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Rhabdomyolysis and COVID-19

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Abstract

This paper seeks to summarize recent research findings concerning the link between rhabdomyolysis and COVID-19. While most commonly known as a respiratory disease, COVID-19 has strong direct effects on the kidneys which presents a serious challenge to treatment and care of patients. New research also suggests that COVID-19 directly damages skeletal muscle tissue as well, and rhabdomyolysis induced as a result of viral attack or secondary factors can also place major strain on the kidneys. Both COVID-19 and rhabdomyolysis can lead to acute kidney injury on their own, and their combined effects can present severe clinical complications. This body of research must be developed further in order to inform patient care techniques and adapt to further mutations in the SARS-CoV-2 virus as the pandemic continues.

Keywords

Rhabdomyolysis, COVID-19, Acute Kidney Injury, Skeletal Muscle, Pandemic

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Abstract

This paper seeks to summarize recent research findings concerning the link between rhabdomyolysis and COVID-19. While most commonly known as a respiratory disease, COVID-19 has strong direct effects on the kidneys which presents a serious challenge to treatment and care of patients. New research also suggests that COVID-19 directly damages skeletal muscle tissue as well, and rhabdomyolysis induced as a result of viral attack or secondary factors can also place major strain on the kidneys. Both COVID-19 and rhabdomyolysis can lead to acute kidney injury on their own, and their combined effects can present severe clinical complications. This body of research must be developed further in order to inform patient care techniques and adapt to further mutations in the SARS-CoV-2 virus as the pandemic continues.

Introduction

SARS-CoV-2 was first reported and studied in China, and has since grown into a global, multi-year pandemic. The virus's severity is generally understood to be related to its effects on the respiratory system, but there is an increasing amount of research demonstrating additional effects, symptoms, and complications related it. One such complication is rhabdomyolysis, which is more often associated with the breakdown of striated muscle tissue rather than lung tissues. A number of proposed mechanisms for this have recently started to be developed, which should be synthesized in order to better inform further research into this developing field.

Rhabdomyolysis is COVID-19 patients is concerning because of the dual severity of both diseases, either of which having the capability to kill the patient. Therefore, the interconnectedness of these diseases will be discussed in this paper as a comparative analysis, with the goal of highlighting similarities and cascading mechanisms. Typical pathophysiology of rhabdomyolysis has to do with the breakdown of skeletal muscle and the impact it has on kidney function, whereas pathophysiology of SARS-CoV-2 has also been found to both directly and indirectly damage muscle and kidney tissue.

Rhabdomyolysis

Rhabdomyolysis is the accumulation of broken-down striated muscle in the kidneys. This buildup stresses the kidneys' elimination ability, and can lead to further systemic damage and

shutdown. The reasons for muscle breakdown are numerous, and can be broadly categorized as traumatic or non-traumatic (Cabral et al., 2020).

Etiology

Trauma and crushing injuries such as natural disasters, vehicle collisions, and even high-voltage electrical injury are common causes of rhabdomyolysis (Cabral et al., 2020) (Brumback et al., 1995). Prolonged compression of blood vessels or immobilization during a traumatic event, coma, surgery, tourniquet application etc. can result in muscle ischemia and hypoxia. Rhabdomyolysis occurs after this compression is relieved, and necrotic debris enters the bloodstream (Khan, 2009).

Rhabdomyolysis also occurs as a result of exertional injury, infections, hyperthermia, drugs, and toxins. Exertion through exercise or other means such as seizures can lead to rhabdomyolysis by combining mechanical and thermal damage to muscle tissue with ATP depletion. Drugs, toxins, and electrolyte imbalances can create conditions such as hypoxia, lowered ATP production ability, increased sarcolemma permeability, and so on. All of these conditions can be exacerbated by genetic disorders, many of such first presenting in childhood (Cabral et al., 2020).

Pathophysiology

From these myriad causes of rhabdomyolysis is a common pathway of events, beginning with destruction of the sarcolemma and depletion of ATP which leads to increased intracellular calcium. From cell membrane destruction, the calcium flows directly past the broken cell wall. From ATP depletion, the lack of ATP to operate the Na^+/K^+ channel means intracellular sodium is exchanged for calcium. This causes persistent muscle contraction and energy depletion that destroys membrane proteins. This then leads to cell lysis, and cell contents make their way into the bloodstream, primarily potassium, myoglobin, and creatine kinase (CK) (Bosch et al., 2009).

In the extracellular space and bloodstream, myoglobin is normally bound to plasma globulins. However, this binding capacity can quickly become overwhelmed, and just 100g of muscle tissue breakdown can lead to precipitation of myoglobin in the glomerular filtrate. When this happens, the renal tubules can become occluded and severe damage can occur. Renal damage also occurs due to the direct cytotoxic effect by myoglobin on renal cells, renal vasoconstriction, urate precipitation, and direct oxidative damage to renal tissue (Cervellin et al., 2017).

Clinical Manifestation and Diagnosis

A rhabdomyolysis patient will have varying presentation of symptoms depending on the severity of the muscle damage. The traditional symptoms of the disease are muscle pain, weakness, and dark-coloured urine. However, the most common complaints from patients are swelling, stiffness, cramping, and muscle pain. Frequently, the muscle groups involved are proximal ones such as thighs, calves, or the lower back. On the systemic level, symptoms such as fever, abdominal pain, nausea and vomiting, and general malaise are commonly described (Cabral et al., 2020).

Diagnosis of rhabdomyolysis relies on laboratory tests, with the key indicator being serum CK level. CK is the most sensitive indicator of skeletal muscle injury, corresponding strongly with the degree of damage or development of compartment syndrome (Huerta-Alardín et al., 2005). However, it does not correlate very much with acute kidney injury (AKI) development (Fernandez et al., 2005). Multiple measurements of CK should be made to watch for increasing or non-declining levels, which would suggest ongoing muscle injury or possibly renal failure (Zimmerman & Shen, 2013).

Another indicator is myoglobin level. Development of rhabdomyolysis means myoglobin content is high enough in urine to change its colour to a red-brown shade. Myoglobin is a useful early indicator of rhabdomyolysis because it appears before CK elevation, but has a short half-life and thus can be missed if disease presentation is delayed (Huerta-Alardín et al., 2005) (Zimmerman & Shen, 2013).

Urinalysis tests are frequently used to detect myoglobinuria. However, the test has low sensitivity and specificity, and so is not considered essential (Zimmerman & Shen, 2013). Abnormalities in electrolyte levels should be monitored along with renal function, as hypokalemia and hypophosphatemia, and especially hyperkalemia need to be identified. Hyperkalemia can lead to cardiac arrhythmia or cardiac arrest and must be addressed. Because of this, hypokalemia should not be corrected unless the patient is symptomatic to minimize risk of calcium phosphate accumulation in the injured muscle. Additionally, around 20-30% of patients will develop hyperkalemia during recovery (Cabral et al., 2020).

Rhabdomyolysis-induced Acute Kidney Injury

Acute kidney injury (AKI) can occur in around 10% of patients who have rhabdomyolysis (Zutt et al., 2014). Glomerular filtration rate with rhabdomyolysis is likely impacted through renal vasoconstriction, tubule obstruction, or direct and ischemic tubule injury. Mitigation of AKI relies first on treatment of the cause of muscle injury, whether it is temperature control, infection treatment, or so on. Appropriate hydration early on and continued is imperative for AKI treatment, with patients often needing up to 10 liters of fluid a day. Once AKI is developed, there is no specific therapy, and dialysis may be needed for correcting metabolic abnormalities (Cabral et al., 2020).

Because of the myriad factors and complications of rhabdomyolysis as well as the associated kidney damage, prognosis of the disease varies widely. Despite this, available evidence indicates excellent prognosis if it is treated early and aggressively. AKI arising from severe injury has a very wide range of mortality rates, from 7-80%. In most cases however, AKI is able to be completely reversed and recovered from in a matter of months (Cabral et al., 2020).

COVID-19

Pathophysiology

Coronavirus disease 2019 (COVID-19) is a virus that targets the respiratory tract when severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) particles enter. The disease presents with fever, dry cough, dyspnea, and diarrhea, and the severity of it can range from asymptomatic infection to multi-organ failure (Ertuğlu et al., 2020). Respiratory failure is the main effect of severe cases. However, evidence points to the kidney as the second most affected organ (Li et al., 2020). SARS-CoV-2 particles have also been shown to spread to other body tissues such as the central nervous system, intestine, and cardiac muscle (Ali & Kunugi, 2021). Morbidity of the disease is also higher in patients with preexisting cardiac conditions, indicating that cellular and tissue function even outside the respiratory tract may be directly impaired (Wang et al., 2020) (Tavazzi et al., 2020).

The SARS-Cov-2 virus functions by binding via spike proteins to cells' angiotensin-converter enzyme receptor 2 (ACE-2 receptors), and subsequently sending viral RNA through this attachment. ACE-2 is highly expressed in particular cell types such as type II alveolar epithelial cells (de Oliveira et al., 2021).

The function of ACE-2 is to turn angiotensin II (AGII) into angiotensin 1-7 (AG1-7). The properties of AG1-7 are vasodilatory, anti-inflammatory, and natriuretic. AGII itself is a

powerful vasoconstriction-inducing hormone, and is synthesized from angiotensin I (AGI) by angiotensin-converting enzyme (ACE). It is also a pro-inflammatory marker. When SARS-CoV-2 uses the ACE-2 receptor to enter a cell, it also downregulates ACE-2 expression, leading to increased levels of AGII due to lack of a negative feedback mechanism turning it into AG1-7. AGII then promotes neutrophil infiltration into organs, production of cytokines, and vascular permeability, with all of these factors leading to tissue and organ damage (Chong & Saha, 2021).

Skeletal Muscle Damage

Muscle soreness (myalgia) is the third most common symptom of the disease after fever and cough. This soreness and subsequent loss of skeletal muscle is still not fully understood in terms of mechanism, but it seems to be the intersection of many factors. Old age, along with metabolic and inflammatory disorders exacerbated by old age increase the chance of muscle damage. Older populations are also the primary patients of COVID-19. Patients with these complications typically have some degree of muscle wasting (sarcopenia). Sarcopenic muscle produces myokines and adipokines, which lead to inflammation and oxidative stress on the tissues. Under these conditions, proinflammatory cytokines are produced, which in great number lead to direct organ and tissue damage, including skeletal muscle (Ali & Kunugi, 2021).

Skeletal muscle also displays ACE-2 receptors (Saud et al., 2021) (Paliwal et al., 2020). Recent evidence points to the ability of the SARS-CoV-2 virus to directly enter skeletal muscle cells via these receptors by using viral spike proteins to attach to them and link the viral envelope with the cell membrane for insertion of viral genetic material. This is notable in that it would suggest that this virus is the first virus capable of directly infecting skeletal muscle fibres (Dalakas, 2020).

Kidney Damage

The kidney is vulnerable to attack from SARS-CoV-2 due to the number of kidney cell types that display ACE-2 receptors. These cells include mesangial cells, the Bowman's capsule parietal epithelium, collecting ducts, and podocytes (de Oliveira et al., 2021). While the full impact of SARS-CoV-2 on the kidney and kidney failure is still under investigation, recent studies have found renal dysfunction to be increasingly linked with the disease. Both albuminuria and proteinuria have been observed in hospitalized patients, and both inflammation and edema have been detected in patients' kidney tissues (Ahmadian et al., 2020). The targeting of the kidney by the virus is reported to be a frequent occurrence (Naicker et al., 2020).

The exact mechanisms of renal involvement are also unclear, but there is a proposed pathway that combines various factors. These factors include direct renal damage from viral action and replication; homeostatic imbalance of the renin-angiotensin-aldosterone system (RAAS); deregulation of the compliment system cascade; and a "cytokine storm" of inflammatory factors and their consequences (de Oliveira et al., 2021).

It is likely that the primary factor leading to AKI in patients with severe COVID-19 is acute renal tubule injury due to hemodynamic instability (de Oliveira et al., 2021). However, in milder cases, where patients have relatively mild respiratory symptoms, no septic shock, and no acute respiratory distress syndrome (ARDS), direct kidney disfunction such as collapsing glomerulopathy has been reported. This suggests that the virus directly or indirectly infects the renal tissue itself (Sharma et al., 2020).

COVID-19 Related Rhabdomyolysis

Recent studies have shown that rhabdomyolysis may be related to COVID-19 as a late-developing complication (Jin & Tong, 2020) (Khosla et al., 2020) or even as a presenting

problem (Valente-Acosta et al., 2020) (Chedid et al., 2020) (Alrubaye & Choudhury, 2020). In influenza infection, rhabdomyolysis has been found to most likely occur as a direct result of viral invasion of myocytes. The mechanism behind COVID-19 related rhabdomyolysis is still unclear, but is thought to be secondary to viral invasion or direct muscle damage induced by inflammatory mediators such as cytokines (Ahmadian et al., 2020) (Bach et al., 2021).

Viral factors are not the only contributor to rhabdomyolysis, so it cannot be ruled out that skeletal muscle damage is due to some other mechanism than viral attack. There is existing literature from before the COVID-19 pandemic describing how the drugs hydroxychloroquine and oseltamivir can lead to the development of rhabdomyolysis. These drugs are used in the treatment of COVID-19, and so should be considered a possible cause of rhabdomyolysis (Borku Uysal et al., 2020).

AKI as an observed clinical event in COVID-19 is more common than rhabdomyolysis diagnoses, with existing reports showing 4-7% of patients developing AKI, which is similar to the development shown in the original SARS outbreak. Preliminary reports of rhabdomyolysis were anecdotal only, and remain a small minority of cases (Solís et al., 2020). AKI occurrence does not necessarily indicate the occurrence of rhabdomyolysis. Conversely, some patients who had not developed AKI have had markers of rhabdomyolysis such as pigment casts and inflammation, which proposes the possibility that extensive sub-clinical renal damage had occurred (Ahmadian et al., 2020). Although rare, rhabdomyolysis in COVID-19 patients is probably underdiagnosed, and should be considered in patients with muscle weakness, dark urine, unexplained hyperkalemia, metabolic acidosis, or disproportionate myalgia (Solís et al., 2020).

Treatment

There is currently no specific treatment for COVID-19 related AKI or rhabdomyolysis. Treatment must be done on the specific symptoms, with consideration to any change in state, especially blood and urine markers. A potential therapeutic approach is the restoration of the impaired RAAS homeostasis in order to reverse the disfunction of that renal mechanism directly caused by viral activity. No matter what treatments are chosen, care needs to be taken to ensure that positive effects outweigh the negative, and the treatments are personalized to each patient (Smarz-Widelska et al., 2021).

Conclusions

The existing body of research on the mechanisms of SARS-CoV-2 still needs to be developed further, especially in regard to damage and impairment of body functions outside the lungs, which are understood to be the primary site of the disease. The pandemic has highlighted the clinical concerns of such a widespread outbreak, such as the lack of resources to manage patients in and out of hospitals, new treatments, and new vaccines. There is an existing case study of a patient developing rhabdomyolysis after receiving the Pfizer vaccine. Such a rare side-effect does not call into question any theory of vaccine usage, but does indicate that unprecedented situations will arise. Various social factors such as vaccine inequality or skepticism must also be addressed in order to eventually end the pandemic. On a per-patient basis, factors can arise rapidly and be treated promptly and with an informed outlook, and this still holds true for a population and international scope.

Just as information gained from previous viral disease outbreaks such as the original SARS, MERS, and influenza has informed current analyses of SARS-CoV-2, these current analyses can inform future perspectives on viral mechanisms. The pandemic is not likely to go away any time soon, and with the various different mutations of the virus being detected, a body

of research that evolves with the changing conditions of the pandemic is much more desirable than a stagnant one.

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