

THE ROLE OF SELENIUM DEFICIENCY IN DILATED CARDIOMYOPATHY IN SAUDI ARABIA

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Background: Selenium deficiency is implicated in the etiology of endemic juvenile dilated cardiomyopathy in China, and in sporadic cases in other countries. The aim of this study was to evaluate the role of selenium deficiency in the pathophysiology of dilated cardiomyopathy in the Saudi Arabian population.

Patients and Methods: Plasma and urine selenium concentrations from 72 Saudi patients with confirmed dilated cardiomyopathy were compared with corresponding values from 70 control subjects of the same national origin who had normal ventricular function.

Results: Plasma and urine selenium concentrations (mean±SD) were 1.34 ± 0.45 and 0.49 ± 0.37 $\mu\text{mol/L}$, respectively, for the patient group, and 1.32 ± 0.41 and 0.60 ± 0.41 $\mu\text{mol/L}$, respectively, for the control group. The differences in the values between the two groups were statistically insignificant.

Conclusion: In the Saudi population, dilated cardiomyopathy is not caused by selenium deficiency. *Ann Saudi Med 1999;19(1):20-22.*

Key Words: Selenium deficiency, dilated cardiomyopathy.

Dilated cardiomyopathy is a disease of unknown etiology characterized by impaired systolic function and increased volume of one or both ventricles. Selenium is an essential element of glutathione peroxidase, an enzyme which is involved in the removal of hydrogen peroxide produced during the lipid oxidation process in the cell.¹ Selenium deficiency has been implicated in the etiology of a form of dilated cardiomyopathy observed in Chinese patients, known as Keshan disease.² The purpose of this study was to determine whether selenium deficiency is the underlying etiologic factor in cases of dilated cardiomyopathy seen in the Saudi Arabian population.

Patients and Methods

The study population consisted of 72 Saudi patients admitted to our hospital over a three-year period, and diagnosed as having dilated cardiomyopathy with significant, global left ventricular systolic dysfunction (ejection fraction ≤ 0.40). The diagnosis was based on history, physical examination, electrocardiogram, chest radiograms, echocardiographic examination and radio-nuclide cineangiography, after exclusion of other etiologies

for congestive heart failure, such as congenital, rheumatic, hypertensive or ischemic heart disease, or pulmonary hypertension. In order to exclude latent coronary artery disease as the cause of left ventricular failure, coronary angiography was also performed in all patients older than 30 years.

The control group consisted of 70 Saudi patients who had been submitted to routine diagnostic cardiac catheterization for other reasons and found to have normal left ventricular systolic function (ejection fraction ≥ 0.60).

In both groups, 10 mL of urine, as well as plasma harvested from a blood specimen, were obtained simultaneously and immediately stored at -80°C until analysis. Selenium concentration in both plasma and urine was determined by atomic absorption spectrophotometry, using a model 975 spectrophotometer equipped with an electrothermal (graphite tube) atomizer (Model GTA-95) and autosampler (all from Varian Techtron Pty. Ltd., Mulgrave, Victoria, Australia). The instrument parameters were set according to the manufacturer's recommendations.³ All analyses were performed in at least four runs, and extreme caution was exercised to ensure that the processes of transfer and dilution were free of contamination. Previous analysis of quality control selenium samples according to the described procedure in our laboratory has confirmed the high linearity ($r > 0.999$) and precision ($\text{CV} < 7\%$) of this assay, with the selenium concentrations of the control samples falling within the acceptable range specified by the manufacturer.

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The study was approved by the Research and Ethics Committees of the Research Advisory Council of this hospital, and was conducted in accordance with the Helsinki Declaration on human experimentation. Written informed consent was obtained from all patients of both groups included in the study.

The data were analyzed using the Statgraphics statistical package (Statistical Graphics Co., Rockville, MD, USA). Comparison of values between the two groups was made using the Student's *t*-test for non-paired data. For categorical variables, the chi-squared test was used. Values are presented as mean \pm standard deviation. The level of statistical significance (two-tailed *P*) was set at 0.05.

Results

There was no difference in age between the patient group (40.3 \pm 15.9, range 13-81 years) and the control group (42.8 \pm 16.2, range 16-82 years). Similarly, there was no statistical difference in the representation of gender between the patient group (49 males, 23 females) and the control group (41 males, 29 females). The majority of patients with cardiomyopathy presented with symptoms of advanced congestive heart failure (New York Heart Association Class II, 14; Class III, 42; and Class IV, 16 patients).

Echocardiographic assessment of the patient group revealed severe dilatation of the left ventricle, with end-diastolic dimension of 70 \pm 9 mm and end-systolic dimension of 60 \pm 10 mm. Functional mitral regurgitation (mild in 35 and moderate in 23) was present in the majority of the patient groups. Significant left ventricular systolic dysfunction was documented in the patient group whose left ventricular ejection fraction by both echocardiography (0.23 \pm 0.07) and radionuclide angiography (0.24 \pm 0.19) was severely depressed. In addition, involvement of the right ventricle in this group was corroborated by a low right ventricular ejection fraction (0.25 \pm 0.09) measured by radionuclide angiography.

The plasma concentration of selenium in the patient group (1.34 \pm 0.45 μ mol/L) was not significantly different from that in the control group (1.32 \pm 0.41 μ mol/L). Similarly, there was no significant difference in urine selenium concentration between the two groups (patients, 0.49 \pm 0.37 μ mol/L; control, 0.60 \pm 0.41 μ mol/L; *P*>0.05).

Discussion

Selenium, an essential element, is a co-factor of the enzyme glutathione peroxidase, which is involved in the removal of hydrogen peroxide molecules produced during the lipid oxidation process in the cells. Because glutathione peroxidase is found in all mammalian cells,⁴ selenium may provide a defense against the buildup of lipid peroxidases

and free radicals that damage cell membranes and macromolecules, such as DNA.

Swine, sheep, cattle and monkeys may develop myocardial disease if selenium and vitamin E deficiencies co-exist. Van Fleet et al.⁵ produced cardiomyopathy in 38 weaning swine by feeding them a semi-synthetic diet deficient in selenium and vitamin E for 13-59 days. After development of the deficiency state, the animals were killed, and gross examination of their hearts revealed hydropericardium and pale streaks and patches of necrosis in the myocardium, especially in the left ventricle. Histopathological examination showed the lesions to be scattered throughout the heart, with the atria most severely affected.

A syndrome of sudden death in calves associated with acute myocardial degeneration in the presence of selenium deficiency was reported by Cawley and Bardley.⁶ These animals, up to two months of age, died suddenly during a period of excitement precipitated by feeding. Postmortem examination revealed patchy myocardial pallor, but no other lesions or evidence of infection. Histopathological studies disclosed the presence of hyperacute myocardial degeneration. Biochemical examinations confirmed selenium deficiency in affected calves. After the deficiency was corrected, no further cases were observed.

Sudden death in young camels caused by acute myocardial degeneration in the presence of selenium deficiency was noted in Prince Mohamed Bin Saud Al Kabir's farm in Tawdehea, located 200 km south of Riyadh (personal communication). Postmortem examination of the hearts of the affected animals, conducted in Germany, disclosed marked enlargement of the left ventricle with histopathologic evidence of myofibrillar degeneration and lysis, similar to that seen in swine with cardiomyopathy induced by selenium deficiency.

Dietary selenium deficiency associated with an endemic form of juvenile cardiomyopathy has been reported in China, and is called Keshan disease.^{2,7,8} In Western countries, a small number of cases of dilated cardiomyopathy complicating selenium deficiency have been reported mainly in patients receiving long-term parenteral nutrition,⁹⁻¹⁴ or in association with other disease states, such as the chronic uremic syndrome,¹⁵ human immunodeficiency virus infection,^{16,17} and autosomal recessive dystrophic epidermolysis bullosa.¹⁸ Selenium deficiency has also been documented in black African women with peripartum cardiomyopathy.¹⁹

The importance of identifying selenium deficiency as the underlying cause of dilated cardiomyopathy is underscored by the demonstrated ability of dietary selenium supplementation to prevent the development of the disease,⁸ and to occasionally reverse its deleterious effects on the myocardium.^{14,16} Thus, in a large, prospective, placebo-controlled study conducted in China,⁸ the incidence of Keshan disease in selenium-supplemented children fell from 2.2% in 1974 to 1% in 1975, while the

corresponding rates for the control group were significantly higher (13.5% and 9.5%, respectively). In 1976, sodium selenite supplements were given to both groups with further decline in the incidence of the disease to 0.32%. In 1977, no new cases of the disease were reported. It should be noted that the daily requirements of elemental selenium remains controversial. Thus, although dietary selenium intake of 40 µg/day is considered as adequate for prevention of Keshan disease, higher intake of 50-200 µg/day²⁰ or even 400-600 µg/day,²¹ have been recommended for treating active conditions.

Dietary selenium deficiency has also been reported to be associated with increased risk of coronary artery disease. Although a prospective epidemiological study in Finland provided evidence of an inverse relation between plasma selenium concentration and the risk of cardiovascular disease,²² convincing proof of such an association can only be obtained from large, controlled, prospective prevention trials.

In conclusion, our data indicate that selenium deficiency is not the underlying etiologic factor of dilated cardiomyopathy seen in the native population of Saudi Arabia.

References

1. Rotruck JT, Pope AI, Ganther HE, Hafeman DG, Swanson AB, Hockstra WG. Selenium biochemical role as a component of glutathione peroxidase. *Science* 1973;179:588-90.
2. Keshan Disease Research Group of the Chinese Academy of Medical Sciences. Epidemiological studies on the etiologic relationship of selenium and Keshan disease. *Chin Med J (Engl)* 1979;92:477-82.
3. McKenzie T. Analytical data for the GTA-95. In: Rothery E, editor. Analytical methods for graphite tube atomizer. Victoria, Australia: Vatan Techtron, 1982;25-48.
4. Burk RF. Selenium in man. In: Prasad A, editor. Trace elements in human health and disease. Vol II. Essential and toxic elements. New York: Academic Press, 1976:105-33.
5. Van Fleet JF, Ferrans VJ, Ruth GR. Ultrastructural alteration in nutritional cardiomyopathy of selenium-vitamin E deficient swine. *Fiber Lesions Lab Invest* 1977;37:188-200.
6. Cawley GD, Bardley R. Sudden death in calves associated with acute myocardial degeneration and selenium deficiency. *Vet Rec* 1978;103:239-40.
7. Li G, Wang F, Kang D, Li C. Keshan disease: an endemic cardiomyopathy in China. *Human Pathol* 1985;16:602-9.
8. Keshan Disease Research Group of the Chinese Academy of Medical Sciences. Observations on effect of sodium selenite in prevention of Keshan disease. *Chin Med J (Engl)* 1979;92:471-6.
9. Johnson RA, Baker SS, Fallon JT, et al. An occidental case of cardiomyopathy and selenium deficiency. *N Eng J Med* 1981;304:1210-2.
10. Quercia RA, Korn S, O'Neil D, et al. Selenium deficiency and fatal cardiomyopathy in a patient receiving long term home parenteral nutrition. *Clin Pharm* 1984;3:531-5.
11. Lockitch G, Taylor GP, Wong LT, et al. Cardiomyopathy associated with nonendemic selenium deficiency in a Caucasian adolescent. *Am J Clin Nutr* 1990;52:572-7.
12. Sando K, Hoki M, Nezu R, Takagi Y, Okada A. Platelet glutathione peroxidase activity in long-term total parenteral nutrition with and without selenium supplementation. *J Parenter Enteral Nutr* 1992;16:54-8.
13. Markus RW. Myopathy and cardiomyopathy associated with selenium deficiency: case report, literature review, and hypothesis. *Md Med J* 1993;42:669-74.
14. Levy JB, Jones HW, Gordon AC. Selenium deficiency, reversible cardiomyopathy and short-term intravenous feeding. *Postgrad Med J* 1994;70:235-6.
15. Bonomini M, Albertazzi A. Selenium in uremia. *Artif Organs* 1995;19:443-8.
16. Kavaneau-McHugh AL, Ruff A, Perlamn E, Hutton N, Modlin J, Rowe S. Selenium deficiency and cardiomyopathy in acquired immunodeficiency syndrome. *J Parenter Enteral Nutr* 1991;15:347-9.
17. Dworkin BM. Selenium deficiency in HIV infection and the acquired immunodeficiency syndrome (AIDS). *Chem Biol Interact* 1994;91:181-6.
18. Melville C, Atherton D, Burch M, Cohn A, Sullivan I. Fatal cardiomyopathy in dystrophic epidermolysis bullosa. *Br J Dermatol* 1996;135:603-6.
19. Cenac A, Simonoff M, Moretto P, Djibo A. A low plasma selenium is a risk factor for peripartum cardiomyopathy. A comparative study in Sahelian Africa. *Int J Cardiol* 1992;36:57-9.
20. Badmaev V, Majeed M, Passwater RA. Selenium: a quest for better understanding. *Alter Ther Health Med* 1996;2:59-62.
21. Yang GQ, Xia YM. Studies on human dietary requirements and safe range of dietary intakes of selenium in China and their application in the prevention of related endemic diseases. *Biomed Environ Sci* 1995;8:187-201.
22. Salonen JT, Alfthan G, Huttunen JK, et al. Association between cardiovascular death and myocardial infarction and serum selenium in a matched pair longitudinal study. *Lancet* 1982;2:175-9.