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EDITORIAL

Energy metabolism and syncope

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The autonomic nervous system is an essential component in the brain regulation of virtually every function of the body. This system is constantly working to maintain equilibrium and health in a manner independent of our control. Therefore, it is no surprise that dysregulation of the autonomic nervous system is associated with various disorders including neurally mediated syncope, a condition that occurs when orthostatic tolerance is impaired due to the inability of the autonomic nervous system to appropriately regulate postural tone, which results in low blood pressure and heart rate leading to loss of consciousness dues to the reduction in blood flow to the brain [12, 14]. This can be triggered by different situations and illnesses but is particularly prevalent in astronauts after return from microgravity [3]. The current strategies used to manage this orthostatic intolerance and syncope have limited efficacy highlighting the need for the development of new approaches. In this issue of the *journal*, De Gioannis et al. tested whether increasing caloric intake can be used as a novel strategy to prevent syncope [6].

Consistent with the well-known cross talk between metabolic and autonomic functions body weight has been suggested as a major determinant of orthostatic response and susceptibility to syncope. This is based on the observation that obese subjects display enhanced orthostatic tolerance whereas individuals with lower-body mass index tend to have higher incidence of orthostatic intolerance and syncope [4]. This was further supported by studies showing that subjects undergoing caloric restriction display a reduction in orthostatic intolerance and syncope [7]. The decrease in caloric intake was suggested as a potential explanation for the high prevalence of orthostatic intolerance in astronauts given that they consume less calories during spaceflight [15].

Based on these findings, De Gioannis et al. [6] hypothesized that increasing caloric intake may improve orthostatic tolerance. To test this hypothesis, the authors performed a well-controlled, double-blind, randomized, cross-over trial where healthy individuals were assigned to either a normocaloric diet (used as control) or a diet with high fat content resulting in excess of ~ 550 caloric intake. Each individual involved in the study underwent both diets for 4 days with a washout period of at least 23 days. Orthostatic intolerance was examined at the end of each dietary intervention using a combination of a tilt table testing and application of lower-body negative pressure, a standard protocol to diagnose orthostatic intolerance and syncope [9]. The authors measured hemodynamic parameters in supine position, then at 60° angle of tilt followed by gradual application of lower-body negative pressure, a maneuver that redistribute blood from upper to lower-body compartments causing central hypovolemia. The time it took each subject to exhibit signs of presyncope was considered as primary endpoint. The hemodynamic response and baroreflex sensitivity before and during orthostatic testing were also compared between the two dietary interventions.

De Gioannis et al. [6] found that overnutrition for 4 days did not cause significant change in blood pressure, heart rate and heart rate variability as well as baroreflex sensitivity in the supine or in the upright position. This is expected as

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such short term caloric excess is unlikely to cause significant weight gain or significantly alter metabolic functions. The hemodynamic and baroreflex sensitivity parameters were also comparable between the two dietary interventions in the initial phase (first 5 min of tilt) as well as during the last phase of the orthostatic test. Importantly, the authors found no difference in the time to presyncope between the two groups. Indeed, it took a near identical time (23.1 and 23.3 min, respectively) for individuals in control group and those on calorie-rich diet to exhibit symptoms of presyncope. These symptoms were defined as decreased brachial systolic blood pressure below 80 mmHg, concurrent decrease in finger blood pressure and heart rate, occurrence of syncope or when the participant either report signs of presyncopal or request to stop the test. Together, these findings demonstrate that in contrast to the authors hypothesis a calorie-rich diet does not appear to be an effective strategy to prevent syncope.

As discussed by the authors, these findings in healthy individuals may not necessarily translate into patients who are prone to syncope. It will be particularly interesting to examine the effectiveness of calorie-rich diet in the management of syncope linked to weight loss or caloric deficit. However, such intervention may need to be implemented for several weeks or months to be able to detect any effect. This will likely lead to weight gain and other metabolic effects that may confound the results. An alternative strategy is to use ingredients other than fat such as carbohydrate as a source of excess calories. It should be noted, however, that ingestion of a high glucose solution was found to decrease the latency to presyncope relative to water alone in healthy subjects [11]. Moreover, excess carbohydrate intake appears to worsen orthostatic tachycardia in patients with orthostatic intolerance and cause syncope in orthostatic hypotensive patients [13]. The mechanism underlying these detrimental effects of carbohydrate in syncope is not clear but could be related to the ability of glucose to cause sympathetic nerve activation [16].

Supplementation with specific nutrients that promote autonomic balance impacting positively cardiovascular function has been suggested as a potential approach for the management of syncope. For instance, increasing salt intake was shown to enhance orthostatic tolerance and reduce syncope or presyncope recurrence rate by increasing plasma volume and improving cerebral autoregulation and sympathetic control of the vasculature [5, 18]. This has led various organizations to recommend salt loading, when not contraindicated, along with increased water intake as a strategy to manage patients with syncope [8]. Deficiency in other nutrients that may influence autonomic function has also been identified as a potential contributor to syncope symptoms. Several studies have shown an association between low vitamin D levels and syncope in a subset of patients [17, 19]. This points to the interesting possibility that vitamin D supplementation may be a useful approach to improve orthostatic response and reduce syncope rate, but this remain to be determined.

Thus, available evidence indicates that deficit in certain nutrients may be the main driver and underlying cause of the prevalence of syncope in conditions such as weight loss induced by caloric restriction or other means. In support of such idea in the observation that orthostatic intolerance and syncope are common in patients undergoing bariatric surgery [1], a condition that is known to cause nutrient deficiency including vitamin D [2, 10]. This case scenario would explain the lack of effect of increasing calories on syncope symptoms reported by De Gioannis et al. [6].

Clearly, there are many unanswered questions and a long road ahead to understand the mechanisms underlying syncope and the link between this disorder and metabolic status. This will require considerably more work, but this is necessary to identify strategies that can be used to effectively manage syncope, a serious health problem. The work of De Gioannis et al. makes an important step in this direction by demonstrating that caloric overload for a limited time is not an effective approach to prevent syncope symptoms.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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