.

Finally, we found a significant correlation between silicon intake and urinary silicon excretion (a surrogate measure of silicon uptake), suggesting that the silicon contents of foods can be used to estimate exposure in future epidemiologic studies. This should allow researchers to estimate the effect of dietary silicon on bone health. A daily minimum requirement (recommended daily intake) for silicon has not been established, but was estimated at 10–25 mg/d on the basis of the 24-h urinary excretion of silicon (17, 20). This value is consistent with our data because we found a mean silicon uptake of 40.9% from foods, and from this value we estimated the mean daily absorption of silicon to be 12.1 and 13.5 mg/d in men and 9.9 and 10.2 mg/d in women in the original Framingham and Framingham Offspring cohorts,

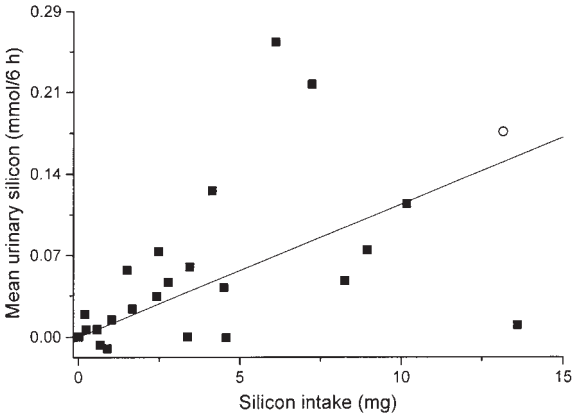

FIGURE 4. Correlation between silicon intake from meals and mean urinary silicon excretion (6-h collections, corrected for baseline silicon excretion) in experimental subjects (studies 1 and 2). The data point from study 1 (○) is the mean of values for 8 subjects after they ingested the test meal containing 13.15 mg Si. The data points from study 2 (■) represent the means of values from 3 subjects after they ingested the different single-item meals. The correlation, r = 0.5, was significant at P = 0.019. The equation for the line is $y = 0.326x$.

respectively. These values would increase slightly if silicon intakes from drinking water were included.

In conclusion, foods are major sources of available silicon for humans. We confirmed that in the Framingham cohorts, daily silicon intakes were markedly higher in men than in women, mainly because of higher beer consumption by men. We showed for the first time that silicon intakes of both sexes decrease with increasing age. Neither silicon deficiency nor a silicon-responsive condition have yet been identified in humans (36), and dietary silicon excess has not been linked to any diseases (32). Future studies can now investigate whether silicon intake influences bone mass.

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Silica and Silicon: Amazing New Health Benefits from this Trace Element

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ESSENTIAL SILICON : THE REGENERATOR

"Silicon is the second most common element on earth, lead only by oxygen, and is the second-most abundant element in the Earth's crust, where it is chiefly found in the form of silica or silicon dioxide.

Silicon is present in important quantity in most of organic tissues, bony tissues, and connective tissues. In the human body, it is in higher concentration (7g) than Iron (Fe) ,Copper (Cu). It potentialize the action of Zinc (Zn) and Copper (Cu) and allows the fixing of Calcium (Ca).

The quantity of silicon in our body diminishes when we age. That is to say the importance of this composite to all the ages, and particularly during the third age to warn and avoid the deteriorations of reticule endothelial tissues , collagen, scleroses by calcification of tissues, weakening of bones and diseases of bone by decalcification (osteoporosis) by continuation of the difficulties of the fixing of calcium.

Silica is one of those elements whose list of benefits keeps growing as time passes. Silica was recognized by the health and science community as an essential trace element in 1972.

What You Need To Know about Silica

Silica deficiency is the causal factor in many degenerative diseases, including Alzheimer's disease and is the missing element in all anti-aging programs.

Research shows that skeletal diseases such as osteomalacia (bad bones), osteoporosis (porous bones and/or spontaneous fractures, as well as shrinkage) although caused by a calcium deficiency, do not respond to calcium therapy alone. Research conducted in Paris, France by noted biophysicist Louis Kervan, and in the United States by Dr. Richard Barmakian shows that fractured bones did not heal at all when high amounts of calcium were present. They heal fair to poorly when moderate amounts of calcium were present. But they heal extremely well when relatively low amounts of calcium were present with an abundance of silica. calcium and vitamin D alone are not sufficient for bone growth, density, strength, and flexibility. silicon is needed to strengthen and increase production of collagen and flexible connective tissue that binds everything together.

Early research, in 1952, by Dr. A. Charnot determined that decalcification (the leeching away of calcium) is always preceded by the complete loss of detectable tissue silica.

Silicon influences the calcification process and the rate at which calcium is deposited in bone. Animals kept on the high silicon diets attained maximal bone mineralization much quicker than did those on low-silica diets."

Silica is a vital mineral that is almost completely over looked by mainstream nutritionists. We are born with an abundance of silica and relatively low amounts of calcium. Then with every advancement in chronological age, the amount of calcium increases and the amount of silica decreases within the body. This is exactly what happens in the aging process. As our silica supply diminishes, the soft tissues become stiff and lose elasticity. They become over calcified!

Additionally, there is a relationship between silica and the rate of aluminum concentration in the brain of Alzheimer’s patients. Many research projects point to the fact that a deficiency of silica in the diet is the causal effect of the increased absorption of aluminum into the body and its ultimate accumulation into the synapses of the brain.
"In their 1997 book, Prescription For Nutritional Healing, James F. Balch, M.D. and Phyllis A. Balch, C.N.C., point out another benefit of silicon to our health as we age. 'Silicon counteracts the effects of aluminum on the body and is important in the prevention of Alzheimer's disease and osteoporosis. Silicon levels are needed in larger amounts by the elderly,' say the Balches."

Research on this remarkable element continues, but a study in 1990 found it an absolute necessity for the proper function of skin, ligaments, tendons, and bones. Silica supplements are taken regularly by millions of people to strengthen and improve their bones, connective tissue, hair, and skin.
Silica adds strength and flexibility. It's obvious why strength and flexibility are essential to skin and bones. It's also important to know that silica supports blood vessel health, making it extremely important in supporting heart health.

Principal constituent of vascular walls , silicon represents an important link for the maintenance of the elasticity of this one. The physiological decrease of the rate of silicon with the age lead to a decrease of the vascular tonicity . At the level of the aortal ones, very rich partitions in élastin (about 40%) and in collagen, one rediscovers mucopolysaccharides that constitute the intermediary matrice between these two first components. These polysaccharides are highly rich in silicium in the human body.

Loepper and Golan studied the relation between the rate of silicium in aortal fabric and arteriosclerosis; they note that all lipid infiltration leads to a decrease of silicon in the arterial partitions. On the other hand, a study conducted by Saddened, Nebla and Nebuloni, concerning 72 61 years old persons and more, showed than in the attained arteries of arteriosclerosis, the rate of silicon is 14 inferior times to the one that was identified on the undamaged arteries. A deficit in organic silicon increases risks of arteriosclerosis, and of coronary diseases. .

Silicon is improve the cardiovascular system, as it is essential to the structural integrity, elasticity and permeability of the arteries. Silica may be useful in reducing blood fats & cholesterol. Artherosclerosis can occur as a result of silicon deficiency whereas silicon is abundant (up to 14 times more) in the arteries of people who are free of heart disease.

"As noted in The Complete Book of Minerals for Health" silica is given due credit by Klaus Schwarz, M.D. Schwarz reviewed a survey of heart deaths in Finland, conducted between 1959 and 1974. The death rate from coronary heart disease in men of eastern Finland was two times higher than men in western Finland. It should be noted that smoking and obesity were relatively the same in both groups. However, another factor impacted the researchers when they checked chemicals in drinking water in both places. Silica was absent from drinking water where coronary heart disease rates were twice as high and definitely present in the other area. Schwarz continues studying silica - this time in fiber, generally regarded as a non-food, which does little more than give bulk to waste matter and hurry it out of the system. As reported in his book, Schwarz studied 337 British men for 10 years and discovered that those who ate the most cereal fiber suffered only one-fifth the heart disease of those who ate the least."

This study has demonstrated that a deficiency in silica could increase the risk of coronary problems. As a matter of fact, the elasticity of the arterial walls is essential to absorb the variations in blood pressure. A supplement of silica is often necessary to restore a normal tonicity to the arteries.

Various studies showed that, with advancing age, silicon disappears from the aorta, the heart's key blood vessel; consequently, connective tissue in it deteriorates.

With the departure of silicon from the interior (intimae) of artery walls, and with the weakening of its connective tissue, comes a greater risk of developing occlusive heart disease."

"In the past generation, many studies have found that deaths from heart disease are far fewer in areas where the water is considered 'hard'. (presence of salts, as of calcium or magnesium.) This was reported as early as the 1960s by Henry Schroeder, then professor of clinical physiology at Dartmouth University Medical School."

In 1939, the Nobel Price winner for chemistry, Professor Adolf Butenant, proved that life cannot exist without Silica. According to his research conducted at Columbia University in 1972, silica is an essential nutrient and must be supplied continuously from food sources.

In the human body, silica is essential for bone formation and the health of connective tissue. Healthy hair, skin, nails and flexible arteries would be impossible without silica. Silica is critical to our well being, but it's difficult to assimilate from a normal diet. Supplementing our silica intake on a regular basis may be extremely beneficial.
Silica supplementation can increase collagen 1 (one) in growing bones. Everyone at every age will benefit from this kind of bone support. As our bodies age they use increased levels of silica but are not able to replenish it as quickly or as easily as when we were young. Silica supplementation becomes increasingly more critical as we get older. Silica is especially important in keeping skin and hair looking young.

By offering silica to the body , assimilation is vastly improved and silica levels can begin to increase. This allows the potential remineralization of bone and could aid in increasing cartilage between joints. As silica levels increase, vascular support increases and the integrity of connective tissue is restored. Silica, when sufficient, may also retard the aging process due to

immune system support.

MUSCULAR , TENDON AND BONE TISSUES

While mineral calcareous (limestone) is prescribed in bony affections (weakness of the bones, slowness of the consolidation of the breaks, lombalgies, rachitism), it is basic that it otherwise replaced, at least be associated with the silica. The Pr Kervran showed that: «... by radio photos, the breaks repair themselves a lot more quickly by extracts of organic silica than by the limestone administration: limestone mineral is a residue, and the organism does not assimilate it; Therefore to re-calcify, this is not limestone mineral that it is necessary to take, but what will allow the organism of "to make" his limestone..

THE CUSTODIAN OF THE BEAUTY OF THE SKIN

The deficit in organic silicon from the forty provokes a dryness and a released of the skin and his lack induces also wrinkles . The elastic fibers crumple and the lines of fractures form the wrinkles.. There again, the organic silicon is one of the essential provisions of synthesis of the collagen fibers and of élastin that allows the skin to preserve or to rediscover his elasticity and his integrity. Once refilled in silicon, the skin rediscovers its youth property and can again fight actively the processes of the ageing. In fact, the presence of the organic silicon in the skin cells revitalizes the collagen and elastin factories, reinforces the cell membranes to arm them against the free radical one and revives the hydro regulation of the cells of the epiderm. The activity of the skin cells is thus relaunched.

The quantity of organic silicon diminishes with the ageing, and this in a irreversible manner, because the human body is incapable TO TRANSFORM the mineral silicon that it ingests (foods, drinks) in organic silicon. Now, mineral silicon IS NOT ASSIMILABLE by the human organism. This is to say the importance of this organic composite to all the ages and particularly during the third age to warn and avoid the deteriorations of reticule- endothelial tissues, collagen, and the scleroses by calcification of tissues, the weakening of the bones, and bony diseases by decalcification (osteoporosis) by continuation of the difficulties of the fixing of calcium.

The works of Zeller and Odier show the essential role that plays the silicon at the connective tissue level . Thus, it was observed that the silicon is essential for the synthesis of the collagen fibers and of elastin in connective tissue. All lack or impoverishment of these tissues in silicon lead to a loss of their elasticity and of their integrity. Organic silicon therefore are indicated to act on wrinkles, vergetures and to improve the elasticity of the skin.

There are many reasons for silica supplementation, including:

1. Silica Inhibits the aging process in tissues
2. Silica helps maintain bone density and strength by facilitating deposits of calcium and minerals into the bone matrix. Strengthens weak connective tissue and improves its structure and function
3. Silica is vital for articular cartilage development. It has an solidifying action (in the ossification process or of bony reminéralisation, and a flexibility and elasticity action on tendons, joints and skin.
4. Silica supports the inner lining of arterial tissue and increases the elasticity of blood vessels. Increases the elasticity and firmness of blood vessels, making them less likely to develop atherosclerosis - when silicon rejuvenates connective tissue, atherosclerotic swelling vanishes
5. Silica can help maintain a youthful skin tone and increase collagen levels.
6. Silica helps hair grow thicker and stronger and nails grow faster and harder.
7. Silica stimulates the immune system to fight off disease-causing invaders – bacteria; viruses; toxins, since it is essential to the triggering process of manufacture of the antigens and antibodies.
8. Silica stimulates cell metabolism and cell formation, has mild disinfecting properties, and is an anti-inflammatory.

Expected Results

- Facilitates deposits of calcium and minerals into the bone matrix
- Aids in remineralizing the skeletal structure
- Aids in articular cartilage development
- Helps to strengthen connective tissue
- Supports the structure and increases the elasticity of blood vessels
- Helps to retain moisture in tissue right under the skin which can help prevent wrinkles
- Helps promote healthy hair, skin & nails

SILICA AND AGE REVERSAL

How and why the body ages has been the subject of many books and postulations. No conclusive data exist, but one thing is

certain: poor nutrition plays a definite role in aging. For some reason yet unknown, aging is associated with a decrease in the silica content of the body. This observation has been interpreted as an indication of why we need to consider silica supplements as we advance in years. This has led many to believe that silica may play a preventive role in aging and premature aging. Considering the role that silica plays in maintaining the youthful appearance of hair, skin, and nails and its many valuable functions in disease prevention, it appears that silica should be more seriously seen as an essential element in the maintenance of youth and vitality of the body.

Taken orally, silica is easily absorbed via the intestinal wall. It is also rapidly and easily excreted; so regular, daily supplementation is important. Because it is water soluble, it does not "build up" in the body. No studies have found any negative effects of "too much" silica. Unfortunately, natural levels of silica tend to drop with age. Regular supplementation could make a significant difference in the quality of your life during later years.

Thus, the silicon associated to vitamins B2, B3, B5, favors the activity of the repressors elements of the cells preventing thus the essential factors or the latent viruses to perturb contained information in the chromosomes carriers of the genes and to develop anarchically. « Silica must be, considered as particularly useful in the preventive treatments of the senescence and cancer ». (Niestlé-piaget)

« One observed that the noxious effects of chemotherapies notably after breast cancer were dramatically reduced by the taken one of organic silicon. Also, in the case of viral hepatitis , one was able to notethat taking organic silicone reduces the high level of transaminases ». (Besbes)

Silica may be indispensable for lungs. Lung tissue function and elasticity are silica dependent. For this reason, silica could be a favorable supplement to orthodox therapies. It can promote mucous flow and reduce coughing. Silica helps support the regeneration of mucous membranes.

Our Bodies Need Silica In our youth, our tissues absorb and maintain high levels of silica -- enabling our bodies to remain very flexible, resilient, and energetic. As we age, our silica levels steadily decline, and we begin to exhibit the traditional signs of aging - including bone, joint and cartilage deterioration; dry, distressed skin; brittle nails, thinning hair, and tooth and gum loss. It is believed that silica supplementation may be a key factor in slowing this process, and may help us maintain a healthier, more youthful, and pain-free body—and in reducing the body's natural recovery time.

Our bodies need boron, magnesium, manganese, potassium, iron and phosphorous in order to assimilate the silica in our system.

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FORMULA:
Bamboo stems, Horsetail, Squid bone Onion, fenugreek, Dandelion roots & leaves, Yellow Dock root, alfalfa, beets, Soybeans, vitamins B2, B3, B5,
Magnesia carb 4 C, Magnesia Mur 5C, Manganum 6C, Phosphorus 9C, Ferrum phos 4C, KaliKali carb 4C, Kali chlor 5C, Calcarea Carb 9C,

Chapter 14
Silicon: The Health Benefits of a Metalloid

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Contents

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Abstract Silicon is the second most abundant element in nature behind oxygen. As a metalloid, silicon has been used in many industrial applications including use as an additive in the food and beverage industry. As a result, humans come into contact with silicon through both environmental exposures but also as a dietary component. Moreover, many forms of silicon, that is, Si bound to oxygen, are water-soluble, absorbable, and potentially bioavailable to humans presumably with biological activity. However, the specific biochemical or physiological functions of silicon, if any, are largely unknown although generally thought to exist. As a result, there is growing interest in the potential therapeutic effects of water-soluble silica on human health. For example, silicon has been suggested to exhibit roles in the structural integrity of nails, hair, and skin, overall collagen synthesis, bone mineralization, and bone health and reduced metal accumulation in Alzheimer's disease, immune system health, and reduction of the risk for atherosclerosis. Although emerging research is promising, much additional, corroborative research is needed particularly regarding speciation of health-promoting forms of silicon and its relative bioavailability. Orthosilicic acid is the major form of bioavailable silicon whereas thin fibrous crystalline asbestos is a health hazard promoting asbestosis and significant impairment of lung function and increased cancer risk. It has been proposed that relatively insoluble forms of silica can also release small but meaningful quantities of silicon into biological compartments. For example, colloidal silicic acid, silica gel, and zeolites, although relatively insoluble in water, can increase concentrations of water-soluble silica and are thought to rely on specific structural physicochemical characteristics. Collectively, the food supply contributes enough silicon in the forms aforementioned that could be absorbed and significantly improve overall human health despite the negative perception of silica as a health hazard. This review discusses the possible biological potential of the metalloid silicon as bioavailable orthosilicic acid and the potential beneficial effects on human health.

Keywords asbestos • dietary silica • medicine • orthosilicic acid • silicon • therapy

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1 Introduction

Silicon is the second most prevalent element in the earth's crust existing primarily as oxygen-containing silica and silicates and accounting for around 27% of elemental mass with oxygen comprising approximately 45% [1–3]. Silica is omnipotent being present in almost all of the earth's minerals, rocks, sands, and clays and exists in myriad chemical forms expressed as quartz, emerald, feldspar, serpentine, mica, talc, clay, asbestos, and glass all of which have different uses [4,5]. Overall, quartz and aluminosilicates are the two most predominant silicates [6]. As an element, silicon has found widespread use in industrial applications often as a component of fabricated steel, a component of abrasives (silicon carbide), a building block of transistors (along with boron, gallium, arsenic, etc.), solar cells, rectifiers, and other

electronic solid-state devices [7]. Industrial applications also include synthesis of glass when derived from sand-based silica, production of computer chips, and as a filler for paint and rubber ceramics, in lubricants, concrete and bricks, as well as being used for medical devices such as silicone implants [5]. Although silicon is used frequently for technical applications, its exposure to humans is fairly limited and largely in chemical forms that are not readily absorbed nor bioavailable.

Silica is used widely in the food and beverage industry as a food additive, i.e., anti-caking agent in foods, clarifying agent in beverages, viscosity controlling agent, as an anti-foaming agent, dough modifier, and as an excipient in drugs and vitamins [5]. Thus, silicon as silica is a dietary component although largely assumed to be inert when provided in forms typically used in the aforementioned applications. Nonetheless, humans are exposed to diet-derived forms of silica suggesting potential capacity for absorption and ultimate bioavailability, which raises the question of whether silicon as a molecular component can exert beneficial, biological effects in humans. Currently, silicon is not recognized as a nutrient in humans although emerging research suggests benefit from consumption of water-soluble forms. To that end, there is renewed growing interest in the potential beneficial effects of silica on human health.

Regarding inadvertent environmental exposure, previous research, in large part, has explored the toxic effects of inhaled crystalline silica and silica-derived asbestos. In fact, silicon has long been recognized as a pulmonary carcinogen with resultant silicosis or asbestosis developing upon prolonged and/or heavy exposure to airborne material [8]. Silicosis is a disease of the lungs caused by continued inhalation of the dust of minerals that contain silica and is characterized by progressive fibrosis and a chronic shortness of breath [9]. Asbestosis is similar in etiology and pathology but distinct as an exposure. While there are intrinsic dangers associated with inhalation of crystalline silica, there are multiple forms of silica in nature that are not toxic. Although non-toxic, the question remains as to the relative water-solubility of different compounds, relative amounts ingested, efficiency of absorption and overall bioavailability. Low-molecular-weight silica can dissolve in water as silicic acid rendering it bioavailable and potentially a beneficial component in humans. Collectively, the lack of understanding of the relative dependence of the physicochemical structure of silica and silicates on water-solubility for absorption has limited overall research interest in aqueous silica. As a result, a clearer understanding of the chemistry of silica, specifically of aqueous orthosilicic acid, is critical to fostering much needed research on potential health benefits.

2 Silicon Biochemistry

2.1 Silicon Distribution and Prevalence in Nature

Chemically, silica is an oxide of silicon and represented by silicon dioxide (SiO_2). Silicon itself is a tetravalent metalloid with chemical properties somewhere in between that of a metal and non-metal element. Its presence is second only to oxygen

in its abundance on earth comprising almost a third of the earth's crust. In its pure form, silicon typically does not exist in a natural elemental state due to its extreme propensity to undergo reactions with ambient oxygen and water. For example, silica, SiO_2, and other oxides, are ubiquitously found in polymerized combinations with metals and embedded in geologic rock formations. Given its omnipotence, overall prevalence and reactivity with other elements, it clearly exists in myriad forms with differing physicochemical properties with some that are toxic and others that are seemingly critical for health.

Silica is largely present in geographical formations and not readily released from these substrates except through natural, but significant, weathering of these structures. Overall, the forms and resultant molecular sizes of polymers and aggregates are dependent on pH and concentrations in aqueous matrices [10]. For example, at low concentrations (<2 mM) silicon exists in a monomeric acidic form (pK_a 9.6) as orthosilicic acid, which imparts a fair degree of water solubility and certainly more than the higher-molecular-weight forms. As concentrations increase, polymerization will occur to form oligomers and eventually colloids, then aggregates and solid amorphous precipitates with a clear concentration dependence on solubility. As one might surmise, the increasing molecular weight and structural complexity restricts water solubility and, as a result, limits potential absorption by humans and animals.

2.1.1 Dietary Sources

Silica exists in the food chain with concentrations tending to be much higher in plant-based foods, i.e., phytolithic, than animal foods [11]. Beverages, however, are the major contributor to dietary silica, or silicon, and include water, coffee, and beer (due to barley, hops, etc.) where fluid ingestion alone can account for ≥20% of intake [12–14]. Beer is the major source of bioavailable silicon for males with concentrations of 9–39 mg/L [14–16]. Silica is also prevalent in municipal water supplies but is particularly high in bottled spring and artesian waters depending on the respective geological source [17]. In fact, beverages alone contribute up to 55% of total dietary intake of silicon as water-soluble silica. Dietary grains and grain products including cereals, oats, barley, wheat flour, pasta, pastries, and polished rice contribute 14% of ingested silicon and vegetables contribute 8% [18]. In the Western diet, major sources of silicon are cereals (30%) followed by fruits, beverages, and vegetables, which together make up 75% of total silicon intake [19]. Processing and refinement of grains remove silicon during the processes but silica-derived food additives can replace the stripped silicon and increase the content although the relative absorptivity of added silicon is questionable. Overall, estimation of dietary intake from all sources is approximately 20–50 mg silicon/day for Western populations but up to ~200 mg/day for populations consuming a more plant-based diet such as populations from India and China [12,18,20–22].

The presence of large amounts of silica in geological formations contributes greatly to the silica content of water. For example, in the United Kingdom, silicon concentrations are ≤2.5 mg/L in north and west Britain but up to 14 mg/L in south

and east Britain [23–25]. Silica is found in fresh water at concentrations of 1–100 mg/L depending on the geographical location, e.g., soil content. Typical municipal water supplies can provide 4–11 mg/L of aqueous silica as noted in a study of the large cities of France. Levels of around 18–20 mg/L occur in the water of large cities of the United States. Bottled waters also contain modest concentrations of silica ranging from 8 to 36 mg/L as noted for the French brands Badoit, Vichy Celestian, and Volvic [26]. Interestingly, bottled water from Malaysia contains 30–40 mg/L silica and from the Fiji Islands contains 85 mg/L silica, more than four times the levels found in fresh water and municipal supplies and over twice that of other bottled waters, presumably due to the leaching of water-soluble silica from volcanic rock. Collectively, aqueous sources provide a wide range of concentrations of water-soluble, bioavailable silica.

There are other dietary sources of silicon including primarily food additives and dietary supplements. For foods, silicon may be added to processed, manufactured, and distributed foods as anticaking agents, thickeners, stabilizers, and clarifying agents, significantly increasing the overall silicon concentration [27]. However, silicates are generally considered to be inert and, as a result, not absorbed to any great extent by humans. In particular, polymeric silicic acids and amorphous silicon dioxide are poorly absorbed. Dietary supplements are an alternative silicon source containing orthosilicic acid or other forms that are presumably modified to a form that is water-soluble, absorbed, and bioavailable although this does not universally apply [28,29]. The estimated overall bioavailability of silicon from supplements ranges from <1 to >50%, a remarkably wide range, and depends on the formulation and concentration [6].

Silica is prevalent in the typical human diet at around 10–25 mg/day and generally considered safe, even if indigestible and non-absorbable. Although a biomarker of silicon status has yet to be developed, approximately 41% of ingested silicon is excreted in urine, which is significantly correlated with dietary consumption of silicon [20,30]. The lack of clear understanding of the myriad of chemical forms of silica and significant, widely communicated likelihood of increased risk of cancer has unduly overshadowed the study of the potential protective effects of silica on human health. It is the intent of this review to provide insight into the chemical properties of silica that may render it bioavailable and beneficial to human health.

Although there are dietary sources of silicon which are thought to exert beneficial effects in humans, there is no recommended dietary allowance (RDA) for silicon and, in fact many do not recognize silicon as a micronutrient essential for life, although 1–2 g is present in the human body [31,32]. However, if one considers the risk assessment of amorphous silicon dioxide as a common silicon source, although non-absorbed, the safe tolerable upper intake level (TUL), a component of the Dietary Reference Intakes (DRIs), is estimated to be 700 mg/day for adults, which is equivalent to 12 mg silicon/kg body weight/day for a 60 kg adult [33]. However, only minimal amounts of silicon become water-soluble and ultimately absorbed, thus the systemic plasma concentration does not increase significantly. The mean dietary silicon intake reported for a Finnish population was 29 mg silicon/day and

for a typical British diet 20–50 mg/day corresponding to 0.3–0.8 mg silicon/kg body weight/day [14,18,34,35]. The estimated dietary intake in the US is 24–33 mg silicon/day with males generally consuming more [20].

2.1.2 Non-dietary Sources

Given the relative prevalence and widespread use of silica, it seems reasonable that there are myriad, diverse sources of and exposures to non-dietary silica/silicon. These occur primarily from exposure to dust, pharmaceuticals, cosmetics, medical implants, and medical devices. Often the forms of silicon occur as silicates or "silicones," synthetic organosilicon compounds that, for the most part, are sparse in the human diet and contribute little silicon overall. Moreover, the forms that do result in exposure are not readily absorbed or biologically useful. For example, some pharmaceuticals can increase exposure of silicon to >1 g/d but the molecular species are largely inert and not absorbed to any significant extent. Examples of silicates include talc, kaolin, and magnesium, calcium, and sodium salts. This seems to be the case with other non-dietary sources such as toiletries, e.g., toothpaste, lipstick, etc., and detergents, tissue implants, etc. [6].

2.2 Silicon Chemical Speciation as Silicates

Silicon is the second most abundant element on earth with properties that are a mixture of both metals and non-metals resulting in classification as an elemental metalloid. As stated previously, silicon is rarely found in its elemental form but rather complexed with oxygen and/or other elements forming silica and silicates. Silicon dioxide, SiO_2, is the oxide of silicon most commonly found in nature as sand or quartz. Generally, a silicate is any compound containing silicon and oxygen as an anion, SiO_4^{2-}, with most in nature existing as oxides although the non-oxygen containing hexafluorosilicate anion, $[SiF_6]^{2-}$, is also often included as a silicate. Chemically, silicate anions can form compounds with numerous, diverse cations, thus this chemical class of compounds is large with formation of aluminosilicates being the most prevalent in nature [36]. Aluminum is the third most prevalent element in the earth's crust and exists in combination with >270 other minerals.

2.3 Silicon Chemistry and Effects on Bioavailability

Silica, SiO_2, is a silicic acid anhydride of monomeric orthosilicic acid (H_4SiO_4) which is water-soluble and stable in aqueous solutions when relatively dilute. Several other low-molecular-weight, but hydrated forms, of silicic acid exist in

aqueous solutions and include metasilicic acid (H_2SiO_3), lower-molecular-weight oligomers such as disilicic acid ($H_2Si_2O_5$) and trisilicic acid ($H_2Si_3O_7$), as well as their hydrated forms pentahydro- and pyrosilicic acids [1]. Depending on the environmental conditions (temperature, pH, and presence of other ions), concentrations, and exposure time, formation of numerous potential polymerized silicic acids is possible through chemical condensation and cross-linking resulting in colloids and gels [37]. It is the lower molecular weight forms, especially the orthosilicic acid that is of the greatest research interest in exerting beneficial effects since this form is preferentially absorbed [38]. In fact, a small human study showed that ingestion of polymeric forms of silicic acid did not increase urinary levels suggesting little absorption, but 53% of ingested orthosilicic acid did increase urinary output indicating absorption [39]. Interestingly, most aqueous silica, i.e., seawater, freshwater, soil water, etc., occurs as orthosilicic acid (H_4SiO_4) making it an important environmental exposure in the context of biological systems due both to its water-solubility and bioavailability [4,40].

As previously noted, orthosilicic acid is water-soluble at relatively low concentrations but polymerizes readily at higher concentrations in excess of 100–200 ppm to form colloids and gels, which are less bioavailable. However, more concentrated solutions of orthosilicic acid can be stabilized to avoid polymerization. In fact, choline-stabilized orthosilicic acid, a liquid formulation, has been developed and approved for human consumption. It is considered non-toxic at high doses with a lethal dose exceeding 5,000 mg/kg body weight in humans and 6,640 mg/kg body weight in animals [41,42]. For a 70 kg human, this translates to a safe level of consumption of 350 g. This stabilized form currently represents the most bioavailable source of supplemental silicon.

3 Silicon and Its Potential Health Benefits

Silicon is the third most abundant trace element in the human body [20,43]. It is present at 1–10 ppm in hair, nails, the epidermis, and epicuticle of hair [44–46]. Considering the natural abundance, presence of bioavailable chemical forms, exposure to humans through diet, it seems more than plausible that there could, and likely is, potential benefit to humans. Whether silicon is an essential micronutrient continues to be debated. It has, however, been reported in the peer-reviewed literature that silicon is actively involved, and perhaps integral, in bone mineralization and prevention of osteoporosis, collagen synthesis, and prevention of the aging of skin, overall condition of hair and nails, reduced risk of atherosclerosis and Alzheimer's disease, as well as other biological effects [47–51].

Interestingly, serum levels are similar to other trace elements and appear to be dependent on life stage, age, and sex with levels of 11–31 μg/dL depending on population assessed and means of analysis [23,52]. A recent study by Jugdaohsingh et al. evaluated host factors potentially influencing the absorption and excretion of dietary silicon. Serum and urine samples were collected from 26 participants

followed by a single ingestion of 17 mg orthosilicic acid. Analyses of samples over the subsequent 6 hours indicated that participant age, sex, and estrogen status did not influence absorption or excretion suggesting more research is needed to better understand the effects of host factors on disposition of dietary silica [53].

3.1 Bone Health and Skeletal Development

Osteoporosis is a leading cause of morbidity and mortality in the elderly and markedly affects overall quality of life, as well as life expectancy. As a result, there is considerable interest in elucidation and use of specific nutrients, non-nutritive dietary components, and/or bioactive compounds of natural origin singly or in combination as a means of mitigating or preventing disease, as well as for maintenance of bone health. Calcium and vitamin D have largely been the primary focus of nutritional prevention of osteoporosis, however, supplementation with other vitamins including B, C, and K has been an area of increased research as well as the use of silicon for maintenance of bone health [54,55].

Osteoporosis is defined as a progressive, debilitating skeletal disorder characterized by low bone mass and deterioration of the microarchitecture of bone [56,57]. Indeed, several key animal studies dating back four decades clearly showed that dietary silicon deficiency caused abnormalities and dysfunction in connective tissues and bone function [58–62]. Numerous human studies have supported a role for dietary silicon in bone health including reduction of the risk for osteoporosis. In a retrospective, clinical study by Eisinger and Clairet, dietary silicon administration induced significant increases in bone mass and bone mineral density of the femur in human females [47]. Moukarzel et al. have also shown a direct relationship between silicon intake and bone mineral density [63]. In osteoporotic participants, supplementation with silicon increased trabecular bone volume and femoral bone mineral density [47,64]. Spector et al. showed in osteopenic and osteoporotic study participants an increase in bone formation markers, i.e., collagen synthesis, and significant increases in femoral bone mineral density [65]. Maehira et al. [66] have shown in mice fed five different calcium sources with differing silicon concentrations that soluble silicate and coral sand, with the highest silicon content, significantly improved bone biochemical and mechanical properties through induced gene expression encouraging correction of the imbalance between bone-forming osteoblastogenesis and suppression of bone-resorbing osteoclastogenesis [66–68]. Others have shown in human osteoblasts that orthosilicic acid-releasing zeolites could induce osteoblastogenesis, formation of extracellular matrix, induced synthesis of ostecalcin and activity of alkaline phosphatase both produced by osteoblasts and reflecting biosynthetic activity of bone formation [69–71]. It has also been shown that silicon supplementation increased hip bone mineral density in men and pre-menopausal, but not post-menopausal, women although a subsequent study showed increased bone mineral density in the spine and femur of both pre- and post-menopausal women currently taking hormone replacement therapy [15,72].

Compelling evidence demonstrates that silicon localizes to bone and that dietary silicon can strengthen bones and, as a result, reduce the risk of osteoporosis [73].

As mentioned before, stabilized preparations of silicic acid have been developed, e.g., choline-stabilized orthosilicic acid, permitting water-soluble preparations with higher concentrations and also markedly enhanced bioavailability. In a randomized controlled animal study, long-term treatment with choline-stabilized orthosilicic acid prevented partial femoral bone loss and exerted a positive, beneficial effect on bone turnover and ultimately bone mineral density [74]. In this study, ovariectomized aged rodents were used suggesting a potential interrelationship between estrogen and bone health and silicon metabolism. A subsequent study by Macdonald et al. found that dietary silicon interacts with estrogen to beneficially affect bone health [72]. Silicon has previously been shown to significantly enhance the rate of bone mineralization and calcification much like vitamin D, although functioning independently [75]. There are potentially conflicting reports since Jugdaohsingh et al. found that silicon supplementation in drinking water did not significantly alter silicon concentrations in the bones of rodents suggesting an additional nutritional cofactor might be absent such as vitamin K in rodents fed a low silicon diet [76].

3.2 Vascular Disease and Atherosclerosis

It has been reported that there are higher incidences of sudden death, cerebrovascular diseases, arterial hypertension, and coronary heart disease in soft water areas of the United States suggesting, in part, that the absence of components presence in hard water, i.e., minerals, may be contributors. As a result, a major research effort has been devoted to identifying potential protective factors in hard water including calcium, magnesium, manganese, and silicon, as examples, all of which are considered potentially beneficial [77].

Silicon is recognized by epidemiologic and biochemical studies as a protective trace element in atherosclerosis. Moreover, the observed decrease in silicon concentrations with increasing age has been suggested to contribute to chronic diseases such as atherosclerosis. The highest concentrations of silica in the human occur in connective and elastic tissues and especially the normal human aorta where it appears to function as a crosslinking agent that stabilizes collagen and presumably strengthens the vasculature [49,78]. Atherosclerosis significantly decreases silicon levels in arterial walls. Moreover, silicon levels decrease just prior to plaque development, which may indicate that silicon deficiencies cause inherent weaknesses in blood vessel walls.

In a study by Trinca et al., the antiatheromatous effect of sodium silicate was tested in rabbits given a standard control diet, an atherogenic diet, and a sodium silicate-supplemented atherogenic diet. Levels of total lipids, cholesterol, triglycerides, free fatty acids, and phospholipids remained unchanged in sodium silicate supplemented rabbits fed an atherogenic diet [79]. In a subsequent study, silicon administered orally or intravenously in rabbits inhibited experimental atheromas normally induced by an

atheromatous diet, decreasing the number of atheromatous plaques and lipid deposits. It was proposed that the preservation of elastic fiber architecture, as well as of ground substance and the lack of free fatty acid accumulation in the aortic intima decreased plaque formation [80]. In a study by Maehira et al. using soluble silica and coral sand, as a natural silicon-containing material, the effect on hypertension, a contributing factor to atherosclerosis, was evaluated in spontaneously hypertensive rats. In rats fed 50 mg/kg dietary silicon for 8 weeks, systolic blood pressure was significantly lowered by 18 mmHg. Provision of soluble dietary silica also suppressed the aortic gene expression of angiotensinogen and growth factors related to vascular remodeling. Silicon also stimulated the expression of peroxisome proliferator-activated receptor-γ, which has antiinflammatory and antihypertensive effects on vascular cells [81]. In a study by Oner et al., dietary silica modified the characteristics of endothelial dilation in aortic rings from rats with modulation of endothelial relaxants and attenuation of smooth muscle cell responsiveness to nitric oxide [82].

Silicon has also been suggested to exert a protective role in atherosclerosis through its effects on blood vessel-associated glycosaminoglycans and collagen integrity and function via its crosslinking capacity [19]. Glycosaminoglycans are long unbranched (linear) polysaccharides consisting of repeating disaccharide units including hyaluronan, chondroitin, dermatan, heparan, and keratan. Silicon is also a constituent of the enzyme prolyl hydroxylase, which synthesizes collagen and glycosaminoglycans. Dietary silicon may facilitate the formation of glycosaminoglycans and collagen and/or serve a structural role as a component of glycosaminoglycans where it crosslinks, and strengthens, polysaccharide chains. Nakashima et al. have noted that the glycosaminoglycan content of the aorta was inversely correlated with the severity of atherosclerosis. Interestingly, they showed that the silicon content in fatty streaks and/or atheroma was significantly higher than in normal human aortic intimal regions suggesting that the increase of silicon in the aortic intima is related to the occurrence and/progression of atherosclerosis [83].

3.3 Neurodegenerative Disease (Alzheimer's Disease)

Metals that can cross the blood brain barrier and generate directly or indirectly oxidative stress can cause significant damage to the neuronal structure of the brain. Aluminum is abundant in the environment but is not a micronutrient. However, ingestion and/or exposures can cause deposition and accumulation in the body, e.g., brain, where it can cause considerable damage. Aluminum, a nonredox-active metal, is a well-known toxicant and its salts can accelerate oxidative damage of neurons. Oxidative stress is one of the critical features in the pathogenesis of Alzheimer's disease and has been demonstrated in brain tissue from Alzheimer's patients. Aluminum is a contributing factor to oxidative stress, as it generates reactive oxygen species (ROS) shown to cause oxidative damage to neurons through interaction with iron, a redox-active metal, and promotion of free radical-generating Fenton reactions, which can increase hallmark aggregation and accumulation of β-amyloid.

Collectively, studies clearly indicate that aluminum promotes oxidative stress capable of damaging neuronal cell death [84].

The molecular pathogenesis of Alzheimer's disease includes many risk factors including extracellular deposition of β-amyloid, accumulation of intracellular neurofibrillary tangles, oxidative neuronal damage and activation of inflammatory cascades [85]. Although the subject of continuing scientific debate, aluminum has been detected in neurofibrillary tangles in the brains of both Alzheimer's and Parkinson's disease patients with dementia and is proposed to play crucial roles as a crosslinker in β-amyloid oligomerization [86–88].

Although the neurotoxicity of aluminum is well-documented, the association with neurodegenerative disorders is the subject of debate as is the potential benefit of consuming silica [89]. Some epidemiological studies, but not all, suggest that silica could be protective against aluminum damage, because silica reduces oral absorption of aluminum and/or enhances its excretion [90–92]. Studies have suggested that oligomeric but not monomeric, viz., orthosilicic acid, silica can prevent aluminum absorption through the gastrointestinal (GI) tract reinforcing the importance of chemical speciation [39]. Silicon readily complexes with aluminum and, in fact, aluminosilicates are the most prevalent silicates in nature. A silicate is any of numerous compounds containing silicon, oxygen, and one or more metals forming essentially a salt of silicic acid. Aluminum silicates are water-insoluble and although the processes involved in aluminum bioavailability are unclear regarding its transport into the central nervous system, numerous reports show that silicic acid can, in fact, reduce aluminum absorption and ultimately deposition and accumulation within the brain. In an epidemiological study, Rondeau et al. examined associations between exposure to aluminum or silica from drinking water and risk of cognitive decline, dementia, and Alzheimer's disease among 1,925 elderly subjects followed for 15 years. The authors concluded that cognitive decline with time was greater in subjects with a higher daily intake or geographic exposure to aluminum from drinking water. An increase of 10 mg/day in silica intake was significantly associated with a reduced risk of dementia [93]. Thus, it appears that the relative concentration of both aluminum and silica in drinking water are important in determining benefit or detriment regarding the risk and/or exacerbation of Alzheimer's disease [94]. Interestingly, soft water contains less silica acid and more aluminum while the converse is true for hard water [25]. In a study by Exley et al. introduction of hard water rich in silica significantly reduced overall aluminum levels in the body presumably through reduced absorption of aluminum as supported by reduced urinary concentrations [95]. A subsequent study showed that drinking up to 1 L of a silicon-rich mineral water daily for 12 weeks fostered urinary removal of aluminum in both control and Alzheimer patient groups without increasing urinary excretion of the micronutrients iron and copper [96]. Moreover, there were clinically relevant increases in cognitive performance in 20% of participants. Gonzalez-Munoz et al. have shown that beer consumption, a rich bioavailable source of silicic acid, can reduce cerebral oxidation caused by aluminum toxicity by, interestingly, modulating gene expression of pro-inflammatory cytokines and antioxidative enzymes [51].

3.4 Diabetes

Type 2 diabetes is a disorder of glycemia based largely on the development of insulin resistance. It has been noted that micronutrients can regulate metabolism and gene expression associated with glycemia thereby potentially influencing the development and progression of diabetes [97]. In a report by Oschilewski et al., administration of silica to BB-rats, prone to spontaneous diabetic syndrome, completely prevented the development of diabetes [98]. Rats were treated with 100 mg silica/kg body weight via intraperitoneal and intravenous routes and observed for weight changes, glycosuria, and ketonuria. The authors showed nearly complete inhibition of the development of diabetes (1 of 31 in treated group versus 9 of 31 for control group) and attribute the protection of silica to reduced infiltration of pancreatic islets by macrophages. Kahn and Zinman showed in a previous study exploring bone health that dietary silicon suppressed bone marrow-derived peroxisome-proliferator receptor-γ, which regulates bone metabolism, but also regulates glucose metabolism where it is a ligand-activated transcription factor and a molecular target of a class of insulin-sensitizing drugs referred to as thiazolidinediones [99].

In the subsequent study, the antidiabetic effects of silicon were investigated in obese diabetic KKAy mice prone to hyperleptinemia, hyperinsulinemia, and hyperlipidemia (50 ppm silicon for 8 weeks). Interestingly, silicon and coral sand, a rich source of silicon, displayed antidiabetic effects through blood glucose reductions and increases in insulin responsiveness, as well as improvement in the responses to the adipokines leptin and adiponectin [100]. The authors report this as a novel function of anti-osteoporotic silicon and suggest use of silicon as a potential antidiabetic agent capable of reducing plasma glucose and reducing the risk of diabetic glomerulonephropathy. There is clearly a need for research into the potential novel therapeutic applications of silicon, as silica, for prevention and management of diabetes.

3.5 Wound Healing

Silica already finds widespread use in medical and surgical applications including tissue engineering for regeneration of tissues, e.g., wound repair and organs. This typically is in the form of collagen scaffolds, which are used as sponges, thin sheets or gels. Collagen, as a long fibrous structural protein, possesses the appropriate properties for tissue regeneration including optimal pore structure, permeability, hydrophilicity and stability *in vivo*. As a result, collagen scaffolds permit deposition and growth of cells, e.g., osteoblasts and fibroblasts, promoting normal tissue growth and restoration [101]. There are studies that suggest that dietary silicon can also exert beneficial effects on wound repair.

The successful healing of wounds requires local synthesis of significant amounts of collagen with its high hydroxyproline content drawing upon amino acid precursors

such as proline and ornithine [102]. In animal studies, silica-deficient diets result in poor formation of connective tissues including collagen and ultimate structural damage. Silica maintains the health of connective tissues due, in part, to its interaction with the formation of glycosaminoglycans where silicon is consistently found and presumed to have an active role. As a result, a deficiency in silica could result in reduced skin elasticity and wound healing due to its role in collagen and glycosaminoglycan formation. Seaborn and Nielsen have reported that silicon deprivation decreases collagen formation in wounds and bone, and decreases ornithine transaminase enzyme activity in liver [103]. In a rodent study, silicon deprivation affected collagen formation at several different stages of bone development, the activities of collagen-forming enzymes, and consequent collagen deposition on other tissues. This has major implications suggesting that silicon is important in wound healing and supports that dietary silicon, as silicic acid, can exert therapeutic effects for this use.

4 Toxicology of Silicon and Silica

4.1 Chemical Forms Contributing to Toxicity

As previously discussed, elemental silicon exists primarily as an oxide largely in the form of silicon dioxide. Silica, SiO_2, is a silicic acid anhydride of monomeric orthosilicic acid (H_4SiO_4), which is water-soluble and stable in aqueous solutions when relatively dilute but can polymerize and complex with numerous minerals to form silicates with aluminum silicate being the most prevalent. Several other low-molecular-weight, but hydrated forms, of silicic acid exist in aqueous solutions and are non-toxic. Forms of silicon that are toxic include long fibrous crystalline forms such as asbestos. Asbestos is a group of crystalline 1:1 layer hydrated silicate fibers that are classified into six types based on different physicochemical features [104]. These include chrysotile [$Mg_6Si_4O_{10}(OH)_8$], the most common and economically important asbestos in the Northern Hemisphere, and the amphiboles: crocidolite [$Na_2(Fe^{3+})_2(Fe^{2+})_3Si_8O_{22}(OH)_2$], amosite [$(Fe,Mg)_7Si_8O_{22}(OH)_2$], anthophyllite [$(Mg,Fe)_7Si_8O_{22}(OH)_2$], tremolite [$Ca_2Mg_5Si_8O_{22}(OH)_2$], and actinolite [$Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$].

Silica occurs in both non-crystalline and crystalline forms where crystalline silica is a basic component of soil, sand, granite, and many other minerals. Crystalline forms technically are physical states in which the silicon dioxide molecules are arranged in a repetitive pattern with unique spacing, lattice structure and angular relationship of the atoms. Crystalline silica forms, viz., polymorphs, include quartz, cristobalite, tridymite, keatite, coesite, stishovite, and moganite. Silicosis largely occurs due to inhalation of one of the forms of crystalline silica, most commonly quartz. All three forms may become respirable size particles when workers chip, cut, drill, or grind objects that contain crystalline silica.

4.2 Routes of Exposure and Safety

The most noted toxicity associated with silica and asbestos are silicosis and asbestosis, respectively. The key route of exposure leading to toxicity is respiratory with progressive, debilitating damage from lengthy and/or heavy inhalation of the dust of silica. In fact, the International Agency for Research on Cancer (IARC) classifies silica as a "known human carcinogen" based on inhalation as a route of exposure. Regarding dietary exposure, there is no evidence of carcinogenesis when silica was fed to rodents for ~2 years (effectively the whole life span) supporting that the route of exposure is more critical than the chemical form. There are reports that magnesium trisilicate (6.5 mg elemental silicon) when used as an antacid in large amounts for years may be associated with the development of urolithiasis due to formation, *in vivo*, of silicon-containing stones although fewer than 30 cases have been reported in the last 80 years [105].

There are other reports of toxicity from oral ingestion of crystalline and amorphous silicates. For example, nephropathy can result from finely ground silicates and nephritis from long-term use of high dose, silica-containing medications as well as kidney damage and kidney stones [106]. There are some reports of increased risk of cancer (esophagus and skin) from silica-rich materials such as millet and seeds [14,107,108]. It is proposed that the overall limitation in absorption of silicon, regardless of level of dietary intake, coupled with efficient elimination significantly limits the potential toxicity of silica. Circumventing this defense mechanism via peritoneal injections of silicon as shown in animals can easily exceed expected urinary output beyond that associated with presumed silicon adequacy [30,109].

4.2.1 Inhalation and Asbestosis

When asbestos fibers are inhaled, most fibers are expelled, but some can become lodged in the lungs and remain there throughout life increasing the risk of asbestosis. Asbestosis is a chronic inflammatory and fibrotic disease affecting the parenchymal tissue of the lungs, referred to as interstitial fibrosis, caused by the inhalation and deposition of fibrous asbestos. Manifestation of the disease occurs typically after high intensity and/or long-term exposure to asbestos as a specific group of airborne crystalline silicate fibers. Asbestos fibers are invisible without magnification because their size is approximately 3–20 μm wide but as small as 0.01 μm. For reference, human hair has a width of ~20–180 μm. Given the omnipotence of asbestosis in technical applications, it is considered an occupational lung disease.

4.2.2 Inhalation and Silicosis

Silicosis is also a form of irreversible occupational lung disease, technically a type of pneumoconiosis that is caused by inhalation of small particles of crystalline silica dust. Inhaling finely divided crystalline silica dust even in small quantities

(the Occupational Safety and Health Administration (OSHA) allows 0.1 mg/m^3) over time can lead to silicosis, bronchitis, or cancer, as the dust becomes lodged in the lungs causing chronic irritation with reduced lung capacity. It is marked by inflammation, pulmonary edema, scarring of the lungs, and formation of nodular lesions in the upper lobes of the lungs with resultant difficulty in breathing. There are several different clinical and pathologic varieties of silicosis, including simple (nodular) silicosis, acute silicosis (silicoproteinosis), complicated pneumoconiosis (progressive massive fibrosis), and true diffuse interstitial fibrosis [110].

4.3 Mechanisms of Toxicity

The molecular mechanism of silica and asbestos-induced carcinogenesis is complex and unclear. Clearly, inhalation is the primary route of exposure leading to toxicity and depends on the shape and size of silica fibers, duration of exposure, and relative dose, as well as lung clearance capacity and individual genetics [111,112]. Several mechanisms have been proposed including the adsorption, chromosome tangling, and oxidative stress hypotheses.

The adsorption theory posits that the surface of asbestos has a high natural affinity for proteins and other biomolecules and presumably disrupts cell function. The chromosome tangling hypothesis argues that asbestos can interact with chromosomes and "tangle" them during cellular division causing clastogenic damage. Probably the most compelling mechanism at this time is the oxidative stress theory, which purports that iron associated with asbestos fibers, once internalized, can contribute to Fenton chemistry with generation of reactive, damaging free radicals and reactive oxygen species. Moreover, deposition of asbestos and silica particles in the lungs can initiate chronic inflammation *via* involvement of phagocytic macrophages, which also produces copious ROS. Although discussed separately, oxidative stress and inflammation are intimately linked and often occur concurrently, thus both occur concomitantly in lung disease.

4.3.1 Oxidative Stress

Cumulative supporting evidence suggests a role for ROS and reactive nitrogen species in the pathogenesis of asbestos- and silica-induced diseases [110,113]. Oxidative damage to the lungs can occur directly through highly reactive hydroxyl radical formation via the Fenton and Haber-Weiss reactions with fiber surface iron, and indirectly through inflammation [114–116]. This route involves the recruitment and activation of ROS-producing inflammatory cells, such as macrophages. Other cell types also participate in the process including mesothelial cells and lung fibroblasts, which also produce ROS species in response to silica and/or asbestos.

Numerous *in vitro* studies have shown the involvement of oxidative stress in damage caused by silica. For example, Liu et al. tested the effects of silica nanoparticles on

endothelial cells by measuring ROS generation, apoptosis and necrosis, proinflammatory and prothrombic properties and the levels of the apoptotic signaling proteins and the transcription factors after exposure to silica nanoparticles (25–200 μg/mL) for 24h [117]. Silica nanoparticles markedly induced ROS production, mitochondrial depolarization and apoptosis in endothelial cells. Others have shown similar results with primary endothelial cells exposed to silica nanoparticles with activation and dysfunction of endothelial cells shown by release of von Willebrand factor and necrotic cell death [118]. In a study of mesothelial cells, exposure to crocidolite asbestos induced oxidative stress, caused DNA damage and induced apoptosis demonstrating that phagocytosis was important for asbestos-induced injury to mesothelial cells [119].

Several human studies have been conducted to determine if oxidative stress results from asbestos exposure using a relatively new biomarker of exposure. Measurement of exhaled breath condensate for markers of oxidative stress is one of the most promising methods available for determining pulmonary damage from environmental exposures [120]. An increase in the exhaled breath condensate concentrations of 8-isoprostane, an oxidative stress marker, has been observed in patients with idiopathic pulmonary fibrosis and in a limited study with asbestos-exposed subjects. Pelclova et al. measured 8-isoprostane, in 92 former asbestos workers with an average exposure of 24 years [114]. The results indicated higher levels of 8-isoprostane in exposed subjects compared to control subjects (69.5 *versus* 47.0 pg/mL) supporting asbestos-induced oxidative stress. In a study involving 83 patients (45 with asbestosis and hyalinosis and 37 with silicosis), concentrations of 8-isoprostane and hydroxynonenal, an oxidative degradation product, were measured in urine and exhaled breath condensate. The results indicated that most markers correlated positively and significantly with lung function impairment [121]. These markers as well as others have been effectively developed to detect and confirm oxidative stress in patients with asbestosis and silicosis [122,123].

4.3.2 Inflammation

There is growing evidence that amorphous silica can cause an inflammatory response in the lung. These crystalline silicates are phagocytozed by macrophages that then release cytokines that attract and stimulate other immune cells including fibroblasts, which are responsible for the excessive production of collagen (fibrotic tissue) that is characteristic of silicosis [10]. In a study by McCarthy et al., exposure of human lung submucosal cells to SiO_2 nanoparticles (10–500 nm) for up to 24 hours increased cytoxicity and cell death, induced pro-inflammatory gene expression and release of pro-inflammatory IL-6 and IL-8, and upregulation of pro-apoptotic genes indicating oxidative stress-associated injury [124]. Bauer et al. also showed that silica nanoparticles caused dysfunction and cytoxicity through exocytosis of von Willebrand factor and necrotic cell death in primary human endothelial cells [118]. In the study by Liu et al., incubation of endothelial cells with 200 μg/mL silica caused increased cell death and the release of numerous, diverse pro-inflammatory mediators (TNF, IL-6, IL-8, and MCP-1) by remaining viable cells [117].

Silica nanoparticles also activated pro-inflammatory gene expression, e.g., NF-κB, and suppressed antiinflammatory gene expression, e.g., Bcl-2. The study collectively showed that silica nanoparticles damaged endothelial cells through oxidative stress via changes in gene expression associated with inflammation. Others have shown the role of IFN-γ in the development of murine bronchus-associated lymphoid tissues induced by silica and activation of NF-κB in silica-induced IL-8 production by bronchial epitehelial cells [125]. Clearly, silicosis is characterized by mononuclear cell aggregation and lymphocytes are abundant in these lesions [126].

Ironically, short-term studies in rodents exposed to crystalline quartz suggested that silicon exposure stimulated the immune system and respiratory defense through activation of neutrophils, T lymphocytes, and NK cells with subsequent increased production of ROS [127–129]. This is thought to enhance the pulmonary clearance of microbes. Intriguingly, silica was shown, at least in rats, to activate and increase proliferation of CD8+ and CD4+ T cells suggesting potential therapeutic use in the future as an immunostimulant for pulmonary disorders. Recently a supplemental anionic alkali mineral complex containing sodium silicate (60% of mass) has been developed and is currently used as immunostimulant in animals including horses, pigs, etc. [130]. The mechanism of action is not known, however, it has been suggested that orthosilicic acid-generating sodium silicate is the bioactive agent responsible for the immunostimulation. Sodium metasilicate has also been shown to be immunostimulatory [131]. The seemingly dichotomous actions of silica represent a conundrum with excessive immunostimulation in silicosis and asbestosis clearly being detrimental but an apparent capacity of silica to also beneficially boost the immune system with consequent ROS production.

5 Potential Medicinal Uses of Silicon and Silicates

The potential medicinal uses of silicon in the form of silica have only recently been recognized particularly with respect to bone health and prevention of neurodegenerative diseases. Data are preliminary yet supportive of potential roles in reducing the occurrence of type 2 diabetes and preserving and producing collagen, e.g., wound repair. Silicon is environmentally prevalent representing the second most abundant element yet the biological availability of silica is limited and distributed unevenly based largely on geographic location and source. As discussed previously, it is the orthosilicic acid that is water-soluble and bioavailable yet overall intake and absorption could be improved. Thus, orthosilicic acid will likely be a prominent therapeutic medicinal agent and, in fact, many potential therapeutic applications have already been presented. For example, silicon appears to play a significant role in maintaining bone health through increased bone formation and increased bone mineral density and maintenance of connective tissues. Silicon, as dietary silica, also inhibits absorption of toxic aluminum, which may contribute to the development of Alzheimer's disease. This occurs at a time when there is increased prevalence of osteoporosis and Alzheimer's disease as populations worldwide become older. Other potential uses include enhancement of immune

function, preservation and health of skin, hair, and nails, and use as potential antidiabetic and anticancer agents.

The development of new formulations of orthosilicic acid or orthosilicic acid-releasing compounds is a promising means of delivering increased concentrations of bioavailable and safe silicon. Choline-stabilized orthosilicic acid is a newly developed, concentrated solution of orthosilicic acid in a choline and glycerol matrix and is promoted as biologically active and the most bioavailable form of silicon. Moreover, choline-stabilized orthosilicic acid has been approved for human consumption and is considered relatively non-toxic with a tolerable upper limit exceeding 5 g/kg body weight [28,41]. There are many other silicon supplements available including extracts of horsetail, which contains 12 mg silicon per tablet of which 85% is suggested to be bioavailable [28,29,65,74,132]. Overall, results of the NHANES III study indicate a median intake of silicon from supplements to be 2 mg/d, but with preparations such as the aforementioned could markedly increase.

A particularly interesting area of research and development has been the emergence and/or use of orthosilicic acid-releasing compounds. Specifically, certain types of zeolites, a class of aluminosilicates with well-described ion (cation)-exchange properties have been shown to release orthosilicic acid [1]. Overall, 191 unique zeolites have been described with over 40 naturally occurring zeolites identified. These are already widely employed in chemical and food industries, agriculture, and environmental technologies but could find much greater use as medicinal and/or nutritional agents. In fact, the biomedical applications of zeolites include, in part, modulation of enzyme kinetics, use in hemodialysis, prevention of diabetes, increased bone formation, function as an antidiarrheal and antibacterial agent and as vaccine and tumor adjuvants [1]. The numerous biological activities of some types of zeolites documented so far is thought to be due, in large part, to the orthosilicic acid-releasing property.

6 Summary and Future Directions

In conclusion, silicon, as silica and silicates, represents a very large family of molecules with potential health benefits but also with potential toxic effects depending on the form, water-solubility, route of exposure, and amount consumed. For example, inhaled particulate fibrous crystalline silica can be toxic and depends heavily on route of exposure and chemical form. Silica can also dissolve in water to form non-toxic bioavailable silicic acids and specifically orthosilicic acid. This form of absorbable silica found in foods and water sources, is readily absorbed, reaches key tissue and organ target sites of action, and is efficiently excreted. The lack of apparent toxicity of water-soluble forms that are consumed, as opposed to inhaled, and the ongoing debate regarding essentiality as a micronutrient have obscured the relative importance of chemical speciation and potential contributions of silica.

Even though water-soluble to some degree, there are limitations to absorption dictated largely by chemical instability, e.g., propensity to polymerize, and maximum

allowable concentrations of water-soluble orthosilicic acids. However, there has been development of acid forms with markedly increased stability and, as a result, significant increased concentrations and bioavailability of silicon. Choline chloride-stabilized orthosilicic acid is a pharmaceutical formulation that is particularly promising but other forms exist including sodium or potassium silicates, and orthosilicic acid-releasing forms such as zeolites.

Further research on silicon is critically needed particularly focusing on the physiological roles of silicon and how this relates to human health, as well as the dependence on chemical speciation. Specifically, ample data exist to support a possible role of silicon in wound repair, atherosclerosis and hypertension, diabetes, several bone and connective tissue disorders, neurodegenerative diseases, e.g., Alzheimer's and Parkinson's disease, and other conditions that occur particularly in the aging population. It is also important to further elucidate biochemical mechanisms of action of silicon-containing molecules, as silicic acids, and to extend testing more into whole body systems. Specifically, larger studies with humans are needed to explore the medicinal and nutritional potential of silicon.

Abbreviations

DRI	dietary reference intake
IARC	International Agency for Research on Cancer
IFN-γ	interferon-γ
IL	interleukin
MCP-1	monocyte chemoattractant protein-1
NF-κB	nuclear factor B
NHANES	National Health and Nutrition Examination Survey
NK cells	natural killer cells
NTF	tumor necrosis factor
OSA	orthosilicic acid
RDA	recommended dietary allowance
ROS	reactive oxygen species
TUL	tolerable upper limit

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SILICON AND BONE HEALTH

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Abstract

Low bone mass (osteoporosis) is a silent epidemic of the 21st century, which presently in the UK results in over 200,000 fractures annually at a cost of over one billion pounds. Figures are set to increase worldwide. Understanding the factors which affect bone metabolism is thus of primary importance in order to establish preventative measures or treatments for this condition. Nutrition is an important determinant of bone health, but the effects of the individual nutrients and minerals, other than calcium, is little understood. Accumulating evidence over the last 30 years strongly suggest that dietary silicon is beneficial to bone and connective tissue health and we recently reported strong positive associations between dietary Si intake and bone mineral density in US and UK cohorts. The exact biological role(s) of silicon in bone health is still not clear, although a number of possible mechanisms have been suggested, including the synthesis of collagen and/or its stabilization, and matrix mineralization. This review gives an overview of this naturally occurring dietary element, its metabolism and the evidence of its potential role in bone health.

Keywords

Silicon; orthosilicic acid; human exposure; dietary sources; silicon metabolism; bone health

Introduction

Osteoporosis is a leading cause of morbidity and mortality in the elderly, and is an increasing drain on healthcare resources (over 1 billion pounds in the UK) (1, 2). The major clinical effect is bone fracture, especially of the femur, but also of vertebrae and the radius, causing pain, disability and loss of independence, and often a rapid sequence of events leading to death (1-5).

The aetiology of osteoporosis is multifactorial, and although genetic and hormonal factors strongly influence the rate of decline of bone mass with age, nevertheless poor nutrition, smoking and excessive alcohol use, and lack of physical exercise all also greatly affect it (1, 3-7). Although ideally these non-genetic factors could be altered, in practice this is difficult, and hence drugs are extensively used to try to slow, or reverse, osteoporosis, now chiefly calcium and vitamin D supplementation, bisphosphonates and oestrogens, and oestrogen receptor modulators (5, 8-11). Osteoporosis is an imbalance between bone resorption by osteoclast cells and bone formation by osteoblasts (2, 12) - oestrogens and bisphosphonates slow bone resorption, by reducing bone turnover, but few drugs (rhPTH, strontium renelate and sodium fluoride being exceptions) can increase osteoblast activity and hence bone formation (2).

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There has also been interest in other bone minerals (magnesium, potassium and fluoride) and nutritional trace elements (zinc, copper, boron and manganese) in the diet; their intake is positively associated with bone mass, while deficiency has been correlated either with reduced bone mass or slow healing of fractures (6, 7, 12-14). Zinc, copper and manganese are essential cofactors for enzymes involved in the synthesis of the constituents of bone matrix (6, 7).

Another trace element that may be important is silicon (Si), but although there is 1-2 g present in the body (the most abundant trace element after iron and zinc, two other elements of physiological importance) its function is still surprisingly unclear. Silicon was long thought to be an inert universal contaminant that 'washes through' biology with no biological or toxicological properties; "a fortuitous reminder of our geochemical origin or an indicator of environmental exposure" (15). Animal studies in the 1970's reported that dietary silicon deficiency produces defects in connective and skeletal tissues (16-18), and that silicon is concentrated at the mineralisation front of growing bone (18). Work over the last 30 years has added to these findings to suggest that dietary silicon may be important, or at least beneficial, for bone formation and to bone health. This review gives an overview of silicon, human exposure to this element, its metabolism and the evidence of its potential role in bone health.

Silicon

Silicon (Si) is a non-metallic element with an atomic weight of 28. It is the second most abundant element in the Earth's crust at 28 wt %, (19, 20) but it is rarely found in its elemental form due to its great affinity for oxygen, forming silica and silicates, which at 92%, are the most common minerals. Quartz (12%) and the aluminosilicates, plagioclase (39%) and alkaline feldspar (12%) are the most prevalent silicates (21). These are present in igneous and sedimentary rocks and soil minerals and are highly stable structures that are not readily broken down except with extensive weathering. Thus natural levels of soluble (available) silica are low. Chemical and biological (plants, algae and lichens) weathering, however, releases silicon from these stable minerals, increasing its bioavailability. Dissolution of Si, from soil minerals in water results in the formation, by hydrolysis, of soluble silica species. Below pH 9, and at a total Si concentration below 2 mM, silicon is present predominately as $Si(OH)_4$ the most stable specie at low Si concentration. This monomeric form of silica, 'monomeric silica', is water soluble and a weak acid (pKa of 9.6), thus also referred to as 'monosilicic acid' or 'orthosilicic acid' (22). At neutral pH, this tetrahedral, uncharged (i.e. neutral) species is relatively inert, but does undergo condensation reactions (polymerisation) to form larger silica (polysilicic acid) species, especially at Si concentrations > 2-3 mM. Indeed, only in very dilute solutions, it is suggested, that the monomer will be found in its pure form, as often the dimer $[(HO)_3Si\text{-}O\text{-}Si(OH)_3]$ is also present (but never > 2%), even in solutions greatly below 2 mM Si (22, 22). Above 2 mM Si, $Si(OH)_4$ undergoes polymerization to form small oligomers (linear and cyclic trimers and tetramers or cyclic decamers) and, at concentration much above 2 mM, small colloidal species will also be present, which upon aggregation will eventually results in the formation of an amorphous precipitate, which at neutral pH (pH 6-7) is a gel (20, 22-24). Thus polymerisation of $Si(OH)_4$ reduces its solubility and hence bioavailability.

Silicon also exists as 'organo-silicon' compounds or silicones, but these synthetic (man-made) compounds are rarely found in the diet and in nature in general. Silicon as $Si(OH)_4$ is inert and until recently was suggested not to take part in any chemical or biological interactions, even though it is known to be actively taken up and transported by some primitive organisms and plants to form elaborate silica exoskeletons and biogenic silica, respectively, and the formation of which is assisted and controlled by proteins and

polysaccharides (25-27). Recently Kinrade et al (28, 29) reported that $Si(OH)_4$ interacts readily with alkyl diols of sugars to form five and six-coordinate Si complexes suggesting that interactions with bio-molecules is possible.

Human exposure to silicon

Human are exposed to numerous sources of silica/silicon including dust, pharmaceuticals, cosmetics and medical implants and devices (see Table 1), but the major and most important source of exposure for the majority of the population is the diet.

Dietary sources

Dietary intake of Si is between 20-50 mg Si/day for most Western populations (30-33); ≥ 2-fold higher than typical intake of iron and zinc. Higher intakes (140-204 mg/day) have been reported in China and India where plant-based foods may form a more predominant part of the diet (34, 35). The intake within different age groups is not well documented (33). It appears to be similar for children (27 mg/day) and adults (29 mg/day) in Finland, although their major sources of intake are different (32). In children the major source is from cereals (68% of total dietary intake), whereas the major source in adult males is from beer ingestion (44%) (30, 32). Intake in females is lower than in males, which is due to the higher intake of beer in males (30, 32, 36). Beer is a highly bioavailable natural source of silicon (see below). Intake also decreases significantly with age in adults (0.1 mg for every additional year) (30, 33).

Drinking water—Silicon in drinking water is derived from the weathering of rocks and soil minerals and since different types of minerals weather at different rates, the concentration of Si in water is dependent upon the surrounding geology. In the UK for example, Si concentrations are low (0.2-2.5 mg/L) in the north and west of Britain (‘highland’ Britain), where the rocks are ‘old’ and well-weathered (37-39), and the water is naturally soft (37). In contrast, Si levels are much higher (2.8-14 mg/L) in the south and east of Britain (‘lowland’ Britain) from the weathering of ‘young rocks’; the water is naturally hard as it is high in dissolved solids and is also alkaline (37, 38, 40, 41). The Si concentration of European mineral waters is within a similar range (4-16 mg/L) to lowland drinking waters and their pH is typically around neutral, or slightly above. Recently, however, higher levels (30-40 mg/L) have been reported in Spritzer and Fiji mineral waters, from natural sources in Malaysia and Fiji respectively.

Drinking water and other fluids provides the most readily bioavailable source of Si in the diet, since silicon is principally present as $Si(OH)_4$, and fluid ingestion can account for ≥ 20% of the total dietary intake of Si (42).

Food sources—Silica in food is derived from natural sources, including adherent soil particles on surfaces of vegetables and from its addition as additives (see below). Natural levels of Si in food are much higher in plant derived foods than meat or dairy products (Table 2). Plants take up and accumulate Si from soil and soil solutions that becomes incorporated as a structural component conferring strength and rigidity to stalks, for example, in grasses and cereals and also in some plants such as horsetail (Equisetum arvensa) where Si is essential (41, 43). Such plants, termed ‘Si accumulators’, are generally the monocotyledons, which include the cereals, grasses (e.g. rice) and some herbaceous plants. These accumulate some 10-20 times more Si than the dicotyledons (e.g. legumes). Indeed, some monocotyledons, such as rice, actively take up and transport Si and silicon-related genes have been recently identified. Plants produce biogenic (phytolithic) silica which is often associated with the polysaccharide/carbohydrate components of the cell wall.

High levels of Si are found in unrefined ('whole') grains such as barley, oats, rice bran and wheat bran (32, 44-46). Upto 50%, of the Si is present in the hulls and husks. Rice hulls, for example, contain 110 mg Si/g, and during manufacturing/industrial treatment these are removed which reduces Si in the refined foods. However, grain products such as breakfast cereals, flour and bread, biscuit, rice, pasta, cake and pastry etc., are still high dietary sources of Si (32, 44, 45) (see Table 2). Barley and hops are used in making beer and the mashing process breaks down their phytolythic silica, into soluble forms, so this beverage is high in Si (32, 44, 47, 42) (Table 3). In comparison wines and liquor/spirits have lower levels of Si (44) (Table 3). Sugar cane also actively takes up Si and refined and unrefined sugars are also high in Si (32, 44).

High natural levels of Si are also present in some vegetables, namely beans (green, Kenyan, French), spinach and root vegetables and some herbs (32, 44). Fruits contain low levels of Si except for bananas and dried fruits and nuts. However, very little Si is digested in the gut and made available from bananas (<2%) (30).

Seafood is also high in Si with mussels having the highest levels (32). Animal and dairy products are low in Si (44) (Table 2), higher levels are found in offal and the less popular food-parts, such as the brain, heart, liver, lung and kidney (32). High levels of Si are also present in arteries, where it maintains the integrity of the lining of the aortic tissue (termed the tunica intima) (48).

Additives—As noted above, Si is also added to manufactured and processed foods as additives, increasing the Si content of these foods. Commonly, this is in the form of silicates such as calcium silicate, sodium aluminosilicate, magnesium hydrogen metasilicate (talc), magnesium trisilicate, calcium aluminium silicate, bentonite and kaolin (49, 50). These silicates are either extracted from their naturally occurring minerals or produced synthetically with tailored properties, namely a high surface area with hygroscopic properties (37). Silicates are thought to be inert and not absorbed in the gastrointestinal tract (37, 49), and, under UK regulations governing silicate additives, are added at less than 2% of the weight of the food (37). Silicates are used as anticaking agents for better flow and storage properties, as thickeners and stabilizers, as clarifying agents in beer and wine, as glazing, polishing and release agents in sweets, as dusting powder in chewing gum and as coating agents in rice (32, 50-52). Silicate additives are thought to be inert and not readily absorbed from the gastrointestinal tract.

Supplements—Silicon is also available as a food supplement in tablet and solution forms. These show varying bioavailability (<1 to >50%) and most show negligible-low bioavailability. Biosil® or choline-stabilised orthosilicic acid (BioMineral NV, Destelbergen, Belgium), is a concentrated solution of orthosilicic acid (2% solution) in a choline (47%) and glycerol (33%) matrix. This is promoted as 'biologically active silicon' and studies in man have suggested that it is a readily bioavailable source of Si (53) and biologically active (54-56). Silica+® (Pharmafood, Belgium) is made from the dry extract of horsetail and contains 12 mg Si per tablet, of which 85% is suggested to be bioavailable. However, studies conducted in man have shown it to be significantly less bioavailable than Biosil® (57). Other supplements available over the counter include Silicea (silicon dioxide; Weleda, UK), Silicol (colloidal silica gel; Saguna, Germany), Silica (silicon dioxide; New Era, UK), Horsetail (horsetail extract; Good n'Natural, UK) and G5 (monomethyl trisilanol in solution; LLR-G5, Ireland).

Data from The Third National Health and Nutrition Examination Survey (NHANES III, 1984-1988) estimated the median intake of Si from supplements to be 2 mg/d (33). The main users of Si supplements were adults (19 y +).

Non-dietary sources

Pharmaceuticals—Silicon is present in some pharmaceuticals. Silicic acid and sodium silicates were administered, orally or intramuscularly, as possible treatments for pulmonary tuberculosis and atherosclerosis in Germany in the early part of this century (37). Later, a silica found in bamboo, was also used as a possible treatment for asthma and tuberculosis (22). In modern pharmaceuticals Si is present mainly in antidiarrhoeals, antacids and in proprietary analgesics such as aspirin. In analgesics, silicates (magnesium silicate and magnesium trisilicates) are present as excipients, which are inert ingredients that hold the other ingredients together, or as desiccants, if the active ingredient is hygroscopic (37, 52, 58). The levels of silicates in these drugs, however, are not well documented and bioavailability is suggested to be negligible. Abusive use, however, can cause inflammation of the kidneys termed ‘analgesic nephropathy’, but it is unclear if this is related to the active ingredient or the excipient (37).

Cosmetics—Silicon is also present in cosmetics and toiletries as a viscosity control agents and as an excipient (52, 59). Silica and silicates (e.g. hydrated silica and magnesium aluminium silicate) are present in toothpaste, creams, lipstick and coloured cosmetics (52, 60). Silicates are also likely to be present, as an excipient, in powdered cosmetics, while in talcum powder the main ingredient is magnesium hydrogen silicate. Phytolithic silica may be present, as a contaminant, in facial scrub and shampoos as often these are plant based, while silicones may be present in some hand and nail creams and in nail varnish.

Dermal absorption of silica/silicates is not well documented and it is thought to be negligible as these compounds are not lipid soluble. In contrast, silicones, in hand and nail creams, for example, are suggested to be readily absorbed.

Gastrointestinal absorption

The main route of entry of silicon in to the body is from the gastrointestinal tract. Indeed, urinary excretion of Si, a good marker of absorbed Si, correlates with dietary intake of Si (30, 61-63). However, the gastrointestinal absorption, metabolism and excretion of silicon is still poorly understood. There are only a few studies investigating the gastrointestinal bioavailability of Si from food, beverages or pharmaceuticals (30, 46, 47, 53, 57, 62-68).

The absorption of silicon, however, is strongly influenced by the form of silica ingested and this is related to the rate of production of soluble and absorbable species of silica in the gastrointestinal tract (30, 53, 64, 69). Biogenic/phytolithic silica is present in plant derived foods, and since these are largely insoluble forms of Si, they were thought to be relatively unavailable (32, 42, 53, 57, 70) until recently (30, 61, 62). However, a mean 41% of ingested Si is absorbed from solid foods and generally the Si content of the food is a marker of its uptake (30), suggesting phytolithic silica is broken down and absorbed. Absorption however requires their breakdown to much smaller soluble species such as orthosilicic acid (30, 61, 62).

Orthosilicic acid is the major silica species present in drinking water and other fluids/ beverages, including beer, so these provide the most available source of silicon to man. It is readily absorbed and excreted; at least 50% of intake (30, 33, 42, 47, 62, 67).

Silicate additives are also present in foods and beverages. As with pharmaceuticals these are added as inert additives or excipients and are thought not to be absorbed. A number of studies, in man and animals, however, have reported marked increases in serum Si concentration or excretion of Si in urine (5-56%) following ingestion of silicates (zeolite A (an aluminosilicate), sodium aluminosilicate, or magnesium trisilicate) suggesting that these

are partly solubilised to orthosilicic acid in the gastrointestinal tract and absorbed (63, 65, 68).

The mechanism of gastrointestinal uptake of silica is not known, but the silica species in the gastrointestinal tract influences its absorption (64), as noted above. Simple uncharged species such as orthosilicic acid will interact very weakly, or not at all, with the mucosally-bound mucus layer, thus will be readily mobile and will permeate easily across the mucus layer. Indeed, orthosilicic acid is readily and rapidly absorbed and excreted in urine, and uptake occurs predominately in the proximal small intestine (62, 64). This is likely to be by the paracellular pathway or small-pore transcellular pathway and is unlikely to be energy dependent. In contrast, charged polymeric silica species will either interact more strongly with the mucus layer, through cation bridges, and thus be less mobile, and/or will be too large to permeate through the mucus layer. Thus, polymeric/colloidal species of silica that are not readily broken down in the gastrointestinal tract will not be significantly absorbed and will be excreted in faeces (64). Other factors that may affect the absorption of silica are discussed below.

Fibre—Kelsay et al. (46), demonstrated that a high fibre diet (fruit and vegetables) reduces the gastrointestinal uptake of minerals, including Si. Urinary excretion of Si was 35% compared with 58% from a low fibre diet; while faecal excretion was 97% and 67% respectively. Both diets, however, produced a negative Si balance, although, this was more negative with the high fibre diet (−14.6 mg/day compared with −3.5 mg/day).

Dietary cations—Carlisle (68), found the silica supplementation to be more effective when rats were fed a low calcium diet, and Nielsen (15), suggested that low dietary calcium enhances the uptake of silica. These results, suggest that, either calcium and silica compete for the same absorption pathway, or that calcium forms insoluble, luminal calcium silicate that reduces silica bioavailability. Magnesium could similarly reduce the bioavailability of silica by forming insoluble silicates, since magnesium orthosilicate is considered the predominant form of silica in urine and possibly in plasma (71). Charnot and Pérès (72), suggested that silica controls the metabolism of calcium and magnesium.

Age—Reduced gastric acid output, as occurs with ageing, is suggested to reduce the ability to metabolise dietary silica. Thus, the gastrointestinal absorption of Si may decrease with ageing (49). Gut permeability, however, increases with ageing, but this is unlikely to significantly enhance Si absorption which is already high. In addition Si intake also seems to decrease with ageing (30, 33). We recently, however, found no marked significant differences in the absorption of Si between young (<40 y old) and elderly (>60 y old) men and women (Sripanyakorn et al., unpublished data).

Endocrine function—Charnot and Pérès (72) suggested that Si metabolism is controlled by steroid and thyroid hormones and that inadequate or reduced hormone or thyroid activity, as occurs with ageing, decreases silica absorption.

Silicon excretion

Silicon absorbed across the intestinal mucosa reaches the blood circulation, but it is not known whether any absorbed silica is retained by the mucosal cells, as occurs with some metal cations, although this is likely to be small. In blood, Si elutes with the non-protein bound fraction suggesting that silica does not associate with plasma proteins or that it forms a weak, easily disassociated interaction (73). Silica will be present as the neutral orthosilicic

acid species which readily diffuses into erythrocytes and other tissues (74), but may also be present as silicates (73) such as magnesium orthosilicate (71).

The main route of excretion of absorbed silica is via the kidneys into urine. Indeed, renal function appears to be an important determinant of plasma Si concentration and with impaired renal function, as seen in uraemic patients for example, plasma Si concentration is significantly elevated compared with normal healthy subjects (3.8 ± 1.74 mg/l vs 0.16 ± 0.04 mg/l in healthy subjects) (40, 41, 70, 73, 75). Both plasma and urinary Si levels correlate with creatinine clearance (61, 62, 76, 77). Berlyne et al. (76) also found that urinary Si correlates with calcium and magnesium levels in urine, again, suggesting that Si may be present as calcium and magnesium silicates. High levels of Si are present in the liver following intracardiac injection of silica in rats, so absorbed silica could also be excreted in bile, and subsequently eliminated in faeces (74). However, this is unlikely to be significant as absorption of Si into serum (area under the curve) correlates significantly with its excretion in urine (61, 62). Furthermore, silicic acid is water soluble and bile is an excretory pathway of lipid soluble molecules. Finally, renal and not biliary or gall bladder stones occur with long-term excessive Si intake.

As silicon is not associated with plasma proteins, it is readily filtered by the renal glomerulus (73, 74), and is eliminated with little tubular re-absorption (71). Much of the absorbed silica is eliminated within 4-8 hr following its ingestion (30,47,61,62,64). Indeed, the renal clearance of Si, is high (82-96 ml/min) (61,62). However, absorbed silica is also likely to be taken up by tissues which may delay its total elimination from the body. Thus, studies in rats, with the ^{31}Si isotope injected intracardially, have demonstrated that most of the Si is readily eliminated from plasma into urine (77% of ingested dose by 4 hr), but some is also distributed between a number of organs, including bone, skin, muscle and testes, but not the brain (78,79). Highest levels of ^{31}Si were found in the kidneys, liver and lungs (78); these were six fold higher compared to the concentration in plasma collected at the same time period. The one study in man, using the ^{32}Si radioisotope, showed that 36% of the oral dose was absorbed and eliminated in urine and although there was no evidence of retention, this was not a balance study as faecal excretion was not measured (65). The possibility, therefore, that some silicon was retained can not be excluded. The only documented balance study in man, investigating Si (46), found a negative Si balance, indicating the difficulty of undertaking such studies. Schwarz and Milne (16) suggested that in healthy, non-silicon deficient animals it is unlikely for Si to be accumulated. However, Si appears to be present in all tissues, including the brain (12-27 μg/g), and the total body burden is several grams, suggesting that at least some ingested Si is accumulated (68,70,73,75,80,81).

Tissue distribution

As noted above, some absorbed silicon is retained by the body as Si is present in all tissues. In addition fasting serum Si concentration is increased with Si supplementation in rats and humans and in the rat bone Si level correlates with dietary Si intake (Jugdaohsingh et al., unpublished data). Tissue levels however vary. In the rat highest levels are found in bone and other connective tissues such as, skin, nail, hair, trachea, tendons and aorta and very much less (10-20 fold less) in soft tissues (19; Jugdaohsingh et al., unpublished data). A similar tissue Si distribution is expected in humans, although this has not been investigated. Silicon is suggested to be integrally bound to connective tissues and their components and to have an important structural role (82) as silicon deprivation studies have reported detrimental effects on these tissues (16,17) as is also speculated to occur with normal ageing with the decline in tissue Si levels. Vice versa, silicon supplementation has been reported to have beneficial effects on these tissues especially bone where much of current work has

concentrated (36,48,54-56, 83-86). The potential importance of Si to bone health is discussed below.

Essentiality

Circumstantial evidence for the essentiality of silicon in animals (see below) and the presence of silica in most cells and in primitive organisms such as bacteria, viruses and fungi suggests that it may have a desirable or even an essential biological role in all organisms (16, 22). For some primitive organisms, such as diatoms, other algae, and sponges silicon is essential for survival and replication and so is actively taken-up and transported from the low levels in their environment (natural waters) (22, 26, 87-90). Similarly, silicon is also essential in some plants, namely rice, oats, barley, maize, cucumber, tobacco and tomatoes, as silicon deficiency reduces their growth and vice versa, addition of silicon improves growth and guards against attack by pathogens (22, 91).

Silicon deprivation experiments in the 1970's, in growing chicks (17) and rats (16), suggested that silica may also be essential for normal growth and development in higher animals, including humans, primarily in the formation of bone and connective tissues. However, these results have not been subsequently replicated, at least to the same magnitude and thus the essentiality of Si in higher animals remains questionable. It is however the most ubiquitous of all trace elements (92) and is present in blood at concentrations similar to physiologically important elements such as iron, copper and zinc (93) and is excreted in urine in similar orders of magnitude to calcium, one of the most important cell signalling molecules and major bone mineral, prompting suggestions that Si may have an important if not essential (biological) role.

Silicon and bone health

There is perhaps no question that silicon appears to have a beneficial role in bone formation and in bone health. Since the findings of Carlisle (17) and Schwarz & Milne (16) of a potential role of silicon in bone and connective tissues, there have been numerous studies over the past 30 years investigating this potential role of dietary silicon. A brief summary of the accumulated evidence is given below; see also Tables 4-6.

Dietary silicon intake and BMD—As mentioned above, the main and most important source of exposure to silicon is from the diet and recently two cross-sectional epidemiological studies from our group have reported that dietary silicon intake is associated with higher bone mineral density (BMD). In the Framingham Offspring cohort we reported that higher intake of dietary silicon was significantly positively associated with BMD at the hip sites of men and pre-menopausal women, but not in post-menopausal women (36). This study was repeated using the APOSS (Aberdeen Prospective Osteoporosis Screening Study) cohort, a women only cohort, and it similarly showed that dietary silicon intake was significantly positively associated with BMD at the hip and spine of pre-menopausal women. We also showed a similar correlation in post-menopausal women but only in those currently on hormone replacement therapy (HRT) (94). A weaker (non-significant) correlation was found in past-HRT users and no correlation in those who had never taken HRT. These two studies suggest that higher silicon intake is associated with higher BMD, a marker of bone strength, and also, a potential interaction between silicon and oestrogen status.

No silicon deprivation studies have been conducted in humans, but, as described above, in laboratory animals Si deprivation resulted in skeletal abnormalities and defects. In chicks, legs and beaks were paler, thinner, more flexible and thus easily fractured (17). In rats,

defects to the skull including the eye sockets was reported as was disturbances and impairment to incisor enamel pigmentation (16). More recent studies by Seaborn and Nielsen (95-100) (see Table 5) and others have not been able to reproduce these dramatic effects but have reported decreases in BMD, mineral content and collagen synthesis, and increases in collagen breakdown, thus confirming Si deprivation has a negative impact on bone.

Silicon supplementation—In osteoporotic subjects silicon supplementation with monomethyl trisilanol resulted in increased bone volume (83) and increases in femoral and lumbar spine BMD (84) (Table 4). In the latter study, silicon was shown to be more effective than Etidronate (a bisphosphonate) and sodium fluoride. A more recent study by Spector et al (56) in osteopenic and osteoporotic subjects, using choline-stabilised orthosilicic acid (ch-OSA), reported a trend for increased bone formation markers in serum, especially PINP (pro-collagen type I N-terminal propeptide) a marker type I collagen synthesis, with increasing dose of ch-OSA. A slight significant increase in femoral BMD was observed with the mid ch-OSA dose (6 mg Si/d).

Similarly in ovariectomised rats, supplementation with silicon or ch-OSA reduced bone resorption and bone loss and increased bone formation and bone mineral content or BMD (54,101,102) (Table 5). Results in chickens showed increased BMD and mechanical strength and in horses (mares) reduced bone-related injuries with silicon supplementation (103-108).

In vitro cell culture studies—Numerous cell and tissue culture studies have also been conducted to determine the mechanisms of silicon's effect on bone (Table 6) (109-119). Studies by Carlisle in the early 80's using chondrocytes and tibial epiphyses from chick embryos reported that silicon increased bone matrix synthesis (non-collagenous matrix polysaccharides and collagen) and that Si dose dependently increased prolyl hydroxylase activity, the enzyme involved in collagen synthesis (109-114). Recent studies with human osteoblast cells and zeolite A, an acid labile aluminosilicate, reported increased osteoblast proliferation, extracellular matrix synthesis, alkaline phosphatase (ALP) activity and osteocalcin synthesis (115-117). More recent studies using orthosilicic acid have also reported increases in type I collagen synthesis and cellular differentiation (118) and in addition increases in the mRNA of these proteins, suggesting potential involvement of Si in gene transcription (118, 119).

Thus tissue and cell culture studies have also suggested that silicon is involved in bone formation by increasing matrix synthesis and differentiation of osteoblast cells. Effects of silicon on bone resorption and osteoclast cell activity has not been well studied. Schutze et al (120) reported that zeolite A, but not separately its individual components (Si and Al), inhibited osteoclast activity (pit number and cathepsin B enzyme activity).

Bone implants and cements—Additional evidence of the involvement of silicon in bone is provided by in vivo and in vitro studies with silicon-containing implants and ceramics such as Si-substituted hydroxyapatites and Bioglass™. Such materials have been shown to bond much better to bone than their non-silicon-containing counterparts due to the spontaneous formation of a biologically active apatite-like layer on their surface (121). Silica on these materials is said to undergo partial dissolution to form an amorphous Si layer and the dissolved Si has been implicated for the in vivo efficacy of these implants as it has been shown to be involved in gene upregulation, osteoblast proliferation and differentiation, type I collagen synthesis and apatite formation. One recent paper reported more ordered collagen fibrils and mature bone formation with Si-substituted hydroxyapatite (122).

Mechanisms—Mechanisms are not clear but it has been suggested, based on the evidence above, that silicon is involved in bone formation through the synthesis and/or stabilization of collagen. Collagen has an important structural role in animals contributing to the architecture and resilience of bone and connective tissue. It is the most abundant protein in bone matrix conferring flexibility and, with elastin, is a major component of connective tissues which is found in skin, cartilage, tendons and arteries, for example. High levels of Si were found to be strongly bound to connective tissues and its components, namely glycoaminoglycans, polysaccharides and mucopolysaccharides (82) implying an integral role for Si. Quite how Si may be involved in collagen synthesis and or its stabilisation is still not established. It has been implicated in gene transcription of type I collagen gene, a cofactor for prolyl hydroxylase the enzyme involved in collagen synthesis, in the utilisation (i.e. gastrointestinal uptake and metabolism) of essential elements that are required for bone and collagen synthesis, such as copper (123), calcium and magnesium and in the scavenging and detoxifying toxic aluminium. Silicon has also been found at the mineralisation front of growing bone (18) suggesting also an involvement in early calcification/mineralization of bone matrix.

Toxicity

The toxicity associated with the inhalation of particulate crystalline silica and silicates, such as quartz, and man-made fibrous silicates (e.g. asbestos) has been extensively studied as long-term exposure causes scarring of the lung, that may lead to reduced lung capacity, lung cancer, and the increased risk of tuberculosis and heart complications. These crystalline silicates are phagocytosed by macrophages that then release cytokines that attract and stimulate other immune cells including fibroblasts, which are responsible for the excessive production of collagen (fibrotic tissue) that is characteristic of silicosis (22).

Oral ingestion of crystalline or amorphous silica/silicates in the diet may also cause toxicity. The inflorescences of Steria italica (millet) promotes oesophageal cancer, while the seeds of the Phalaris family of grass (e.g. canary grass, Phalaris canariensis) promote skin tumours (42, 124, 125). Finely ground silicate minerals from eroded acid granite in drinking water has been linked to ‘Endemic or Balkan Nephropathy’, which is inflammation of the kidneys (interstitial nephritis), found in confine parts of the Balkans (Yugoslavia, Bulgaria and Romania) (63). Long-term use of high doses of silicate containing drugs, such as analgesics and antacids (magnesium trisilicates) could cause damage to the renal kidney tubules and lead to chronic interstitial nephritis (63). As noted previously, the high levels of silica in these drugs can lead to the formation of renal stones/calculi which are responsible for kidney damage. Formation of silica stones/calculi (urolithiasis) is also a common problem in cattle and sheep who ingest large quantities of silica daily, since grass consists of 2% silica by weight, and drink very little water (22, 37). However, ingestion of amorphous silica is not associated with toxicity in the rat (33).

Chronic haemodialysis patients are potentially at risk from the accumulation of silicon (73, 75, 81). The high silicon levels of these patients have been associated with nephropathy, neuropathy, chest disease, bone diseases and liver disease (73, 75, 81).

However for much of the population with normal renal function the normal intake of dietary silicon from foods and water has not been associated with any known toxicity (33). There are no known symptoms or diseases of silicon excess or deficiency in humans.

Conclusion

Silicon is a major (naturally occurring) trace element in the human body derived predominantly from the diet. The intake and metabolism of which has only recently been determined. We ingest between 20-50 mg/day in the Western world, greater than two-fold our intake of iron and zinc and it is excreted in similar magnitude to calcium, suggesting more than a role as a 'ubiquitous contaminant'. Indeed accumulated evidence over the last 30 years suggests an important role in bone formation and bone and connective tissue health. Mechanisms are unclear but evidence exists of its involvement in collagen synthesis and/or its stabilization and in matrix mineralization. However much still remains to be understood on this potential biological role of silicon. Whether silicon has an essential role in man, as it has in lower animals also remains to be established. Establishment of a biological role for this element will have important implication for nutrition as a preventative measure, or Si containing supplements as a treatment, for bone and connective tissue diseases.

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Table 1

Human exposure to silicon

Sources	Exposure Levels	Comments
Soil	28% of the Earth's crust	Locked up in minerals (e.g., quartz, aluminosilicates). Inert, insoluble and very little is bioavailable (even to plants). Only released with weathering.
Dust	No data avilable.	Wide variety and forms (crystalline and amorphous). Inhaled; not readily solubilised; retained in the lungs and does not participate in the general metabolism of Si in the body.
Water	0.8-35 (median: 6.2) mg/L (freshwater), 0.001-0.3 mg/L (marine) 0.2-14 mg/L (tap), 4-40 mg/L (mineral/spring)	Most readily bio-available source (50-80%), as Si present as soluble OSA. Intake can make up 20-30% of daily Si intake, may be higher from mineral waters.
Diet	13-62 mg/d (Western countries) 143-204 mg/d (India), 139 mg/d (China)	Major contribution from plant-based foods (cereals, grains and some fruits & vegetables) and little from dairy and meat. Mean bioavailability is ~41%. Cereals, grains & products: 49±34%; Fruits & vegetables: 21±29% (bananas: 2.1%)
Dietary additives	≤ 2% food weight (UK)	Silicates (Mg, Ca & Al). Extracted from natural minerals or synthetics. Suppose to be inert and not absorbed from the GI tract.
Dietary supplements	Variable: 0.02 to 60 mg/g. Horsetail 9-17 mg/g	Colloidal, gels, plant-based, etc. Bioavailability is low, << 20% for most; BioSil (stabilised-OSA; BioMinerals NV, Belgium), ~30%; Monomethyltrisilano (LLR-G5, Ireland) is similar to OAS, at least 50% bioavailable.
Pharmaceuticals	Main components of antacids ($Mg_2Si_3O_3$; 250 mg/g), anti-diarrhoeal (Al & Mg silicates; 80% wt), and as excipients in proprietary analgesics	Can greatly increase exposure (> 1g/d) but are suppose to be inert & not absorbed. 5-10% at most is absorbed. Long term use can lead to silica stones and kidney damage (Dobbie and Smith 1982).
Cosmetics/ Toiletries	No data available. Excipients and viscosity agents.	Toothpaste, creams (silicones), lipstick, coloured/powdered cosmetics & talcum powder (Mg hydrogen silicate). Dermal absorption suggested to be low as silicates are not lipid soluble, but silicones in hand and nail creams are. Dermal absorption of aluminosilicates is linked to podoconiosis an inflammatory disease.
Other sources (e.g, detergents, tissue implants, etc.)	No data available	Exposure is low/minor for most individuals.

OSA= orthosilicic acid; GI= gastrointestinal

Table 2

Food sources of silicon

Food Groups	Si (mg/100g)	Range	Comments
Cereals Grains & Products			
Breakfast Cereal (n=16)	7.79 ± 6.31	1.34–23.36	11 of the 18 foods with high Si content (> 5mg/100g) are from this group. Silicon is almost solely present in the outer skin (husks/hull) of the grain. Oat bran has the highest Si content as it consist of the husk/ hull.
Bread/Flour (n=15)	2.87 ± 1.60	0.34–6.17	
Biscuit (n=5)	1.56 ± 0.56	1.05–2.44	
Rice (n=8)	1.54 ± 1.00	0.88–3.76	
Pasta (n=7)	1.11 ± 0.47	0.62–1.84	
Fruits			
Raw& canned (n=33)	1.34 ± 1.30	0.1–4.77	Bananas, pineapples and mangoes are high.
Dried (n=3)	10.54 ± 5.44	6.09–16.61	
Vegetables (n=49)	1.79 ± 2.42	0.1–8.73	High in Kenyan beans, green beans, runner beans, spinach and coriander.
Legumes (lentils, pulses, etc.; n=11)	1.46 ± 1.23	0.38–4.42	Lentils and Soya/tofu are high.
Nuts & Seeds (n=4)	0.78 ± 0.82	0.28–1.99	
Snack Foods (crisps, candy, etc; n=3)	1.97 ± 2.15	0.47–1.01	
Milk & Milk Products (TDS & n=3)	0.31 ± 0.21	0.07–0.47	Low Si content
Meat & Meat Products (TDS)		0.1–1.89	Low Si content

Table adapted from Powell et al. (44); TDS= Sample four the Food Standard Agency total diet study

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Table 3

Silicon in beverages

Food Groups	Si (mg/100g)	Range	Comments
Beverages (non-alcoholic)			
Tap water (n=11)	0.37 ± 0.13	0.095–0.61	Mineral waters > tap water
Mineral & Spring waters (n=14)	0.55 ± 0.33	0.24–1.46	Tap waters > carbonated drinks
Tea & Coffee (n=6)	0.51 ± 0.28	0.24–0.86	
Fruit juices (n=11)	0.38 ± 0.53	0.05–1.5	
Fizzy/Carbonated (n=6)	0.15 ± 0.04	0.11–0.19	
Milk based (n=6)	1.30 ± 1.40	0.2–3.96	
Beverages (alcoholic)			
Beers (n=76)	1.92 ± 0.66	0.9–3.94	No correlation with alcohol content, type of beer, type of storage/ packaging or geographic origin (Sripanyakorn et al., 2004).
Wines (n=3)	1.35 ± 0.85	0.68–2.31	
Port/Sherries (n=2)	1.24-1.26		
Liquor/Spirits (n=11)	0.13 ± 0.04	0.06–0.20	

Table adapted from Powell et al. (44)

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Table 4

Effect of dietary silicon on bone health; human studies

Studies	Methods	Study findings
Silicon supplementation		
Schiano et al. (83)	Osteoporotic subjects; oral, 5.5 mg/d × 20 d/mo for 3 mo (n=14) & im, 16.5 mg/wk for 4 mo (n=16)	↑ trabecular bone volume
Eisinger & Clairet (84)	Osteoporotic females (n=8); im, 100 mg/wk for 4 mo	↑ femoral BMD (4.7 ± 6.3%) >> sodium fluoride and Etidronate
Reffitt et al., (unpub. 2002)	Females with low bone mass (n=6); oral, 28 mg Si/d for 12 wk	↑ spine BMD (2.5%)
Spector et al. (56)	Females with low bone mass (n=114); oral, 0, 3, 6 & 12 mg Si/d as ch-OSA + Ca (1 g/d) & Vit D3 (800 IU)	Trend for ↑ bone formation markers with increasing Si dose & significant ↑ femoral BMD with 6 mg/d
Epidemiological Studies		
Jugdaohsingh et al. (36)	Cross-sectional study of the Framingham Offspring cohort, (Framingham, MA, USA); 1251 men & 1596 women (306 pre-menopausal).	Higher hip BMD with higher Si intake in men, pre-menopausal women, but not post-menopausal women
Macdonald et al. (94)	Cross-sectional study of the Aberdeen Prospective Osteoporosis Screening Study (APOSS, UK); 3199 pre-menopausal & early post-menopausal women.	Si intake is positively associated with BMD at the spine and significantly at femur in pre-menopausal women and post-menopausal women currently taking HRT

↑ = increase; ch-OSA = choline stabilized orthosilicic acid; im= intramuscular injection

Table 5

Effect of dietary silicon on bone health; studies in laboratory animals

Studies	Methods	Study findings
Rats		
Low silicon Diets		
Seaborn & Nielsen (95-97)	− Si vs. +Si (25-50 μg/g diet)	↓: body wt, skeletal Ca, tibial BMD, formation markers, plasma & bone Si
Seaborn & Nielsen (98,99)	− Si vs. +Si (10 & 35 μg/g diet)	↓: body wt, mineral content (femur, tibia & vertebrae), hydroxyproline conent of tibia
Nielsen & Poellot (100)	− Si vs. +Si (35 μg/g diet)	↑: bone resorption
Ovariectomy & Si Supplementation		
Hott et al. (101)	OVX + Si (120 μg/kg Bwt)	↓ osteoclast surface area (SA), ↑ osteoblast SA & MAR, ↓ bone loss, ↑ bone vol
Rico et al. (102)	OVX + Si (500 μg/g feed)	↑: body wt, longitudinal growth of femur, mineral content of femur & 5th vertebrae
Calomme et al. (54)	OVX + ch-OSA (1 mg Si/kg Bwt)	↑: body wt, serum & urine Si, partial increase in BMD at femur and lumbar spine
Chickens		
Merkley & Miller (103)	+Si (75 mg/l in drinking water)	stronger tibia & humeri, ↑ ash content of humeri
Roland (104)	+Si (0.75% Na aluminosilicate)	↑ egg production
Calomme et al. (105)	+Si (135 mg/kg Bwt/2 d) as ch-OSA	↑ serum Ca, total BMC (8%), BMD: midshaft (4%), distal metaphysis (5%), hip (6%)
Horses		
Nielsen et al. (106)	+Si	↓ bone related injuries in quarter horses
Lang et al. (107)	+Si (0.22 kg/d)	↑ serum & milk Si levels, ↑osteocalcin, ↓ collagen breakdown
Calves		
Calomme & Vanden Berghe (108)	+Si (<5% Si as ch-OSA)	↑: serum Si, skin hydroxyproline content

−Si = Si deficient diet; +Si = Si supplementation; OVX = ovariectomy; Bwt = body weight, ch-OSA = choline stabilized orthosilicic acid; BMC = bone mineral content; BMD = bone mineral density; SA= surface area; MAR= mineral apposition rate ↑ = increase; ↓ = decrease

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Table 6

Effect of dietary silicon on bone health: tissue and osteoblast cell culture studies

Studies	Methods	Study findings
Chick Embryos		
Carlisle & Alpenfels (109)	Paired frontal bones (low (6.6 μM) vs 2.2 mM for 12 d)	↑: dry weight (23%); collagen (43%), calcium content (14%), bone matrix polysaccharide (60%; d 8)
Carlisle & Alpenfels (110)	Paired proximal & distal tibial cartilaginous epiphyses (12 d)	↑: dry weight (42%; d 8); collagen (60%; d 8) vs ↓ in low Si group, ↑ matrix polysaccharides (63-140%)
Carlisle & Garvey (111)	Chondrocytes from epiphyses (18 d)	↑: procollagen hydroxyproline (243%), matrix polysaccharide (152%) – not due to cell proliferation
Carlisle & Suchil (112)	Paired tibial cartilaginous epiphyses (12 d)	↑: dry weight (44%), cartilage (400%; d8), hexosamine, proline, hydroxyproline & non-collagenous protein
Carlisle & Alpenfels (113)	Paired tibial cartilaginous epiphyses (12 d)	↑: proline synthesis (11-16 fold) with Si,
Carlisle et al. (114)	Prolyl hydroxylase from frontal bones (0.2, 0.5 & 2 mM Si; 8 d)	↓: proline and hydroxyproline synthesis in low Si dose dependent increase in activity (5-10 fold)
Human Osteoblast Cells		
Brady et al. (115)	From trabecular bone & MG-63 cell line (Zeolite A; 0.1-100 μg/ml)	↑: Cell proliferation (124-270%), ALP activity (144-310%)
Mills et al. (116)	Zeolite A	↑: Cell proliferation & extra cellular matrix
Keeting et al. (117)	From trabecular bone (Zeolite A; 0.1-100 μg/ml)	↑: Cell proliferation (62%), ALP (50-100%), osteocalcin (100%)
Reffitt et al., (118)	Cell lines (MG-63 & HCC1), bone marrow aspirates & dermal fibroblasts (10-50 μM Si as OSA; 3 d)	↑: type I collagen (40-80%), ALP activity (40%), osteocalcin (40%), ALP mRNA & osteocalcin mRNA
Arumugam et al. (119)	Osteoblast cells extracted from trabecular bone (5-50 μM Si as OSA; 20 h)	↑: mRNA type I collagen (2-2.5 fold)

↑ = increase; ↓ = decrease; ALP= alkaline phosphatase

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