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Letter to the Editor / Editöre Mektup

SGLT-2 inhibitors should be reconsidered by WADA due to their potential performance-enhancing effects

Potansiyel performans artırıcı etkileri göz önüne alındığında, SGLT-2 inhibitörlerinin WADA tarafından yeniden değerlendirilmesi gerekir

Şahhan Kılıç, Süha Asal

Ministry Of Health Çorlu State Hospital, Cardiology, Tekirdağ, Turkey

In recent years, as athletic performance appears to have approached its physiological limits, elite athletes have increasingly sought ways to optimize their competitive edge. Among these strategies, the misuse of pharmacological agents has become a significant ethical and medical concern. To ensure fair competition and athlete safety, the World Anti-Doping Agency (WADA) publishes an annually updated Prohibited List. Diuretics are included not only because of their ability to mask the presence of other prohibited substances, but also due to their capacity to induce rapid weight loss, both of which undermine the spirit of sport and create unfair advantages.

Despite exhibiting similar osmotic diuretic properties, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, such as dapagliflozin, are not currently listed among prohibited substances. Originally developed for the treatment of type 2 diabetes, SGLT-2 inhibitors have gained widespread use in heart failure and cardiometabolic disorders. These agents promote glycosuria and natriuresis, leading to fluid loss, reduced body weight, and lower plasma volume, features that may provide a competitive edge in endurance or weight-class-based sports.

Our recent experimental study, which investigated the effects of dapagliflozin and sacubitril/valsartan on exercise performance in rats, revealed that dapagliflozin significantly enhanced swimming endurance and motor coordination compared to controls (1). Notably, a statistically significant improvement in performance emerged after the ninth swimming session ($P < 0.001$), accompanied by enhanced outcomes in rotarod tests. Echocardiographic evaluations further supported improved cardiac function in the treatment groups. These findings indicate that dapagliflozin may act as a true performance enhancer, beyond its therapeutic role.

The potential ergogenic effects of SGLT-2 inhibitors can be explained through multiple physiological mechanisms. These include increased hematocrit and erythropoietin levels (improving oxygen delivery), enhanced mitochondrial fatty acid oxidation, stimulation of ketone body production, and a shift toward insulin-independent energy metabolism. These adaptations contribute to more efficient energy utilization in both cardiac and skeletal muscle. Furthermore, a meta-analysis has demonstrated that SGLT-2 inhibitors significantly improve cardiorespiratory fitness, which may further enhance endurance performance (2). In addition, sympathetic nervous system inhibition may result in reduced heart rate and blood pressure, further optimizing cardiovascular performance under physical stress (3,4).

WADA's rationale for banning diuretics is not limited to their masking potential; they are also prohibited due to their ability to create unjust advantages and their contradiction of the core values of fair play and integrity in sport. From this perspective, SGLT-2 inhibitors share similar performance-related properties and warrant the same scrutiny.

Given the easy accessibility of SGLT-2 inhibitors and their expanding use even in non-diabetic individuals, the risk of misuse among athletes cannot be overlooked. Notably, the anti-anginal agent trimetazidine with less robust performance-enhancing evidence, was added to the WADA Prohibited List in 2014 for similar reasons (5). In contrast, dapagliflozin's effects have now been demonstrated experimentally with clear and measurable performance

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Correspondence / Yazışma: Şahhan Kılıç · T.C. Sağlık Bakanlığı Çorlu Devlet Hastanesi, Kardiyoloji Kliniği, Tekirdağ, Türkiye · drsahhankilic@gmail.com

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improvements. This calls for a reassessment of the regulatory status of SGLT-2 inhibitors.

In conclusion, we propose that SGLT-2 inhibitors be re-evaluated by WADA for possible inclusion in the Prohibited List, particularly considering their diuretic effect and potential for enhancing physical performance. Further independent investigations and expert consensus will be instrumental in guiding this regulatory decision. However, the current scientific evidence strongly supports the need for vigilance and action in this regard.

Conflict of Interest / Çıkar Çatışması

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