1.2 Environmental Chemistry of Endemic Diseases

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Introduction

Human health, especially in rural populations in developing countries, can be seriously affected by parasitic diseases, communicable diseases as well as nutritional diseases. Parasitic disease such as malaria with one to two million deaths per year, 300 million infected, and two billion at risk, and schistosomiasis with 200 million affected, and around 500 million at risk are widely reported and studied (1). Communicable diseases, including water borne diarrhoeal diseases, seriously affect people with around five million deaths in young children each year and are again well recognised (2). Nutritional diseases on the other hand have in recent years not received the same publicity, yet many serious consequences result. It has been estimated that around 800 million people are seriously malnourished, 800 to 900 million are anaemic with an iron deficiency and around seven million have vitamin A deficiency (2).

Vitamin deficiencies, together with iodine deficient goitre, the selenium responsive Keshan and Kaschin-Beck diseases and those where excess levels of fluoride, arsenic or selenium seriously affect health are referred to as 'endemic diseases'. They are not, however, restricted to individual countries but the term is used to distinguish diseases with a chemical aetiology from biologically mediated communicable or parasitic diseases.

In this report, emphasis will be placed on endemic fluorosis, iodine deficient goitre, Keshan and Kaschin-Beck diseases.

Fluorides and Fluorosis

The intake of excess concentrations of fluorides, whether from drinking water, ingestion of food or inhalation of high fluoride smoke or dusts, gives rise to fluorosis in animals and humans. Plants too are affected but will not be discussed here.

Dental fluorosis, the mottling of teeth at relatively low concentrations of fluoride, occurs on all continents and is widespread (3). It usually arises from drinking well waters containing elevated concentrations of fluoride ions. No accurate data exist on the total numbers of people affected but a recent report suggests the numbers exceed 80 million and could be as high as 100 million (4). In China, some 85 million people are at risk from high fluoride levels and 38 million people are reported to have dental fluorosis, while in India the number affected is around 25 million.

High fluoride concentrations in soils, rocks and waters, particularly well waters, occur throughout the world. High fluoride levels and hence dental fluorosis, where exposure to fluoride exceeds approximately 1.5 to 2 mg l^{-1}, is often thought of as being a disease of tropical climates. Accordingly, the disease extends in geographical belts extending from Turkey into the eastern Mediterranean and into Africa, particularly the east coast nations, and down to South Africa. Other belts extend from Turkey across to India, China, Korea and Japan. Dental fluorosis also occurs in South America, including Bolivia, Argentina and Equador. In earlier years, dental fluorosis was recorded at locations in the temperate countries across Europe and the Americas.

Traditionally, fluorosis is considered to arise from drinking high fluoride surface, shallow- and deep-well waters although drinking special high fluoride teas and intake of high fluoride salt in some South East Asian countries can markedly increase the intake. In parts of China 'brick tea' contains up to 600 mg kg^{-1} giving rise to a concentration in solution of 3 mg l^{-1}. High fluoride salts typical of China, Thailand, Myanmar and Vietnam can give rise to a daily intake of 4-5 mg fluoride. Inhalation of high fluoride smoke from coal combustion provides another major exposure route.

The incidence of dental fluorosis varies enormously depending on exposure and nutritional status in particular. In Thailand at one location, up to 92% of the subjects examined showed dental fluorosis where the water contained 1.0-1.6 mg l^{-1} fluoride (5). Not surprisingly, incidence of dental fluorosis varies throughout China, but is recorded in all 28 provinces, autonomous regions and municipalities of the country except Shanghai (6). Fluorosis distributions have been mapped in detail in China based on the exposure route, ie. deep-well water, shallow-well water, high fluoride coal smoke, etc. Less detailed maps have also been produced for other parts of the world, particularly for affected states in India.

Dental fluorosis is particularly widespread in people from many regions of the Rift Valley throughout the east coast of Africa. In Kenya, for example, fluorosis is a health problem of major concern. Nair and Gitonga (7) have estimated that around 10 million people are potentially at risk, but further data is required to ascertain annual variations in concentrations and the contribution of fluoride in drinking water to total exposure.

Skeletal fluorosis, where osteoscherosis, ligamentous and tendinous calcification and extreme bone deformity result, is also global in scope. In China, some two million people and in India, approximately one million people, suffer from this incapacitating disease. Although normally considered as a disease of the elderly due to continuous fluoride exposure over long periods of time, skeletal fluorosis has been reported in locations also in children particularly in Tanzania. Skeletal fluorosis would normally be considered at fluoride concentrations above approximately 10 mg l^{-1} in water, but nutritional level, calcium intake, etc, modify human response. Skeletal fluorosis incidence, as with dental fluorosis, varies markedly from location to location.

Although fluorosis is well known as an endemic disease throughout the world, the numbers affected would appear to be increasing due to population growth, particularly in Africa. Despite the use of alternative low fluoride waters in parts of China and India the disease is still serious.

The development of extensive low cost defluoridation techniques is still required for areas where alternative sources of low fluoride water are unavailable. Extensive work is necessary to understand the aetiology of the disease, its exposure routes and to reduce the incidence of both dental and skeletal fluorosis around the world.

Iodine Deficient Goitre

Iodine deficient goitre, despite being a well recognised endemic disease, still affects over 150 million people around the world from a population exposed to low iodine of around 800 million to 1 billion people (8). Endemic goitre occurs on all continents and in many countries, particularly throughout the Third World. Iceland is one of the few countries where goitre has not been described. It is thus a disease of serious proportions although the iodization of salt has reduced the incidence of goitre in the developed world to relatively low numbers. More than 43 million people in South East Asia suffer mental and physical impairment due to iodine deficiency (9). Under severe iodine deficiency, ie. less than 20 $\mu g\ day^{-1}$, cretinism results. It has been estimated that over 3 million people suffer of iodine deficient cretinism. The incidence of cretinism varies in China between 0.01 to 1.09% of the groups surveyed.

High iodine levels cause thyrotoxicosis and hence iodine-induced goitre due to reduced thyroid uptake of iodine although this situation is much less common than iodine-deficient goitre. High-iodine goitre is typical of coastal areas in China and Japan where intakes of seaweeds or vegetables pickled in kelp salt are consumed (10). This contrasts with the iodine-deficient goitre which is greatest in areas of high mountains and plateaus, especially those far from the influence of the maritime atmosphere with its elevated levels of iodine.

The critical intake band is around 50-100 $\mu g\ I\ day^{-1}$, with water as a source accounting for 10-20% of the exposure. For children, adolescents and pregnant women, the daily intake should exceed 150 $\mu g\ day^{-1}$. Concentrations of iodine in urine or in head hair are ready monitors of iodine exposure. Values of around $0.5 \pm 0.25\ \mu g\ I\ g^{-1}$ hair can be found in iodine-deficient areas compared with 'normal' values of around $1 \pm 0.2\ \mu g\ I\ g^{-1}$ hair (11).

'Normal' soils range around 5-10 $\mu g\ I\ g^{-1}$ d.w. with plant values less than 1 $\mu g\ I\ g^{-1}$ d.w. (12). Data from a range of countries shows that the incidence of endemic goitre is light around 1 $\mu g\ I\ g^{-1}$ d.w. soil, but becomes serious with an incidence of approximately 40% when the vaue is around 0.4 $\mu g\ I\ g^{-1}$ soil. The exact relationship varies with the other exposure routes of iodine including total diet and water iodine intakes.

The incidence of goitre is still high in Asia despite many attempts at increasing iodine intake via iodinated products, injection of iodinated oils, etc. In China alone, goitre occurs in 28 provinces,autonomous regions and municipalities, except Shanghai. Based on surveys of 213 million people, the incidence has been calculated to be 19.8 million. In India the number affected is 40 million while serious incidences of the disease occurs throughout Asia and South East Asia particularly (13).

As with the incidence of fluorosis, iodine-deficient goitre occurrences have been carefully studied and mapped throughout China (14) and more generally on the global scale (8).

Keshan Disease

The endemic cardiomyopathy, Keshan Disease, named after Keshan County, Heilongjiang Province, has been reported since the early 1930s from many areas of China and extends into Inner Mongolia and the Democratic People's Republic of Korea (North Korea) (14). Early stone tablets describe characteristic symptoms from different areas of China. The disease has been reported in 15 provinces and in 309 counties in a belt from south-west to north-east China. The criteria for diagnosing Keshan Disease include acute or chronic cardiac insufficiency, heart enlargement, 'gallop rhythm', arrhythmia and ECG changes. Histopathologically, it is characterised by multifocal necrosis and fibrous replacement of the myocardium. The disease effects children usually under 10 years of age and women of child-bearing age living in rural areas, but the incidence rate among age classes varies between adjacent counties. Pronounced annual fluctuations of disease incidence have been noted throughout China (14, 15).

Acute and subacute incidence of Keshan Disease and the resultant death rate varies between villages, counties and provinces as well as with the year of occurrence. The disease was especially prevalent around the years 1960 and 1970 (14, 15). Overall, the death rate has decreased over a 20-year period in North China from 40.25% to 12.97% (average 21.03%) (16). An incidence rate of up to 11% in susceptible age groups and a fatality rate of up to 80% has been reported in earlier times although the disease incidence has declined markedly in recent years (14).

Epidemiological studies have shown that the disease occurs in low selenium environments, resulting in a low dietary intake. Approximately, 15 $\mu g\ d^{-1}$ is the critical dietary intake value (17) and can be compared with a median intake of 74 $\mu g\ d^{-1}$ for some U.S citizens (18) and up to 210 $\mu g\ d^{-1}$ in Japan for example (19). Selenium concentrations in water, soil and crops from Keshan Disease areas are low and have been mapped across the country. Selenium in top soils from, for example, the 'deficient' red-brown earths, purplish soils and drab earths contain 0.09, 0.06 and 0.08 $\mu g\ g^{-1}$ respectively , giving rise to a concentration in rice and maize of around 0.017 and 0.014 $\mu g\ g^{-1}$. Rice and maize from a non-disease area contains approximately 0.07 and 0.05 $\mu g\ g^{-1}$ respectively.

It is of interest that the selenium concentration in rain water when measured at intervals from the coast near Changle to Yengshou in the interior in a north-east direction, following the prevailing wind, actually increased from 0.18 ng ml^{-1} to 0.43 ng ml^{-1} (20). Selenium concentrations in soil on the other hand , show an inverse relationship with that in rain. Indeed, experiments on the microbial volatilisation of selenium from Chinese soils show that higher rates occur on the low selenium soils rather than on the 'normal' soils, thus perhaps helping to explain significant selenium loss from soils already geochemically low in the element (21). At peak loss it was calculated that up to 0.07 g yr^{-1} mu^{-1} selenium could be lost (1 mu equals approximately one-sixth of an acre). Selenium in hair is a useful biological indicator of selenium status. Selenium concentrations in hair for individuals from a Keshan Disease purplish soil area averages 0.123 µg g-1 (n = 492) compared with 0.366 µg g^{-1} (n = 183) from a non-disease area, north-west brown desert soil (22).

Hair selenium concentrations in individuals from Keshan Disease areas in Kalaqin Qi, Inner Mongolia where selenium was sprayed over crops increased during the trials. Control hair from Keshan Disease patients was approximately 0.160 µg g^{-1} compared with hair from people in the selenium sprayed area of 0.3 to 0.5 µg g^{-1}. Selenium intake for staple foods from the control areas was 6.7 µg d^{-1} compared with non-affected areas of 18.1 µg d^{-1} and 63.4 µg d^{-1} from the sprayed areas.

Preventative trials, especially with sodium selenite tablets, selenized salt or selenium-supplemented fertilizers and hence supplemented crops, have been carried out throughout China over a number of years.

The results clearly show that selenium supplementation has a protective effect; the longer the period of supplementation the greater the benefit. Based on a large number of supplementation trials throughout China and Inner Mongolia, it is now accepted that the major aetiological factor in Keshan Disease is a deficiency of selenium.

Kaschin-Beck Disease

140 years have elapsed since Kaschin-Beck Disease was reported by I M Urenskii from the Transbaikalia region, Urov River area of east Siberia. The disease was named after two Russian scientists who were involved in its early description although it is often referred to as Urov Disease in Russia. Historical records referring to the joint deformations and dwarfism show that it has been known for over 300 years at least in Shaanxi Province, China.

The disease occurs in 15 provinces and 303 counties of China including the Tibetan autonomous region extending into North Korea, Inner Mongolia, Japan and Russia (14). The distribution of the disease is mostly contiguous, but some discrete areas occur. Likewise, some 'health islands' occur within disease affected areas. Some two million people exhibit clinical symptoms of the disease and around thirty million live in affected areas in China alone. The disease incidence fluctuates annually and in recent times new disease areas are still being reported.

The basic pathological change with the disease, commencing mainly in children of five to thirteen years, is the multiple degeneration and necrosis of articular cartilage and the growth plate which results in permanent disabilities. In severely affected areas, children two to three years of age are affected, while in lightly affected areas, new cases occur after ten years of age.

Kaschin-Beck Disease (deformans endemica) is regarded as an endemic, chronic high-incidence and degenerative osteoarthrosis whose aetiology is still incompletely understood (14). In Russia, it was proposed that a strontium-calcium imbalance was implicated in the disease as well as high phosphate and manganese contents (23), although further studies are not definitive.

In recent years, three theories have been advanced to account for the disease in China. One theory implicates mycotoxins in contaminated grain produced by the fungus *Fusarium oxysporum*. The mycotoxin theory, although popular for a time, seems now to receive less support although a higher incidence of fungal contaminated grain was reported from disease areas than from non-disease areas.

An implication that well water is involved in the aetiology of the disease is the second theory based on a decrease in the disease incidence following the provision of alternative sources. For example, a change from shallow well water for affected villages in two areas in Jilin Province, to deep well water reduced the humic acid level to a value similar to non-disease areas. This was accompanied by a high recovery rate and the absence of new cases in previously affected villages (24). Likewise, a change from shallow well water to deep well water in Linyou County, Shaanxi Province, decreased the disease incidence over a two-year period until no new cases occurred, whilst in affected villages still supplied with shallow well water, the incidence of Kaschin-Beck Disease actually increased (25). In this latter trial, the authors considered that the increase in selenium content of the well water from 0.08-0.09 ng ml^{-1} to 1.16-1.38 ng ml^{-1} was the responsible factor rather than a decrease in humic acids.

Other studies have implicated humic acids in the aetiology of the disease though the effect may be an indirect one as humic acids bind selenite and reduce the available selenium in water.

The thirds and most widely supported theory to explain the aetiology of Kaschin-Beck Disease involves an imbalance of chemical elements in the ecological environment, especially a deficiency of selenium (26). Evidence for this view comes from the occurrence of the disease on low selenium soils in China and thus, there is a comparable but not identical distribution as with Keshan Disease.

Tan Jianan et al consider that values of selenium in hair of <0.120 µg g^{-1} are characteristic of Kashin-Beck Disease areas, while >0.2 µg g^{-1} indicate disease free areas.

Since Kaschin-Beck Disease occurs on low selenium soils, many selenium supplementation trials, both large and small scale, have been reported over the years from the most severely affected counties. Recent trials have been monitored by an X-ray examination of hand-bone development as well as using hair and blood as indicators of the selenium status. In one study involving 437,000 three- to six-year old children from seven endemic counties in Heilongjiang Province, sodium selenite was given orally as tablets (0.5 mg once per week) for three successive years, and the disease followed by X-ray examination (27). The detection rate decreased following treatment from 40.82% to 8.66%.

In another study involving 1,000 children in 20 severely affected endemic areas in Yungshou County, Shaanxi Province lasting from 1980-1987, the X-ray positive detection rate dropped from 63.6% to 21.9% following selenium supplementation (28). Selenium-enriched yeast has also been shown to exert a protective effect in a study of 180 five- to fifteen-year old children in Fengning County, Hebei Province.

Conclusions

Despite the intensification of human health concerns and interventions around the world, serious nutritional diseases still occur on a large scale, incapacitating hundreds of millions of people. Supplementation trials with iodine and selenium illustrate their relationship with goitre and Keshan Disease respectively, but the chemical aetiology of Kaschin-Beck Disease, despite being selenium responsive, is still uncertain. Greater emphasis needs to be placed on epidemiological surveys of such diseases. At the excess level, endemic fluorosis is a disease which is global in scope although alternative water sources and blending of waters have virtually eliminated the disease from western Europe and North America. In a number of developing countries, however, endemic fluorosis is increasing in line with increases in populations principally exposed to high-fluoride waters. Low cost defluroridation processes are still urgently required for locations where alternative water sources are unavailable. Such environmentally-related diseases will continue to assume global prominence over the next decade despite improvements in health care in some countries.

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