Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology 35 (2024) 76–80

Contents lists available at ScienceDirect

Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology

journal homepage: www.ap-smart.com

Original Article

Serum vitamin D insufficiency is correlated with quadriceps neuromuscular functions in patients with anterior cruciate ligament injury: A preliminary study

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A R T I C L E I N F O

Keywords:
ACL
knee extensors
25(OH)D
Neuromuscular deficits

A B S T R A C T

Background: This study aimed to investigate the correlations of serum vitamin D insufficiency with quadriceps neuromuscular function in patients with anterior cruciate ligament (ACL) injury.
Methods: A cross-sectional study was conducted. Eighteen patients with a primary, unilateral ACL injury who had insufficient serum vitamin D concentrations (<30 ng/ml) were recruited for the study. Bilateral quadriceps neuromuscular function, including maximal strength, the speed of rapid contraction, and inhibition, were measured on an isokinetic dynamometer with the hip and the knee joint flexion at 90° and 45°, respectively. Quadriceps strength was measured by maximal voluntary isometric contractions (MVIC); the speed of rapid contraction was quantified by the rate of torque development (RTD), which was divided into the early ($RTD_{0\text{-}50}$) and the late phase ($RTD_{100\text{-}200}$); quadriceps inhibition was quantified by the central activation ratio (CAR). Serum vitamin D concentration was quantitatively determined by serum 25(OH)D concentration measured by the 25(OH)D ELISA kit. The Spearman rank correlation analysis was used to examine the correlation between the vitamin D concentration and bilateral quadriceps MVIC, $RTD_{0\text{-}50}$, $RTD_{100\text{-}200}$, and CAR, respectively.
Results: The results of Spearman rank correlation analyses showed that the serum 25(OH)D concentration was significantly correlated with bilateral quadriceps MVIC (injured: $r = 0.574$, $p = 0.013$; uninjured: $r = 0.650$, $p = 0.003$) and $RTD_{0\text{-}50}$ ($r = 0.651$, $p = 0.003$), and CAR ($r = 0.662$, $p = 0.003$) on the uninjured limb. However, no significant correlations were found between the serum 25(OH)D concentration and the other outcomes.
Conclusions: The serum vitamin D concentration correlates with quadriceps neuromuscular function in patients with ACL injury who had vitamin D insufficiency.

1. Introduction

Anterior cruciate ligament (ACL) injuries are prevalent in sports medicine.[1] Unfortunately, due to the compromised knee function, management of ACL injury has not yielded satisfactory success in returning patients to their pre-injury level of sports participation.[2,3] Impaired quadriceps neuromuscular function is the primary problem that impedes patients' recovery after ACL injury.[4] Evidence shows that poor strength, lower speed of force production, and inhibition in the quadriceps are related to poor knee function at the time of RTS.[5–7] Quadriceps inhibition is also a factor that hampers the effectiveness of quadriceps neuromuscular training.[8] In addition, the above quadriceps neuromuscular impairments is detrimental to long-term joint health.[9] Therefore, approaches to restoring quadriceps neuromuscular function in patients with ACL injury warrant further exploration.

Quadricep strength is determined by muscle size, length, muscle fiber type, Ca^{2+} homeostasis, the properties of fiber-tendon attachment, cortical activation, motoneuron recruitment, etc.[10] The speed of force production in the quadriceps is usually quantified by the rate of torque development (RTD), which is often divided into the early and late phases because the two phases are determined by different physiological factors. Early quadriceps RTD is predominantly related to the excitability of

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https://doi.org/10.1016/j.asmart.2023.11.001
Received 7 August 2023; Received in revised form 1 November 2023; Accepted 2 November 2023

corticospinal and spinal projections to the quadriceps, while late RTD is more related to the morphology of the muscle.[11–13] Quadriceps inhibition, which manifests as the inability to fully activate the muscle despite maximal exertion, is caused by both central and peripheral neural inhibition after ACL injury. Knee pain, swelling, and loss of sensory afferent from the knee joint can cause reduced corticospinal and spinal excitability, resulting in poor muscle activation during dynamic movements.[14]

Vitamin D is a fat-soluble vitamin acquired by diet or produced in the skin under sunlight and has biological effects on skeletal muscle and the nervous system. After further metabolisms in the liver and kidney, its primary circulating form, 25hydroxyvitaminD (25(OH)D), is released into circulation.[15] 25(OH)D is the main form of vitamin D measured in serum, with levels of <20 ng/ml representing deficiency, levels between 20 and 30 ng/ml representing insufficiency, and levels >30 ng/ml representing sufficiency.[16] It has been proved that serum vitamin D concentration is associated with the cross-sectional area of skeletal muscle, the proportion of Type II fiber, and the expression of myostatin messenger RNA.[17–19] In addition, vitamin D also acts on the central and peripheral nervous systems. The influences of Vitamin D deficiency on the nervous system were reported to be associated with a reduction in the production and release of neurotrophic factors,[20] decreased motoneuron excitability,[21] decreased nerve conduction velocity,[22] and neuromuscular junction denervation.[19]

The prevalence of Vitamin D insufficiency in patients with ACL injury is reported as 56%–76.5 %,[23,24] which is significantly higher than that in the age-matched general population (20–40 %).[25] Until now, evidence on the effects of vitamin D concentration on the recovery from ACL injury is inconsistent. Barker and colleagues found that vitamin D insufficiency hinders quadriceps strength recovery after ACLR(23). However, the study by Gupta et al. reported that the circulating vitamin D level has no effects on functional outcomes following ACLR.[26] Furthermore, whether vitamin D insufficiency is associated with quadriceps neuromuscular function in patients with ACL injury is still unknown. Regarding the biological effects of vitamin D on skeletal muscle and the nervous system, which were matched with physiological determinants of quadriceps neuromuscular function, we hypothesized that vitamin D insufficiency was associated with poor quadriceps neuromuscular function in patients with ACL injury. Thus, the objective of this preliminary study was to investigate the correlations of serum vitamin D concentration with maximal strength, RTD, and inhibition in the quadriceps in patients with ACL injury who had vitamin D insufficiency. Since vitamin D is easily modified with supplementation, understanding the association between vitamin D level and quadriceps neuromuscular function may inspire a potential way to improve quadriceps neuromuscular function in patients with ACL injury.

2. Methods

2.1. Study design

A cross-sectional study was conducted.

2.2. Participants

The study was approved by the ethics committee from***(No.**** blinded for review purposes). Informed consent was obtained from all the participants, and all the procedures were conducted in accordance with the Declaration of Helsinki. Participants were screened and recruited from the orthopaedics clinic in the **** Hospital from March 2021 to July 2022. Participants were eligible and included if they met all the following criteria: 1) Aged from 18 to 40 years old. 2) Sustained a primary, unilateral ACL rupture. 3) Had a pre-injury activity level not less than the Tegner Scale of 6.4) Had a body mass index (BMI) less than 29 kg/m^2 5) Had vitamin D insufficiency (the serum 25(OH)D concentration<30 ng/ml). Participants were excluded if they 1) Had previous traumatic knee injuries or surgeries to either knee joint. 2) Sustained concomitant bone fractures, Bucket handle meniscus tear [diagnosed by magnetic resonance imaging (MRI)], full-thickness chondral lesions, and multi-ligamentous ruptures. 3) Had any metabolic disorders. The rupture of the ACL was diagnosed by an orthopeadic surgeon and further confirmed with MRI. All the assessments in this study were taken before the start of the standard preoperative rehabilitation in our hospital.

2.3. Outcome measurements

2.3.1. Quadriceps neuromuscular function

Quadriceps neuromuscular function in this study included quadriceps strength, RTD, and inhibition. The measurements were conducted on both the injured and the uninjured limbs in our participants, as bilateral impairments in quadriceps neuromuscular function were found in patients with ACL injury.[27] The uninjured limb was measured first, followed by the injured limb in all outcomes. All quadriceps neuromuscular functions were measured on a Biodex dynamometer (Biodex System 4, Biodex Medical Systems Inc., New York, USA) via isometric contractions with the knee flexion at 45° and the hip flexion at 90°, respectively.[28]

2.3.1.1. Quadriceps strength. After 5 min of warm-up on a stationary bicycle, quadriceps strength was measured through maximal voluntary isometric contractions (MVIC). All participants were stabilized with straps placed over the trunk, pelvis, and thigh to isolate knee movement. Three sub-maximal voluntary contractions were performed before the formal test for familiarization and further warm-up. Then, participants were instructed to perform three 5-s MVICs with a rest period of 30s between each contraction, and participants were given verbal encouragement of 'kick as fast and hard as possible' during the contractions. The highest peak torque among the 3 contractions was collected as the MVIC and normalized by body mass for analysis.

2.3.1.2. Quadriceps RTD. Quadriceps RTD was derived from the torque-time curves recorded in the MVIC test.[29] The early and the late RTD were retrieved and calculated as the average slopes of torque versus time curve from 0 to 50 ms ($RTD_{0\text{-}50}$) and 100–200 ms ($RTD_{100\text{-}200}$), respectively.[30] The onset of a contraction was identified as the torque≥20Nm.[31] The highest $RTD_{0\text{-}50}$ and $RTD_{100\text{-}200}$ were picked and normalized to body mass. The 0–50 ms and 100–200 ms of RTD were chosen because the physiological determinants of the 2 periods are significantly different.[32] In addition, they play different roles in functional performance and knee function in patients with ACL injury. Impaired $RTD_{0\text{-}50}$ increases the likelihood of an ACL injury and relates to poor knee function,[33,34] while impaired $RTD_{100\text{-}200}$ negatively affects sports performance.[35]

2.3.1.3. Quadriceps inhibition. Quadriceps inhibition was measured by the superimposed burst (SIB) technique, which is a technique that delivers a series of electrical stimulation percutaneously to the quadriceps during an MVIC that causes a transient increase in muscle torque.[36] Central activation ratio (CAR), which is calculated as MVIC/(MVIC + stimulation provoked torque (SPT), was the outcome of the SIB technique used to quantify quadriceps inhibition. CAR of 1 means the full activation of the quadriceps without any inhibition. Thus, a higher CAR indicates fewer quadriceps inhibition.

Participants were given at least 5 min of rest after finishing the MVIC test to avoid muscle fatigue. Two self-adhesive electrodes [ValuTrode (7.5 × 13 cm), Axelgaard manufacturing, CA, USA] adhered to the quadriceps along the femoral nerve.[37] All the participants were instructed to perform another three repetitions of 5s extension MVICs, and they had a 1-min rest interval between each contraction. A supramaximal electrical stimulus (100 pulses/s, 600μs pulse duration, 10 pulses train) was automatically delivered to the quadriceps at the 3rd second during the MVIC by a software-controlled (Signal 7.05a, CED Software, Cambridge, UK) constant-current electrical stimulator (DS7R; Digitimer, Welwyn Garden City, UK). The determination of the supramaximal electrical stimulus has been described previously.[27] To assure the maximal exertion of the participant, a successful trial was defined as the quadriceps torque prior to the electrical stimulation achieving greater than 90 % MVIC. The above SIB protocol showed excellent reliability.[27] The maximal CAR among 3 successful trials was collected and used for further analyses.

2.3.2. Serum vitamin D concentration

A non-fasting venous blood sample was obtained between 10:00 and 11:00 on the day of quadriceps assessments to measure the concentration of circulating 25(OH)D for individual participants.[38] The obtained blood sample was immediately centrifuged at 4200 rpm for 10 min at 4 °C and separated into serum samples. The serum sample was stored at −80 °C until the analysis. The quantitative determination of serum 25 (OH)D concentration was measured by the 25(OH) Vitamin D ELISA kit (Abcam ab213966) with 3 trials in each sample.

2.4. Statistical analysis

The normality of the data was checked by the Shapiro–Wilk test. Descriptive statistics were represented by median, 25th percentile, and 75th percentile. The Spearman rank correlation analysis was used to examine the correlation between the vitamin D concentration and bilateral quadriceps MVIC, $RTD_{0\text{-}50}$, $RTD_{100\text{-}200}$, and CAR, respectively, after confirming the linear relationships between the vitamin D concentration and the quadriceps neuromuscular outcome by scatter plots. SPSS (Version 26.0, IBM Corp) was used for all statistical analyses. To label the strength of the association, a correlation coefficient (r) of 0–0.19 was regarded as very weak, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong, and 0.80–1.0 as very strong.[39] The level of significance was set as $P < 0.05$.

3. Results

A total of eighteen eligible participants (14 males and 4 females) with a median age of 28.0 (21.8, 33.3) years old, BMI of 22.9 (22.1, 25.0) Kg/m^2, and a pre-injury Tegner scale of 7.0 (6.0, 9.0) were included in the study, and all the participants were able to complete all the assessments and entered the statistical analyses. The median serum 25(OH) D concentration of the participants was 15.95 (10.58, 19.45) ng/ml. The demographical data and the results of all quadriceps neuromuscular measurements can be found in Table 1.

The results of the Spearman rank correlation test showed that the serum 25(OH)D concentration had moderate to strong correlations with quadriceps MVIC on both the injured ($r = 0.574$, $p = 0.013$) and the uninjured limbs ($r = 0.650$, $p = 0.003$), $RTD_{0\text{-}50}$ on the uninjured limb ($r = 0.651$, $p = 0.003$), and CAR on the uninjured limb ($r = 0.662$, $p = 0.003$). The scatter plots of the significant findings can be found in Fig. 1.

A. The correlation between circulating vitamin D concentration and quadriceps MVIC on the injured limb; B. The correlation between circulating vitamin D concentration and quadriceps MVIC on the uninjured limb; C. The correlation between circulating vitamin D concentration and quadriceps $RTD_{0\text{-}50}$ on the uninjured limb; D. The correlation between circulating vitamin D concentration and quadriceps $RTD_{100\text{-}200}$ on the uninjured limb. The solid line in each figure represents the best-fit line, and the dashed line represents the 95 % confidence interval.

On the contrary, no correlations were found between $RTD_{100\text{-}200}$ either on the injured limb ($r = 0.348$, $p = 0.157$) or the uninjured limb ($r = 0.296$, $p = 0.232$), $RTD_{0\text{-}50}$ ($r = 0.292$, $p = 0.240$), or CAR ($r = 0.389$, $p = 0.111$) on the injured limb and the 25(OHD)D concentration.

Table 1
Demographics and results of quadriceps neuromuscular function (N = 18).

Outcome	No.		
Gender (male/female)	14/4		
Concomitant meniscal injuries	4		
	25th quartile	Median	75th quartile
Age (years)	22.1	28.0	33.3
BMI (Kg/m^2)	22.1	22.9	25.0
Pre-injury Tegner Activity Score	6.0	7.0	9.0
Time from injury (weeks)	4.0	6.0	12.5
MVIC on the injured limb (Nm/kg)	1.63	2.01	2.16
MVIC on the uninjured limb (Nm/kg)	2.07	2.31	2.48
$RTD_{0\text{-}50}$ on the injured limb (Nm/kg/s)	4.68	8.87	11.70
$RTD_{0\text{-}50}$ on the uninjured limb (Nm/kg/s)	5.00	8.75	11.44
$RTD_{100\text{-}200}$ on the injured limb (Nm/kg/s)	2.32	3.11	4.21
$RTD_{100\text{-}200}$ on the uninjured limb (Nm/kg/s)	3.45	3.76	4.55
CAR on the injured limb	0.897	0.941	0.968
CAR on the uninjured limb	0.921	0.936	0.963
Circulating Vitamin D concentration (ng/ml)	10.58	15.95	19.45

4. Discussion

To the best of our knowledge, this study is the first one that revealed the correlations between serum vitamin D concentration and quadriceps neuromuscular function in patients with ACL injury. Consistent with our hypothesis, in this preliminary study, we found moderate to strong positive correlations between vitamin D concentration and bilateral MVIC, as well as $RTD_{0\text{-}50}$ and CAR on the uninjured limb.

Many studies have investigated the relationship between serum vitamin D concentration and quadriceps strength. However, results regarding a positive relationship between them are inconsistent across studies.[23,40–42] The inconsistency may be attributed to different populations of interest, different measurement methods for quadriceps strength, and the ignorance of diurnal fluctuations in the serum vitamin D concentration in some studies.[38] Studies focusing on the relationship between vitamin D concentration and quadriceps strength in ACL-deficient patients are quite limited. Like our study, the positive relationship between serum vitamin D and quadricep strength was also reported by Barker et al.[23] Barker et al. found that quadriceps strength recovery from pre-to post-ACLR was hindered by vitamin D insufficiency (<30 ng/ml). Thus, the positive correlations of serum vitamin D concentration and bilateral quadriceps strength found in our study indicate that increasing vitamin D concentration may be a possible way to facilitate quadriceps strength recovery in patients with ACL injury.

Our study found positive correlations of vitamin D concentration with $RTD_{0\text{-}50}$ and CAR on the uninjured limb. On the contrary, significant correlations were not found on the injured limb. We speculated that one possible reason for the non-significant correlations on the injured limb was the adverse influences caused by knee pain and swelling on the injury-sided quadriceps after the traumatic knee injury. It has been demonstrated that pain and swelling after an ACL injury can induce decreased excitability of the motor neuron pool in the quadriceps,[14] which is related to impaired $RTD_{0\text{-}50}$ and quadriceps inhibition. Deficits in $RTD_{0\text{-}50}$ and inhibition were found in the bilateral quadriceps previously in patients with ACL injury,[27,43] and the uninjured (contralateral) limb (11.8 %) has a twice fold of a second ACL injury incidence than the injured (ipsilateral) limb (5.8 %).[44] As quadriceps neuromuscular deficits may be risk factors for a second ACL injury on the contralateral limb, increasing vitamin D concentration may be considered as a way to enhance quadriceps neuromuscular function on the uninjured limb and decrease the risk of sustaining a second contralateral ACL injury. Apart from the above possible reason, we must mention that this study is a preliminary study, so the small sample size may underestimate the

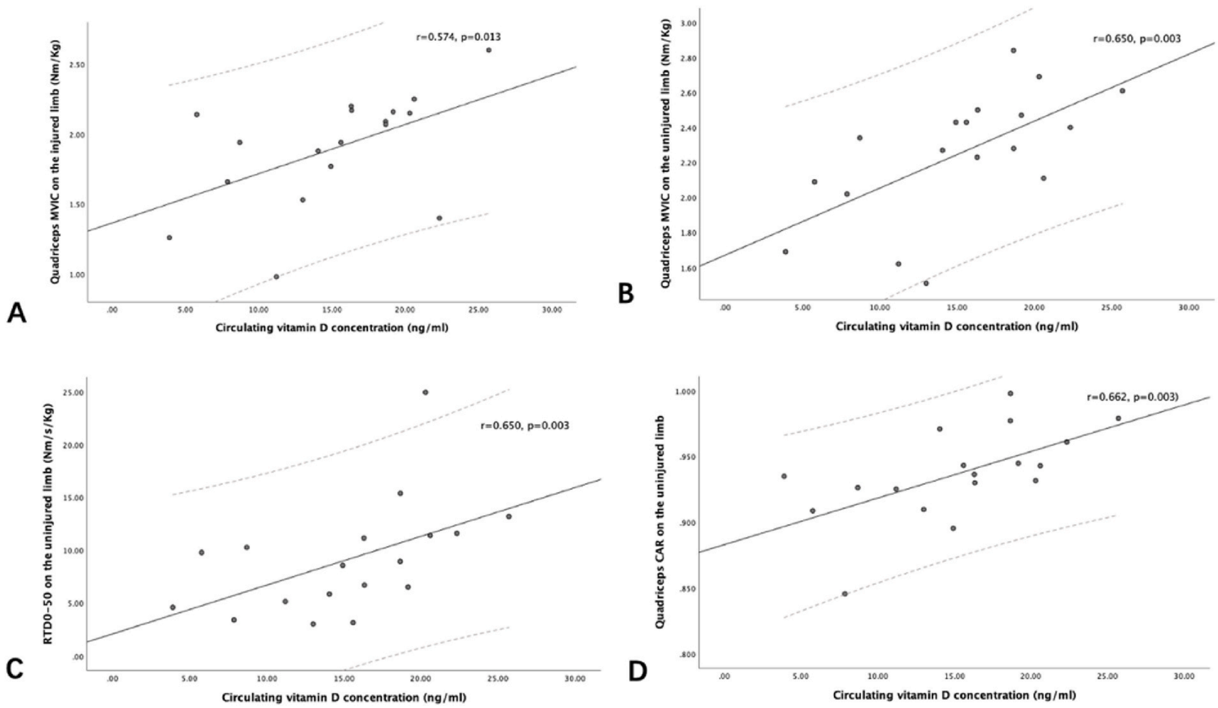

Fig. 1. Correlations between the vitamin D concentration and quadriceps neuromuscular function.
A. The correlation between circulating vitamin D concentration and quadriceps MVIC on the injured limb; B. The correlation between circulating vitamin D concentration and quadriceps MVIC on the uninjured limb; C. The correlation between circulating vitamin D concentration and quadriceps $RTD_{0\text{-}50}$ on the uninjured limb; D. The correlation between circulating vitamin D concentration and quadriceps $RTD_{100\text{-}200}$ on the uninjured limb. The solid line in each figure represents the best-fit line, and the dashed line represents the 95 % confidence interval.

relationship between serum Vitamin D level and quadriceps $RTD_{0\text{-}50}$ and inhibition on the injured limb.

Our study did not find significant correlations between serum vitamin D concentration and $RTD_{100\text{-}200}$ on the injured or the uninjured limb. Except for our study, only the study by Huang et al. investigated the relationship between vitamin D concentration and quadriceps RTD in Asian athletes.[45] This study found that RTD was significantly lower in athletes with vitamin D deficiency than those with sufficient vitamin D status, but there was no difference in RTD between athletes with insufficient and sufficient vitamin D status.[45] Based on the above, we inferred that the level of $RTD_{100\text{-}200}$ in the quadriceps would be interfered only in patients with vitamin D deficiency.

Our study also has some limitations. Firstly, a cross-sectional study was conducted, so we could not tell the longitudinal relationships between the serum vitamin D level and quadriceps neuromuscular function in patients with ACL injury due to the limitation of our study design. Secondly, the serum 25(OH)D concentration fluctuates on an annual basis, so the positive correlations found in our study may have variations in different seasons year-round. Thirdly, quadriceps-related outcomes were only measured at a single functionally related position.[28] Given the length-force and the angle-force relationships in the muscle, different testing positions may influence the results. Last but not least, this study has a small sample size, which possibly makes the results underpowered, so this study mainly intends to start further discussions on this topic. Larger-scale correlational studies to enhance the conclusions are needed. Besides, more cohort and randomized controlled trials are warranted to investigate whether modulating serum vitamin D concentration to a sufficient level can enhance quadriceps neuromuscular function in patients with ACL injury.

5. Conclusion

The serum vitamin D concentration was correlated with maximal strength, the early phase of rapid contraction, and inhibition in the quadriceps on the uninjured limb, as well as maximal quadriceps strength on the injured limb among patients with an ACL injury who had insufficient vitamin D status.

Authors' contribution

JHQ drafted the manuscript and completed data analyses; CYC collected data; GCWM assisted in drafting the manuscript and data analyses; XH collected consent forms and collected data; MQY assisted in drafting the manuscript; MDC assisted in drafting the manuscript; QWW collected data; JPN, PSHY recruited subjects; MTYO initiated the study and was in charge of the subject recruitment.

Ethics approval and consent to participate

The study was approved by the Joint Chinese University of Hong Kong- New Territories East Cluster Clinical Research Ethics Committee (No.2019.488). Informed consent was obtained from all the participants, and all the procedures were conducted in accordance with the Declaration of Helsinki.

Consent for participation

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study did not have any funding support.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

List of Abbreviations

ACL: anterior cruciate ligament
ACLR anterior cruciate ligament reconstruction
BMI body mass index
CAR central activation ratio
MRI magnetic resonance imaging
MVIC maximal voluntary isometric contraction
RTD rate of torque development
$RTD_{0\text{-}50}$ rate of torque development from 0 to 50 ms from the onset of a contraction
$RTD_{100\text{-}200}$ rate of torque development from 100 to 200 ms from the onset of a contraction
RTS return to sports
SPT stimulation provoked torque
25(OH)D 25-hydroxy-vitamin D

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