Vitamin D Deficiency Rickets and Osteomalacia in Israel

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The vitamin D nutritional status is determined more by previous exposure of the skin to sunlight than by dietary intake of vitamin D [1]. As such, humans do not have additional dietary requirements for vitamin D when sufficient sunlight is available. The effectiveness of sunlight, however, depends upon several factors, such as the season of the year, latitude, pollution, skin pigmentation (which affects the synthesis of vitamin D) and, lastly, exposure of the skin, which is restricted by certain populations' religious and traditional strict dress codes. Under these conditions, vitamin D deficiency may be found in certain populations even in sunny areas, and vitamin D supplementation becomes essential to prevent rickets and osteomalacia.

Vitamin D deficiency rickets was historically considered to be rare in sunny Israel. This contention was refuted by studies that have emerged over the past two decades, demonstrating that the prevalence of vitamin D deficiency is unexpectedly high in Israel among certain populations. Up to 35% of the population of elderly people in Israel was found to be vitamin D deficient or insufficient [2,3]. Notably, up to 80% of elderly patients with hip fractures had vitamin D deficiency [4]. Such deficiency may well result from several factors: elderly people spend most of their time indoors and are much less exposed to sunlight than are young people. There is also evidence that aging decreases the capacity of human skin to produce vitamin D [5] and that the elderly suffer from intestinal malabsorption of fat-soluble vitamin D [6].

Vitamin D deficiency rickets and osteomalacia has also been reported in Bedouin women of child-bearing age living in the Negev Desert, as well as in their newborn infants [7,8]. This has been ascribed to sunlight deprivation due to the traditional dress code that requires them to cover the body and face, their diet containing foods rich in phytate – which appears to chelate calcium and vitamin D – and a diet poor in vitamin D and calcium-rich foods.

Another group of vitamin D-deficient subjects in Israel was found among young ultra-Orthodox Jewish women [9]. As high as 40% of women after delivery of their infants in an ultra-Orthodox Jewish maternity hospital were found to have vitamin D deficiency or insufficiency compared to only 16% at another hospital in the same area [10]. Since the ultra-Orthodox and the non-Orthodox populations of this study live in the same metropolitan area, and since dietary behavior patterns contribute little to the nutritional status of vitamin D [1], the authors of this study attribute the higher prevalence of vitamin D deficiency or insufficiency among these women to their modest religious dress code, which decreases exposure of the skin to sunlight.

In the present issue of *IMAJ*, Ginat-Israeli et al. [11] describe a 2 year old boy and a 7 month old female inflant with nutritional rickets, both of whom were born in Ethiopia and immigrated with their families to Israel. The boy was the sixth child born to his mother and the female baby was her mother's tenth child. The boy was breast-fed for 13 months and thereafter subsisted on only a peanut-based snack; the girl was fed only diluted cows' milk. Their diets were therefore poor in both vitamin D and calcium. Furthermore, these children did not receive supplements of vitamin D as is customarily provided for infants during their first year of life in Israel.

Mothers' milk contains negligible amounts of vitamin D [12]. The principle quantity of vitamin D required by the infant during the first months of life had been furnished by the mother through the placenta. Thus, when pregnant women are deficient in vitamin D, their offspring are liable to be born deficient in vitamin D and to develop rickets. Although concentrations of 25-hydroxyvitamin D were not measured in these women, it may be assumed that they were deficient in vitamin D during their pregnancy and this may well be the major cause of vitamin D deficiency in their babies. Support for this notion comes from Fogelman et al. [13], who described vitamin D deficiency and hypocalcemia during pregnancy and lactation among Ethiopian women immigrants to Israel. The reasons for hypocalcemia and vitamin D deficiency among these Ethiopian women were apparently their dark skin, a factor that reduces the penetration of light required for the production of vitamin D, and their impaired nutrition, which was characterized mainly by the low intake of calcium (about one-fifth of the recommended daily amount).

In addition to vitamin D deficiency, dietary calcium deficiency is a major factor contributing to the development of rickets in Africa [14]. The typical African diet is poor in calcium and rich in grains, which contain inhibitors of calcium absorption such as phytates, oxalate and phosphate. Nutritional rickets is common in Ethiopia and in other African countries and may lead to significant morbidity, such as pneumonia (rachitic pneumopathy) [15], and increased mortality rate. Finally, vitamin D deficiency in these Ethiopian women (as well as in the Bedouin and ultra-Orthodox Jewish women) may stem from the high pregnancy rate that may cause further depletion of vitamin D stores in women already at risk.

The high prevalence of vitamin D deficiency among the above-mentioned populations at risk raises the question of whether vitamin D supplements should be given to these groups on a routine basis even in a sunny country such as Israel.

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Capsule

Nurturing a T cell brigade

The treatment of cancer by introducing tumor-fighting T cells into patients has gained some success for certain types of malignancy. But it has been difficult to produce enough of such T cells and to maintain their *in vitro* reactivity within the patient. In an attempt to overcome these shortcomings, Brentjens et al. (*Nature Med* 2003;9:279) transduced fresh human T cells with a chimeric antigen receptor (CAR) whose external domain recognizes CD19: a surface protein that is expressed in many B cell malignancies. In culture, these CAR+ T cells efficiently killed CD19-bearing tumor cells, retaining this activity even after extensive expansion. Infusing these expanded T cells into immunodeficient beige mice resulted in the eradication of a previously engrafted Burkitt lymphoma. Successful *ex vivo* activation, expansion, and *in vivo* survival of transduced T cells required interleukin-15 and the co-stimulatory surface molecule CD80. Finally, T cells taken from patients with chronic lymphoid leukemia, after modification with the same CAR, were capable of killing autologous tumor cells in culture, suggesting that translation of this work to the clinic might be feasible.

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Capsule

Transplantation and tumors

Improvements in immunosuppressive drugs and organ storage technology have enhanced the success rate of organ transplantation, but these surgeries still place recipients at elevated risk of certain malignancies, including Kaposi sarcoma (KS). Because KS is caused by human herpesvirus type 8 (HHV-8), development of this tumor in the transplant setting has been attributed to activation of latent virus in the host or transmission of free virus from the donor organ. In a small study of kidney transplant recipients, Barozzi et al. present highly suggestive evidence that KS can also arise through transmission and engraftment of donor tumor cells or their progenitors. Presumably such cells would normally be eliminated by immune surveillance, but the immunosuppressed state of the organ recipients may allow their uncontrolled proliferation. This finding not only underscores the importance of screening donor organs for HHV-8 but is likely also to renew interest in earlier speculations that sexual transmission of KS in AIDS patients may sometimes occur through direct transfer of shed tumor cells.

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