# META-ANALYSIS OF 327 CASES OF EXERTIONAL RHABDOMYOLYSIS.

*Metanálise de 327 casos de rabdomiólise induzida por exercício*

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## RESUMO

A rabdomiólise induzida por exercício (ER) é uma condição potencialmente grave que geralmente requer hospitalização e hidratação intravenosa para prevenção de complicações como a insuficiência renal aguda. A literatura deste assunto é predominantemente de relatos de casos. O presente artigo compila os dados de 327 casos de ER publicados no período de dez anos (2008-2017). Houve predominância de jovens do sexo masculino com relato de exercícios que incluíram longa duração, alta carga ou alto número de repetições, acima das capacidades físicas dos indivíduos. A tríade clássica de mialgia, urina escura e fraqueza muscular foi relatada apenas em 17% dos pacientes. O início dos sintomas ocorreu em média 2 dias após o exercício (com variação de 0 a 14 dias). Níveis médios de creatina quinase sérica de 71.277 U/L foram relatados na admissão e os níveis médios de pico de 85.778 U / L relatados por volta do terceiro dia após o dano muscular (até 1.454.952 U/L). Os músculos mais freqüentemente envolvidos foram nas extremidades inferiores (41%), mas a ER foi relatada em quase todas as regiões do corpo. Insuficiência renal aguda foi relatada em 7% dos casos. O conhecimento dos principais aspectos da fisiopatologia dessa doença é importante para o delineamento de medidas preventivas, principalmente junto aos profissionais e às pessoas envolvidas na prática de atividades físicas.

**Palavras-chave**: rabdomiólise, exercício físico, meta-análise

## ABSTRACT

Exertional rhabdomyolysis (ER) is a potentially serious condition that usually requires hospitalization and intravenous hydration to prevent complications such as acute renal failure. The literature on this subject is predominantly of case reports. This paper compiles data of 327 cases of ER published over the ten-year period (2008-2017). There was a predominance of young men with reports of exercises that included long duration, high load or high number of repetitions, above the

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physical abilities of the individuals. The classic triad of myalgia, dark urine and muscle weakness was reported only in 17% of the patients. Symptom onset occurred on average 2 days after exercise (ranging from 0 to 14 days). Mean serum creatine kinase levels of 71,277 U/L were reported at admission and mean peak levels of 85,778 U/L reported around the third day after muscle damage (up to 1,454,952 U/L). The most frequently involved muscles were in the lower extremities (41%), but ER was reported in almost all body regions. Acute renal failure was reported in 7% of cases. Knowledge of the main aspects of the pathophysiology of this disease is important for the design of preventive measures, especially among professionals and people involved in physical activity.
**Keywords**: rhabdomyolysis, physical exercise, meta-analysis

## INTRODUCTION

Regular practice of physical exercises can aid in weight control, as well as in the treatment of various diseases. The recommendation has been widely accepted in the scientific environment, with proven benefits in the prevention and treatment of several pathological conditions in the cardiovascular sphere [1], pulmonary [2], metabolic [3] and cerebral [4]. However, exercising in an exaggerated and inadequate manner may pose health risks [5]. Muscle injury known as rhabdomyolysis is a potentially serious clinical problem, which has been associated with different exercise modalities such as running [6], strength training [7], spinning [8] and cross-fit [9]. The points in common seem to be the intensity of the exercise that is inappropriate to the practitioner's physical condition [10] and probably a genetic predisposition [11], and may also be influenced by the use of substances such as medications [12], stimulants [13] and illicit drugs [14]. However, there are still gaps in knowledge on this issue; mitochondrial metabolic imbalance [15] and tissue ischemia, among others, have been described as probable mechanisms related to rhabdomyolysis [16].

Clinical features of this disease may include severe myalgia, muscular weakness and darkening of the urine, a few days after the exercise was performed, therefore, it is important to have a high degree of suspicion on the part of the physicians for this condition. Cases of rhabdomyolysis have been observed in different muscle groups, even of small size which may sometimes hamper diagnosis [17]. Laboratory investigation usually demonstrates serum elevation of creatine phosphokinase (CPK) levels (beyond five times the upper limit is the usual level considered as rhabdomyolysis) and myoglobinuria as the main findings. Imaging methods such as ultrasound, scintigraphy and magnetic resonance imaging have also been used to visualize the muscle injury in this syndrome [18]. The main and most feared complication of rhabdomyolysis is renal

failure and sometimes dialysis may be required [19] in its treatment, besides adequate hydration. The present article aims to consolidate the data of published cases of exertional rhabdomyolysis (ER), in order to contribute to a better understanding of its pathophysiological mechanisms.

## MATERIALS AND METHODS

### *Data sources and study selection*

The PubMed-Medline database was searched for case reports and series of cases published from January 01, 2008 up to December 31, 2017. The following search terms were used: "rhabdomyolysis" AND "physical exercise", OR "exercise-induced rhabdomyolysis" OR “exertional rhabdomyolysis”. Titles, abstracts and full-text publications were obtained and screened for original data on clinical and laboratorial features after ER. Exclusion criteria were: 1. Non-exertional rhabdomyolysis; 2. Experimental studies. No language restrictions were applied. Secondary references were also included if they matched all criteria.

### *Data extraction and quality assessment*

The following data were extracted from the selected articles: age, gender, type of exercise, symptoms, levels of serum CPK, muscles compromised, and development of acute renal failure.

### *Data synthesis and analysis*

Risk factors were associated with clinical endpoints by cross-tabulation. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a spreadsheet calculation – Episheet [20]. A P value of less than 0.05 was considered significant.

## RESULTS

The Medline search strategy resulted in a total of 65 articles in that database. After the inclusion of secondary references and exclusion of unrelated or duplicated articles, we achieved a total of 85 articles reporting a sample of 327 patients with exertional rhabdomyolysis in this period [7, 8, 13, 17, 21-101]. Those cases originated from 24 countries of all five continents, with a predominance of published cases from USA (132 patients), Norway (65), China (40), South Korea (23) and Spain (14).

The number of cases of ER reported annually on the initial period of 2008-2012 was 68 versus 259 on the period of 2013-2017. The main features of reported cases of ER are displayed in table 1.

Most of the reported cases occurred in young people, after an intense or unaccostumed exercise. The most frequently reported activities were weight training / weightlifting / resistance training. We found a predominance of cases of ER in the male gender and the most reported symptom was myalgia. The classic triad of myalgia, dark urine and muscle weakness was reported in 17% of the patients. The onset of symptoms

occurred in 2 days (average) after exercise (range 0-14 days). Serum CPK average levels of 71,277 were reported on admission, and average peak levels of 85,778 U/L reported around the third day after muscle damage (up to 1,454,952 U/L).. Myoglobinuria was reported in only 51 patients (16%). Considering clinical features (pain, weakness, tenderness) and imaging studies (when available), muscles most frequently involved were in lower extremities (40%), but ER was reported in almost all muscles of the body. Acute renal failure was reported in only 7% of cases. The risk of developing renal failure was not statistically significantly increased in patients of male gender (RR:1,90; CI:0,59 – 6,17; p=0,2653) aged 30 or more (RR:1,64; CI:0,69 – 3,88; p=0,2688) with the classic triad of symptoms (RR:1,78; CI:0,66 – 4,75; p=0,2655) or with levels of CPK superior to 5,000 U/L (RR:1,43; CI:0,36 – 5,73; p=0,6051). Associations with other causes were also reported, such as medications, endocrine dysfunction, infections, metabolic and genetic disorders. The treatment was based on hydration and rest, and some articles discussed protocols of patients discharge and return to physical activities [90].

**Table 1: Features of cases of exertional rhabdomyolysis**

| Age | Number of patients | Percentage |
|---|---|---|
| 0 - 10 | 2 | 0,61% |
| 11 - 15 | 10 | 3,06% |
| 16 - 20 | 44 | 13,46% |
| 21 - 25 | 50 | 15,29% |
| 26 - 30 | 17 | 5,20% |
| 31 - 35 | 15 | 4,59% |
| 36 - 40 | 5 | 1,53% |
| 41 - 70 | 5 | 1,53% |
| Not Informed | 179 | 54,74% |
| **Gender** | | |
| Male | 157 | 48,01% |
| Female | 82 | 25,08% |
| Not Informed | 88 | 26,91% |
| **Exercise** | | |
| Weight training / Weightlifting / Resistance training | 72 | 22,02% |
| High number of Repetitions / Strenuous exercise | 71 | 21,71% |
| Regular physical activity | 42 | 12,84% |
| Spinning | 41 | 12,54% |
| High intensity resistance training | 20 | 6,12% |
| Crossfit | 12 | 3,67% |
| Race / Run | 11 | 3,36% |
| Military selection/Military training/Ruckmarch | 10 | 3,06% |
| Ultrarunner | 6 | 1,83% |
| Electrostimulation | 5 | 1,53% |
| Football match / Football practice | 5 | 1,53% |
| Abdominal Crunches | 4 | 1,22% |
| Other types (less than 1% each) | 28 | 8,56% |
| **Muscles involved** | | |
| Lower extremities | 133 | 40,67% |
| Upper extremities | 103 | 31,50% |
| Chest | 16 | 4,89% |
| Abdominal | 12 | 3,67% |
| Lumbar | 11 | 3,36% |
| Diffuse | 4 | 1,22% |
| **Acute Renal Failure** | 23 | 7,03% |
| **Death** | 1 | 0,30% |

## DISCUSSION

We recognize that this review has many weaknesses, as the relative high number of reports that do not display some data, and the publication bias. Not all cases of ER are published, and maybe this number of cases is underestimated. Nevertheless, the reported data are not bad. The increasing number of people committed to exercising may improve the global health status, but also brings along the increase in the number cases of ER when the practice is exaggerated. Maybe there has been an increase in the number of journals interested in publishing case reports or small series, and the increased number of published cases of ER might not reflect a real increase in incidence over the years. On the other

hand, this increase could also be explained by the higher frequency on exercise modalities of higher risk. The consolidation of the data on exercises types showed a vast majority of cases occurring after an effort that could be long in time, with high number of repetitions or too intense. The disproportion between previous physical conditioning and the specific exercise routine seems to be the main cause of ER, in line with results found in literature [10]. This is true not only in sedentary people but also in athletes [65, 71]. The higher frequency of ER in young people may reflect not only the higher levels of physical activity at this age range, but also a psychological aspect that makes those young people go beyond their physical abilities posing them a higher risk of developing ER. The predominance of male gender could be the reflexion of the higher number of men involved in the activities. Also, when we look at specific exercise modalities like spinning we find female gender more predominant. We also observed the presence of environmental and body conditions that could predispose to this disease. Previous conditions as infection, use of drugs or genetic or metabolic disorders are important aspects to be remembered in the evaluation of the patients [16, 57, 102, 103].

There are essentially two pathways that lead to ER, the mechanical (muscle tension related) and the metabolic (cellular energy depletion) [91]. As observed in metabolic myopathies, a cellular energy crisis is the final pathway of rhabdomyolysis. With energy collapse, the ion pumps fail, leading to an influx of calcium, membrane rupture and liberation of intracellular components like myoglobin in the blood stream, leading to its deposition in the renal tubules, with consequent renal failure. The development of ways of protecting the mitochondrial energy supply is a promissory research field. We also found a non statistically-significant lower risk of acute renal failure in females, along with the less frequent occurrence of ER in this gender probably because of hormonal features [104,105].

The clinical features of rhabdomyolysis are classically described as myalgia, dark urine and weakness but also muscle edema, fatigue, nausea and other general symptoms may occur [89], making it important to have a high clinical suspicion of this condition when there is a story of possible muscle damage. Some studies emphasize the aid of imaging methods as ultrasound or magnetic resonance imaging on diagnosing ER [36, 92], but it will be confirmed by the elevation of serum CPK levels. We found CPK has a wide range of amplitude and a typical temporal profile. However, the magnitude of initial CPK level elevation does not seem to be a relevant factor in the development of acute renal failure. The treatment of ER is based on muscle rest, hydration, in some cases urine alcalinization, and monitoring for compartment syndrome and acute renal failure [100].

We strongly believe that the most important single factor for the prevention of ER is education of people towards the rational use of their bodies concerning a gradual scaling of exercises or a gradual return to training after a period of inactivity. In some populations of higher risk, like military [63, 73, 91, 95] or athletes [85], this is of even higher importance. The knowledge from physical education professionals about the possibility of rhabdomyolysis is essential to promote early diagnosis and avoid complications through immediate referral for early treatment in suspected cases.

The benefits of physical activity are widely proven, so the preservation of muscular system's health means a better function to the whole body. Therefore, it is important to preserve this extremely important system to permit us to have a longer and better quality of life.

## CONCLUSION

Exertional rhabdomyolysis is a serious and potentially fatal condition, and it is of great importance the knowledge of the clinical features, pathophysiological mechanisms, and therapeutic protocols of this disease. The efforts toward prevention are still the most cost-rewarding, and should be directed to education of people interested on the practice of physical activity but also towards professionals involved to provide adequate counseling.

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