The use of creatine and the development of deep vein thrombosis. A scoping review

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ABSTRACT

Deep vein thrombosis (DVT) is the development of blood clots in the deep veins of the extremities, classically described secondary to periods of inactivity. In some reports, creatine supplementation in the context of dehydration has been demonstrated to increase the likelihood of the development of DVTs in patients who were otherwise healthy. The purpose of this study is to conduct a scoping review of incidences of DVTs related to creatine supplementation and urge future research to investigate the mechanism of this adverse effect. Following the standard PRISMA guidelines for scoping reviews, the authors searched PubMed and Google Scholar using the terms "deep vein thrombosis", "DVT", and "creatine intake or supplementation." All relevant articles were included if they described an association between DVT and creatine supplementation. Once included, each study was qualitatively analyzed for relevant information. Any dispute of the articles for inclusion or exclusion were discussed until consensus was achieved. Four articles were included within this review from the case report and case series literature. While these articles reaffirmed the overall safety of creatine, there is an emphasis on ensuring adequate hydration in those taking this supplement. This should provoke further research into the role that creatine and other exercise supplements might play in provoking deep venous thrombosis. This evidence has the potential to change the advice of healthcare professionals to ensure they stress the importance of adequate hydration with the use of workout supplements.

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Introduction

Deep vein thrombosis (DVT) is classically described as the development of blood clots in the deep veins of the extremities, after long periods of inactivity. The classic triad of symptoms including erythema, swelling, and pain of the affected lower extremity made worse by simple dorsiflexion of the foot (Homan's Sign).[1-3] DVTs can become life or function threatening when they re-enter the venous circulation becoming a pulmonary embolism, the third leading cause of cardiovascular death.[1-3] In more rare circumstances, where a portal between the venous and arterial system exist, such as a patent foramen ovale, the DVT can become an embolism for the development of a large vessel occlusion stroke.[4]

Significant risk factors for DVTs include significant lower extremity fracture, pregnancy, oral contraceptives (and other hormonal therapies), and immobility, with complex pathophysiology.[5-8] Hereditary risk factors include antithrombin deficiency, Factor V Leiden, and polymorphisms within the promoter region of the protein C gene, such as C2405T and A2418G.[9,10] While it was previously though that hyperhomocysteinemia (homocysteine levels of greater than 15 micromoles per liter) increased the risk for DVT, the actual revision it that only very high levels of homocysteine are recognized to be associated with thrombotic events.[11] Lindstrom *et al.* has recently expanded on the existence of 16 new possible genes that have been linked to coagulation, anticoagulation, platelets, erythrocytes, and inflammation, although more research is still required.[12]

DVT most commonly arises in areas with disturbed blood flow, such as pockets that are adjacent to valves of the deep veins

in the legs.[13] Thrombophilia, central venous catheters, obesity, cancer, and advanced age have also been shown to increase the risk of DVT.[14-16] Although DVT is most commonly seen in older demographics, adolescents and young healthy patients can also experience unprovoked episodes of DVT.[17] A case outlined by Varkey *et al.* has been related to increased turbulent blood flow, inferior vena cava absence, and protein excess that can increase the risk of venous thrombosis.[18] This paper discussed how creatine supplementation might have been the provoking factor, a statement which they backed with citations from the case report literature.[18]

Purpose

The purpose of this study is to conduct a scoping review of the incidence of deep vein thrombosis (DVT) related to creatine supplementation and urge future research to investigate the mechanism of this adverse effect.

Methods

Due to the plethora of research concerning creatine as a supplement, it was determined that a scoping review was the best for the purpose of this study. This scoping review followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[19]

A Google Scholar search of "deep vein thrombosis" and "creatine" yielded over 8,400 results, upon which search terms were modified and narrowed down. A Google Scholar search of "deep vein thrombosis" and "creatine supplementation" yielded 113 results. A search for "deep vein thrombosis" and "creatine intake" yielded 5 results. A Google Scholar search of "DVT" and "creatine supplementation" yielded 38 results. A PubMed search "creatine" and "deep vein thrombosis" yields 26 results. Articles were included if they specifically addressed the occurrence of DVT in patients stemming from creatine supplementation.

Articles were assessed using the following inclusion criteria: i) articles must be written in English; ii) full-text copies of the studies were available via open-access or through library access via an affiliated organization; iii) studies were written and published before May 19, 2024. Exclusion criteria included: i) studies not discussing deep vein thrombosis, creatine, or creatine supplementation, or ii) articles that were not in peer reviewed journals.

Once included, each study was qualitatively analyzed for the following relevant information: presenting symptoms of each case, corresponding age and gender, the researchers' analysis of the relationship between DVT, dehydration and creatine supplementation. All this information was collated in duplicate into an Excel spreadsheet. Given the rarity of such case reports, critical appraisal of each study was deemed inappropriate.

Results

The search results yielded 182 results from the two databases of which 4 papers ultimately fit inclusion criteria (Figure 1). None of the results from PubMed were included. These four papers detailed 3 case reports and 1 case series of 2 patients that experienced unprovoked DVTs in the setting of creatine supple-

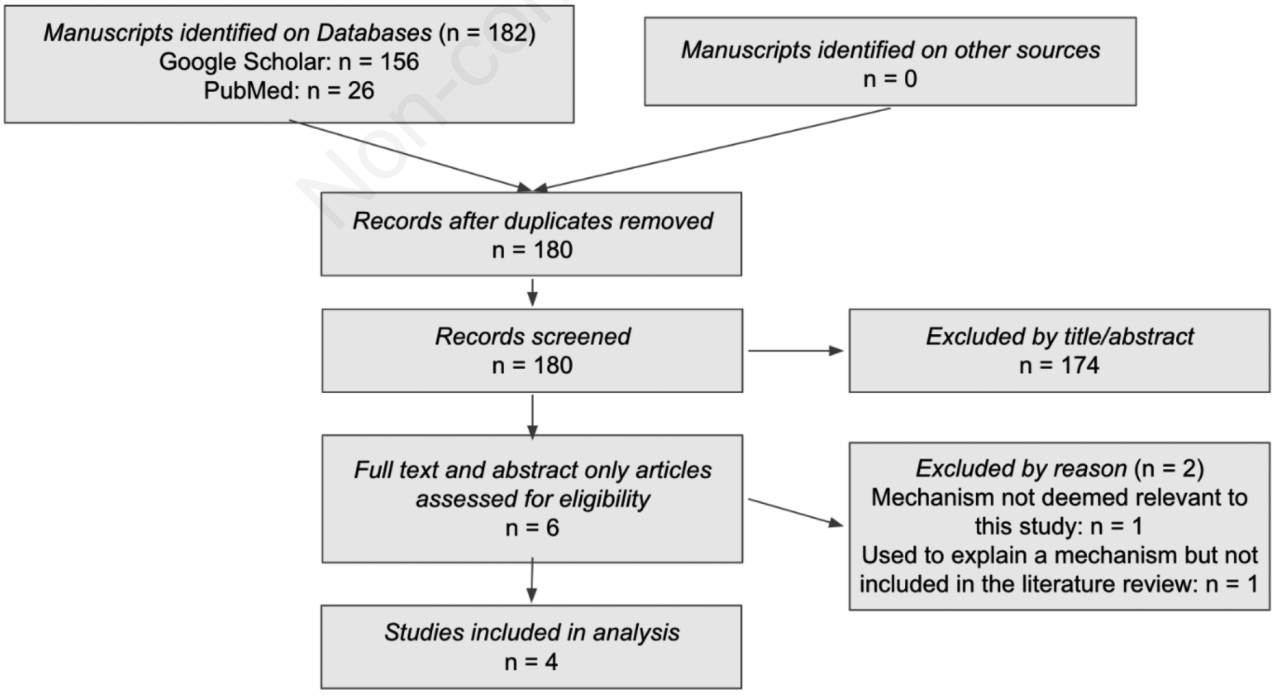

Figure 1. PRIMSA flowchart for manuscript evaluation.

mentation. One extra article was used in order to reference a possible mechanistic example but did not include a case study. None of the studies reported any financial disclosures or conflicts of interest.

Varkey *et al*. present a case report of a 22-year-old male with an unprovoked DVT associated with creatine supplementation in the setting of anatomical aplasia or acquired atrophy of the inferior vena cava.[18] The patient came in for left-side inguinal pain and left lower extremity pain most noticeable at the upper thigh. After extensive testing, it was determined that the patient had a venous malformation The authors posit that pathophysiology of creatine supplementation and unprovoked DVT involves increased turbulent flow in the setting of IVC absence along with excess protein that may increases the risk of venous thromboembolism. Special screening for unprovoked DVTs with normal clotting profile and negative family history of coagulopathy must be done in this patient population and excess protein supplementation must be cautioned according to appropriate levels of evidence.[18]

Lee *et al*. describe a similar situation where a young, otherwise healthy patient presented with an unprovoked pulmonary thromboembolism and DVT that was possibly linked to creatine supplementation in the setting of extreme dehydration.[20] The patient presented with sudden onset dyspnea and chest pain associated with a 1-week history of left calf swelling with no pain. He had no family history of coagulation disorders and all laboratory studies regarding coagulation came back normal. The authors propose that creatine exerts an osmotic effect, allowing water to move into the muscle. This decreases the water within the blood, leading to dehydration, which can increase the risk of developing a DVT.[20]

Tan *et al*. presents a case series of an 18-year-old male with a one-week history of headache accompanied by emesis who had a venous thrombosis of the superior sagittal sinus, right transverse sinus, and right internal jugular vein and a 31-year-old male with a five-day history of left lower leg swelling and pain who had a DVT of the lower extremity, both with active lifestyles.[21] The first patient noted that he became thirstier after beginning to take creatine and had no head or neck congenital abnormalities, family, or personal history of venous clots before or abnormal lab studies. The second patient just traveled on a 5-hour flight, but otherwise had a negative contributing history. The paper highlights the dehydration risks of creatine should be discussed and cautions young athletes who are at risk of dehydration or do not adequately hydrate about long-term creatine supplementation.[21]

Moussa *et al*. details a case report of an otherwise healthy young patient who developed a central artery occlusion and presented with a 1-month history of a painless blind spot in his right eye. All coagulation studies were normal along with family history of coagulation disorders.[22] In the setting of dehydration and creatine supplementation, a young healthy patient contracted a right-sided venous thrombosis of the central artery and had previously suffered through an episode of rhabdomyolysis several years previously. The authors of this case report young athletes must be warned about potential dehydration effects that put them at higher risk of getting unprovoked DVTs and other occlusions as creatine becomes more popular among this population. Creatine supplementation leads to increased levels of phosphocreatine and phosphocreatine is what leads to the osmotic effect of drawing water into the muscles.[22]

Discussion and Conclusions

A molecule of creatine is composed of 4 carbon atoms, 9 hydrogen atoms, 3 nitrogen atoms, 2 oxygen atoms and comes from the guanidino phosphagen family.[23] It then undergoes a reaction with creatine kinase (CK), a member of the family of phosphagen kinases that help regulate energy metabolism. While there are three main isoforms of CK, the vast majority found within humans are cytoplasmic CK and mitochondrial CK.[23] CK catalyzes the combination of creatine and an inorganic phosphate from adenosine triphosphate (ATP), leading to the creation of phosphocreatine and adenosine diphosphate (ADP).[24] This important reaction regulates the ADP pool and increases readily available energy in the form of phosphocreatine, which buffers oxidative phosphorylation and provides intracellular energy transport.[25]

It is well known that creatine leads to dehydration by creating an osmotic gradient drawing water in muscles that could potentially invite turbulent flow. This turbulence reduces the efficacy of the flowing blood in the venous circulation leading to increased likelihood of the formation of a DVT.[26] It is important then, as posited by multiple studies, to inform young athletes that adequate hydration while supplementing with creatine is important.

Although rare, DVT from creatine supplementation is a seemingly easily preventable issue, if proper hydration is observed. However, these cases are also few and far in between and should be handled on a case-by-case basis. The overwhelming amount of research on creatine supplementation safety, including the position of the International Society of Sports Nutrition (ISSN),[27] illustrates the use of creatine in a normal healthy adult with proper hydration practices should still be considered safe. The most recent ISSN position statement on creatine safety is in line with most current findings.[27] Nevertheless, the ISSN could provide additional guidance to adequately hydrate athletes and temper creatine usage considering the data supported by this review.

The limitations of the study include the paucity of literature investigating this phenomenon and its associated pathophysiology, as only qualitative information and associations are available from these studies. The evidence provided by case reports or a case series of two young adults is not causative; only trends and associations can be observed.

Based on the current literature (*Supplementary Table 1*), this paper provides a clear additional statement that those taking creatine ought to ensure they are appropriately hydrating themselves to ensure they are not at an increased risk of venous thrombosis. This paper serves as a word of caution to those who may not understand the role of proper hydration when supplementing a diet with creatine.

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Online supplementary material:
Supplementary Table 1.