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SILICON AND BONE HEALTH

R. JUGDAOHSINGH

Rayne Institute, Gastrointestinal Laboratory, St Thomas' Hospital, London SE1 7EH; Department of Nutrition, King's College London, 150 Stamford Street, London SE1 9NN; MRC Human Nutrition Research, Elsie Widdowson Laboratory, Fulbourn Road, Cambridge CB1 9NL. Tel: (+44) 207 188 2506; Fax: (+44) 207 188 2510; ravin.jugdaohsingh@kcl.ac.uk

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.

Key words: 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).

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,

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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

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%; Monomethyl-trisilano (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

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

Table 2
Food sources of silicon

Food Groups	Si (mg/100g)	Range	Comments
Cereals Grains & Products	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.
Breakfast Cereal (n=16)	2.87 ± 1.60	0.34–6.17	
Bread/Flour (n=15)	1.56 ± 0.56	1.05–2.44	
Biscuit (n=5)	1.54 ± 1.00	0.88–3.76	
Rice (n=8)	1.11 ± 0.47	0.62–1.84	
Pasta (n=7)			
Fruits	1.34 ± 1.30	0.1–4.77	Bananas, pineapples and mangoes are high.
Raw& canned (n=33)	10.54 ± 5.44	6.09–16.61	
Dried (n=3)			
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

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

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
Wines (n=3)	1.35 ± 0.85	0.68–2.31	storage/packaging or geographic origin (Sripanyakorn et al.,
Port/Sherries (n=2)	1.24_1.26		2004).
Liquor/Spirits (n=11)	0.13 ± 0.04	0.06–0.20	

Table adapted from Powell et al. (44)

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

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 x 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

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-

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

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

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, ↓: proline and hydroxyproline synthesis in low Si
Carlisle et al. (114)	Prolyl hydroxylase from frontal bones (0.2, 0.5 & 2 mM Si; 8 d)	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

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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