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<Abstract>

-Silica urolithiasis in dogs is mainly caused by silica-rich drinking water.
-Specific brands of pet food are also associated with silica urolithiasis.
-The type of silica molecule (not the amount of silica) in the food might be the crucial factor resulting in silica urolith formation.

Silica urolithiasis is relatively rare in dogs. Silica uroliths account for about 0.1–4% of canine urinary calculi worldwide [1], and 1.7% of canine urinary calculi in Japan [2]. From 2008-2009, however, four of the 12 urolithiasis cases seen at Kagoshima University were found to involve silica uroliths. The report provided by Hill's Urolith Analysis Service in Japan showed that requests for urinary calculus analyses from the southern Kyushu area accounted for only 4% of all requested canine urolith analyses from 2009 to 2010 in Japan. However, 20% of the canine silica urolithiasis cases in Japan occur in this region [2]. We believed that the food and lifestyle of the dogs in this area was similar to that of dogs from other areas in Japan. Thus, we attempted to clarify the epidemiology of silica urolithiasis in southern Kyushu area.

To do this, we sent questionnaires to 22 veterinarians in Kagoshima Prefecture, which is in southern Kyushu, and collected data on the 30 dogs that were reported as having been diagnosed with silica urolithiasis. Fourteen of the 30 dogs lived in Kirishima City (population 128,000), six lived in Kagoshima City (population 606,000), and four lived in Aira City (population 76,000) (Figure 1).

Of course, this is a biased sample; however, there seemed to be a regional epidemic of silica urolithiasis in dogs. For example, although we sent questionnaires to most of the veterinarians in Kagoshima City, the incidence of silica urolithiasis in Kagoshima City was relatively low and five of the six cases occurred in the northern part of the city (Figure 2). We also asked the owners of the dogs with silica calculi, through their

Figure 1. Distribution of silica calculus in Kagoshima area (30 cases).The distribution of cases of canine silica urolithiasis does not seem be associated with human population. Although Kagoshima City is the most populated city in the region, silica urolithiasis occurred mostly in Kirishima City. It also occurred in Soo, Shibushi, and Kanoya, which are all relatively sparsely populated areas.

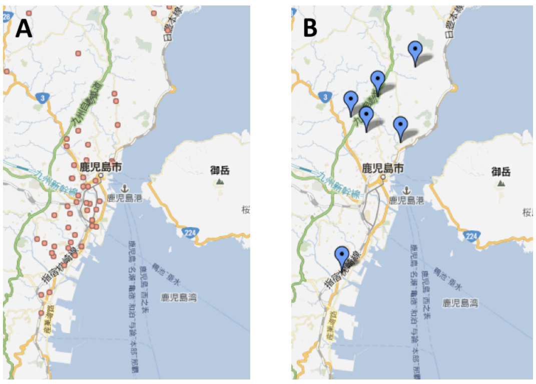

Figure 2. A: Distribution of animal hospitals in Kagoshima City (red circles). B: Distribution of silica urolithiasis cases in Kagoshima City. Although animal hospitals are evenly distributed throughout the city, silica urolithiasis cases mainly occurred in the northern part of the city.

attending veterinarian, about aspects of the dog's lifestyle that may be associated with the development of silica calculi. These included the brand of pet food fed, habits such as eating soil or other unusual foods, and the type of drinking water provided. All of the dogs were fed commercially available dog foods, only one dog was known to eat soil, and all of the dogs except one drank tap water. This led us to suspect that tap water was a potential causative factor in the silica urolithiasis cases in this area.

Southern Kyushu has many volcanoes. Mt. Sakurajima in Kagoshima is one of the most active volcanoes in the world; it erupted approximately one thousand times in 2012. Mt. Shinmoedake erupted in 2011. It is believed that the silica concentration in river water and underground water is high in volcanic areas (Edogawa river office homepage: www.ktr.mlit.go.jp/edogawa/study/woodbook/woodbook/item06/sirika.htm). In the Kagoshima area, most of the tap water is supplied by relatively small wells. For example, in Kagoshima City, tap water is supplied from three river water sources and more than 100 underground or sump water sources. In Kirishima City, which has no river water source, there are more than 60 underground or sump water sources. Japan does not regulate measurement of the silica content of tap water. We measured the silica concentration in tap water from Kagoshima and other areas of Japan using the molybdenum-blue method. The silica concentration in the tap water in Kagoshima was markedly high compared with the concentrations in tap water in other areas of Japan.

As shown in Figures 3 and 4, the mean silica concentrations were 62.3 mg/l and 78.8 mg/l in Kagoshima City and Kirishima City,

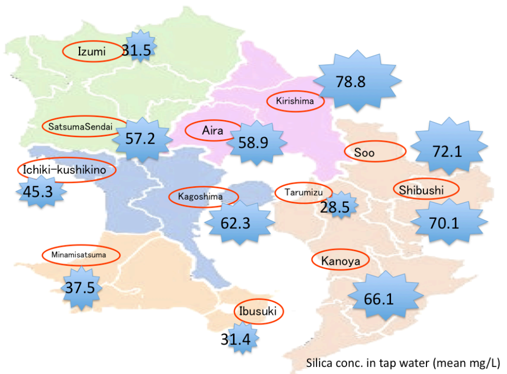

Figure 3. Silica concentrations in tap water in Kagoshima Prefecture. Water sampling sites were arbitrarily selected. The silica concentrations are high in the areas where silica urolithiasis cases occurred.

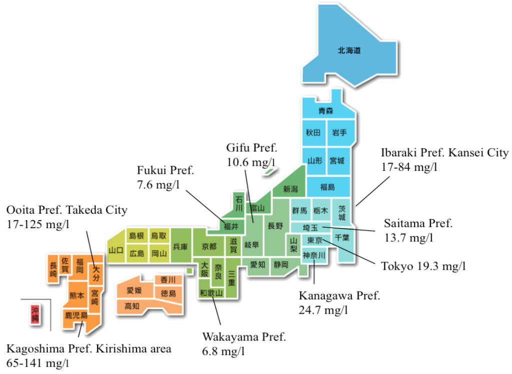

Figure 4. Silica concentrations in tap water in Japan. Water sampling sites were arbitrarily selected. The concentrations are markedly high in Kagoshima. There are also some other places where the silica concentrations are high (e.g., Oita, Ibaraki).

respectively, while in Tokyo (river water source), the concentration was 19.3 mg/l. Thus, there are some "silica hot spots" where the concentration of silica in tap water is high (e.g., in Oita, Ibaraki). The distribution of silica calculi hot spots is similar to the distribution of hot springs in Japan (Figure 4, 5). However, in Ibaraki, the silica concentration in the tap water is high despite a lack of hot springs. The reason for this is likely that we obtained a tap water sample from Chikusei City, where the tap water is supplied in part by a deep well. The silica concentrations in Japanese tap water ranged from 16.8–83.8 mg/l; these differences probably reflect the source of tap water.

From these epidemiological facts, we speculated that the silica urolithiasis seen in dogs in southern Kyushu is caused by the tap water. However, there is no direct evidence of this yet and there are still some questions that remain to be answered. For example, we changed the drinking water of the dogs kept in our hospital from tap water (high silica) to

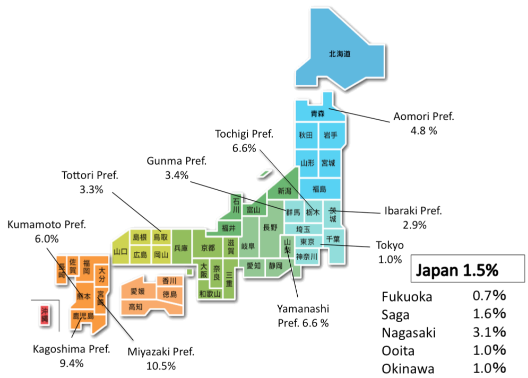

Figure 5. Silica calculi as a percentage of total urinary calculi in the prefectures of Japan. The epidemic areas (areas with higher percentages of silica calculi) are also places that are famous for having hot springs.

bottled water (low silica) and then measured urine silica concentrations 3 days later. The urine silica concentrations before and after changing the water were not significantly different. This may be because of the low sensitivity of our assay (molybdenum-blue method). Other assays, which use radioisotopes, provide a successful measurement of blood and urine silica concentrations [3]. Another question is why only a small population of dogs in silica hot spots such as Kirishima area was affected by silica urolithiasis. Furthermore, why do the silica urinary calculi seem to only dogs? Many humans also drink tap water in the areas that we studied; however, silica urinary calculi are not common in people in this area and there is only one case report associating water intake and silica urolithiasis in humans [4]. In that report, a baby who was fed powdered milk dissolved in silica-rich water developed silica urinary calculi. Although we do not yet know the answers to these questions, we do have a hypothesis.

The solubility of silica in water is about 120 mg/l at 20 °C and pH 7.0. At higher temperatures, silica becomes more soluble. The temperature of underground water is higher than that of surface water, especially in volcanic areas. Therefore, if underground water is saturated with silica, that same water is oversaturated at the lower temperatures that occur at ground level. Oversaturated silica may precipitate or disperse as colloid. To confirm this, we asked Dr. Miho Takahashi (Tokyo University of Marine Science and Technology) to analyze the dissolved silica molecules in tap water in Kirishima by FAB-MS. Indeed, the ratio of linear tetramer ($Si_4(OH)_9O_4^-$)/cyclic tetramer ($Si_4(OH)_7O_5^-$) was higher than that in normal unsaturated silica solution, which indicates that the water was once oversaturated [5]. Silica is absorbed from the intestine when it is dissolved in water. For example, the silica in beer is well absorbed and excreted in the urine [6], but silica is poorly absorbed from food with a high silica content (such as oats) [7]. Thus, dogs usually do not develop silica urinary calculi after eating garden stones or soil, even though these often contain large amounts of insoluble silica complexes. To dissolve the silica (including colloid) requires heating or alkaline conditions. The pH in the intestine of dogs is higher than in humans, and can sometimes reach pH 8.5) [8]. Therefore, we

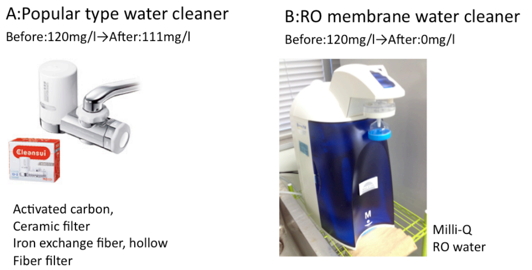

Figure 6. Removal of dissolved silica was attempted using two different water purification systems. A widely used water purifier did not remove the dissolved silica from silica-rich well water. An RO membrane water purifier (Milli-Q) removed the silica.

hypothesize that the tap water in epidemic areas is sometimes oversaturated with silica and that this water includes both soluble and colloidal silica. The dogs drink the tap water, and if the pH in the intestine is high, the colloidal silica dissolves and is then absorbed from the intestine leading to an excess of silica excreted in the urine and resulting in the formation of calculi.

It is relatively easy to remove silica from drinking water, but it does require specific knowledge of how to do it. We tested several types of water purification systems and found that a widely used type of water purifier, which uses activated carbon, ion exchange fibers, and a hollow fiber filter, does not effectively remove the silica from tap water. On the other hand, a reverse osmosis membrane type water purifier (RO purifier) removes almost all of the silica in the water (Figure 6). However, regular maintenance of the water purification system may be necessary in areas with silica-rich water. Another way to prevent the formation of silica calculi is to give the dog bottled water containing only a low level of silica. Since the silica concentration is usually not listed on the bottle's label, the manufacturer should be contacted. Bottled water collected from

Table1 Silica conc. in Bottled Water

Brand	Water obtaining place	Silica
Evian	France	12.5
Volvic	Not labeled	28.4
Brand A	Fiji	137.8
Brand B	Hokuto City (Yamanashi Pref.)	45.9
Brand C	Kobayashi City (Miyazaki Pref.)	113.9
Brand D	Hita City (Ooita Pref.)	137.8
Brand E	Kirishima City(Kagoshima Pref.)	269.1

Table2 Silica Calculus in Dogs Living not Epidemical Area

Dog No.	Living Area	Food	Drinking Water	Affected year
Dog#1	Tokyo	Pet Food Brand A	Tap water	2004
Dog#2	Chiba Pref.	Pet Food Brand A	Tap water (clreaned)	2003
Dog#3	Tokyo	Pet Food Brand A	Tap water	2003
Dog#4	Tokyo	Pet Food Brand A	Tap water (clreaned)	2001
Dog#5	Hyougo Pref.	Pet Food Brand B	Bottled water	2011

volcanic areas or from deep wells may contain high concentrations of silica; however, this silica is sometimes removed during purification process. Evian is a brand of bottled water with a low silica content (Table 1).

Silica urolithiasis sometimes occurs in areas where the silica content of tap water is low. Through the internet, we were able to contact five independent owners of dogs that were affected by silica urolithiasis while living in low-silica areas. We sent them questionnaires about drinking water, food, and lifestyle factors that may be associated with silica urolithiasis. Only one owner routinely gave their dog well water. Surprisingly, at the time that they developed silica urolithiasis, four of the five affected dogs were fed the same brand of pet food. All of the dogs were affected between 2002 and 2005 (our investigation was done in 2012), therefore we could not obtain samples of the actual food that they ate. However, we did analyze the silica content of the same brand of pet food. It is known that silica is contained in the raw materials used in pet foods: rice husks, corn gluten, and beet pulp [9-11]. Almost all pet foods include silica rich these materials, and the silica content of the brand that had been fed to the affected dogs was no higher than that of control pet foods (Table 2). All of the pet foods that we investigated included enough amount of silica. However, to form urinary calculi the silica must be absorbed, and to be absorbed the silica must be in a soluble form. In humans, almost all silica uroliths are formed in people who are treated with magnesium silicate (magnesium trisilicate) as an antacid [12]. It may be that it is not the amount of silica contained in the food, but the type of silica molecule in the food that is the crucial factor in cases of silica urolithiasis associated with pet food.

Table3 Silica Contents in Dry Pet Food

Pet food brand	Crude fiber content	Silica content
Science Diet Light	18.50%	717ppm
Royal canin	21.10%	1820ppm
Brand A	4%	1280ppm
Brand B	8.50%	2370ppm
Brand C	4,3%	2670ppm

Acknowledgements

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