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Meta-analyses

# The effect of glutamine supplementation on athletic performance, body composition, and immune function: A systematic review and a meta-analysis of clinical trials

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SUMMARY

*Background & aim:* This systematic review and meta-analysis of available evidence was conducted to obtain a conclusive result on the effects of glutamine supplementation on athletes.
*Methods:* Systematic review and meta-analysis. Data related to body mass, lean body mass, body fat percentage, Vo2 max, lymphocytes, leukocytes and neutrophil counts were extracted to determine the effects of GLN on performance outcomes.
*Data Sources:* The literature search was conducted across the databases Pubmed, Scopus, ISI Web of Science, SID (Scientific Information Database) and Cochrane Central Register of Controlled Trials, covering a period up to January 2017.
*Eligibility Criteria for Selecting Studies:* Clinical trials evaluating glutamine supplementation outcomes on athletes aged over 18 were included.
*Results:* A total of 47 studies were included in the systematic review, and 25 trials matched the inclusion criteria for the meta-analysis. According to the meta-analysis, glutamine has a significant effect on weight reduction (WMD = −1.36 [95% CI: −2.55 to −0.16], p = 0.02). Moreover, neutrophil numbers were reduced following glutamine intake at doses greater than 200 mg/kg body weight (WMD = −605.77 [95% CI: −1200.0 to 52.1]; P = 0.03). Also, supplementation by glutamine dipeptide resulted in higher blood glucose after exercise (WMD = 0.51 [95% CI: 0.18, 0.83] mmol/l; P = 0.002). There was no association between glutamine ingestion and other outcomes investigated.
*Conclusion:* According to this meta-analysis, generally, glutamine supplementation has no effect on athletics immune system, aerobic performance, and body composition. However, the current study showed that glutamine resulted in greater weight reduction. In addition, the present study suggests that the efficacy of glutamine supplementation on neutrophil numbers could be affected by supplement type and dose.


## 1. Introduction

Maintaining athletic performance is an issue constantly considered by trainers and athletes [1]. Nowadays, athletes employ several approaches for success in competitions, and the use of pharmaceutical or nutritional products are the most common among them. Some of the reasons mentioned by athletes for using these products include: increased performance, accelerated recovery, and reduced muscle damage [2]. It has been frequently suggested by various studies that nutritional supplements can increase athletic performance [3]. Physical performance is highly related to muscle function and muscle protein synthesis. Muscle protein degradation has an important role in determining muscle strength [4]. Amino acids are muscular building blocks and are used

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as a source of energy for skeletal musculature [5]. There is scant evidence to suggest that nonessential amino acids stimulate muscle protein synthesis. However, glutamine (GLN), which is a nonessential amino acid, is different. Certain well-regarded scientific studies have shown GLN supplementation to have specific benefits, including supporting the immune system, increasing glycogen production, anticatabolic effects, and increasing the absorption of water and electrolytes [6]. In laboratory animals, a direct relationship has been shown between free GLN levels in muscle, and the rate of muscle protein synthesis [7]. Sustaining a positive protein balance and the anabolic effects of GLN supplementation may potentially improve athletic performance (namely power, vertical jump performance, or overall muscle strength) due to the enhancement of muscle mass [3].

GLN is the most abundant amino acid in plasma and skeletal muscles. About 60% of the total free amino acids in skeletal muscles [8,9] and 20% of plasma amino acids [10] consist of GLN. This amino acid may be used for the synthesis of other amino acids, proteins, nucleotides and a number of other biological molecules [11]. In addition, it is essential for homeostasis (including fluid balance, pH, regulating body temperature, and heart rate), and optimal function of some body tissues, especially the immune system and gastrointestinal tract [10]. This amino acid is the most important fuel source for certain immune cells and may have a special effect on immune stimulation [12]. For years it has been assumed that immune cells use glucose as a fuel [13], but in the early 1980s, it was found that these cells use GLN equally and in the same way as glucose [14]. Recently, the role of GLN in immunosuppression has become a lively topic. A decrease in plasma GLN is associated with immune suppression after intensive exercise and in overtraining syndrome [15]. However, there is no direct evidence demonstrating that reduced plasma GLN following exercise or due to overtraining syndrome is associated with impaired immune function [16]. Based on limited studies, GLN increases the number of circulating lymphocytes and macrophages. Besides, a relationship has been identified between plasma GLN level and resistance to viral infection in nonathletes [17,18].

Decreases in plasma GLN levels after prolonged exercise may be ascribable to an increase in bodily demand and a greater GLN uptake by tissues than normal. Plasma GLN levels can decline due to reduced production or decrease in the release of GLN by muscles [16]. Despite existing claims about the effects of GLN on enhancing athletic performance and improving the immune system, the results of these studies remain conflicting. This study was conducted to evaluate the effect of GLN supplementation (in comparison to a placebo) on athletic performance, body composition, and immune function, in clinical trials.

## 2. Methods

This study follows the guidelines and PRISMA statement for reporting systematic reviews and meta-analyses of studies. Table 1 shows the PICOS (population, intervention, comparator, outcome, and setting) criteria used to perform the systematic review. Due to the study type (meta-analysis and systematic review), ethical approval was not necessary according to local legislation. The study protocol was registered on PROSPERO (registration number: CRD42016038438).

**Table 1**
PICOS (population, intervention, comparator, outcome, and setting) criteria used to perform the systematic review.

| PICOS | Criteria |
|---|---|
| Population | Healthy active subjects |
| Intervention | Glutamine supplementation |
| Comparator | Placebo group |
| Outcome | Immune function; Athletic performance; Body composition; Blood markers (growth hormone, blood glucose, and Creatine kinase) |
| Setting | Clinical trials |

### 2.1. Literature review

Two authors (AR and ER) independently performed an extended literature search of the following databases: Pubmed, Scopus, ISI Web of Science, SID (Scientific Information Database) and Cochrane Central Register of Controlled Trials and Cochrane Library database. All studies published as original full-text articles covering a period up to January 2017 were searched. No restriction was applied to publication year, and all studies published in English or Persian were included. The following medical subject heading terms and words were used as search strategies, in all possible combinations: glutamine, dipeptide, L-glutamine, L-Alanyl-L-Glutamine, sustamine, oral glutamine, supplement of glutamine, glutamine supplementation, athletes, exercise, sport, training, athletics, body composition, muscle mass, lean mass, lean body mass, fat mass, body mass, weight, immune function, immune, immune response, immunity, white blood cell, lymphocyte, leukocyte, neutrophil, cytokine, performance, aerobic performance, anaerobic performance, power, strength, endurance, resistance, Vo2, growth hormone, GH, glucose, creatine kinase, CK, creatine phosphokinase", phosphor-creatine kinase, CPK. For expanding the search, "related article" function was applied and the reference lists of selected articles were searched for extra articles.

### 2.2. Study selection

Any treatment by GLN or its dipeptide (as L-Alanyl-L-Glutamine or sustamine), either individually or in combination with any other artificial substance, considered as "glutamine supplementation".

The following eligibility criteria were applied: a) Studies enrolling patients over 18; b) Athletes following regular exercise regimes; c) Controlled trials; d) GLN or L-Alanyl-L-Glutamine supplementation; e) Trials that reported at least 1 of the outcomes considered in the present study; f) Written in English or Persian. All studies were considered, irrespective of whether GLN was given in powder forms, pills or as a sports drink.

Trials with the following criteria were excluded: a) Observational studies (cohort study, case–control study, ecological studies, case reports, and case series); b) GLN supplemented in combination with other nutrients with potential metabolic activity (for example amino acids, nucleotides, creatine and omega-3 fatty acids); c) Articles without full-text availability, opinion pieces, review articles and editorials.

### 2.3. Data extraction

An electronic database was designed to obtain all relevant trials data. The data were extracted separately by 2 investigators (AR and ER), and in the event of disagreement AM cross-examined doubtful data, with a decision being made after reaching to an agreement. Following Information extracted from the studies: first author, country of origin, year of publication, study type (parallel or crossover), gender, blinding, GLN dosage, administration method, period of supplementation, the regimen of the control groups, type of sport/exercise, and various outcome measurements.

The primary purpose of this systematic review and meta-analysis was to evaluate if GLN supplementation could affect athletic performance, immune function and body composition based

on clinical trials conducted so far. All related studies have been reviewed, and the following were the most frequent measurements used for conducting the meta-analysis. Data related to body weight, lean body mass, and body fat percentage were extracted before and after supplementation for evaluating the effects of GLN supplementation on body composition. For athletic aerobic performance, Vo2 max data were extracted. Data related to lymphocyte, leukocyte, and neutrophil counts was used for determining the effects of GLN on immune function. As a secondary endpoint of the analysis, the effects of GLN on concentrations of GH, CK and blood glucose was considered, which are indirectly related to sport performance and body composition. The quality of the studies was evaluated by 2 separate reviewers (AR and ER) based on the Jadad score [19].

### 2.4. Statistical analysis

The effect size, as estimated by the mean difference (MD), was used to perform the fixed method meta-analysis. A random-effects meta-analysis was carried out for each measurement where there was a significant heterogeneity between studies [20]. Heterogeneity was assessed using the $I^2$ index, and by testing the null hypothesis that all studies reveal a common effect size. Heterogeneity was considered low if $I^2 < 30\%$, moderate if $I^2 = 30–75\%$, and high if $I^2 > 75\%$ [21]. To identify the potential sources of heterogeneity, stratified analyses were performed according to the following indicators: GLN dosage (≥0.2 g/kg/day or <0.2 g/kg/day), duration of GLN supplement (acute or chronic), supplement type (glutamine or sustamine), and study quality (low or high). Acute supplementation included interventions that were conducted in a single day. Moreover, studies classified according to sport type into the following groups: Endurance and team sports (e.g. soccer, track and field, altitude training, Repeated High-Intensity Endurance Test, rowing, cycling, running, and military training); Wight class and aesthetic sports (e.g. wrestling, judo, gymnastics and Resistance training). For all the analyses, the presence of a different effect between subgroups was tested for.

Funnel plots were used to visually inspect for the presence of publication bias. In addition, for further investigation of publication bias, Begg's rank correlation and Egger's linear regression tests were used. All analyses were carried out using Stata, version 12 SE (Stata Crop, College Station, TX, USA). *P*-values <0.05 were considered statistically significant.

## 3. Results

### 3.1. Study characteristics

As shown in Fig. 1 the early electronic search resulted in 1066 studies, after duplicate removal. Following a title and abstract screen, 996 studies were excluded due to reporting unrelated data, including animal subjects, being review articles, and being written in neither English nor Persian. Overall, 68 studies were evaluated

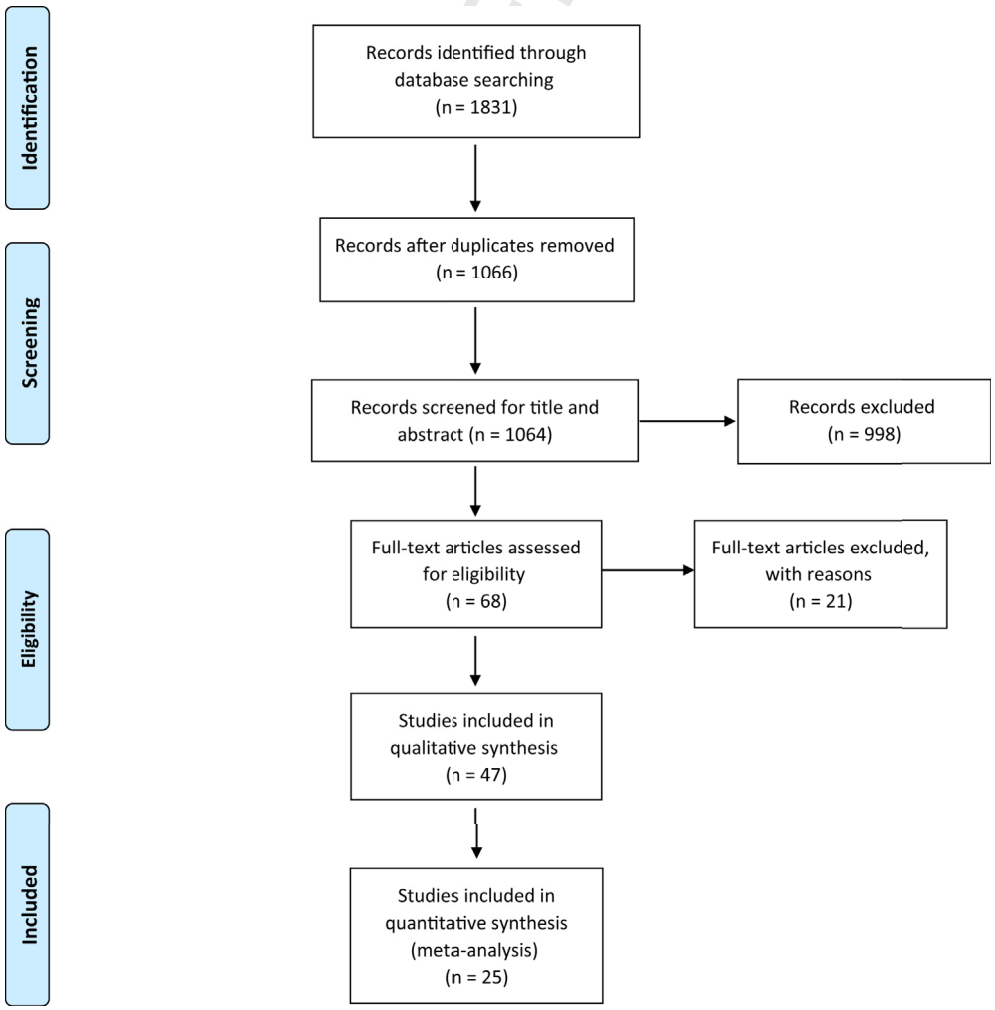


**Fig. 1.** Flow diagram of literature search according to the PRISMA statement.

for eligibility, and 21 studies were excluded for the following reasons: a) Used a combination preparation with other ergogenic aids or amino acids [5,15,22–30]; b) Did not report measurements related to the aims of this study [31–39]; and c) Were not performed on human subjects [40]. From 47 trials included in the systematic review, 25 of them met the inclusion criteria for meta-analysis. Table 2 summarizes the information on all the trials included in the systematic review. A total of 29 studies (62%) employed a parallel study design, whereas 18 studies (38%) used a cross-over design. Most studies (n = 37) were conducted on male subjects, 8 trials involved both male and female participants, and 2 recruited only females. The majority of the trials tested the effects of GLN in acute supplementation (n = 23), while the duration of intervention in 16 studies was fewer than 4 weeks, and in 7 trials was longer than 4 weeks. Dosages of GLN supplements are not directly comparable, as in some studies authors adjusted the supplement according to participants' weight, while in others there was no difference in dosage according to weight. Based on the Jadad score, in more than half of the trials (n = 27), the study quality was high, but 20 trials received a poor score due to a lack of randomization or double-blinding.

## 4. Glutamine supplementation and immune function

### 4.1. Qualitative synthesis

Overall, 20 studies considered the effect of GLN supplementation on immune function [1,12,14,16,18,41–55]. One study showed a significant reduction in the incidence of infection following 7 days of GLN ingestion in athletes [18].

One study showed that the ratio of CD4+ helper/CD8+ suppressor cells significantly decreased in the placebo group than in the GLN group [41]. On the other hand, in one study, CD8+ reduction due to GLN supplementation resulted in a significant increase in the ratio of CD4+/CD8+, while this ratio remained unchanged in the control group [54]. However, in 4 studies, the numbers of CD4+ and CD8+ were not different between the GLN group and the placebo group [14,42,43,48]. In one study, the percentage of T-cells was significantly greater in the GLN group exclusively 16 h post-exercise, in comparison to the placebo [14]. Also, a study showed a significant elevation in post-training Natural Killer (NK) activity in athletes who received GLN supplementation [54]. However, three studies found no effect of GLN supplementation on NK cell activity [14,43,44].

One study that evaluated the effect of GLN supplementation on B cell counts found no difference between the experimental and control groups [14]. The effect of GLN supplementation on the change of salivary immunoglobulin A (s-IgA) was not significant in 3 studies [1,12,47]. Also, some studies found no difference between the GLN group and placebo in plasma levels of Ig M [52,54], IgA [50,52,54] and IgG [50,52,54]. However, one study reported that nasal IgA was greater in athletes receiving GLN compared to the placebo [47].

In 10 studies that considered the effect of GLN on total leukocyte counts, 8 studies found there was no significant difference in total leukocyte numbers after GLN supplementation compared to a placebo [14,16,41,43,45,48–50]. Two of the studies indicated that leukocyte numbers considerably increased following GLN intake, compared to the placebo [51,52]. Nine studies that examined lymphocyte numbers reported no difference between the GLN and the placebo group [14,16,41–45,48,49]. In six studies, GLN supplementation did not affect the change in neutrophil numbers [16,42,43,45,48,49]. One study showed that neutrophil numbers were less enhanced in the GLN group, compared to the placebo [44]. Sasaki and colleagues found that after one week (but not two weeks) following GLN supplementation, neutrophil numbers increased significantly after exercise, although in the placebo group there was a little reduction in neutrophil numbers compared to pre-exercise [50]. Also, another study reported greater increases in neutrophil numbers in the GLN group [52]. Three studies reported that GLN supplementation had no effect on monocyte numbers [43,48,49].

Also, according to studies that investigated the link between of GLN supplementation and athletes' immune function, there was no difference in the plasma concentration of complements (C3, C4 [50,52] and C5a [14]), C-reactive protein (CRP) [14], neopterine [14], Interleukin-6 (IL-6) [14], interferon-γ (IFγ) [14], concanavalin A (ConA) stimulated proliferative response [43], lymphokine activated killer (LAK) [42–44], phytohaemagglutinin stimulated lymphocyte (PHA) proliferative response [42,43], and phagocyte activity [50,52] between the GLN and placebo groups. However, one study showed a greater plasma level of IL-6 immediately after exercise, in the GLN group compared to the placebo [46]. Moreover, two studies showed that the peripheral blood mononuclear cells (PBMC) level of IκBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) increased in response to exercise in the GLN group [53,55]. Two studies also indicated a greater heat shock protein 70 (HSP70) expression in the GLN group when compared to a placebo [53,55]. Also, Zuhl and colleagues reported that plasma levels of tumor necrosis factor alpha (TNF-α) were significantly lower in the GLN group compared to placebo [55].

### 4.2. Quantitative synthesis

Nine trials, including 173 subjects (n = 89 treated and 84 controls) provided data on leukocyte numbers for meta-analysis [14,16,41,44,45,48,49,51,52]. Among these, 4 trials [14,16,41,44] were acute and 5 were longer-term intervention [45,48,49,51,52]. As shown in Fig. 2a, GLN supplementation did not reveal a significant leukocyte-increasing effect, compared to placebo (mean difference = 198.07 [95% CI: −749.1, 1145.3] n/μl; P = 0.68). Moderate heterogeneity was observed among the studies ($I^2$ = 64.5, P = 0.004). The subgroup analysis of study duration (acute or chronic supplementation), quality (high or low) and supplement dose (<200 mg/kg body weight/day or ≥200 mg/kg body weight/day) shows that heterogeneity was significant in trials with chronic intervention (n = 5, $I^2$ = 79.6, P = 0.001), with supplement dose above 200 mg/kg BW (n = 4, $I^2$ = 83.4, P < 0.001), in weight class and aesthetic athletes (n = 4, $I^2$ = 82.9, P = 0.001), and in low quality studies (n = 3, $I^2$ = 81.6, P = 0.004). Also, subgroup analysis suggested that leukocyte numbers reduced in acute intervention and increased in chronic intervention, but none of them were significant statistically (Table 3). Sensitivity analysis suggests no difference in the results, following the exclusion any of the trials. A funnel plot (Fig. 3A) demonstrated no publication bias of trials in investigating the effect of GLN supplementation on leukocyte numbers (Egger's test P = 0.95; Begg's test P = 0.53).

Overall, 8 studies provided enough data regarding the effect of GLN supplementation on neutrophils numbers (n = 84 treated and 81 controls). According to the meta-analysis, GLN supplementation did not significantly affect the neutrophils numbers, compared to the placebo group (mean difference = −112.70 [95% CI: −389.7, 164.3] n/μl; P = 0.42; Fig. 2b). There was low heterogeneity between studies ($I^2$ = 24.6, P = 0.23). Five studies conducted in chronic duration and 3 were acute intervention. The subgroup analysis of study duration (acute or chronic) showed that there was no significant difference between acute (P = 0.58) or chronic (p = 0.47) supplementation of GLN on neutrophil counts. Similar results were seen for two groups of sport type. Supplement doses of more than 0.2 gr/kg BW GLN resulted in a significant decline in

**Table 2**
Characteristics of the included trials.

| Author (year) | Country | Study design | Gender | Blindness | Quality | No. of population | No. of intervention/ placebo | Intervention duration | Supplement type | Placebo type | Supplement dose | Outcomes | Sport type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Castell, L. M. et al. (1996) [18] | Belgium | Parallel | Male and female | Double | High | 151 | 72/79 | Acute | GLN + mineral water | Maltodextrin | 5 gr | Immune function | ultra-marathon or marathon runners, Rowers |
| Castell, L. M. et al. (1997) [14] | Belgium | Parallel | Male and female | Double | High | 18 | 10/8 | Acute | GLN + mineral water | Maltodextrin | 100 mg/kg | Immune function | Ultra-marathon or marathon runners, rowers |
| Castell, L. M. et al. (1997) [41] | Belgium | Parallel | Male | Double | High | 18 | 10/8 | Acute | GLN + water | Maltodextrin | 5 gr | Immune function | Marathon runners |
| Rohde, T. et al. (1998) [42] | Denmark | Parallel | Male | Single | Low | 16 | 9/7 | Acute | GLN | CHO-free lemonade | 400 mg/kg | Immune function | Marathon runners |
| Rohde, T. et al. (1998) [43] | Denmark | Cross-over | Male | Single | Low | 8 | 8/8 | Acute | GLN | CHO-free lemonade | 900 mg/kg | Immune function | – |
| Haub, M. D. et al. (1998) [56] | USA | Cross-over | Male | Double | High | 10 | 10/10 | Acute | GLN | Sucrose | 30 mg/kg/day | Performance | physically active subjects |
| Walsh, N. P. et al. (2000) [16] | England | Cross-over | Male | Single | Low | 7 | 7/7 | Acute | GLN | Sugar-free lemon drink | 42 gr | Plasma glucose, Immune function, performance | Cycle |
| Akbarnejad, A. et al. (2001) [10] | Iran | Parallel | Male | Single | Low | 21 | 7/7 | 1 week | GLN | Did not intake anything | 300 mg/kg/day | Performance | Wrestling |
| Candow, D. G. et al. (2001) [57] | Canada | Parallel | Male and female | Double | High | 31 | 17/14 | 6 weeks | GLN | Maltodextrin | 900 mg/kg of lean body mass/day | Body composition | Resistance training 2–4 times a week |
| Krzywkowski, K. et al. (2001) [44] | Denmark | Cross-over | Male | Double | High | 10 | 10/10 | Acute | GLN | Maltodextrin | 17.5 gr | Immune function, Plasma glucose Growth hormone | Elite athletes |
| Krzywkowski, K. et al. (2001) [12] | Denmark | Cross-over | Male | Double | High | 11 | 11/11 | Acute | GLN | Maltodextrin | 17.5 gr | Immune function | endurance trained sportsmen |
| Bruce, M. et al. (2001) [58] | England | Cross-over | Male | Double | Low | 7 | 7/7 | Acute | GLN + Artificially sweetened beverage | Artificially sweetened beverage | 125 mg/kg | Performance, Glucose | Cyclist |
| Banaeifar, A. (2003) [45] | Iran | Parallel | Male | Single | Low | 20 | 10/10 | 1 month | GLN | Lemonade | 50 mg/kg/day | Immune function | Wrestler |
| Lehmkuhl, M. et al. (2003) [3] | USA | Parallel | Male and female | Double | High | 29 | 10/9 | 8 weeks | Creatine monohydrate + GLN | Creatine monohydrate | 4 gr/day | Body composition | Track & field |
| Finn, K. J. et al. (2003) [59] | USA | Parallel | Male | Double | High | 18 | 9/9 | 12 days | GLN + Artificially sweetened beverage | Artificially sweetened beverage | 350 mg/kg/day | Body composition | Wrestler |
| Hiscock, N. et al. (2003) [46] | Denmark | Cross-over | Male | Double | Low | 8 | 8/8 | Acute | GLN | Maltodextrin | 3.5 gr | Immune function, Plasma glucose | Healthy trained |
| Krieger, J. W. et al. (2004) [47] | USA | Parallel | Male and female | Double | High | 13 | 6/7 | 2 weeks | GLN | Sugar-free lemon drink | 100 mg/kg/day | Immune function, performance | Runner |
| Marwood, S. et al. (2007) [60] | England | Cross-over | Male | Single | Low | 8 | 8/8 | 2 days | GLN | Sugar-free lemon drink | 125 mg/kg/day | performance | Cyclist |
| Dabidi Roshan, V. et al. [1] | Iran | Parallel | Male | Double | High | 23 | 12/11 | Acute | GLN | Sugar-free lemon drink | 100 mg/kg | Immune function | Students |
| Alijani, E. et al. (2008) [48] | Iran | Parallel | Female | Double | High | 30 | 10/10 | Acute | GLN | Maltodextrin | 14 gr | Immune function | Athletics |
| Ziaee, V. et al. (2008) [49] | Iran | Parallel | Male | Single | Low | 21 | 7/7 | 1 week | Creatine monohydrate + GLN | Creatine monohydrate | 300 mg/kg/day | Immune function | Wrestler |
| Favano, A. et al. (2008) [61] | Brazil | Parallel | Male | Double | High | 16 | 9/7 | Acute | GLN | Maltodextrin | 3.5 gr | Performance | soccer |
| Hoffman J. R. et al. (2010) [62] | USA | Cross-over | Male | Single | Low | 10 | 10/10 | Acute | Sustamine | Water | 200 mg/kg 50 mg/kg | Blood factors | Physically active subjects |

(*continued on next page*)

**Table 2** (*continued*)

| Author (year) | Country | Study design | Gender | Blindness | Quality | No. of population | No. of intervention/ placebo | Intervention duration | Supplement type | Placebo type | Supplement dose | Outcomes | Sport type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ghanbarzadeh, M. et al. (2011) [63] | Iran | Parallel | Male | Single | Low | 20 | 10/10 | 8 weeks | GLN + water + sugar | Water + sugar | 100 mg/kg/day | Performance, Body composition | Soccer |
| Ghasemi, A. et al. (2011) [64] | Iran | Parallel | Male | Single | Low | 10 | 5/5 | 4 weeks | GLN + water | Water + glucose | 28 gr. Twice/week | Blood factors | Student athletes |
| Street, B. (2011) [65] | England | Parallel | Male | Single | Low | 15 | 7/8 | 4 days | GLN | Maltodextrin | 300 mg/kg/day | Performance, Blood factors | drop jumps (eccentric exercise) |
| Hoffman J. R. et al. (2012) [66] | USA | Cross-over | Female | Double | Low | 10 | 10/10 | Acute | Sustamine | Water | 1 gr/day 2 gr/day | Performance | Basketball |
| Hakimi, M. et al. (2012) [67] | Iran | Parallel | Male | Double | High | 30 | 15/15 | 8 weeks | GLN | Starch | 350 mg/kg/day | Blood factors, Body composition | Nonathlete healthy young male students |
| Rowlands, D. S. et al. (2012) [68] | New Zealand | Cross-over | Male | Double | High | 8 | 8/8 | Acute | GLN | Glucose, sodium citrate, orange flavor, and filtered water | 9.9 gr | Performance, Blood factors | cycle & triathlete |
| Karami, S. et al. (2013) [69] | Iran | Parallel | Male | Double | High | 14 | 7/7 | Acute | GLN | Not mentioned | 500 mg/kg | Blood factors | Soccer |
| Sasaki, E. et al. (2013) [50] | Japan | Parallel | Male | Single | Low | 26 | 13/13 | 2 weeks | GLN | Not mentioned | 3 gr/day | Blood factors, Immune function | Judo |
| Khorshidi-Hosseini, m. et al. (2013) [70] | Iran | Parallel | Male | Double | High | 14 | 7/7 | Acute | GLN + Sweetener + water | Sweetener + water | 250 mg/kg/day | Performance | physical education students |
| Piattoly, T. et al. (2013) [6] | USA | Parallel | Male | Double | High | 12 | 6/6 | 6 days | GLN | Carbohydrate | 300 mg/kg/day | Performance | Cyclist |
| Abbasalipour, M. et al. (2014) [51] | Iran | Parallel | Male | Double | High | 14 | 7/7 | 15 days | GLN | Not mentioned | 300 mg/kg/day | Immune function | Elite wrestler |
| Nomura, T. et al. (2014) [52] | Japan | Parallel | Male | Single | Low | 35 | 18/17 | 9 days | GLN | Not mentioned | 6 gr/day | Immune function, Body composition, CK, | Judo |
| da Silveira, C. L. et al. (2014) [71] | Brazil | Parallel | Male | Double | High | 32 | 10/12 | 12 weeks | GLN | Corn flour | 300 mg/kg/day | Performance | Military police officers |
| Caris, A.V. et al. (2014) [72] | Brazil | Cross-over | Male | Double | High | 9 | 9/9 | 3 weeks | GLN | Corn starch + lactose | 20 gr/day | Blood factors | Colorado Altitude Training |
| Koo, G. H. et al. (2014) [73] | Korea | Cross-over | Male | Single | Low | 5 | 5/5 | 1 weeks | GLN | Not mentioned | 6 gr/day | Blood factors | Elite rowing athletes |
| Rahmani-Nia, F. et al. (2014) [74,75] | Iran | Parallel | Male | Double | High | 17 | 9/8 | 2 days | GLN | Maltodextrin | 100 mg/kg/day | Blood factors, performance | Untrained healthy |
| Pruna, G. J. et al. (2014) | USA | Cross-over | Male | Double | High | 12 | 12/12 | Acute | Sustamine | Electrolyte drink (Cho, Na, K) | 0.6 gr 1 gr | Performance | Endurance runners |
| Zuhl, M. et al. (2014) [53] | USA | Cross-over | Male and female | Double | Low | 8 | 8/8 | 2 weeks | GLN | Sugar-free lemon drink | 900 mg/kg of fat-free mass | Immune function | University student athletes |
| Legault, Z. et al. (2014) [76] | Canada | Cross-over | Male and female | Double | High | 16 | 16/16 | 3 days | GLN | Maltodextrin | 300 mg/kg/day | Performance | Eccentric exercise |
| Zuhl, M. et al. (2015) [55] | USA | Cross-over | Male and female | Double | Low | 7 | 7/7 | Acute | GLN | Sugar-free lemon drink | 900 mg/kg of fat-free mass | Immune function | Trained endurance athletes |
| Mccormack, W. P. et al. (2015) [77] | USA | Cross-over | Male | Double | High | 12 | 12/12 | Acute | Sustamine | Sports drink (Cho, Na, K) | 300 mg/500 ml 1 g/500 ml (250 ml every 15 min) | Blood factors | Endurance runners |
| Song, Q. H. et al. (2015) [54] | China | Parallel | Male | Single | Low | 24 | 12/12 | 6 weeks | GLN | Not mentioned | 10 gr/day | Immune function | Swimmers |
| Najarzadeh, A. et al. [78] | Iran | Parallel | Male | Double | High | 80 | 40/40 | Acute | GLN | Maltodextrin | 100 mg/kg BW | CK | University student athletes |
| Nakhostin-Roohi, B. et al. [79] | Iran | Parallel | Male | Double | High | 19 | 9/10 | 1 Week | GLN + Sweetener + water | Sweetener + water | 150 mg/kg/day | CK | Young active |

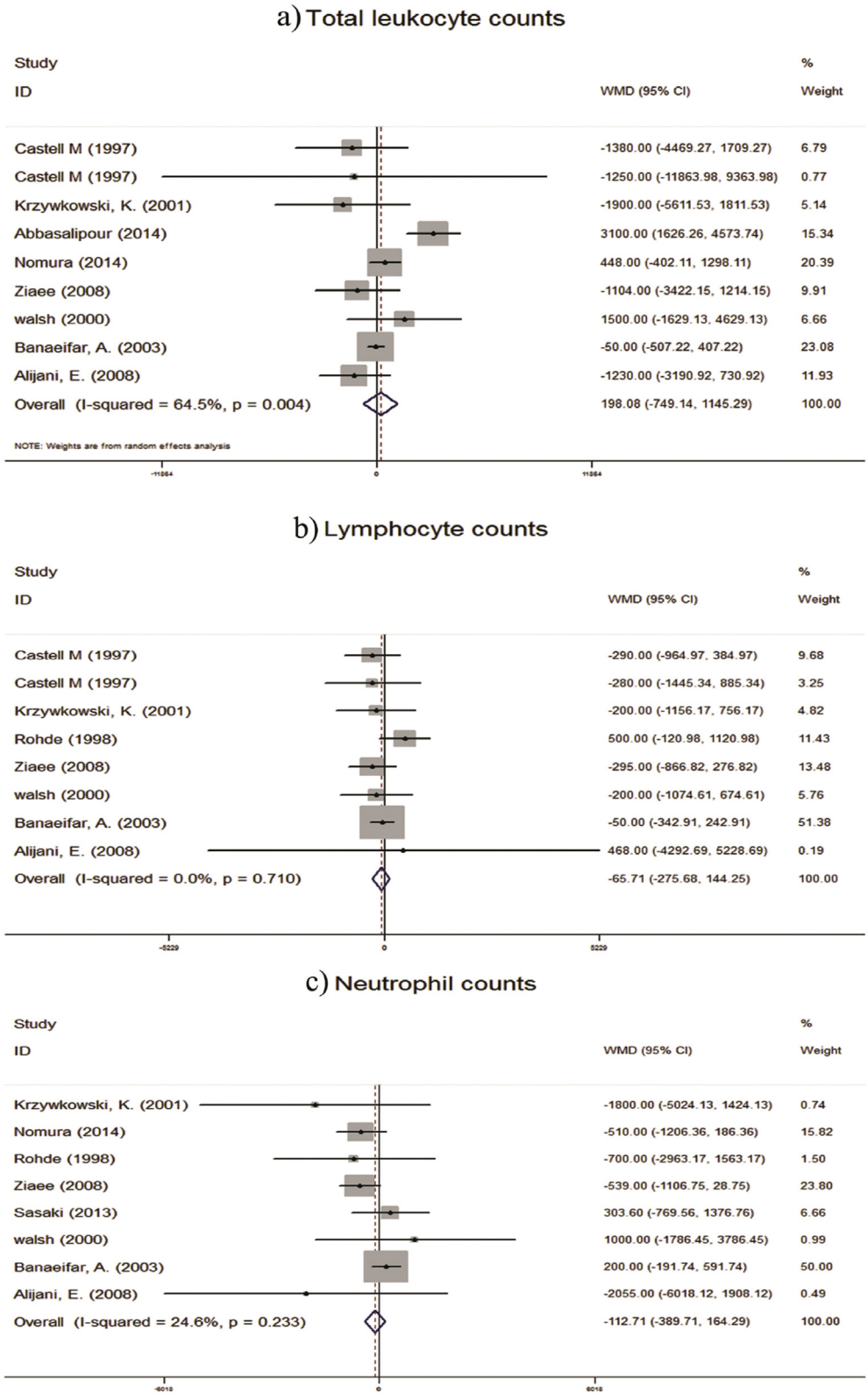


**Fig. 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of GLN supplementation on immune function**. A, leukocyte; B, lymphocyte; C, neutrophil. Square size shows the weight of study in pooled analysis and horizontal bars reflecting the 95% confidence interval.

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**Table 3**
Overall estimates of meta-analysis on the effect of glutamine on study outcomes.

| Outcomes | Subgroups | No. of trials | References | WMD (95% CI) | P-value | $I^2$ (%) | P-value for heterogeneity |
|---|---|---|---|---|---|---|---|
| **Immune function** | | | | | | | |
| Leukocyte (n/μl) | | 9 | [14,16,41,44,45,48,49,51,52] | 198.07 (−749.1, 1145.3) | 0.68 | 64.5 | 0.004 |
| Study duration | Acute | 4 | [14,16,41,44] | −486.94 (−2300.1, 1375.2) | 0.60 | 0.0 | 0.48 |
| | Chronic | 5 | [45,48,49,51,52] | 181.33 (−194.6, 557.3) | 0.34 | 79.6 | 0.001 |
| Supplement dose | <200 mg/kg BW | 5 | [14,16,41,45,52] | 59.25 (−336.5, 455.1) | 0.76 | 0.0 | 0.60 |
| | ≥200 mg/kg BW | 4 | [44,48,49,51] | 780.32 (−230.2, 1790.9) | 0.13 | 83.4 | <0.001 |
| quality | Low | 3 | [41,44,51] | 1794.90 (542.7, 3047.1) | 0.005 | 81.6 | 0.004 |
| | High | 6 | [14,16,45,48,49,52] | −0.37 (−386.0, 385.26) | 0.99 | 0.0 | 048 |
| Sport type | Endurance and team | 5 | [14,16,41,44,48] | −839.29 (−2200.0, 511.01) | 0.38 | 0.0 | 0.60 |
| | Weight class and aesthetic | 4 | [45,49,51,52] | 653.85 (−595.79, 1903.50) | 0.50 | 82.9 | 0.001 |
| Neutrophil (n/μl) | | 8 | [16,42,44,45,48−50,52] | −112.70 (−389.7, 164.3) | 0.42 | 24.6 | 0.23 |
| Study duration | Acute | 3 | [16,42,44] | −430.79 (−2000.0, 1111.8) | 0.58 | 0.0 | 0.41 |
| | Chronic | 5 | [45,48−50,52] | −102.10 (−383.6, 179.4) | 0.47 | 45.6 | 0.11 |
| Supplement dose | <200 mg/kg BW | 5 | [16,42,45,50,52] | 51.91 (−268.0, 371.8) | 0.75 | 3.2 | 0.38 |
| | ≥200 mg/kg BW | 3 | [44,48,49] | −605.77 (−1200.0,-52.1) | 0.03 | 0.0 | 0.57 |
| Sport type | Endurance and team | 4 | [16,42,44,48] | −644.49 (−2100.0, 793.05) | 0.38 | 0.0 | 0.50 |
| | Weight class and aesthetic | 4 | [45,49,50,52] | −154.94 (−612.21, 302.31) | 0.52 | 53.3 | 0.09 |
| | Lymphocyte (n/μl) | 8 | [14,16,41,42,44,45,48,49] | −65.71 (−275.7, 144.2) | 0.54 | 0.0 | 0.71 |
| Study duration | Acute | 5 | [14,16,41,42,44] | −3.31 (−358.5, 351.8) | 0.98 | 0.0 | 0.43 |
| | Chronic | 3 | [45,48,49] | −99.22 (−359.5, 161.1) | 0.45 | 0.0 | 0.73 |
| Supplement dose | <200 mg/kg BW | 5 | [14,16,41,42,45] | −21.11 (−253.7, 211.5) | 0.85 | 0.0 | 0.44 |
| | ≥200 mg/kg BW | 3 | [44,48,49] | −262.2 (−750.4, 225.9) | 0.29 | 0.0 | 0.94 |
| Quality | Low | 2 | [41,44] | −260.06 (−811.5, 291.35) | 0.35 | 0.0 | 0.88 |
| | High | 6 | [14,16,42,45,48,49] | −32.75 (−259.8, 194.3) | 0.77 | 0.0 | 0.54 |
| Sport type | Endurance and team | 6 | [14,16,41,42,44,48] | −0.71 (−354.93, 353.51) | 0.99 | 0.0 | 0.57 |
| | Weight class and aesthetic | 2 | [45,49] | −100.92 (−361.62, 159.77) | 0.44 | 0.0 | 0.45 |
| **Body composition** | | | | | | | |
| Body mass | | 5 | [3,52,59,63,67] | −1.36 (−2.55, −0.17) | 0.02 | 0.0 | 0.93 |
| Supplement dose | <200 mg/kg BW | 3 | [3,52,63] | −1.45 (−2.67, −0.23) | 0.02 | 0.0 | 0.89 |
| | ≥200 mg/kg BW | 2 | [59,67] | 0.95 (−5.06, 6.72) | 0.78 | 0.0 | 0.82 |
| Quality | Low | 2 | [52,63] | −1.47 (−2.69, −0.24) | 0.02 | 0.0 | 0.78 |
| | High | 3 | [3,59,67] | 0.95 (−4.63, 6.54) | 0.73 | 0.0 | 0.96 |
| Sport type | Endurance and team | 2 | [3,63] | −1.47 (−2.69, −0.24) | 0.01 | 0.0 | 0.69 |
| | Weight class and aesthetic | 3 | [52,59,67] | 0.63 (−4.52, 5.79) | 0.81 | 0.0 | 0.96 |
| | Fat mass | 5 | [3,52,59,63,67] | 1.01 (−0.19, 2.22) | 0.09 | 0.0 | 0.58 |
| Supplement dose | <200 mg/kg BW | 3 | [3,52,63] | 1.61 (0.09, 3.12) | 0.03 | 0.0 | 0.55 |
| | ≥200 mg/kg BW | 2 | [59,67] | −0.01 (−1.99, 1.97) | 0.99 | 0.0 | 0.81 |
| Quality | Low | 2 | [52,63] | 1.64 (0.11, 3.17) | 0.03 | 7.3 | 0.29 |
| | High | 3 | [3,59,67] | −0.02 (−1.98, 1.94) | 0.98 | 0.0 | 0.97 |
| Sport type | Endurance and team | 2 | [3,63] | 1.96 (0.30, 3.63) | 0.02 | 0.0 | 0.69 |
| | Weight class and aesthetic | 3 | [52,59,67] | −0.03 (−1.78, 1.71) | 0.96 | 0.0 | 0.97 |
| | Lean body mass | 5 | [3,52,57,59,67] | 0.38 (−2.94, 3.71) | 0.81 | 0.0 | 0.99 |
| Supplement dose | <200 mg/kg BW | 2 | [3,52] | −0.002 (−4.76, 4.76) | 0.99 | 0.0 | 0.77 |
| | ≥200 mg/kg BW | 3 | [57,59,67] | 0.77 (−3.75, 5.29) | 0.73 | 0.0 | 0.94 |
| **Aerobic capacity** | | | | | | | |
| $Vo2_{max}$ (ml/kg/min) | | 3 | [10,63,71] | 0.96 (−5.1, 3.2) | 0.65 | 68.7 | 0.04 |
| **Blood factors** | | | | | | | |
| Glucose (mmol/l) | | 8 | [16,44,62,69,72,77] | 0.27 (−0.24, 0.78) | 0.29 | 88.5 | <0.001 |
| Quality | Low | 3 | [16,62] | 0.43 (−0.10, 0.96) | 0.11 | 31.0 | 0.23 |
| | High | 5 | [44,69,72,77] | −0.46 (−0.55, −0.36) | <0.001 | 91.6 | <0.001 |
| Supplement dose | <200 mg/kg BW | 3 | [62,77] | 0.45 (0.11, 0.78) | 0.008 | 0.0 | 0.95 |
| | ≥200 mg/kg BW | 5 | [16,44,62,69,72] | −0.51 (−0.61, −0.41) | <0.001 | 87.3 | <0.001 |
| Supplement type | Glutamine | 4 | [16,44,69,72] | −0.01 (−0.65, 0.57) | 0.96 | 87.0 | <0.001 |
| | Sustamine | 4 | [62,77] | 0.51 (0.18, 0.83) | 0.002 | 0.0 | 0.52 |
| CK (UI/l) | | 3 | [50,52,73] | −20.29 (−86.55, 45.97) | 0.54 | 0.0 | 0.67 |
| GH (ng/l) | | 3 | [44,64,67] | 0.17 (−1.50, 1.85) | 0.83 | 64.2 | 0.06 |

WMD, weight mean difference; BW, body weight; CK, creatine kinase; GH, growth hormone.

neutrophil numbers (n = 3, mean difference = −605.77 [95% CI: −1200.0, 52.1] n/μl; P = 0.03). Sensitivity analysis did not provide any further information. The funnel plot did not show any publication bias between trials (Egger's test P = 0.36; Begg's test P = 0.80; Fig. 3B).

Eight studies reported the effect of GLN supplementation on lymphocyte numbers. Five studies were acute duration and 3 were chronic. The meta-analysis on the mean change of lymphocyte numbers after GLN or placebo supplementation in plasma was conducted on 141 subjects (73 treatments and 67 placeboes). It was found that GLN supplementation did not significantly change lymphocyte numbers compared to placebo (mean difference = −65.71 [95% CI: −275.7, 144.2] n/μl; P = 0.54; Fig. 2c). Heterogeneity was not obvious among studies ($I^2$ = 0.0, P = 0.71). The effect sizes were constant in the sensitivity analysis. There were no any differences between doses ≥0.2 gr/kg/day and <0.2 gr/kg/day of GLN on lymphocyte numbers. Similarly, the lymphocyte numbers did not significantly change with GLN supplementation in either the subgroups of study duration (acute or chronic supplementation), sport type (endurance and team sports or weight class and aesthetics), and study quality (high or low). For trials considering lymphocyte numbers, neither Begg's (P = 0.57) and Egger's test (P = 0.64), nor a visual inspection of the funnel plot showed any publication bias (Fig. 3C).



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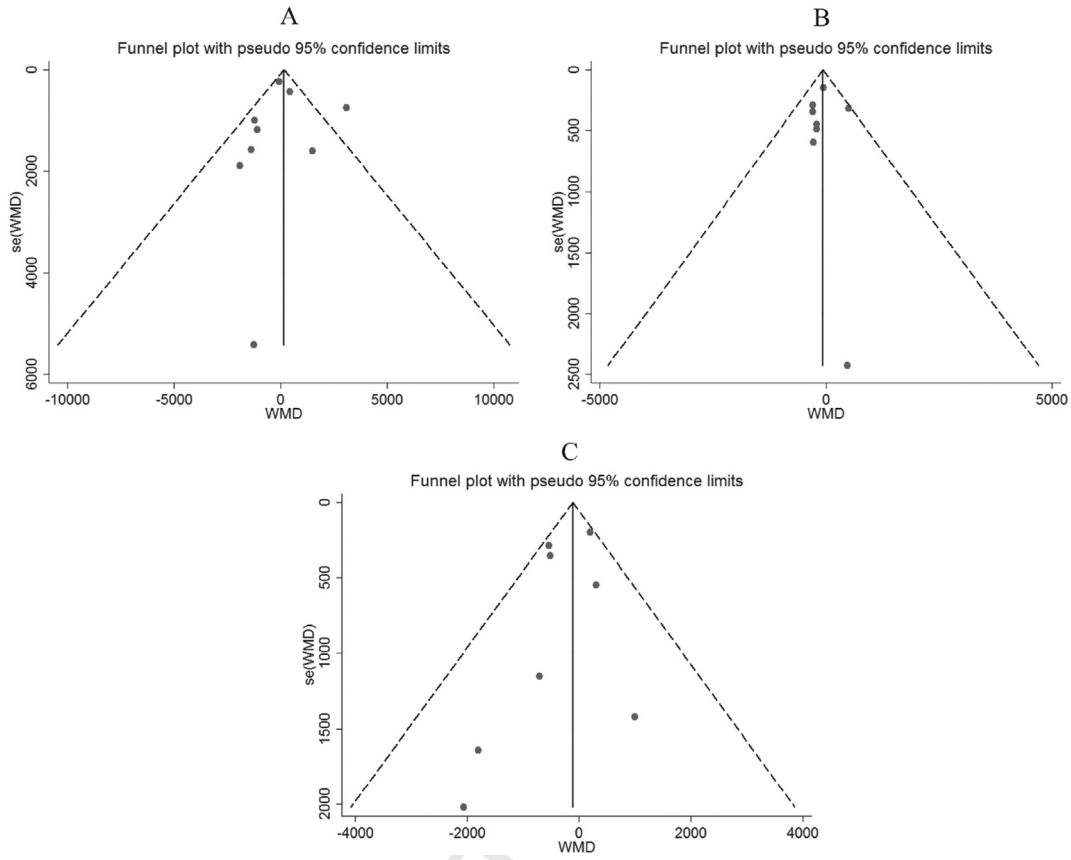


**Fig. 3. Funnel plots detailing publication bias in the studies selected for analysis**. A, total leukocyte counts; B, lymphocyte counts; C, neutrophil counts. WMD: Weight Mean difference. Visual inspection of funnel plots indicating that there is no publication bias among studies.

## 5. Glutamine supplementation and body composition

### 5.1. Qualitative synthesis

In total, 6 studies [3,52,57,59,63,67] investigated the results of GLN supplementation on body composition. One of these studies examined the effect of a mixture of GLN and creatine on body composition, which showed that in both the creatine monohydrate and creatine monohydrate plus GLN groups, body mass and LBM (measured by skinfolds) increased more than in the placebo group ($p = 0.016$). Fat mass and percentage of body fat presented no significant changes over time [3]. Nomura and colleagues found that post-practice body weight decreased significantly, pre- and post-intervention for both the GLN and the placebo groups ($p < 0.01$ for all) [52]. Candow and colleagues found GLN supplementation during 6 weeks of resistance training had no significant effect on body composition [57]. Also, a 12-day period of intervention resulted in a remarkable loss of body weight ($p < 0.001$), lean body mass ($p < 0.001$), and fat mass ($p < 0.001$) in both intervention and control groups, but there were no significant differences between two groups [59]. Two studies showed that body weight and lean body mass significantly increased following 8 weeks of GLN supplementation, and a decrease in body fat percentage was observed during this period [63,67].

### 5.2. Quantitative synthesis

Overall, 6 studies provided enough data to evaluate the effect of GLN supplementation on body composition. The duration of all these studies was more than a day and they were chronic studies. Five studies including a total of 122 subjects (62 treated and 60 controls) investigated the effect of GLN supplementation on fat mass and body weight. In addition, 5 studies (including 69 subjects in the GLN group and 64 controls), examined the effects of GLN on lean mass. These studies suggested an inverse association between GLN consumption and body weight (mean difference = −1.36 [95% CI: −2.55, −0.16] kg, $p = 0.02$, Fig. 4a). There was no heterogeneity among the studies ($I^2 = 0.0\%$, $p = 0.93$). Sensitivity analysis showed that this significant relationship disappears (mean difference = 0.75 [95% CI: −4.19, 5.70] kg) by eliminating the study of Ghanbarzadeh et al. [63].

No association was observed between GLN consumption and fat (Fig. 4b) or lean mass (Fig. 4c) (mean difference = 1.01 [95% CI: −0.19, 2.22] kg, $p = 0.09$, and mean difference = 0.38 [95% CI: −2.94, 3.71] kg, $p = 0.81$, respectively), and there was no heterogeneity between studies ($I^2 = 0.0\%$, $p = 0.58$, and $I^2 = 0.0\%$, $p = 0.99$, respectively). According to the subgroup analysis, a significant increase in body fat mass was observed in low quality studies (n = 2, mean difference = 1.64 [95% CI: 0.11, 3.17] kg, $p = 0.03$). Similar results were also found in studies which supplemented GLN at doses lower than 0.2 gr/kg BW (n = 3, mean difference = 1.61 [95% CI: 0.09, 3.12] kg, $p = 0.04$) and endurance and team sport type (n = 3, mean difference = 1.96 [95% CI: 0.30, 3.63] kg, $p = 0.02$). Although it appears that only one study returned these results [63], a sensitivity analysis did not confirm this. There were no significant differences in the effects of GLN intake on lean body mass, after dividing the groups by study quality and supplement dose. Sensitivity analysis did not show any change in the results related to fat mass and lean body mass.

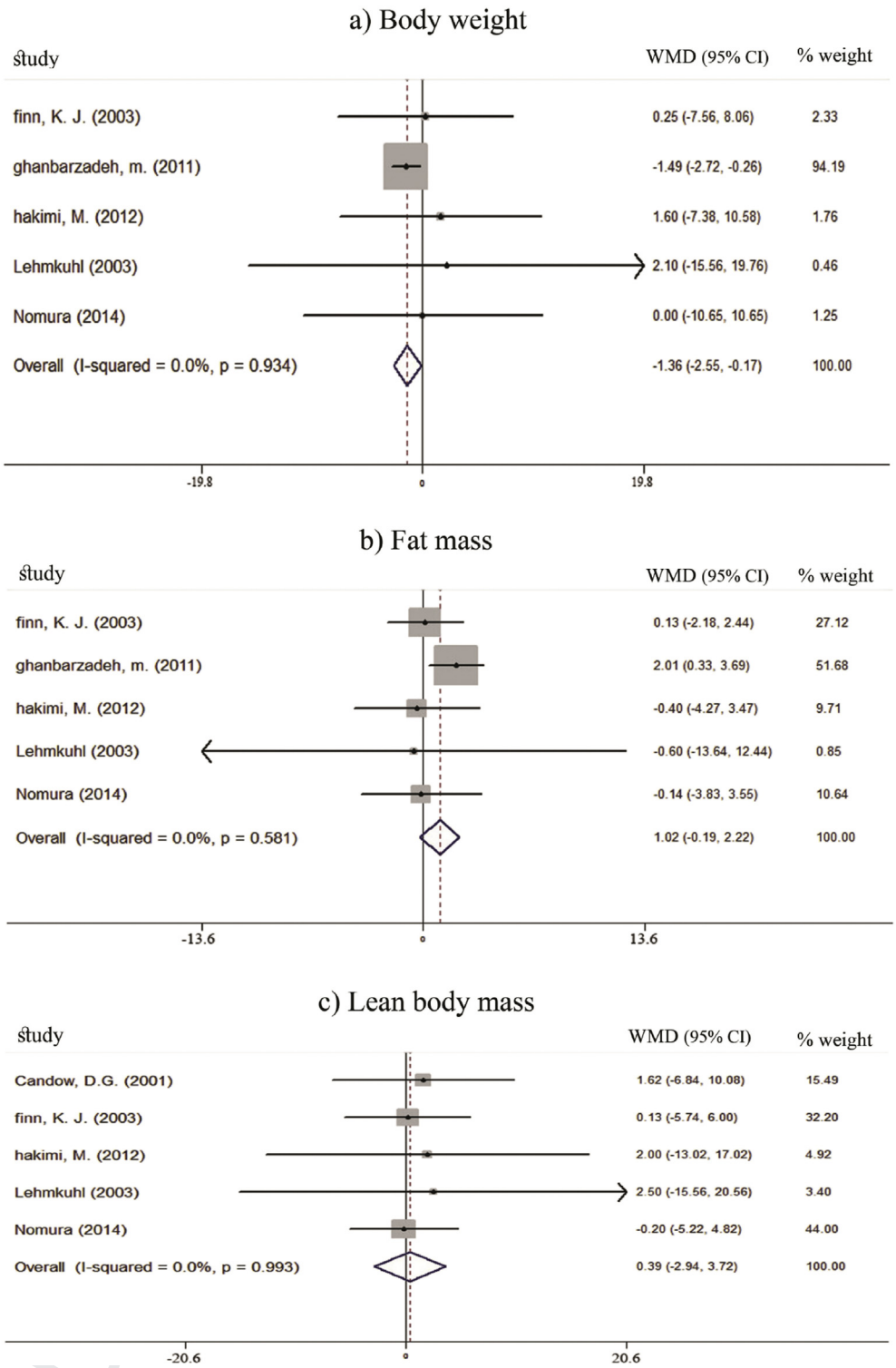


**Fig. 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of GLN supplementation on body composition**. A, body weight; B, fat mass; C, lean body mass. Square size shows the weight of study in pooled analysis and horizontal bars reflecting the 95% confidence interval.

## 6. Glutamine supplementation and athletic performance

### 6.1. Qualitative synthesis

According to our systematic review, 16 trials investigated the effects of GLN supplementation on different aspects of athletic performance.

Two studies reported that GLN supplementation had no effect on aerobic capacity, as evaluated by $VO_2$max, compared to placebo groups [10,71]. One study concluded that GLN supplementation did not affect oxygen consumption and energy expenditure during exercise. GLN also had a trivial effect on exogenous glucose oxidation rate, relative to a control group [68]. In addition, two studies found that pulmonary oxygen consumption ($VO_2$), mean

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response time of % hemoglobin (Hb; as an indicative of muscle deoxygenation kinetics), respiratory exchange ratio, and expired ventilation were not different between the GLN and placebo groups [58,60]. However, in one of these studies, the mean response time of $VO_2$ was faster in the GLN group. Moreover, taking GLN during the early phase of exercise increased muscle oxygen consumption, %Hb and oxidative metabolism [60]. One study also showed that GLN supplementation had a significant enhancement effect on aerobic power ($VO_2$max) [63]. In three studies no significant difference was observed between GLN and placebo groups in heart rate measurements [47,58,66].

Three studies found a significant increase in peak, minimum and mean anaerobic power (Rast or Wingate test) following GLN supplementation compared to a placebo [6,63,70]. On the other hand, in one study the authors did not find any significant relationship between GLN supplementation and improvement in anaerobic performance (measured by shuttle run test), upper limb muscle strength (evaluated by pushups), lower limb muscle strength (evaluated by horizontal jump), flexibility (determined by the sit and reach test), and abdominal muscle endurance (determined by sit-up test) [71]. According to one study, the lactate threshold and lactate tolerance did not change following GLN supplementation, in comparison with placebo groups [10].

A study carried out on basketball players showed that GLN supplementation resulted in a significant improvement in a shooting drill, shooting performance and visual reaction time, although there was no difference between trials in lower body reaction, motor response, vertical jump power and player loads. In this study, low and high doses of GLN had a similar effect [66]. In contrast, another study that compared rehydration with two doses of L-Alanyl-L-Glutamine (low dose and high dose) and a simple electrolyte drink, indicated that visual, physical and motor reaction times were likely to be faster with a low dose of L-Alanyl-L-Glutamine than in other trials. Also, this study showed a possible advantage for high doses of supplements in terms of the number of successful shots. With both low and high doses of supplementation, an improvement in lower body response time was observed. There was no difference in cognitive performance between trials [80].

One study suggested a significantly greater peak torque (as an indicator of strength) over 96 h after exercise, for the GLN group compared to a placebo group [65]. Another study found that GLN supplementation resulted in higher peak torque post-exercise only in male gender [76]. Two studies showed that the rating of perceived exertion (RPE) inclined to be greater in the GLN group compared to the placebo [16,68].

One study showed that GLN supplementation caused an improvement in total distance covered and duration of tolerance [61]. Two other studies showed that subjects who received GLN supplements experienced less fatigue than the placebo group and that the mean time until fatigue or exhaustion was longer for athletes in the GLN group [6,61]. In contrast, one study reported a small increase in leg muscle tiredness with GLN supplementation, compared to glucose or a placebo [68]. Additionally, two studies indicated that GLN makes no significant difference in fatigue perception in comparison to placebo [56,70].

One study considering the effect of GLN supplementation on surface electromyography (sEMG; an indicator of muscle fatigue and muscle damage) concluded that there was no difference between GLN and placebo groups, with sEMG decreasing significantly after exercise in both groups [74].

In one study, GLN supplementation did not affect the timing and magnitude of the soreness, although it diminished soreness more rapidly than in the control group [65]. Also, Rahmani-Nia and colleagues did not observe any effect of GLN supplementation on muscle soreness compared to a placebo [74]. In another study, a lower rate of knee extensor and muscle soreness was noted in the GLN group compared to the placebo group [76].

### 6.2. Quantitative synthesis

Overall, only 3 studies (56 subjects; 27 in treatment and 29 in the placebo group) remained to be included in the meta-analysis, according to the inclusion criteria. It was found that GLN supplementation had no significant effect on Vo2max compared to placebo (mean difference = −0.96 [95% CI: −5.1, 3.2] ml/kg/min; P = 0.65; Fig. 5a). There was moderate heterogeneity among studies ($I^2$ = 68.7, P = 0.04). Sensitivity analysis did not give any further information.

## 7. Glutamine supplementation and blood markers

### 7.1. Qualitative synthesis

Six trials studied the effect of GLN supplementation on blood glucose, and none of them found significant associations [16,44,62,69,72,77].

Four studies were found relevant to the outcomes of GLN supplementation on growth hormone levels. Three of these studies found no effect of GLN supplementation on growth hormone [44,62,64], but Hakimi and colleagues [67] showed 0.35 gr/kg/day GLN over 8 weeks caused significantly greater increases in blood GH in the GLN group compared to the placebo group.

Among 8 studies that investigated the effect of GLN supplementation on blood CK, one study showed serum CK decreased 1 week after the intervention, compared to pre-intervention [50]. Another study indicated that 6 g/day GLN supplementation over 1 week caused a lower level of CK in the GLN supplementation group in the recovery stage compared to the immediately after exercise ($p < 0.05$) [73]. Six studies found no significant relationship between GLN supplementation and blood CK after exercise [52,62,65,74,78,79].

### 7.2. Quantitative synthesis

Data from 6 studies [16,44,62,69,72,77], including 56 treatments and 56 controls, was used to explore the effects of GLN on blood glucose immediately after exercise. Two studies tested two different doses of GLN on blood glucose levels [62,77], therefore each dose was entered in the analysis separately. Overall, 8 effect sizes were entered to compare the relationship between GLN supplementation and blood glucose post-exercise. There were no differences between low and high doses of GLN in affecting blood glucose [77]. According to these studies, GLN intake in athletes did not correlate with blood glucose levels (mean difference = 0.27 [95% CI: −0.24, 0.78] mmol/l; P = 0.29; Fig. 5b). There was a high heterogeneity between these studies ($I^2$ = 88.5%, $p < 0.001$). Potential sources of variation were evaluated by subgroup analysis, and it was found that supplement doses of more than 0.2 gr/kg BW and supplement form (glutamine or sustamine) could be sources of heterogeneity ($I^2$ = 87.3%, $p < 0.001$; and $I^2$ = 87.0%, $p < 0.001$, respectively). The study quality subgroup analysis did not provide further information in detecting sources of heterogeneity. Subgroup analysis showed that, supplementation by glutamine dipeptide (sustamine) has more efficiency in maintaining blood glucose after exercise compared to supplementation by glutamine (0.51 [95% CI: 0.18, 0.83] mmol/l; P = 0.002 vs. −0.01 [95% CI: −0.60, 0.57] mmol/l; P = 0.96). However, in high-quality studies, plasma glucose levels were significantly lower in the GLN group compared to the placebo group (n = 5, mean difference = −0.46 [95% CI: −0.55, −0.36] mmol/l; P < 0.001). All studies included



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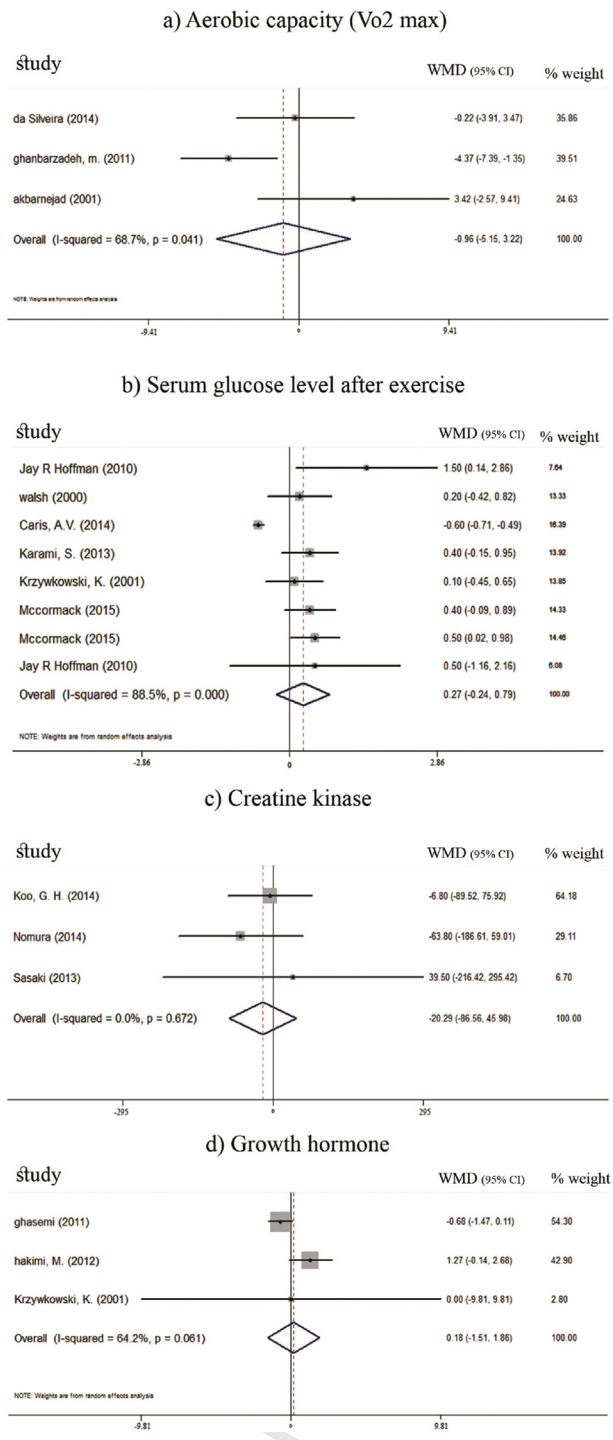


**Fig. 5. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of GLN supplementation on aerobic capacity and blood markers**. A, $Vo_2max$; B, Serum glucose post-exercise; C, creatine kinase; D; growth hormone. Square size shows the weight of study in pooled analysis and horizontal bars reflecting the 95% confidence interval.

"endurance and team sports" athletes. Sensitivity analysis did not provide further information.

Studies on 66 subjects from 3 studies [50,52,73] (36 treatments and 35 control) did not show a significant effect of GLN on blood CK after exercise (mean difference = −20.29 [95% CI: −86.55, −45.97] UI/l; P = 0.54; Fig. 5c). One study indicated no effect of dose on blood CK changes [62]. There was no significant heterogeneity between trials ($I^2$ = 0.0%, P = 0.67). Sensitivity analysis did not show any change in results.

A meta-analysis carried out on three studies [44,64,67], including 30 treated participants and 30 controls, did not find any significant effect of GLN on blood GH immediately post-exercise (mean difference = 0.17 [95% CI: −1.50, 1.85] ng/l; P = 0.83; Fig. 5d). Articles were statistically heterogeneous ($I^2$ = 64.2%, p = 0.06). Subgroup analysis did not find any source of heterogeneity.

## 8. Discussion

In the present meta-analysis, L-glutamine supplementation was not associated with a significant change in the athletes' immune function (leukocyte, lymphocyte and neutrophil counts), aerobic capacity (Vo2max), body composition (fat mass and lean body mass), and plasma levels of glucose, CK and GH after exercise. However, GLN supplementation resulted in a significant weight reduction in athletes.

### 8.1. Immune function

Although moderate exercise stimulates many of the immune system functions, high-intensity exercise may suppress various immune parameters by reducing s-IgA secretion, neutrophil numbers, T and NK cells function as well as change in phagocyte activation [81]. Early studies found that heavy-load exercise can lead to a decrease in athletes' immune function, and proposed that GLN effects are likely to prevent this condition [82]. According to the meta-analysis, GLN did not affect leukocyte, lymphocyte, and neutrophil numbers. However, GLN supplementation in doses more than 0.2 gr/kg BW significantly reduced neutrophil numbers, compared to a placebo. Further, compared with high-quality studies, leukocyte counts were significantly higher in low-quality studies. At the other extreme, some studies reported a significant alteration in immune function following GLN ingestion. The following effects were variously reported with GLN supplementation as compared to a placebo: a decline in the incidence of infection in athletes [18]; changes in the ratio of CD4+/CD8+ [41,54]; increase in the percentage of T-cells [14]; elevation in natural killer activity [54]; increase in nasal Ig-A [47]; enhancement of leukocyte numbers [51,52]; change in neutrophil counts [44,50,52]; increase in IL-6 [46]; elevation in IκBα [53,55]; increase in HSP70 expression [53,55]; and lower plasma levels of TNF-α [55]. It is likely that long-term stress due to overtraining leads to a reduction in GLN synthesis and at the same time increases the body's GLN demands [54]. It has been shown that the immune system needs GLN as an energy source, and that it is also needed for construction of nucleic acid. Additionally, lymphocytes and macrophages require this amino acid for the proliferation and differentiation [83]. Moreover, GLN supplementation can ameliorate stress-induced intestinal permeability, which causes an increase in pro-inflammatory plasma proteins (i.e., TNF-α, IL-6, IL-7), activation of the NF-κB pathways, and endotoxin leakage. In these ways, GLN can play a protective role in the stabilization of the intestinal wall [55]. Nevertheless, most of the studies failed to demonstrate any significant effect of GLN intake on the values of CD4+ and CD8+ [14,42,43,48], NK cells activity [14,43,84], B cell counts [14], s-IgA [1,47,84], plasma levels of Ig A, M and G [50,52,54], leukocyte numbers [14,16,41,43,45,48–50], lymphocyte counts [14,16,41–45,48,49], neutrophil numbers [16,42,43,45,48,49], monocyte numbers [43,48,49], plasma concentration of complements [14,50,52], CRP [14], neopterine [14], IL-6 [14], IFγ [14], ConA stimulated proliferative response [43], LAK [42–44], PHA proliferative response [42,43], and phagocyte activity [50,52]. Based on these findings, it is

more likely that GLN does not affect immunosuppression, as has been remarked by athletes. Although the study duration and supplement dose are important factors to cause the desired effect, this meta-analysis found that there was no difference in acute or chronic intervention duration. However, in some studies, changes in immune function varied over different times [14,50]. Also, the supplement dosage made some difference, as described earlier, in terms of neutrophil numbers.

### 8.2. Body composition

According to our research, GLN supplementation has no significant relationship with lean body mass and fat mass, but there was an inverse correlation with body weight. Consistent with the meta-analysis, several studies found no correlation between consuming GLN and body composition [52,57,59]. However, some studies have shown contrary results. Hakimi [67] and Ghanbarzadeh [63] showed that GLN supplementation increases body weight and lean mass, and significantly reduces fat mass. Lehmkuhl and colleagues [3] suggested that both body mass and LBM increased, while fat mass did not show any significant change after an 8-weeks GLN supplementation. One reason for this variation could be the differences in the amount of GLN intake. As Lehmkuhl [3] showed, adding 4 g of GLN to creatine monohydrate did not change body weight and LBM significantly, compared to creatine monohydrate alone, though that this may have been due to an inadequate dose of GLN. For GLN to have a significant effect on increasing muscle GLN synthetase [63] and on subsequent increases in muscle protein synthesis and muscle mass maintenance [7], the amount of GLN must be high enough to increase plasma GLN levels [85].

The results collected in this paper demonstrate an inverse association between the intake of GLN supplements and body weight. This relationship disappeared following eliminating one of the studies [63]. This weight loss may either be caused by the intensity of the training program [63] or the effect of GLN on reducing body fat. GLN can mediate lipid metabolism and thereby have an impact on the amount of fat tissue [63]. Weight loss may also be due to the effect of exercise on body fluid balance [52]. Another reason for the differences in study results on the effects of GLN on body composition could be due to the differences in the mixture of supplements [63]. Considering the duration of the studies, all studies that included in the meta-analysis were chronic intervention.

### 8.3. Athletic performance

This meta-analysis concluded that GLN supplementation has no effect on the aerobic performance of athletes. Also, there was no effect of GLN on oxygen consumption, oxygen kinetics in muscles, energy cost and aerobic capacity [10,58,60,68,71]. Furthermore, GLN showed no effect on heart rate and thus does not affect muscular blood supply [47,58,66]. In contrast to these findings, some researchers have found a significant relationship between GLN supplementation and a faster mean Vo2 response time, and increases in muscle oxygen consumption, muscle deoxygenation kinetics, oxidative metabolism, and aerobic power [60,63]. It might be that GLN helps to preserve phosphocreatine and glycogen in muscle oxidative fibers as a tricarboxylic acid cycle intermediate metabolite [63]. Overall, though, it appears that GLN plays a minor role in improving athletic aerobic ability.

Studies about the effects of GLN on anaerobic performance present more conflicting evidence. Several studies reported a significant improvement in anaerobic power [6,63,70], strength [65,76], perceived exertion [16,68], reaction time and shooting performance [66,80]. At the other extreme, some studies failed to find a significant relationship between GLN ingestion and anaerobic performance, muscle strength, flexibility, lactate threshold, motor response, vertical jump and lower body reaction [10,66,71]. In general, it seems that GLN has a positive effect on some aspects of anaerobic power and strength. Additionally, based on previous studies, it may be effective in enhancing athletes' tolerance and exercise duration prior to fatigue [6,61]. Furthermore, GLN helped to diminish muscle soreness more quickly [65,76]. However, in some trials, GLN did not affect athletic endurance [56,70,71,74], nor the time nor intensity of muscle soreness [65,74], and in some cases, unfavorable consequences were even observed [68]. GLN has several effects on the immune system and maintaining the body's protein balance, as well as perhaps playing an important role in cellular regulatory systems [86]. GLN possibly also improves muscle function by alleviating inflammatory responses due to exercise [87]. Also, the reduction in protein degradation caused by GLN leads to an increase in the size of fast twitch fibers and enhances buffering capacity [88]. In addition, it is suggested that GLN improves muscle strength and anaerobic power through a number of other functions, such as: increasing muscle cell hydration, which reduces the release of CK, inflammatory processes, and cell lesions [89,90]; reducing sensitivity to dehydration by contributing to a more efficient fluid and electrolyte uptake [66]; promoting muscle glycogen re-synthesis during the recovery period [38]; and reducing plasma lactate concentration [68]. The discrepancies that have been observed in different studies may be due to the form and dosage of supplements, the study duration and quality, the difference in the type and intensity of exercise, and the gender of the participants. For example, some GLN derivatives, such as sustamine, are more stable than GLN itself [91]. Furthermore, combining GLN with maltodextrin has been shown to be more effective than administering the two separately [70]. Also, contrasting results were obtained in one study comparing the effects of GLN on strength between male and female participants [76].

### 8.4. Blood markers (CK, GH, glucose)

The results of the current meta-analysis indicated that GLN supplementation did not significantly affect blood glucose, growth hormone, and creatine kinase levels.

Since there was significant heterogeneity between studies related to blood glucose and growth hormone, the results did not reflect factual findings, while the studies of creatine kinase did not have any heterogeneity. The heterogeneity between studies related to glucose was not abolished by performing subgroup analysis, but the supplement dosage and form were identified as sources of heterogeneity. In line with the meta-analysis, most of the studies did not find a significant correlation between the consumption of GLN and blood glucose [16,44,62,69,72,77]. Among these studies, one study showed higher levels of blood glucose in the placebo group compared to the supplementation group [72] – this may be due to the administration of maltodextrin to the placebo group, while the intervention group was given only GLN. Thus, it is possible to conclude that differences in the type of placebo and intervention duration can lead to different results. Further, this meta-analysis also showed that supplementation by sustamine, but not glutamine, may help athletes in maintaining blood glucose post-exercise. This can be the result of enhancing muscle glutamine uptake by supplementation in dipeptide form [92] that can increase glucose availability. In addition, another amino acid that presents in this dipeptide, alanine, is a gluconeogenic amino acid and may have a contribution to increasing blood glucose levels [93]. Another potential factor that can affect the results from glucose levels, is sport type. All studies that investigated the effect of glutamine on



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blood glucose after exercise recruited endurance and team sport athletes.

Among the studies in relation to GH, one study showed increased levels of this hormone in response to GLN [67]. Other studies also indicated that GLN can increase resting levels of GH [94,95], but not post-exercise levels [95]. Also, the stimulatory role of GLN in growth hormone release can be seen during prolonged critical illness when GLN levels drop below the normal range [96]. The type of exercise also affects the growth hormone response to GLN. Some studies have shown that GLN supplementation during prolonged heavy endurance training has no effect on increasing serum GH [64].

Creatine kinase is a marker of muscle damage that increases in the blood after exercise and is closely linked to energy metabolism [73]. Consistent with other studies [50,52,65,74], the meta-analysis found no effect of GLN supplementation on blood levels of CK, but Koo et al. [73] have shown that GLN reduces CK levels. The reduced levels of serum CK after GLN supplementation may be due to the cellular hydration state. The transportation of GLN into the cell is sodium-dependent. The subsequent entry of water into the cell and release of potassium from the cells [90,97] influences the cellular volume and hydration status, which causes cellular resistance against lesions, and decreases the release of intracellular enzymes such as CK [89,90].

## 9. Conclusion

This systematic review and meta-analysis suggested that GLN supplementation has no effect on leukocyte, lymphocyte and neutrophil counts. Although some studies reported that GLN significantly affects immune function, most studies found no association between GLN ingestion and immunosuppression. Considering the effect of GLN supplementation on athletic performance, it appears that GLN does not affect aerobic performance, but regarding anaerobic performance and strength it could not be determined decisively because of the limited number of studies. Additionally, GLN may have some effects in diminishing muscle soreness more quickly, but it should be confirmed by meta-analysis and needs more studies. In relation to body composition, this study showed that GLN resulted in greater weight reduction, but that the ratio of fat mass and lean body mass did not change. Regarding the post-exercise blood markers, this study found that supplementation in the form of dipeptide, but not glutamine alone, may result in an improvement in blood glucose post exercise. However, because of the low number of studies, this cannot be concluded firmly. There were some limitations in present study including lack of adequate studies to perform the meta-analysis in all areas regards to athletic performance (anaerobic performance, strength, flexibility, etc.), studies in non-English languages that was not possible to be extracted, inadequate information provided by some studies. Moreover, in the meta-analysis, it is not possible to analyze the various measurement parameters for a feature together and this can cause more limitations in interpreting the results. There is a need for more randomized clinical trials to determine whether GLN has a significant effect on athletic performance, immune function, and body composition, or not. Moreover, the present study suggests that the efficacy of GLN supplementation could be affected by the study duration, quality, and supplement dose and type.

## Compliance with ethical standards

Ramezani Ahmadi A, Rayyani E, Bahreini M, and Mansoori A declare that they have no conflict of interest. For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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