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Can Creatine Hydrochloride be an Alternative Molecule to Creatine Monohydrate for Athletes with Weight Gain Restrictions?

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Abstract: *Creatine monohydrate (CrM) supplementation is not recommended for athletes with weight-gain restriction due to its significant water retention adverse effect. Because of this CrM limitation, creatine hydrochloride (CrHCl) was presented in the market. Compared to CrM, CrHCl possesses a different pharmacokinetic and, in theory, could not promote weight gain similar to CrM. However, several aspects related to the stability and efficiency of this new CrHCl molecule need to be investigated and compared to the traditional CrM. This article reviewed the experimental articles that evaluated both weight and body water gain after CrM or CrHCl supplementation. Also, we discuss the possible limitation on performance enhancement of CrM in physical activities where bodyweight influences performance. We will propose CrHCl as an alternative creatine supplement source for the athlete's population, which has weight-gain restrictions. Finally, we will indicate several research questions that must be answered before the CrHCl recommendation for the population of athletes with weight gain restrictions.*

Keywords: *Creatine monohydrate, creatine hydrochloride, weight-gain restrictions, athletes.*

1. INTRODUCTION

Creatine monohydrate (CrM) supplementation increases athletic performance due to improvement in energy availability [1] and its metabolic acidosis buffering ability [2, 3, 4]. The literature describes CrM supplementation as an ergogenic aid. However, due to its low solubility in water, it produces weight gain [5]. Performance improvement outside laboratory tests, such as runners, gymnastics athletes, and fighters (which are divided by weight classes), is not presented in the literature [6, 7]. It can also produce an ergolytic effect in athletes from collective sports modalities where sudden weight gain can interfere in their athletic performance [8, 9].

A new form of creatine (Cr) was released in the sports supplement market (creatine hydrochloride-CrHCl) claims to solve the adverse effect (water retention) caused by CrM supplementation [10]. Compared to CrM, CrHCl is supposedly intended for athletes with weight gain restriction because it is 40 times solubility and relative greater bioavailability (~50% more), therefore better pharmacokinetics [10, 11]. However, there is a lack of information on the ergogenic features of CrHCl in the literature; therefore, studies that prove the efficiency of CrHCl are necessary.

This review will discuss the possible limitation of CrM (weight gain and body water retention)in its implications onphysical activity (PA),where bodyweight influences athletic physical performance. Thus, we will propose CrHCl as an alternative Cr supplement source for the athlete's population, which has weight gain restrictions. Finally, we will indicate several research questions that must be

answered before the CrHCl recommendation for the population of athletes with weight gain restrictions.

2. IS CRM INDICATED FOR ATHLETES WITH WEIGHT GAIN RESTRICTION?

However, studies with CrM supplementation on endurance performance are controversial. Some studies report improvements [12], and others do not [9, 12]. These different results in endurance activities seem to be related to the fact that CrM supplementation promotes weight gain [6].

Cr is considered the most used and studied sports ergogenic aid [13]. It is well documented that CrM ergogenic effects can be seen after a specific supplementation protocol (300mg/kg/day, divided into four daily doses) during ≥5 days [14, 15]. The ergogenic effects of Cr supplementation (due to an increase in the intracellular PCrstores) are well documented, especially in high-intensity intervals PA or in a single short-duration bout exercise [6, 15, 16]. Virtually all the evidence related to the Cr ergogenic benefits is derived from CrM [15], a relatively low-cost molecule compared to the other types of Cr salts.

Weight gain related to CrM supplementation has been reported since 1926 [5]. Some studies that present results of physical tests in which bodyweight influences performance do not present the Cr ergogenic effects [9, 15, 17]. Are these weight gain ergolytic for runners? For example, it has been shown that despite improving energy metabolism, CrM supplementation promotes a greater collagen degradation and purine production in both long-distance and multiple sprints running [9]. The authors attributed these findings to the weight gain effect induced by the CrM supplementation protocol, i.e., it seems that with this protocol, there is greater cartilages degradation in both knees and ankles (due to the increase of the impact in these joints); also, it demands more energy to move the extra weight (which results in greater purine production).

Generally, in activities where bodyweight is eliminated from the tests (e.g., in medium and long-term cycle ergometers in a laboratory environment), ergogenic effects of CrM supplementation are demonstrated [3, 18, 19, 20]. However, when bodyweight is a variable that can influence performance, for example, running or swimming in a field test, the performance benefits are low [6, 7]. For example, a recent meta-analysis [6] observed that studies with field tests (e.g., jumping, swimming, running) have lower effect size values than laboratory tests type (e.g., cycle ergometers); the authors also speculated that this discrepancy is related to the increase in bodyweight promoted by CrM supplementation. Because CrM promotes water retention throughout the body, increasing the bodyweight after the supplementation protocol (see Table 01), CrM is avoided by swimmers, fighters, and long-distance runners or athletes of collective sports in moments close to competition, whereas body weight is a determining factor.

The studies in Table 01 are the results of our search in the literature with the keywords *creatine* and *total body water* in PubMed and their citations in google scholar. In the search, we identified 16 randomized placebo-controlled studies that assessed body water retention and associated weight gain after ≥5 days of CrM supplementation.

Table1. *Studies exploring the effect of creatine supplementation on water retention and weight gain.*

Studies	Participants	Supplement protocol	Total body Water/ Weight gain
(Powers et al., 2003) [21]	16 healthy resistance-trained (RT) men (age 23y) and women (age 22y).	25 g/d of CrM for 7 days (loading phase) and 5 g/d for the remaining 21 days.	↑*/↑
(Kreider et al., 1998) [14]	14 football players (age 19y) submitted to RT and football training.	15.75 g/d of CrM for 28 days.	↔#/↑
(Francaux & Poortmans, 1999) [22]	9 healthy male subjects (age 22.0 y) submitted to a RT.	21 g/d of CrM for 5 days (loading phase) and 3 g/d for the remaining 58 days.	↑#/↑

(Kutz & Gunter, 2003) [23]	17 active males (age 22.9 y) submitted to a lower limbs RT.	30 g a day of CrM for 2 weeks and 15 g a day for the remaining 2 weeks.	↑#/↑
(Bemben, Bemben, et al., 2001) [24]	9 active males (age 19.4 y) submitted to a RT.	20 g/d of CrM for the first 5 d, followed by 5 g/d for the 8 weeks.	↑#/↑
(Bemben, Tuttle, et al., 2001) [25]	11 healthy, sedentary, college males (age 19.4 y)	20 g/d of CrM for the first 5 d, followed by a 5g/d for the next 5 d.	↔#/↔
(Grindstaff et al., 1997) [26]	10 healthy swimmers' men and women (age 15y).	21 g/d of CrM for 9 d.	↔#/↔
(Kern et al., 2001) [27]	10 healthy males (age 18 to 40y).	21 g/d of CrM for 5 days (loading phase) and 10,5 g/d for the remaining 28 days.	↑#/↑
(Kilduff et al., 2004) [28]	11 endurance-trained males (age 27.5y)	20 g/d of CrM for 7 d	↑#/↑
(Easton et al., 2007) [29]	12 endurance-trained males (age 31y)	20 g/d of CrM for 7 d	↑#/↑
(Rawson et al., 2011) [30]	14 healthy physically active men and women (n=4, age 21y).	0.03 g/kg of body weight of CrM per day for 6 wk.	↔#/↔
(Volek et al., 2001) [31]	10 healthy physical active males (age 21y).	0.3 g/kg/ of body weight of CrM per day for 7 d.	↑#/↑
(Powers et al., 2003) [32]	12 healthy aerobically trained males (age 23y).	25 g/d of CrM for 5 days (loading phase).	↑#/?
(Ribeiro et al., 2020) [33]	14 healthy trained males (age 21.8 y) submitted to a RT.	20 g/d of CrM for the first 5 d, followed by a 3g/d for the next 51 d.	↑#/↔
(Deminice et al., 2016) [34]	7 soccer players (age 21.8 y) submitted to a RT.	0.3 g/kg/ of body weight of CrM per day for 7 d.	↑*#/↑

**, direct assessment; # estimated assessment with BIA; ?, data not reported. Changes reported in this table are pre to post CrM supplementation. All studies are two-arm designs controlled by placebo supplementation (crossover studies or studies associated CrM with other supplements to add body water gain were excluded).*

With the data from the studies presented in Table 01 we found that there is a significant difference after CrM when compared to placebo condition (Figure 01) in total body water (CrM= 3.75 ± 2.52%, PLA= 0.75 ± 1.28%, mean difference= 2.75%, p< 0.00) and weight gain (CrM= 1.61 ± 1.13%, PLA= 0.37 ± 0.40%, mean difference= 1.13%, p< 0.00). The data in Figure 1 show great heterogeneity between studies, which may be related to differences in methodological approach such as participant samples (sedentary and trained in endurance or resistance training) and supplementation dosage protocols. However, the values of bodyweight gain after CrM supplementation (~1.3%) are similar to those reported by a systematic review performed previously [6].

We also identified a positive and significant correlation between dose size and weight gain (r= 0.62, p= 0.02), but not for dose size and total body water gain (r= 0.27, p= 0.35). Previous studies have

been demonstrated that CrM increases muscle glycogen content [35] and total skeletal muscle mass (which may involve the addition of protein, glycogen, and water content in the muscle tissue) [33]; this may account for the significant correlation between weight gain and dose size.

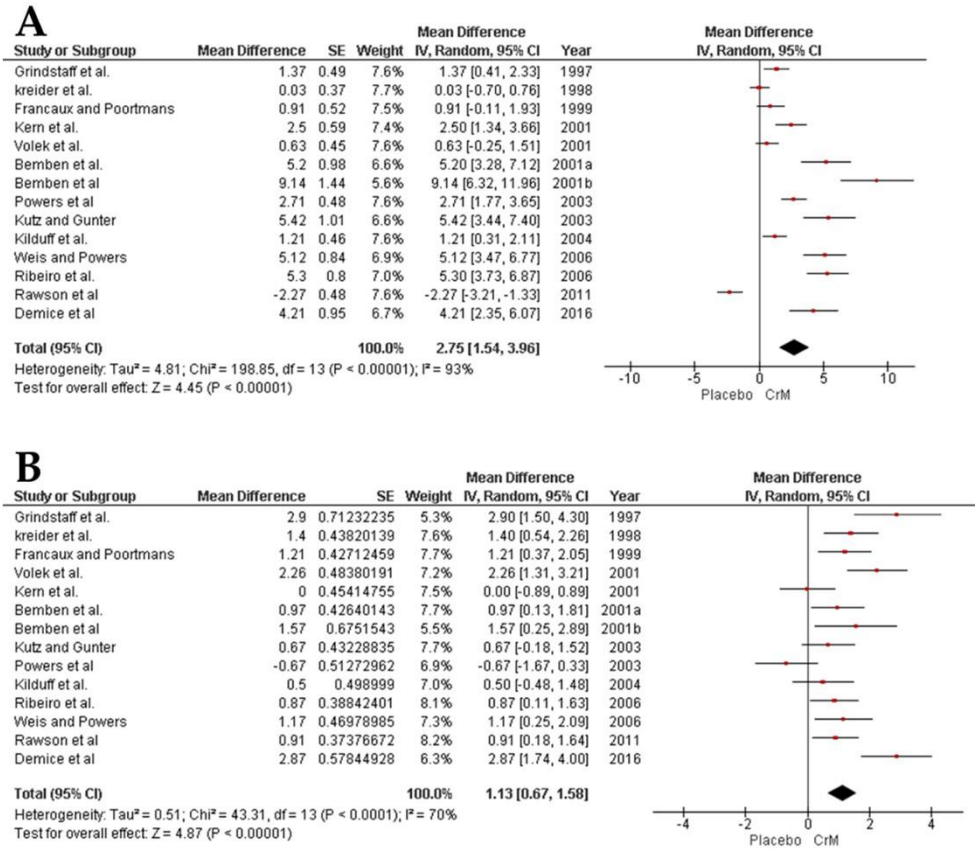

Fig1. *Comparison of percent change in total body water (Figure A) and weight gain (Figure B) after creatine or placebo supplementation.*

Our literature search indicates that CrM supplementation can increase the mean weight gain by 1.61 ± 1.13% after the supplementation periods. In the linear regression presented in Figure 02 (from data of 14 studies presented in Table 01), for each ~0.0049g of CrM supplemented, we have a bodyweight gain of 0.378%. Therefore, an athlete could gain 1.08% of weight gain after a protocol of 5g/day during 28 days of CrM supplementation or ~1.89% of bodyweight gains after 20g/day for seven days followed by 5g/day for 21 days. The bodyweight gain may be linked to the physicochemical properties of CrM and its pharmacokinetic characteristics [36], which we will further discuss in the next section.

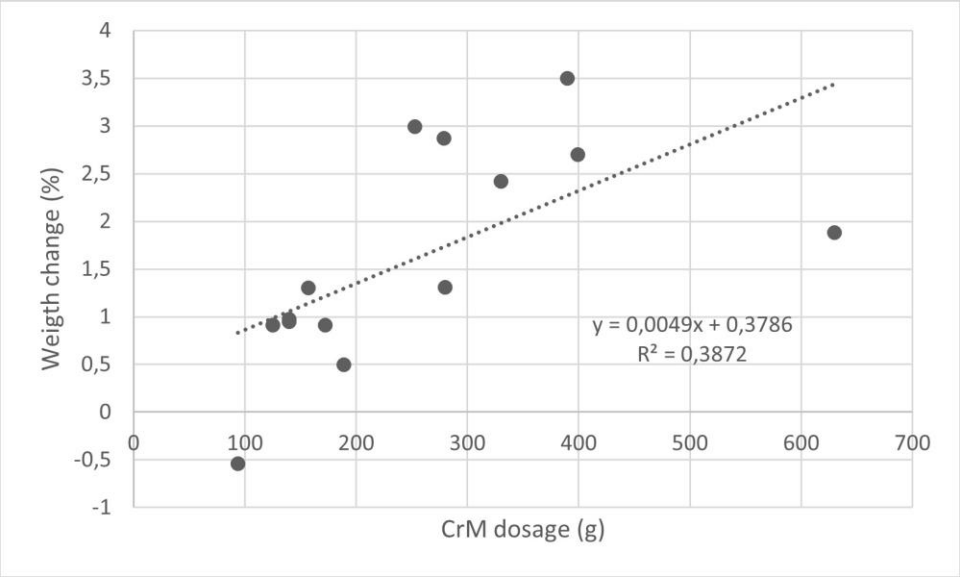

Fig2. *Linear regression between the total dosage of CrM supplementation and weight gain*

Athletes and coaches should assess whether this weight gain (from the CrM supplementation)can mitigate possible performance enhancement from physical training or, in fact, the metabolic improvement from Cr supplementation can outrun the weight gain (that is, athletes with restricted weight gain and their coaches should evaluate pre- and post-supplementation performance and verify if the benefits of CrM supplementation outweigh the weight gain).

3. IS CRHCL INDICATED FOR ATHLETES WITH WEIGHT GAIN RESTRICTION?

The sports supplement industry uses this aspect of CrM (i.e., weight gain) to propose new types of Cr salts. Among the suggested Cr, the most promising appears to be CrHCl, which has a reported solubility around 40x greater than CrM [10]. Studies have shown that CrHCl is a stable molecule in the digestible tract [37] with a faster absorption than CrM [10]. The greater CrHCl solubility and relative greater bioavailability (~50% more), therefore better pharmacokinetics [10, 11]. Such pharmacokinetic change would theoretically imply lower doses (CrHCl: 2.5 g/day *versus* CrM= 5 g/day) [38] to achieve the same muscle saturation effect in 30 days; this would imply lower water retention and lower bodyweight gain. Therefore, future studies are required to test whether the suggested dosage for CrHCl increases muscle concentrations similarly to CrM as found in the literature.

It is important to highlight that their salt forms extensively affect the physicochemical and biological properties of active pharmaceutical ingredients or molecules. Therefore, the choice of a particular salt formulation is based on numerous factors such as molecular chemistry, intended dosage form, pharmacokinetics, and pharmaco dynamics of the agent. The appropriate salt can improve the overall therapeutic and pharmaceutical effects of a molecule. However, the incorrect salt form can have the opposite effect on pharmacokinetics and consequently on bioavailability and can be quite detrimental to molecule development [39]. The HCl salt has been used in the development of products such as drugs or supplements in order to lower its pH and improve its solubility in water, and also to increase its bioavailability in blood plasma after oral administration, so the dose needed to reach plasma levels of the bioactive product is much lower in the HCl salt when compared to the monohydrate compound [11]. Assuming that 2.3g of CrHCl would induce muscle saturation equivalent to 5g/day of CrM (this hypothesis needs to be verified yet), and according to the linear regression data presented in Figure 2, thirty days of 2.3g CrHCl supplementation (suggested elsewhere [11] could result in a 0.53% bodyweight gain (i.e., halved the effect of Cr-induced weight gain).

To our knowledge, there is only one study (from our laboratory) that evaluated body water retention and weight with CrHCl [40]; see Table o2. Yoshioka et al. [40] evaluated 11 Olympic gymnastics

athletes during CrM or CrHCl supplementation and found an increase in weight and gain in total body water after CrM. Interestingly, it identified weight loss and no change in total body water after CrHCl supplementation. Yoshioka et al. [40] used a counterbalanced and cross-over design; however, the protocol supplementation had a short washout period (only thirty days). In addition, performance (1RM in upper and lower limbs) was similar in the two supplementation protocols. Due to the short washout period, it is hard to conclude about performance or weight gain after CrHCl. Therefore, future studies will be necessary to replicate this experiment in a longer washout period or two-arm design with large sample size.

Two other studies from our laboratory (Table 02) assessed performance and body composition after CrHCl supplementation and compared it with CrM after resistance training [41] and endurance training [42] protocols. In both studies, we did not identify participants' bodyweight changes. It should be noted that the bodyweight of the participants in the endurance studies was verified one day after a 10km run in a field test at a ~25°C (we believe that dehydration may have interfered with post-supplementation induced gain in bodyweight). Both studies showed an increase in endurance performance and 1RM test when compared pre- to post-supplementation, but not when compared with placebo. Future studies solve this issue by increasing the sample size and, therefore, improving the statistical power for these comparisons.

Table2. *Studies comparing CrM and CrHCl on body composition.*

Studies	**Participants and intervention**	**Supplement protocol**	**Total body Water/ Weight gain**
(Yoshioka et al., 2019) [40]	11 males' elite gymnastics athletes submitted do intense training blocks (age 18 to 25 y)	5g CrM for 30 days followed by 30 days of placebo supplementation then more 30 days of 1,5g of CrHCl or 30 days of 1,5g of CrHCl followed by 30 days of placebo supplementation then more 30 days of 5g of CrM.	CrM= ↑#/↑; CrHCl= ↔#/↓
Santana et al. (2017) [42]	11 physical active individuals (both genders) submitted to endurance training (age 20-30 y).	CrM (N=6): 20g/day per 7 days followed by 5 g/day per 21 days; CrHCl (N=5): 6g/day per 7 days folloede by 1.5 g/day per 21 days.	CrM= ?/ ↔ CrHCl= ?/ ↔
De França et al. (2015) [41]	10 physical active individuals (age 20 to 40 y) submitted to RT	5g of CrM or 5g CrHCl or 1.5gcreatine HCl/day, Creatine HCl-2 (HCl-2) = 1.5 g of creatine HCl/day 5g of CrM or 5g of CrHCl or 1.5g CrHC for 28 days	CrM= ?/ ↔; CrHCl 5g= ?/ ↔; CrHCl 1.5g= ?/ ↔

A recent study [43] tested 3 and 20 g of CrM and 3 g of CrHCl for seven days on the vigor, power, plasma levels of testosterone (T), cortisol (C), and the ratio T/C. The increase in explosive power, upper-body strength, lower-body strength, T, decrease in C, and improvement in T/C occurs only in 20g CrM, but not in 3g of CrM or CrHCl. This study suggests that short-term supplementation with 3 grams of CrHCl is insufficient to induce ergogenic effects. The study did not report changes in the participants' body composition.

We did not identify in PubMed or Google Scholar other studies published in peer-reviewed journals that compared CrHCl with placebo in terms of performance or body composition variables. Therefore, we cannot draw conclusions from experimental studies to confirm if CrHCl is suitable for athletes with restricted weight gain. As already discussed, we identified a positive correlation between CrM supplementation dosage size and weight gain. However, the ergogenic effect of CrM supplementation when compared to placebo is unquestionable. So, an open question remains: "the ergogenic effect of Cr supplementation always results in weight gain?" The low dose (1.5g/day) suggested by the CrHCl manufacturers used in the three studies mentioned in Table 2 did not induce weight gain. However, it also did not increase athletic performance when compared to placebo supplementation. Therefore, there is still no consistent data demonstrating that the 1.5g dose of CrHCl induces an ergogenic effect when compared with placebo supplementation.

Also, many other questions remain open. For example, checking the CrHCl stability is essential to know its ergogenic potential, as done with Creatine ethyl ester (CrEE). It has recently been shown that CrEE is highly unstable because it undergoes cyclization in plasma by transforming it into creatinine (i.e., in an inactive molecule for athletic performance purposes) [44]. As a result, efficiency for CrEE increases muscle Cr pool is missing [45]. From these findings, it was concluded that CrEE does not serve as an ergogenic resource [1, 46].

To verify the CrHCl molecule stability, thus, its ergogenic potential, we must follow three stages in vitro and another stage in vivo.

- 1st stage in vitro:

First, the verification of the different pK_a values of CrHCl because it is known that the stability of the Cr molecule is related to its pK_a. This variable determines its protonation/deprotonation or non-enzymatic cyclization, i.e., Cr can be transformed into creatinine [44, 46]. For example, CrEE had pK_a values (pK_{a1}= 2.30 and pK_{a2}= 5.25) below blood pH (pH= 7.4) and muscle (pH= 6.8), which causes ions H^+ loses (by deprotonation) from their structure due to its low isoelectric point (pI= 3.7) [46]; CrM, on the other hand, is more stable because it pKa values (pK_{a1} 2.79 and pK_{a2} 12.1) provide a pI=7.4, which is similar to blood plasma and muscle cell [46].

Data from CrHClpK_a are scarce. However, the information available on its first pK_a (i.e., pK_{a1}= 6, in water at 25°) and its high solubility (i.e., 48x) when compared to CrM [10] raise the hypothesis that its pI is lower than physiological pH. The low CrHCLpI (below physiological pH) makes it highly soluble when compared to CrM; however, it can also make it potentially unstable (i.e., susceptible to deprotonation at human physiological pH). The CrHCl molecule may be stable even with low pI if it is a protected protonation/deprotonation or cyclization molecule; however, there is no data to prove this stability.

- 2nd stage in vitro:

After verification of CrHClpI, the next step would be to verify their stability in simulated environments of digestion situations and blood plasma, as done by Hageböck*et al* [37].

- 3rd stage in vitro:

To verify if CrHCl supplementation is phosphorylated by Creatine Kinase (CK) with similar efficiency to CrM, as already verified on another occasion by Ravera *et al*. [47].

- 1st stage in vivo:

If CrHCl is stable at different pHs and a CK pro-nutrient, the next step would be to check its stability in blood plasma after oral ingestion. Also, to determine the daily intake, it is necessary to verify if there is an increase in muscle tissue and its magnitude when compared to CrM standard recommendation. It has been estimated that 30 days of ~2.3 g/day of CrHCl may be sufficient to increase muscle Cr pool, similarly to ~5g/day dosage of CrM [11]. If empirical experiments demonstrate that this CrHCl dosage is efficient to increase Cr muscle poof, it is likely to mitigate the weight gain effect.

Last but not least, evaluating the safety of HCl supplementation is also necessary due to the risk of oesophageal or dental damage due to the chronic oral HCl salt intake [48].

If CrHCl has a positive evaluation in these previews' stages mentioned, then the evaluation of its effectiveness in sports performance related to impairment due to weight change can be tested.

In summary, there is still no scientific evidence for its effectiveness in several parameters such as stability in blood plasma after oral intake, safety, increased concentrations in muscle tissue, or efficiency as an ergogenic supplement. In other words, there is still insufficient evidence to guarantee that CrHCl is an ergogenic molecule, as well as CrM [1, 6, 16, 49].

4. CONCLUSIONS

Athletes with weight gain restrictions might not benefit (i.e., increased athletic performance) from CrM supplementation since this molecule induces significant body water retention and weight gain. Athletes with restricted weight gain and their coaches should evaluate pre- and post-supplementation performance and verify if the benefits of CrM supplementation outweigh the weight gain. CrHCl seems to bring the solution to the weight gain effect. However, research is still needed to test its physiological stability and ergogenic potential. For example: to verify if CrHCl supplementation is a stable physiological molecule, increases muscle PCr pool, and if CK phosphorylates it with similar efficiency to CrM. More important, there is no data demonstrating the improvement in athletic performance of CrHCl when compared to placebo supplementation. After verifying these assumptions, the athletic performance verification studies, particularly in athletes with a restriction for weight gain, become valid.

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AUTHOR CONTRIBUTIONS

Designed the study, literature search, data analysis, and wrote the first draft (Elias de França and Erico C Caperuto). Added important intellectual content writing, criticizing, and correcting previous versions of the manuscript (Ronaldo VT dos Santos, Vinícius B Hirota, and André R Fukushima); all authors approved the final version of the manuscript.

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