Research Paper

The Effect of the Acute Use of Different Doses of Glutamine Supplementation on Serum Testosterone and Cortisol Levels Following Exhaustive Exercise in Young Men

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ABSTRACT

Background: Anabolism has a major contribution in increasing proteolysis and muscle mass of athletes. This study was done to investigate the impact of the acute use of different doses of glutamine supplementation following exhaustive physical activity on cortisol and testosterone levels in young male athletes.

Methods: Following a semi-experimental design, 24 male athletes with a mean age of 22.35±1.79 years were randomly selected and divided into two intervention groups (glutamine; 0.1 and 0.6 gr/kg body weight (BW) and a placebo group (10 g of dextrin dissolved in 500 mL water), each with eight subjects. Serum levels of cortisol and testosterone were measured immediately, 90 minutes, and 24 hours following the test. Data analysis was done using paired t-test and repeated measures analysis of variance at $P<0.05$.

Results: Bruce protocol significantly increased cortisol levels immediately after physical activity ($P<0.05$). Cortisol levels significantly decreased in subjects receiving glutamine at 0.6 g/kg Bw ($P=0.03$) and 0.1 g/kg BW ($P=0.02$) 90 minutes and 24 hours following the protocol. Meanwhile, testosterone levels only increased in cases who received glutamine at 0.6 g/kg BW 24 hours following the protocol ($P=0.02$).

Conclusion: According to the results of this study, taking a glutamine supplement at a dose of 0.6 g/kg body weight after exhausting activities is probably effective in maintaining an anabolic profile.

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Introduction

The primary goals of coaches and athletes are optimal athletic performance and reaching peak performance. Increasing muscle strength, rapid recovery, and maintaining the anabolism profile are critical to achieving this goal. On the other hand, it is well-established that intense exercise is associated with an increased likelihood of infectious diseases and respiratory problems [1]. Muscle fatigue and weakness are common during intense training. Exercise training significantly affects the endocrine system and hormone secretion, depending on the intensity, duration, type, and exercise method [2]. Biologically, managing known hormonal responses to exercise activities is essential to endure the pressure of sports activities [3]. Physical preparedness plays a significant role in responding to stress [4]. Some catabolic hormones (e.g. cortisol) increase during intense, short-term physical exercise. In other words, the body secretes cortisol in response to stressful events, indicating increased catabolism and stress. Enhanced cortisol levels increase protein metabolism and gluconeogenesis in the liver and kidney. Alternation in these hormones affects the body's immune system [4]. It has been shown that stress hormones have a significant disruptive effect on the immune system and inflammation. Disrupted cortisol secretion patterns affect day-to-night cortisol levels, leading to more cortisol secretion [5].

Testosterone is a critical steroid-based anabolic hormone with several biological effects in males and females [5]. The impact of physical exercise on testosterone response has been well-established in males. Testosterone affects protein anabolism, increasing primary metabolism by 5% to 10%. However, the effect of physical exercise on cortisol and testosterone levels is still unclear [5]. Prior studies have indicated that resistance training boosts testosterone levels [6]. On the other hand, some studies have reported that testosterone levels did not decrease after exhaustive training or change statistically significant [5, 7]. Therefore, the measurement of testosterone and cortisol is recommended as an essential hormonal criterion to determine physiological pressure post-training [5]. Decreased testosterone levels indicate increased catabolic trends. A more than 30% reduction suggests excessive exercise, meaning poor recovery post-training [4, 8]. Testosterone plays an essential role in fatigue during exercise. Generally, exhaustive exercises can increase testosterone release, leading to fatigue. Decreased plasma glutamine levels have been reported in response to different stress situations, including constant exercise, trauma, and hunger. Irregular exercise patterns and intensive excursive training exacerbate this process. Stressful events are associated with increased circulation of cortisol, leading to gluconeogenesis [9].

Glutamine, initially a nonessential amino acid, can become an essential amino acid synthesized in skeletal muscles during illness. Most metabolic organs, such as the liver, intestines, and skeletal muscles, control glutamine secretion and its blood circulation [10]. However, muscle activity can alter glutamine availability, which feeds immune cell function. Therefore, low plasma glutamine levels caused by intense exercise are associated with impaired immune function in athletes [5, 8, 9]. Changes in metabolic factors during exercise, such as plasma glutamine, may alter some hormones and neurotransmitters, like cortisol and testosterone. Considering the anti-catabolic role of glutamine [5], its supplementation may affect the levels of cortisol and testosterone [5, 11-13]. Glutamine stands out as one of the most marketed dietary supplements for athletes.

The daily intake of glutamine from dietary protein ranges from 3 to 6 g/d. Glutamine is the most abundant amino acid in plasma and muscles, accounting for 60% of all free amino acids in skeleton muscles and 20% in plasma. It is the building block for synthesizing amino acids, proteins, nucleotides, and several biological molecules [1]. Other significant functions of glutamine are increased growth hormone secretion, intensifying protein synthesis, and strong anti-catabolic properties [14]. Also, its role in increasing glycogen synthesis and decreasing ammonia accumulation contributes to its anti-fatigue function [15].

Maintaining positive protein balance, fluid balance, anti-catabolic effects, and anabolic properties of glutamine supplementation may improve athletic performance (i.e. strength, vertical jump performance, or overall muscle strength) by increasing muscle mass [11]. Recently, researchers have paid attention to the contribution of glutamine in suppressing the immune system. This research shows that declined glutamine levels are associated with the suppression of the immune system after intense exercise and those suffering from excessive exercise syndrome [15]. However, no direct evidence supports the association between decreased levels of glutamine and impaired immune function following exercise or excessive exercise syndrome [16]. A few studies have reported that glutamine increases the number of lymphocytes and circulating macrophages. In addition, an association between plasma glutamine levels and viral infection resistance has been identified in non-athletes [17, 18].

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Nevertheless, the evidence regarding the effect of glutamine on increasing exercise performance is still inconclusive. One study indicates that supplementation with glutamine (0.1 g/kg BW) after exhaustive exercise had no significant impact on cortisol reduction [16]. Another study shows that high cortisol levels are associated with decreased glutamine in football players [17]. Córdova-Martinez et al. (2021) reported that glutamine supplementation (0.3 g/kg BW) after severe activity had no significant effect on cortisol and testosterone levels in young basketball players [5]. The observed results can be attributed to differences in treatment protocols, encompassing severity, duration, type, and glutamine dose. Studies employing ergometers or treadmill report that exercise mode, muscle type, and glutamine dose may affect hormonal responses [3-5, 9].

As cortisol is a well-accepted biomarker of exercise-induced physiological stress, investigating the association between cortisol response and testosterone levels would hold valuable insights. Despite various studies on the association between physical exercise and cortisol and testosterone levels, limited evidence regarding their response pattern to glutamine is available. In addition, while these biochemical factors have been studied as biomarkers of exercise-related physiological stress, each has a unique response to physical exercise, depending on its origin. Also, most studies have investigated the effect of a single dose of glutamine and used a sole examination protocol assessing cortisol and testosterone levels. Evidence suggests that glutamine administration is associated with its increased plasma concentrations within a few hours, depending on the received dose. Therefore, this study intended to investigate the effect of different doses of glutamine administration on serum cortisol and testosterone levels following exhaustive physical activity in young males.

Materials and Methods

Employing a quasi-experimental design, the study participants were allocated into three groups (one placebo and two interventions). Repeated measures were used to collect data. The current applied research followed a double-blinded framework.

The study population included male football players in Qazvin Province, Iran, with at least 3 years of playing at professional and semi-professional levels. Before entering the study, all participants provided written informed consent after receiving a comprehensive introduction to the study protocol. Also, they were asked to fill out a questionnaire, which included information on their years of experience, type of exercise, history of injury, and suffering from a special disease. Then, they filled out the health questionnaire, 24-hour reminder food questionnaire, and the supplementation checklist. One week before initiating supplementation, participants' personal and physiologic characteristics were collected, including age, height, weight, body mass index (BMI), fat percentage, and resting heart rate. These data were used for data homogenization. The inclusion criteria were set at an age between 18 and 24 years, a BMI between 20 and 25 kg/m^2, and the absence of cardiovascular diseases, diabetes, and joint diseases. The exclusion criterion was using any drugs or supplements, such as vitamins and herbal or chemical supplements. Participants were divided into three groups (one placebo and two interventions), each with 8 subjects. Those in the intervention groups received glutamine, 0.1 and 0.6 g/kg body weight (BW). The sample size was selected based on the statistical population, with no predetermined sample size. All tests and measurements were performed in the Exercise Physiology Laboratory of the Imam Khomeini International University of Qazvin.

All participants were asked to warm up for 5 minutes before Bruce's exhaustive protocol (BEP) [8]. The protocol contains 7 steps, each lasting for 3 minutes. The protocol began with a 10% incline at 2.7 km/h. Then, both pace and angle were increased gradually. HP-Cosmos treadmill (Germany) was used as the running surface area. This study used a glutamine supplement produced by Optimum Nutrition Company of USA. The supplement group received 0.1 and 0.6 g/kg BW of glutamine and 500 mL mineral water immediately after exhaustive exercise [18]. The placebo group received a bottle of mineral water (500 mL) containing 10 g of dextrin (2%) (Table 1).

Table 1. Administration of the supplement and placebo

Group	Intervention	Dose
Glutamine (0.1 g/kg BW)	Glutamine	0.1 g/kg BW of glutamine, along with 500 mL mineral water
Glutamine (0.6 g/kg BW)		0.6 g/kg BW of glutamine, along with 500 mL mineral water
Placebo	Dextrin	10 g of dextrin (2%) dissolved in 500 mL mineral water (similar to the supplement in terms of color and taste)

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Initially, the arterial blood sample was collected from an artery of the right hand in a fasting state (12 hours fasting) in the early morning before supplementation. The second blood sample was taken immediately after the BEP, and the third and fourth were taken 90 minutes and 24 hours after the BEP.

Serum cortisol levels were measured by radioimmunoassay assay (using a French Imunotech kit) with a sensitivity of 0.36 µg/mL. Blood testosterone levels were measured using the ELISA method (Marburg kit, Germany) with a sensitivity of 0.24 µg. Blood samples were centrifuged for one minute at 2000 rpm and kept at -76°C.

The Shapiro-Wilk test was applied to test the normal data distribution, which indicated normal distribution. The independent t-test was used to test for intra-group differences. The paired t-test was used to evaluate the mean difference between study groups compared to the pre-test. To assess changes in four stages of measurement and perform intra-group comparisons, the paired t-test was used. Also, repeated measure analysis of variance and post hoc test was used for inter-group comparisons. Statistical significance was considered when the P<0.05. Data analysis was performed using SPSS software, version 23. Graphs were drawn using Graph Pad software, version 8 at a significance level of <0.05.

Results

Table 2 presents descriptive statistics of the participants.

Individual characteristics of the participants are described in Table 2. The independent t-test showed no significant difference between the study groups, and the three groups were homogenous.

As shown in Table 3, repeated measures analysis of variance showed a significant difference in cortisol levels between the glutamine groups (0.6 g/kg BW; P=00.03, and 0.1 g/kg BW; P=0.02) and testosterone levels in the glutamine group (0.6 g/kg BW; P=0.02). Also, there was a significant difference in the placebo group concerning cortisol levels. In addition, this test showed a significant difference between the three groups concerning cortisol (P=0.04) and testosterone (P=0.02) levels at different measurement times (i.e. before the intervention, immediately after the intervention, 90 minutes after the intervention, and 24 hours after the intervention). Therefore, the Bonferroni test was used to evaluate intra-group differences at different times (Figures 1 and 2).

Discussion

This study investigated the effect of different doses of glutamine supplementation after an exhaustive physical activity on cortisol and blood testosterone levels. Skeletal muscle tissue is the primary source of glutamine and releases glutamine at approximately 50 mmol per hour in the fed state. The effects of acute exercise on plasma glutamine concentrations largely depend on the duration and intensity [19]. Plasma glutamine levels significantly decrease after long hours of physical activity [20]. This study showed that exhaustive activity significantly increased cortisol levels immediately after exercise, consistent with similar studies [2, 4, 5]. Overall, 0.6 g/kg BW of glutamine supplementation could reduce cortisol levels compared to 0.1 g/kg BW of glutamine and placebo. In addition, receiving 0.6 g/kg BW of glutamine supplementation caused a significant reduction in cortisol levels compared to 0.1 g/kg BW of glutamine and placebo after exhaustive physical exercise for up to 24 hours.

As shown in Figure 1, supplementation was more effective 24 hours after the activity. The highest reduction in cortisol levels was found in the glutamine group (0.6 g/kg BW) 24 hours after the activity compared to 90 minutes. Prior studies have reported more effectiveness of glutamine supplementation at 2, 24, 48, and 72 hours, indicating its gradual effect [5]. Córdova-Matins et al. [5], Kazemi et al. [20], Hakimi et al. [21], and Karami et al. [22] reported similar results.

Table 2. Descriptive statistics of the participants before the intervention

Variables	Placebo	Glutamine (0.1 g/kg BW)	Glutamine (0.6 g/kg BW)	P
Age (y)	22.2±2.07	21.2±75.70	21.1±50.40	0.14
Height (cm)	181.87±2.64	175.2±75.91	175.2±10.15	0.09
Weight (kg)	71.6±37.54	73.5±93.50	69.4±78.81	0.21
Fat (%)	17.1±5.85	16.1±75.83	16.1±12.53	0.08
BMI (kg/m²)	22.2±5	2±23.5	22.1±5.5	0.19

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Table 3. Results of the repeated measure analysis of variance

Variables	Baseline Data Differences Between Study Groups				P			
	Time	0.1	0.6	Placebo	Inter-group Comparisons			Intra-group
					0.1	0.6	Placebo	
Cortisol (µg/mL)	Before the intervention	13.85±2.78	14.10±2.17	13.69±2.9	0.02#	0.03#	0.01#	0.04*
	Immediately after the intervention	18.92±3.13	19.36±3.40	19.54±3.9				
	90 minutes after the intervention	16.82±2.51	17.19±2.91	19.90±1.15				
	24 hours after the intervention	14.90±3.14	13.70±2.39	15.18±1.16				
Testosterone (µg/mL)	Before the intervention	5.95±1.05	6.26±1.22	6.11±0.98	0.06	0.04#	0.08	0.02*
	Immediately after the intervention	5.48±1.10	5.98±0.71	5.90±0.98				
	90 minutes after the intervention	5.49±0.032	6.14±0.51	6.11±0.82				
	24 hours after the intervention	5.70±0.12	6.88±0.64	6.20±0.78				

#Intragroup differences, *Differences between groups.

In a study on young basketball players, Córdova Matins et al. reported that receiving glutamine immediately after intense activity correlated with reduced cortisol levels [5]. Similarly, Kazemi et al. reported that consuming glutamine and carbohydrates reduced cortisol levels 24 hours after physical activity compared to the placebo group [20]. In a study on the effect of glutamine supplementation in non-athletes following an 8-week plan, Hakimi et al. reported a significant reduction in glutamine levels [21]. Karami et al. (2017) reported that glutamine consumption reduced cortisol levels after three stages of 20-minute running with an intensity of 80% of maximum heart rate, consistent with the present study's findings [22]. Dobeidi Roshan et al. assessed 24 young males and concluded that 0.1 g/kg BW of glutamine supplementation did not reduce cortisol levels [16].

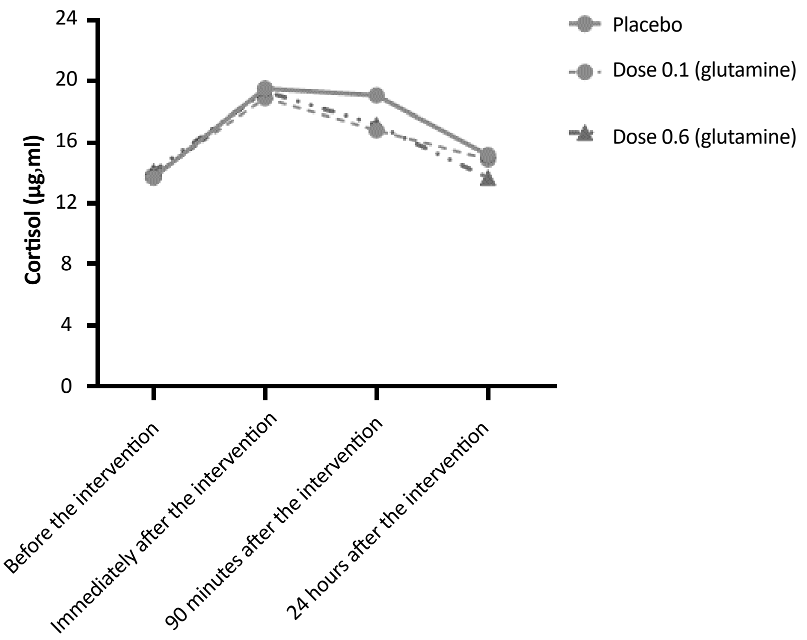

Figure 1. Comparing the mean cortisol levels in study groups at different measurement times

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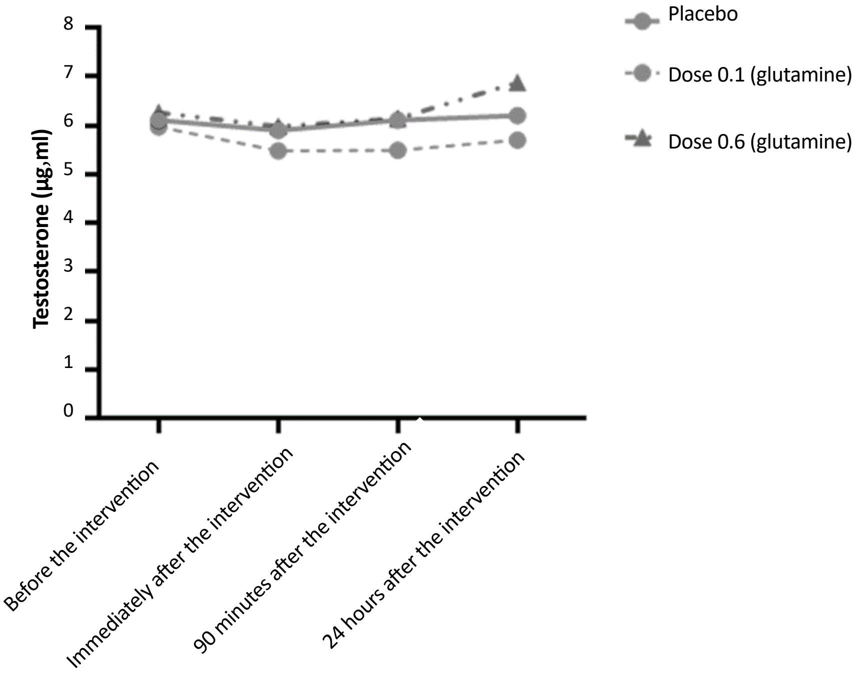

Figure 2. Comparing the mean testosterone levels in all three groups at different measurement times

The observed difference can be attributed to glutamine dose and the use of saliva samples. The observed effect can be attributed to greater availability of glutamine, increased energy consumption due to glutamine consumption, increased glutamine synthesis ratio, positive glutamine balance in the blood circulation, and increased antioxidant capacity [16]. This improved hormonal response may significantly reduce muscle glycogen during exercise, leading to an advanced anabolic environment that results in muscle adaptation and recovery. In addition, glutamine supplementation enhances the availability of amino acids, which may lead to increased absorption of amino acids by muscles, increasing pure protein balance in muscles and an improved anabolic environment [1, 11].

As cortisol reduction is associated with low plasma levels of glutamine, such associations may be accompanied by an enhanced need for glutamine to modulate the immune system and stimulate the cellular divisions involved in anabolic processes. Glutamine feeds immune cells and contributes to repairing mechanisms. In this context, a significant role of glutamine amino acid in athletes is increasing growth hormone and reducing proteolysis in exhaustive exercise activities. Transporting glutamine across the plasma membrane stimulates a process that depends on sodium, leading to increased water absorption and potassium release. Cell swelling increases resilience to external damage and reduces the secretion of enzymes that cause cell damage, leading to the increased ratio of anabolic to catabolic hormones. Cortisol is a good physiological biomarker of stress and function of the hypothalamus-pituitary-adrenocortical axis [23]. As calcium can activate cellular proteases and positive reports regarding taurine's effect on hemostasis and calcium buffering, glutamine supplementation may improve cellular damage indices after traumatic exercise [9]. In addition, it may play a positive role in maintaining muscle hydration by absorbing water, which prevents increased cortisol levels and anabolic growth [24].

Compared to the placebo and 0.1 g/kg BW of glutamine, 0.6 g/kg BW administration of glutamine could significantly increase testosterone levels 24 hours after exhaustive exercise. Similar results were reported by Córdova-Martines et al. [5] and Hakimi et al. [21]. Córdova-Martínez et al. reported that receiving glutamine immediately after exhaustive activity was associated with increased testosterone levels in young basketball players, compared to the controls. However, the increase was not statistically significant [5]. Kazemi et al. reported that glutamine and carbohydrate supplementation increased testosterone levels compared to the placebo group [20]. Hakimi et al. administered both carbohydrates and glutamine [21]; therefore, caution should be taken when generalizing their findings. The impact of exercise type on testosterone response [4] and the unchanged testosterone level immediately after and 90 minutes following the BEP are significant findings [1]. Testosterone can promote muscle protein synthesis [5] by binding androgen receptors and stimulating muscle satellite cells, highlight-

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ing its vital role, as gene transcription is the primary goal of protein synthesis [25]. The findings support the optimal effect of supplementation on testosterone.

In this study, the testosterone pattern indicated good recovery, and the anabolic profile was maintained, which is helpful for hard training and competition. In addition, low cortisol levels seem necessary to control the inflammatory response following exercise [9], which is helpful for optimal muscle repair and regeneration during recovery and improving performance [13]. Decreased plasma levels of glutamine following prolonged exercise can be attributed to increased hepatic absorption of glutamine for gluconeogenesis, the synthesis of acute-phase proteins, and or increased glutamine absorption from the kidney to prevent acidosis [9]. Increased glutamine absorption by active leukocytes may also facilitate reducing plasma levels of glutamine after prolonged exercise; however, some evidence supports this issue [13]. It is assumed that the decline in glutamine, caused by heavy exercise, negatively affects the access of immune cells to glutamine, demanding glutamine to produce energy and nucleotide biosynthesis [24]. Therefore, this hypothesis can be used to explain exercise-induced immune disorders and increased susceptibility to infection in athletes [25].

Glutamine is not added to commercial sports drinks mainly because of its relative instability in solutions. Due to the osmotic gradient, drinks containing glucose and sodium cause increased water transfer from the intestine to circulation. Glutamine is absorbed by the intestinal epithelial cells by sodium through sodium-independent mechanisms. It has been shown that the addition of glutamine to oral rehydration solution results in increased solution absorption. Glutamine is thought to be relatively safe and well-tolerated by most people. Meanwhile, caution should be taken by those suffering from kidney diseases. No adverse reaction has been reported to short-term glutamine supplementation at 20-30 g within a few hours [1]. Further studies are required to evaluate the findings of the present study.

Herein, some limitations and challenges must be considered before applying the findings. The research did not include the studied topic in different training programs with various intensities. Another important limitation is not using different doses of glutamine supplementation at multiple periods. The next limitation of this study is not measuring plasma cytokines and glutamine, which might have increased the accuracy of immune system monitoring. Last but not least, the small number of participants in each group, relatively short study period, lack of comprehensive control of participants' nutrition, and overlooking psychological factors and participants' sleep duration are among other significant limitations.

Conclusion

This study demonstrated that timely administration of 0.6 g/kg BW of glutamine supplementation results in an acceptable balance between cortisol and testosterone responses. Therefore, the authors recommend its consumption after exhaustive exercise. We assume that controlling these specific parameters helps prevent inflammation and stress caused by highly intense exercise. Glutamine supplementation facilitates recovery following exhaustive activities associated with increased cortisol levels, with a high risk of muscle damage.

Ethical Considerations

Compliance with ethical guidelines

The research purpose and methodology of the present study was approved by the Research Ethics Committee of Imam Khomeini International University (Code: IR.IKU.REC.7219).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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