



EDITORIAL

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Volume 339:1156-1158

[October 15, 1998](#)

Number 16

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Kashin–Beck Disease — Expanding the Spectrum of Iodine-Deficiency Disorders

Selenium, as selenocysteine, is an integral component of two important enzymes — glutathione peroxidase and iodothyronine deiodinase — that are present in many tissues, including the thyroid gland. Glutathione peroxidase catalyzes the breakdown of hydrogen peroxide, thereby protecting against oxidative damage. Iodothyronine deiodinase catalyzes the deiodination of thyroxine to triiodothyronine, a more potent thyroid hormone. Iodine is not an integral component of any enzyme, but it is an integral component of thyroxine and triiodothyronine. Selenium and iodine are thus linked biochemically because both are involved in thyroid hormone production.

Selenium and iodine are also linked geographically, most notably in Asia. Severe deficiency of both iodine and selenium occurs in a region extending from northeastern China and adjacent regions of Siberia and Korea to southwestern China, including Tibet, although iodine deficiency occurs in a considerably larger area and affects many more people.^{1,2,3} Severe deficiency of both elements also occurs in Central Africa, in the Democratic Republic of the Congo. There, as in China, iodine deficiency is more widespread.⁴ Severe iodine deficiency occurs in other regions of Africa and in South America, but nowhere else is selenium deficiency as severe as in China and Central Africa. These are also the only regions in which clinical or biochemical abnormalities have been attributed to selenium deficiency.

What are the clinical consequences of selenium deficiency? Three disorders have been associated with it: Keshan disease, Kashin–Beck disease, and (when it occurs in combination with iodine deficiency) hypothyroid cretinism. Keshan disease is a cardiomyopathy affecting mostly young and middle-aged women.^{1,2} It is characterized by multifocal myocardial necrosis and fibrosis and leads to cardiogenic shock and congestive heart failure. The name derives from Keshan County in northeastern China, the site of a large outbreak of the disease in the 1930s, but people living in other regions of selenium deficiency in China also have been affected. Keshan disease can be prevented, though not treated, by selenium supplementation, and widespread supplementation and probably also more varied diets have led to its near-disappearance in China.^{1,2}

The second disorder associated with selenium deficiency is Kashin–Beck disease, named for two investigators who studied affected patients in Siberia in the 19th century. It is an osteoarthropathy of the hands and fingers, elbows, knees, and ankles in children and adolescents.^{1,2} It is characterized by necrosis of growth-plate and epiphyseal chondrocytes and proliferation of surrounding chondrocytes, and it leads to a hypertrophic osteoarthropathy and, in some subjects, to short stature. Kashin–Beck disease occurs in the same regions of China as Keshan disease, but it is more common and its prevention requires more selenium.⁵ The frequency of Kashin–Beck disease in China, like that of Keshan disease, is decreasing, probably because of changes in diet; this trend has made it difficult to document benefit from selenium supplementation alone.

The third disorder is hypothyroid cretinism. In some regions of Central Africa, iodine deficiency and selenium deficiency

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coexist,⁴ and deficiency of selenium may explain why those with cretinism also have hypothyroidism. Traditionally, cretinism has been divided into neurologic and hypothyroid cretinism.⁶ Neurologic cretinism is characterized by motor rigidity, a shuffling gait, deaf-mutism, and mental retardation, but not by hypothyroidism. It is a consequence of the effects on fetal neural development of iodine deficiency and hypothyroidism in the mother during early pregnancy. Hypothyroid cretinism is characterized by hypothyroidism, mental retardation, and growth retardation. It is a consequence of iodine deficiency and hypothyroidism in infancy. Few people with cretinism of either type have goiter, but both types of cretinism occur in regions in which goiter is endemic. This categorization of cretinism is overly simplistic; the clinical manifestations overlap in many regions where goiter is endemic,⁷ and there is no reason to believe that iodine deficiency would affect only mothers (and their fetuses) or only infants. Yet both types of cretinism can be prevented by iodine supplementation.

Still, Central Africa is one area in which virtually all people with cretinism are hypothyroid. The concomitant selenium deficiency, with a resulting deficiency of the two selenium-containing enzymes, could contribute to the hypothyroidism in two ways. A deficiency in glutathione peroxidase could result in oxidative damage to the thyroid by hydrogen peroxide, which is produced in increased amounts in the thyroid gland of iodine-deficient subjects as a result of stimulation by thyrotropin.⁸ A deficiency in iodothyronine deiodinase could result in decreased production of triiodothyronine in many tissues. Selenium deficiency may actually protect against neurologic cretinism by decreasing the conversion of thyroxine to triiodothyronine in the mother, so that more thyroxine is available for transfer to the fetus and conversion to triiodothyronine in the fetal brain.⁸

Given the facts that selenium deficiency and iodine deficiency occur in the same regions of China and that goiter can occur both in people with Keshan disease and in those with Kashin-Beck disease,³ might iodine deficiency exacerbate or even cause some of the disorders attributed to selenium deficiency? In this issue of the *Journal*, Moreno-Reyes et al. describe the results of a study of iodine and selenium metabolism in children and adolescents in 11 villages in Tibet in which many of the subjects had Kashin-Beck disease and 1 village in which none had the disease.⁹ Severe iodine and selenium deficiency was present in all the villages. Among the subjects with Kashin-Beck disease, the investigators found more severe iodine deficiency and more hypothyroidism (with some cretinism) than among the unaffected subjects from the same villages and those from the village in which there was no Kashin-Beck disease; the severity of selenium deficiency was similar in the three groups.

These findings suggest that Kashin-Beck disease results from the combination of selenium and iodine deficiency. The Kashin-Beck type of osteoarthropathy is not a feature of endemic goiter, hypothyroid cretinism, or sporadic hypothyroidism in children. The latter disorders are characterized by growth retardation, delayed skeletal maturation, and in severe cases, epiphyseal dysgenesis, but not by chondronecrosis. Kashin-Beck disease has not been described among selenium-deficient persons with hypothyroid cretinism in Central Africa (but selenium deficiency is somewhat less severe there than in China), nor has it been described in subjects in whom iodine sufficiency has been demonstrated.

How might combined iodine and selenium deficiency affect cartilage? One possibility is that growth-plate cartilage is not only especially dependent on locally produced triiodothyronine but also sensitive to oxidative damage. Thus, deficiency of iodothyronine deiodinase and glutathione peroxidase might result in a combination of local thyroid hormone deficiency and cellular injury that could cause chondronecrosis. The combined deficiency may affect other tissues as well, but if it does, the changes are less obvious than those of Kashin-Beck disease or of endemic cretinism. Alternatively, the combined-deficiency hypothesis could be all wrong, and the culprit could be some other nutritional deficiency, a contaminant of food, or an unknown environmental factor.

Iodine deficiency is a serious problem worldwide. Its clinical consequences — endemic goiter and cretinism — reflect not only the severity of iodine deficiency, but also the effects of constituents of food and of selenium deficiency on thyroid hormone biosynthesis and metabolism. Foods such as cassava and millet contain substances that can be converted to thiocyanate, which inhibits thyroid hormone biosynthesis and therefore magnifies the effect of iodine deficiency.¹⁰ Selenium deficiency can result in thyroid injury and decreased extrathyroidal triiodothyronine production. If Moreno-Reyes et al. are correct, Kashin-Beck disease is more a clinical consequence of iodine deficiency than one of selenium deficiency. If so, then iodine supplementation should

prevent not only endemic goiter and both hypothyroid and neurologic cretinism but also Kashin–Beck disease.

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