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Carotenoids and healthy aging: the fascination continues

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Red, orange, and yellow pigments, known as carotenoids, are widespread and abundant in nearly all organisms in the plant and animal kingdoms. Animals, with rare exception, are unable to synthesize carotenoids and obtain them by consuming plants. There are >1000 carotenoids in nature, of which >30 have been described in human milk and serum. From the 1830s through 1930s, major carotenoids in the human diet were identified in plants: carotene from carrot, lutein from plant leaves, lycopene from tomato, zeaxanthin from corn, and cryptoxanthin from papaya. During the same period, carotenoids were isolated from animal biofluids and tissues such as plasma, human milk, placenta, corpus luteum, adipose, and macula luteum. The chemical structures of many carotenoids were elucidated by Paul Karrer (1889–1971) (1). Conjugated double bonds allow carotenoids to serve as potent antioxidants by quenching singlet oxygen and reactive oxygen species. Carotenoids are also involved in gap junctional communication, growth factor signaling, cell growth and differentiation, and immunoregulation (2).

The prevention of sarcopenia (i.e., age-related loss of muscle mass and function) is a goal of healthy aging, because sarcopenia is associated with falls, loss of independence, hospitalization, and mortality. In this issue of the *American Journal of Clinical Nutrition*, Sahni et al. (3) present results from ∼2400 participants in the Framingham Offspring Study (FHS) that expand observations on the relation of carotenoids and vitamin E with declines in physical function. Higher dietary intake of carotenoids was associated with lower decline of grip strength and increased gait speed, 2 indicators of sarcopenia. They could not replicate these findings in ∼3800 participants from the Cardiovascular Health Study (CHS). However, there were large age differences between FHS (33–88 y) and CHS (≥65 y). Changes in physical function over time may differ in older compared with younger individuals. It would be interesting to know if the association between carotenoid intake and physical function were to remain significant in FHS participants aged ≥65 y. The dietary assessment in FHS was conducted using a detailed FFQ, whereas CHS used a brief FFQ that did not provide intake estimates of individual carotenoids and vitamin E.

There is recent evidence that carotenoids protect skeletal muscle. Biological mechanisms implicated in sarcopenia include altered fatty acid metabolism, dysregulation of mitochondrial ATP production, increased production of reactive oxygen species, and telomere shortening—all of which have been related with carotenoids. Dietary lycopene supplementation in mice modulated the expression of skeletal muscle fiber types and upregulated genes involved in fatty acid synthesis (4). In mouse myoblasts, lycopene stimulated proliferation and enhanced mitochondrial ATP production (4). Astaxanthin, a pinkish-orange carotenoid derived from marine animals, stimulated mitochondrial biogenesis in insulin-resistant skeletal muscle (5), reduced skeletal muscle damage after ischemia-reperfusion injury (6), attenuated exercise-induced damage in mouse skeletal muscle (7), and protected against oxidative stress in rat skeletal muscle after vigorous exercise (8). Astaxanthin mitigates oxidative stress and protects against mitochondrial dysfunction (9). Telomere shortening was found in patients with sarcopenia (10), and low circulating carotenoids were associated with telomere shortening (11). Future work is needed to gain insight into how carotenoids may relate to other hallmarks of aging (12) such as cellular senescence, epigenetic alterations, genomic instability, and dysregulated nutrient sensing in skeletal muscle.

The authors concluded that their findings need to be replicated before conducting a clinical trial evaluating the effect of dietary antioxidants/carotenoids on muscle strength and function. A large number of studies in diverse populations and systematic reviews show that adherence to healthy diets that are rich in carotenoids or high consumption of fruit and vegetables has a protective relation against reduced muscle strength, poor physical performance, and frailty (13–16). In addition, numerous studies, including many by our group, show that higher circulating carotenoids, considered the strongest biomarker of fruit and vegetable intake, independently predict lower risk of decline in muscle strength and walking speed and lower risk of disability and mortality (17–19).

The question is: do we really need a clinical trial? It would be costly and long in length given the nature of the outcome of interest (i.e., age-related change in muscle strength and gait speed). The protective effects of a diet rich in carotenoids on muscle strength and function may require a long exposure of many years to decades, a period that is not realistic for a clinical trial. Using a single dietary component approach (e.g., carotenoids) may not capture the complexity of the effect of nutrients and bioactive components within a whole diet and, in turn, their relation with muscle health and function. Furthermore,

Supported by NIH R01 AG057723 and R21 HL153471.

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First published online January 20, 2021; doi: https://doi.org/10.1093/ajcn/nqaa364.

a clinical trial is unlikely to change dietary recommendations for older adults, since a high intake of carotenoid-rich fruit and vegetables is already advocated by such groups as the American Heart Association, the American College of Cardiology, the American Cancer Society, and the World Health Organization for the prevention of cancer, heart disease, and other adverse aging outcomes.

An ideal diet promotes optimal health and longevity. For example, 2 traditional diets, the Mediterranean diet and Japanese washoku diet, are rich in dietary carotenoids and associated with healthy aging. Washoku is based on the principle that each meal should contain 5 colors: red, yellow, green, black, and white (20), with the first 3 colors generally reflecting foods that are rich in carotenoids. In addition, there is a reference diet recently proposed by the EAT-Lancet Commission (21). The "planetary health diet" was based on the best nutritional evidence available for optimizing health. The planetary health diet is rich in carotenoids, as the diet emphasizes a high intake of fruit, dark green vegetables, and red and orange vegetables (21). The health benefits of fruit and vegetables may be attributed to the synergy or interactions of the nutrients and many bioactive compounds, including carotenoids. Humans are living longer than ever, but longer lives are accompanied by a greater burden of late-life disease. An immense amount of data links carotenoid intake to the prevention of aging-related conditions and diseases. Adherence to high intakes of fruit and vegetables remains a substantial challenge and may ultimately affect the health of an aging population worldwide.

The authors' contributions were as follows—BB and RDS: contributed substantially to the review of the paper and literature, conceptualization, and writing the editorial.

Author disclosures: The authors report no conflicts of interest.

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