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Article type : Review

Sodium citrate supplementation: an updated revision and practical recommendations on exercise performance, hydration status and potential risks

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/TSM2.174

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Running title: Citrates in performance and hydration

Keywords: exercise, physical activity

Abstract

Based on the assumption that a significant buffering capacity is able to attenuate the negative pH changes associated with high intensity physical exercise, numerous studies have been focused on the effects the exogenous administration of sodium citrate (SC) on human performance. However, the exact mechanisms of action of citrates have never been accurately described and results obtained so far often failed to demonstrate a significant advantage, mainly to an unfavorable relationship between achievable benefits and risk of side effects. In recent years, new evidence has emerged on the fields of use of SC supplementation in sports thus providing the theoretical basis for its use after dehydrating exercise to promote a fast fluid recovery. The aim of this review is to highligths recent experimental observations that could provide new interest in this buffering agent.

Introduction

Among the different nutritional strategies to improve performance, some ergogenics aids are based on the capacity to modify the acid/base balance by counteracting the accumulation of hydrogen ions (H^+) that occurs during high intensity muscle contractions. During exercise, the arising of energy demand is mainly satisfied by the anaerobic glycolysis followed by lactic acid production. Lactic acid immediately dissociates into H^+ and lactate ions (Lac-) and this chemical event causes the acidification of the intrecellular muscular environment. In particular, the exercise-induced acidosis occurs when the production of H^+ overcomes the capacity of skeletal muscle disposal, and this event is followed by different consequences on cell energetics leading to muscle fatigue and performance reduction [1–3]. As shown by several studies[4,5], acidification is mirrored by a significant decrease of muscle pH from ~7.1 (at rest) to ~6.5 after high-intensity exercise until exhaustion. In a low pH environment the activity of some glycolytic enzymes can be reduced, lowering the rate of ATP production[6]. In addition, extra H^+ interferes directly with the muscle contraction by competing with calcium ions for the troponin binding site[7], and affects the oxidative

phosphorylation as well as the resynthesis of phosphorylcreatine[8]. Taken together these phenomena are fundamental for the onset of muscle fatigue, even though an exact mechanistic explanation of the process has not been provided yet, remaining an object of debates and investigations[9,10].

In basal conditions, inside/outside the cells, the body maintains the pH balance in a physiological range, thanks to intracelullar buffers (phosphates, proteins and dipeptides present in the cytosol), extracellular buffers, and dynamic buffering systems that involve renal and respiratory mechanisms[11]. In addition, there are buffers that can directly accept or release H^+ to prevent dramatic changes in pH; in the muscular environment the balance is also maintained by lactate-proton transporters called monocarboxylate transporter 1 (MCT1) and 4 (MCT4) carrying H^+ from the muscles to the blood where the chemical buffering system is mainly composed of bicarbonate (HCO_3^-)[12]. These endogenous regulation mechanisms are usually highly efficient but, in certain conditions, as in the case of very high intensity exercise (Vo_2Max>90%), they can quickly become overloaded[13]. Therefore, in the last century there was a strong focus on the use of buffer supplements capable of inducing blood alkalosis to study their mechanisms of action and possible benefits on physical performance. Among these, supplementation of beta-alanine, sodium bicarbonate, sodium citrate (SC) and sodium/calcium lactate have been used in order to increase the extracellular buffering capacity with encouraging results in some cases and conflicting in others[14,15]. Several authors have recently provided useful information on the use of these supplements, suggesting dosages, intake times and possible side effects[16–18]. However, on the specific effect of SC no updated reviews are available at present and the most recent published article[19], based on a previously meta-analysis[20], only described general factors that influence individual responses to extracellular buffers, without suggesting strategies to optimize supplementation strictly referred to SC. Considering that some interesting findings have emerged in recent years regarding SC optimal intake timing, administration form and doses to improve fluid balance in dehydrated athletes, with potential positive consequences on performance, the purpose of this work is to provide an updated review on the latest SC experimental results and to summarize some practical evidence-based recommendation in relation to SC mechanisms of action.

Mechanisms of action

Sodium bicarbonate and SC are the most common options to improve blood buffering capacity but the SC supplementation has shown less gastrointestinal (GI) distress[18]. After the intake, SC rapidly dissociates in body fluids, into the constituent ions: Na^+ and $citrate^{3-}$. Citrate contains three functional groups of carboxylic acid which, due to the relatively low pK values of each at physiological pH, are completely ionized giving a large overall negative charge (-3). The citrate anion is expelled from the plasma and involves a variation in the ratio between strong cations and strong anions altering the electrical balance. In order to restore electric neutrality, the $[H^+]$ is decreased and $[HCO^{3-}]$ increases, resulting in a rise in pH and in an alkalotic state[21,22]. The increase in pH facilitates the disposal of lactate from the muscle during exercise by the monocarboxylate transporters, improving the contractile capacity of the muscle[23–25] and thus favoring an increase in performance compared to the same dose of $NaHCO^{3-}$. However, while sarcolemma is particularly impermeable to HCO^{3-}, citrate can penetrate this membrane through different systems involving specific transporters[24,26]. The citrate flow through the inner mitochondrial membrane occurs through a citrate transporter protein (CTP), while in the tissues different transporters belonging to the SLC13 gene family have been identified that allow citrate absorption from the blood[27]. Further information on the mechanisms of transport of SC through the membranes was described by Mycielska and collaboratorsin 2009[28]. Citrate is a fundamental substrate for cellular metabolism in different energy processes: it is an intermediate of the Krebs cycle; it carries acetyl CoA from the mitochondria to the cytosol; it interferes with glycolysis by inhibiting phosphofructokinase (PFK). According to some authors, the inhibitory effect on glycolysis could affect short-term performance (less than 180 sec) but disappear with long-term exercise in which higher lactate production arises[29]. Since such mechanisms have never been established in humans, further high-quality studies are needed to understand the final role of citrate in muscle during exercise.

According to a study by Street and coll., the alkalosis observed after SC ingestion reduces the interstitial K^+ accumulation released by the muscle during intense exercise[30]. The accumulation of K^+ contributes to the manifestation of fatigue[2,31]and reduces muscle excitability[32]. It has been suggested that a lowering of the interstitial $[K^+]$ during exercise is associated with an improved performance[33]. Furthermore, the impact on the electrolyte balance following the intake of SC also affects some hormones. In a recently published study[34], lower values of aldosterone and cortisol were found after SC ingestion, probably due to increase $[Na^+]$ and reduced $[K^+]$, the first being

considered a weak stimulus whereas the latter a strong stimulus for aldosterone secretion[35,36] (Figure 1).

Dose and Timing

Back in the early 19th century, the ergogenic effect of some substances capable of modifying the blood pH was already hypothesized[37–39]. In 1953 Johnson and Black from the University of Maryland, were pioneers in the study of the effect of these compounds to increase physical performance but results obtained on SC (5 g) or sodium bicarbonate (3.5 g) assumption failed to show performance advantages in young male runners[40]. Since then, increasingly higher doses have been used to understand SC benefits and tolerability. 40 years after the study of Johnson and Black, findings from McNoughton et al. showed a linear increase of blood bicarbonate following SC doses in the range from 0.1 to 0.5 g*kg^{-1}bw but only the dose of 0.5g *kg^{-1}bw appears to be the minimal effective required for performance enhancement during anaerobic cycle ergometer test of 1 min[41]. The suggested dose of 0.5 g*kg^{-1}bw (35 g for a subject of 70 kg) appeared to be the most appropriate in subsequent trials by other authors[22,42,51,43–50], very much higher than the 5 g in single dose bolus used by Johnson and Black[40]. However, a later slow decline in the interest for new investigations on the potential role of SC as ergogenic aid derived from a meta-analysis published in 2011, showing the lack of a clear effect on performance (0.0±1.3%) from a typical SC dose of 0.5 g*kg^{-1}bw[20]. Despite this, the authors pointed out that in the majority of the studies considered, the ergogenic effect was evaluated 60-120 min after ingestion, while the peak in blood bicarbonate was observed at least 180 min after SC ingestion. Therefore, the timing factor could be critical in the lack of significant benefits.

In recent years, two studies published by Urwin blunted any doubts about the optimal timing of SC ingestion for the maximal achieveble change in blood pH to hypothesize an ergogenic effect due to acute supplementation[52,53]. In 2016 the first SC dose-response study in absence of exercise was published[52]. Urwin et al.[57] measured blood pH, blood bicarbonate concentration and gastrointestinal symptoms at rest and at 30 min intervals after supplementation of three SC dosages (0.5; 0.7 and 0.9 g*kg^{-1}bw) for 240 minutes post-ingestion. For each of SC doses used in the study, blood bicarbonate concentration was significantly higher ($p<0.001$) than baseline (90 min post-ingestion) while the peak blood pH was observed between 180 min to 215 min after ingestion. However, in this study no significant differences were observed in blood bicarbonate concentration at all SC doses used ($p<0.05$). These findings provide two fundamental pieces of

evidence: 1) SC can induce a significant alkalosis for several hours achieving a blood pH peak after at least 3 hours from ingestion; 2) higher doses than 0.5g*kg^{-1}bw may not provide any additional buffer capacity. Similar results have also been reported in another paper recently published by Urwin et al.[53]. This latest study compared the effects of two different forms (water solution Vs capsules) of SC (0.5 g*kg^{-1}bw) on blood pH, blood carbonate and GI symptoms for 240 minutes post-ingestion, in physically active participants. Compared to baseline, a significant increase of blood pH and bicarbonate to peak ($p<0.001$) was observed, both for capsules and water solution. More importantly, the stronger buffer effect following capsules ingestion was not expected [higher peak blood pH ($P < 0.001$) and blood carbonate ($P= 0.013$)]. However, for capsules ingestion, the time to reach the peak values of blood pH and blood carbonate was significantly higher than for water solution. Notably, focusing on individual data following SC intake, an important aspect emerging from this study regarded the wide variability of responses between subjects. This can be due to not only the different form of SC administered, but also because of a different inter-individual alkalotic peak in terms of blood pH, blood bicarbonate concentration or both, as reported by Gough et al.[54]. Based on this evidence, future more accurate studies should take into account the opportunity of considering a personalized buffer capacity of each participant in order to tailor the strategy of SC supplementation and definitely establish its potential effect[55].

Effects on exercise

It is important to note that several hours after SC intake the buffer potential appears higher than an equimolar dose of sodium bicarbonate (higher concentration of HCO_3^-). This effect is probably due to the presence of three negative charges in the molecule (while bicarbonate ions have only one) which dispose of H^+ and increase [HCO_3^-][56]. This evidence reinforces the hypothesis that timing and dosage of SC ingestion may represent key features to achieve significant functional improvement during exercise and their adequate combination probably lacks when a change in pH is not associated with an ergogenic effect[30,57–63]. In fact, some initial results suggest that to supplement SC at the dose of 0.5 g*kg^{-1}bw or higher with a timing above 90 min is able to improve endurance performance(3 km and 5 km time-trials in elite multidisciplinary athletes and well-trained college runners respectively) in presence of controlled experimental conditions in double-blind randomized trials [22,45]. However, findings from other field studies suggested that the

ergogenic effect of SC supplementation on running performance may not occur in the real competitive world[46,48]. For example, acute SC assumption induced alkalosis and plasma volume expansion by improving water retention but this was not associated with ergogenic effects in a running race of 5000 m, performed in warm environment and that involved non-heat acclimated endurance-trained males. However, in this study the authors pointed out that, considering the inter-individual difference of the impact of SC on performance, the likelihood of benefits was higher than that of harm[48].

Another determinant of the effect may be the duration of the endurance trial. In fact, findings from a study published in 1996, showed that the use of SC (90 min before trial rides) improved 30 km cycling time-trial (TT) performance in trained male cyclist[43]. Shabort et al. showed that SC ingestion failed to improve cycling performance in male cyclist involved in 40 km TT, but in this case exercise was performed only 60 min post-supplementation[58]. Acute SC supplementation (0.5 $g*kg^{-1}bw$) administered 120 min before a 200 m swimming race did not show a significant improvement of performance in all swimmers and only a modest amilioration of time was detected in half of the swimmers (those who were older and with greater body mass)[49]. Linossier et al. demonstrated that, compared to the placebo, SC had a significant ergogenic effect on supramaximal efforts as evidenced by the increased exhaustion time (by 15%) in active students[44] performing a cycle ergometer test at 120% peak oxygen uptake. As far as we know, only one study evaluated the effects of SC supplementation in subjects who performed a sustained isometric contraction[64]. The results suggested that SC ingestion (0.4 $g*kg^{-1}bw$) was an ergogenic aid during a prolonged isometric knee extension to 35% of the maximum voluntary contraction (MVC) in healthy active male subjects (age 25-35). Recently some researchers have shown the ability of SC to improve tennis performance[51]. A larger amount ($p<0.001$) of competitions won in the simulated game was observed for the SC condition against the placebo condition (SC: 8.0±1.6 against PLA: 6.0±1.7) in ten Brazilian nationally-ranked young male tennis players. The main findings of this investigation supported the hypothesis that alkalotic state induced by SC (0.5 $g*kg^{-1}bw$) would increase performance since a positive correlation ($r=0.70$) between pH level and games won was reported. This finding showed SC supplementation as an effective ergogenic aid to improve skilled tennis performance but it should be stressed that the number of sets won could also be due to technical and tactical determinants capable to impact on the final result.

Citrates to promote rehydration and weight gain

In 2004, results from Oopik et al. suggested that the ingestion of SC (0.5 g*kg^{-1}bw in 1.5 litres of solution) did not improve performance in trained male runners during a 5 km of running race, but supplementation determined fluid retention (approximately 1% of body mass), and an increase in plasma volume and pH compared to pre-exercise values[46]. The higher plasma volume was an expected phenomenon due to the sodium load induced by the citrate beverage. Furthermore, the body weight gain induced by SC ingestion was maintained throughout the duration of the test. Importantly. these findings open up a new scenario in which SC supplementation could be useful to prevent the decline in performance due to fluid loss and dehydration. For example, in athletes involved in combat sports it is common practice to lose body weight quickly before a match and then increasing it a few hours after the weigh-in[65]. Although this practice entails considerable health risks, it continues to be widely used. From a study conducted on combat sports athletes during the 2013 high Spanish national championships, 84% of participants were hypohydrated at weigh-in and among them, 50% were severely hypohydrated[66]. In addition, severely dehydrated athletes reported declined neuromuscular performance when compared to what observed after 13-18 h of rest and rehydration. Findings from Timpmann and collaborators suggested that dietary SC supplementation improves hydration following a 5% rapid loss of body mass in trained wrestlers; in particular, results showed that the addition of SC (0.6 g*kg^{-1}bw) to a high carbohydrate diet stimulated regain of bw by increasing plasma volume during the 16-hour recovery period[67]. Similar results obtained by Aedma and collaborators showed that the ingestion of a higher dose of SC (0.9 g*kg^{-1}bw in 17h) reduced both fluid loss by increasing water retention and perceived fatigue in trained wrestlers in conditions simulating a competition day[68]. Even in this case the supplementation was not associated with significant increase in performance measured as peak power. As enhanced plasma volume may improve endurance performance by fighting against the increase in core body temperature[69], recent studies investigated the potential benefits of SC ingestion in endurance sports performed in warm environmental conditions[34,48,70]. Mora-Rodriguez and Hamouti focused on the importance of pre-exercise plasma volume expansion in endurance performance following the ingestion of saline solutions and showed that acute plasma volume expansion in the range of 7-8% can improve performance of 20% on average[69]. Suvi et al., for the first time, studied the impact of SC ingestion on cycling performance during 40 km of TT in a warm environment[70]. Similarly to the Timpmann study[67], participants consumed SC (0.6 g*kg^{-1}bw) in a 16h rest period after losing 4% of their bw through exercise in the heat, and before 40 km TT the plasma volume was 7.8 % higher in the SC group compared to 0.9 % observed in

the placebo group. Therefore, SC ingestion during 16h recovery period enhanced rehydration, promoted water retention, and increased plasma volume but had no effect on thermoregulation and 40 km cycling TT performance in dehydrated endurance athletes in warm environment[70]. Furthermore, a very recent study by Suvi with the same experimental data of 2018, pointed out that a change in aldosterone secretion may arise from SC supplementation before, during, and after exercise even in absence of a significant improvement in performance[34]. Based on the above, SC supplementation has the potential to improve hydration but whether this change may be associated with performance gain remains to be established, particularly in athletes involved in multiple close events in warm environments where the rest periods to rehydrate are limited.

Possible side Effects of citrate consumption

One of the most important topics related to nutritional supplementation for improving performance is the presence of possible side effects caused by the ingestion of specific products. The typical harm effects observed taking citrates are a large intensity-range of GI disorders, nausea and bloatedness. Indeed, citrates are strong osmolar compounds that could easily retain water within the intestine when the modality of assumption isn't thoughtful. Furthermore, risks associated with a specific supplement can cover its ergogenic effects. In the 1994 study by Cox and Jenkins, ventilatory and blood data confirm that significant changes in circulatory acid-base balance occurred with SC consumed prior to an interval exercise[42]. However, this failed to improve repeated 60 s of sprint performance probably due to the strong nausea experienced by all but one subject of the study. An increase in gastric dumping was reported by a study on runners performed a race of 3000 m[22]. Subjects experienced also diarrhea and increased flatulence but performance time was significantly shorter ($p<0.05$) for the SC trial than the placebo trial. A third study on endurance performance in well trained college runners underlined side effects of SC, such as nausea and thirst, in 12 subjects, couppled to headache in two of them[45]. Moreover, all 17 subjects reported an urge to defecate or diarrhoea after SC ingestion. However, they remarked that these disturbances were mild, transient and linked to the first hour after supplementation. Although SC is considered by the scientific literature to be a more tolerable substance compared to sodium bicarbonate[18], its potential to cause GI problems should not be underestimated as underlined by Oopik in 2008[71]. The results of this study suggest that SC administered in 800 ml of solution in the amount of 0.4 $g*kg^{-1}$bw can cause severe side effects (15 out of 17 females runners) and is not associated with improvement of performance in 1500 m competitive running race[71]. All the studies

mentioned above used SC powder in solution with water or sugar-free beverages. In 2014 Vaher used capsules of SC, instead of water solution, to investigate performance in 5000 m runs[48]. The subjects ingested gelatine capsules containing either SC (0.5 g*kg^{-1}bw) or placebo. The capsules were ingested within 30 min with a bolus of still water. Then, the subjects were allowed to rest for 120 min before the 5000 m run started. Although the performance was not significantly enhanced, the study underlined that ingesting SC in gelatine capsules with a bolus of water is less likely to induce GI distress than administering the equal dose in water solution. On the other side, if the number of gelatine capsules to swallow is very high it can cause problems by itself[68]. The first randomized cross-design trial on this topic was published by Urwin[53] in 2019. The primary aim of the study was to compare the effect of 0.5 g*kg^{-1}bw of SC administered through two different modes (solution or capsules) on blood alkalosis and GI symptoms over a 240 min post-ingestion period. Participants ingested (in a 30 min period) 0.5 g*kg^{-1}bw of SC in gelatine capsules with 750 ml of the sport drink or diluted in 750 ml sport drink as powder. All participants co-ingested the dose with a meal rich in carbohydrate (CHO) to reduce GI distress[72]. For both ingestion modes, GI symptoms were significantly elevated compared to baseline at each point from 30 to 120 min after ingestion and the authors concluded that capsules and powder were very similar to produce GI distress. The overall minor nature of GI symptoms in the study[58], as similar as another recent dose-response study[52], suggests that a low incidence of GI symptoms is obtainable when SC is administered as capsules and co-ingested with a CHO-rich meal. In addition, the capsules allowed higher alkalosis peak in the 150-240 min time frame and were more palatable compared to solution. The only con of taking capsules seems the fact that they can cause "loss of appetite" more frequently than solution, probably due to the number of capsules ingested and the greater protein content compared to powder[68]. Nevertheless, this effect on the appetite is very mild and not very relevant for practical application and for reaching peak performance in high-intensity exercises. The association of SC and stimulants, such as caffeine, does not seem to enhance GI effects at least in subjects which GI transition time is prolonged[50].

Perspective

In our opinion, the high probability of gastrointestinal side effects overcomes the ergogenic effects that potentially may be achieved through acute SC supplementation. In the case a tentative of a SC supplementation should be put in practice, Table 1 provide practical recommendations for a potential ingestion protocol. Overall, although the interest in the use of SC in sports seems to be

declined compared to other buffering agents, we believe there are still some aspects to investigate that we summarize in the following key points:

- Considering the early encouraging findings highlighting SC-related weight maintenance under several conditions of dehydration, further studies are certainly needed to investigate the ergogenic effects in sports where fluid loss negatively affects performance.
- Given the wide variability of individual response observed in the available studies, the possibility of creating a personalized timing of supplementation should also be explored.
- All published studies used protocols that contemplate the ingestion of SC in a short intake period (from a few minutes to about 16 hours). New trials investigating the long-term effects of SC on fatigue, hydration status and performance are missing and encouraged.
- All the available studies on this topic were conducted in young subjects (on average 20-30 years old). The lack of data on elderly people may suggest that future investigations should be designed to detect the effects on SC administration on performance and hydration status in master athletes.

Acknowledgements

English writing assistance was provided by Maria Douvli Smith (MD). This study was supported by

crowdfunding #Sport4Therapy to GD. The authors declare no conflicts of interest.

Figure legend

Figure 1. Representative depiction of dissolved sodium citrate fate.

Figure 1. Representative depiction of dissolved sodium citrate fate. The dissolved citrate enters the muscle cell membrane and is directly recruited into the Citric Acid cycle to increase the metabolic energy. The Na+, instead, remains in the plasma restoring the electrochemical balance. This process results in K+ loss causing an alteration of the stress-hormonal pathway, inhibiting the aldosterone synthesis in the renal cell.

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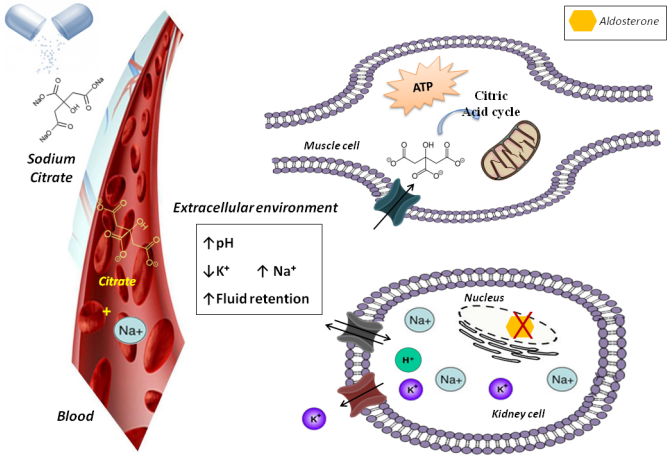
Table 1 – Practical recommendations for a SC supplementation

DOSE	0.4-0.5 g*kg^{-1}bw of SC. Higher doses (0.6-0.9 g*kg^{-1}bw) in a short ingestion period increase the risk of GI distress, but fluid retention may be obtained if the rapid bw recovery is the goal.
FORM	Prefer gelatine capsules to solutions (liquid plus powder).
TIMING	SC should be ingested at least 3 hours prior to exercise, in order to achieve peak alkalosis and minimize GI symptoms.
OTHER ADVICE	Ingesting a CHO rich meal with the SC based supplement can help as possible "protection" strategy to avoid GI distress.



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