to the editor: In a recent paper by Higashida et al. (5), the authors report that very large doses of antioxidant vitamins do not prevent the exercise-induced adaptive responses of muscle mitochondria, GLUT4, and insulin action to exercise. As clearly stated in the paper, their data disagree with those reported by three independent research groups from Germany (14), Australia (17), and Spain (4).

Using a significantly different experimental protocol regarding exercise training intensity and duration, antioxidant supplementation (doses and types of antioxidants), and molecular parameters analyzed (mRNA vs. protein levels), Higashida et al. compared their data with ours and came to exactly the opposite conclusions, i.e., that antioxidant vitamin supplementation does not have an inhibitory effect on the adaptive responses of skeletal muscle to exercise. Regarding our study published in the American Journal of Clinical Nutrition (4), we found a very significant increase (~186%) in endurance time in rats after training (6 wk), which was dramatically blunted when the animals were supplemented with vitamin C (~26% increment). Endurance capacity is directly related to mitochondrial content, which is why we decided to determine the mitochondrial biogenesis cascade in skeletal muscle in our animals, and we found that it was significantly hampered. Although we found a dramatic effect of vitamin C on endurance time in animals, we did not find the same effect on \( \dot{V}O_2 \) \(_{\text{max}} \) in either the animal study or the human study. This is clearly stated and discussed in the introduction, results, and discussion sections of our paper. However, Higashida et al. did not run any performance tests in their study; moreover, they misquoted a few times the results obtained in our human study.

Training studies, including the data published by Higashida et al., conducted to determine whether antioxidant vitamins improve exercise performance, have generally shown that supplementation is useless (3, 7, 13, 18, 20). However, recent evidence shows that they can be worse than useless. Several studies suggest that antioxidants may have detrimental effects on performance. As early as 1971, it was shown that vitamin E supplementation (400 IU/day for 6 wk) caused unfavorable effects on endurance performance in swimmers (15). The authors concluded: “There is no evidence here to suggest that vitamin E has any beneficial effect on endurance performance. Indeed the evidence, if anything, suggests that the vitamin has an unfavourable effect.” Malm and coworkers (10, 11) showed, in two consecutive studies, the...
deleterious effects of ubiquinone-10 supplementation on the performance of humans after a high-intensity training program. In 2002, it was shown that supplementation of racing greyhounds with 1 g vitamin C/day for 4 wk significantly slowed their speed (12). Moreover, in a human study, the negative effects of ascorbic acid supplementation on the adaptive responses of endogenous antioxidant enzymes and stress proteins were demonstrated (8). Furthermore, it has been shown that supplementation with ascorbic acid to prevent delayed-onset muscle soreness after exercise does not preserve muscle function but hinders the recovery process, thereby being detrimental to future performance (2). Finally, in our animal study, we found that vitamin C supplementation decreases training efficiency because it prevents exercise-induced mitochondrial biogenesis (4). Similar conclusions have been recently achieved by a US-based research group (6). The authors found that inhibition of a free radical-generating enzyme (xanthine oxidase) by allopurinol severely attenuates exercise activation of the mitochondrial biogenesis pathway in skeletal muscle. Thus, in our opinion and contrary to the considerations of Higashida et al., there is growing evidence of the negative effects of antioxidant supplementation in exercise performance in both animal and human studies.

The evidence on the detrimental effects of antioxidant supplementation when given to patients and healthy people (non athletes) is, if possible, more robust. In 2007, Bjerlakovic et al. looked at data from sixty-seven studies on antioxidant supplements and they concluded that beta carotene, vitamin A, and vitamin E supplementation seemed to increase the risk of death (1). This data confirmed previous reports showing that long-term vitamin E supplementation may increase the risk for heart failure in patients with vascular disease or diabetes mellitus (9). When a 6-wk aerobic exercise training program was applied in patients with hypertension, supplementation of antioxidants (vitamins C and E and α-lipoic acid) led to an enhancement of blood pressure and an inhibition of exercise-induced flow-mediated vasodilatation (19). Finally, one of us (M. Ristow) showed that antioxidant supplementation with vitamins C and E prevents the induction of molecular regulators of insulin sensitivity and endogenous antioxidant defense by physical exercise (14).

A significant number of both healthy and sick individuals are taking antioxidant supplements in the belief that these will improve their health and prevent or ameliorate diseases (1). Moreover, a large proportion of athletes, including elite athletes, take vitamin supplements, often large doses, seeking beneficial effects on performance (16). The complete lack of any positive effect of antioxidant supplementation on physiological and biochemical outcomes consistently found in human and animal studies raises questions about the validity of using oral antioxidant supplementation in both health and disease.

The vast majority of experimental evidence clearly advises against this supplementation. Thus, we unreservedly confirm the conclusions
derived from our previous research (4, 14) and disagree with Higashida et al. In our opinion, antioxidant supplements are, at the least, useless.