

The occurrence of myocarditis after the administration of vaccines against COVID-19: Systematic review

A ocorrência de miocardite após administração de vacinas contra COVID-19: Revisão sistemática

La aparición de miocarditis tras la administración de vacunas contra COVID-19: Revisión sistemática

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Abstract

Introduction: COVID-19, a disease whose etiological agent is the SARS-CoV-2 virus, is a disease that, in addition to causing respiratory complications, also causes other complications, such as cardiovascular and thromboembolic diseases. And, after the use of vaccines produced and launched in record time, there were several reports of myocarditis related to vaccination campaigns in several countries around the world. **Objective:** To investigate the possible relationship between vaccination against COVID-19 and the occurrence of cases of myocarditis. **Methods:** Systematic review, search in the Pubmed database for articles published between January 2020 and March 2022. Articles from clinical and observational studies with humans were included. Articles that related adverse reactions to the vaccine other than myocarditis, and those that did not specifically relate the vaccine to myocarditis were excluded. **Results:** 19 articles were selected. The total number of patients was 63, of which 60 were men, aged between 12 and 60 years, with chest pain as the main symptom and, in the majority, with onset 2 to 60 years old. 3 days after administration of the second dose of COVID-19 mRNA vaccine. The course of the disease was mostly mild and with rapid resolution of symptoms. **Conclusion:** Even with the search for evidence of the pathophysiological mechanism involved after vaccine administration and the development of acute myocarditis, there is still no evidence to prove this cause-effect relationship, beyond temporality. However, it is possible to confirm the temporal relationship between the mRNA vaccine and the development of myocarditis as adverse effects.

Keywords: SARS-CoV-2; Covid-19; Myocarditis; Vaccine; Adverse effects.

Resumo

Introdução: A COVID-19, doença cujo agente etiológico é o vírus SARS-CoV-2, é uma doença que além de causar complicação respiratória, também acarreta outras complicações como, por exemplo, doenças cardiovasculares e tromboembólicas. E, após a utilização de vacinas produzidas e lançadas em tempo recorde, houve vários relatos de miocardites relacionadas às campanhas de vacinação, em diversos países no mundo. **Objetivo:** Investigar a possível relação entre a vacinação contra a COVID-19 e a ocorrência de casos de miocardites. **Métodos:** Revisão sistemática, busca na base de dados Pubmed artigos publicados entre janeiro de 2020 a março de 2022. Foram incluídos artigos de estudos clínicos e observacionais, com seres humanos. E excluídos artigos que relacionassem reações adversas da vacina que não fosse miocardite, e aqueles que não relacionassem especificamente a vacina com miocardite. **Resultados:** foram selecionados 19 artigos. O total de pacientes foi de 63, dos quais 60 eram homens, com idade entre 12 a 60 anos, com dor torácica como principal sintoma e, na maioria, com o início 2 a 3 dias após a administração da segunda dose da vacina de mRNA COVID-19. O curso da doença foi principalmente leve e, com rápida resolução dos sintomas. **Conclusão:** Mesmo com a busca por evidências do mecanismo fisiopatológico envolvido após a administração da vacina

e o desenvolvimento de miocardite aguda, ainda não há evidências que comprovem essa relação causa-efeito, além da temporalidade. No entanto, é possível confirmar a relação temporal entre a vacina de mRNA e o desenvolvimento de miocardite como efeitos adversos.

Palavras-chave: SARS-CoV-2; Covid-19; Miocardites; Vacina; Efeitos adversos.

Resumen

Introducción: la COVID-19, enfermedad cuyo agente etiológico es el virus SARS-CoV-2, es una enfermedad que, además de causar complicaciones respiratorias, provoca otras complicaciones, como las enfermedades cardiovasculares y tromboembólicas. Además, tras el uso de vacunas producidas y lanzadas en tiempo récord, hubo varios reportes de miocarditis relacionados con campañas de vacunación en varios países del mundo. **Objetivo:** Investigar la posible relación entre la vacunación contra la COVID-19 y la aparición de casos de miocarditis. **Métodos:** Revisión sistemática, búsqueda en la base de datos Pubmed de artículos publicados entre enero de 2020 y marzo de 2022. Se incluyeron artículos de estudios clínicos y observacionales con humanos. Se excluyeron los artículos que relacionaban reacciones adversas a la vacuna distintas a la miocarditis y aquellos que no relacionaban específicamente la vacuna con la miocarditis. **Resultados:** Se seleccionaron 19 artículos. El número total de pacientes fue de 63, de los cuales 60 eran hombres, con edades entre 12 y 60 años, con dolor torácico como síntoma principal y, en su mayoría, con inicio 2 a 60 años 3 días después de la administración de la segunda dosis de la vacuna de ARNm COVID-19. El curso de la enfermedad fue en su mayoría leve y con rápida resolución de los síntomas. **Conclusión:** Aún con la búsqueda de evidencia del mecanismo fisiopatológico involucrado después de la administración de la vacuna y el desarrollo de miocarditis aguda, aún no hay evidencia que demuestre esta relación causa-efecto, más allá de la temporalidad. Sin embargo, es posible confirmar la relación temporal entre la vacuna de mRNA y el desarrollo de miocarditis como efectos adversos.

Palabras clave: SARS-CoV-2; Covid-19; Miocarditis; Vacuna; Efectos adversos.

1. Introduction

The years of 2019 and 2020 are marked as the beginning period of the SARS-CoV-2 pandemic, causer of COVID-19 disease. The virus SARS-Cov and SARS-CoV-2 belong to a subfamily Coronavirinae, in the family Coronaviridae and of the Nidovirales order, but their structures and pathology characterized are different. In the viral structure of SARS-CoV and SARS-CoV-2, the difference is mainly in the S protein, ORF8 protein and ORF3b protein (Mendes et al., 2020).

In comparison with SARS-CoV-1 that caused severe acute respiratory syndrome (SARS) between 2002 and 2003, the SARS-CoV-2 virus in addition to the respiratory complication, causes cardiovascular and thromboembolic complications (Bozkurt et al., 2021). And, therefore, it seems to have more relevant systemic complications. One of the complications is myocarditis, that is an inflammatory condition of the heart muscle that causes chest pain, dyspnea on exertion, palpitations, elevation of troponin, cardiac magnetic resonance imaging and altered electrocardiogram as signs and symptoms indicative of the disease (King et al., 2021; Gargano et al., 2021). The cause of cardiac muscle damage may come from an incorrect immune response of the host and unrestrained activation of innate immune pathways, causing an increase in pro-inflammatory cytokines, endothelial dysfunction and thrombus formation; the cause is not necessarily related to the direct invasion of the virus (Bozkurt et al., 2021).

During the pandemic, with the significant mortality of more than 3 million people in the world, there was the emergency production of specific vaccines for Covid 19, among them: Pfizer-BioNTech COVID-19, Moderna, Janssen e Coronavac (Rosner et al., 2021). Vaccines in general stimulate the immune system to produce antibodies against a particular pathogen, providing preventive protection against the infection. Therefore, throughout the spread of SARS COV 2, different forms of vaccines were created to combat the virus, such as the above, from viral RNA or inactivated virus, among other strategies (Muthukumar et al., 2021; Singh et al., 2021).

The cases of myocarditis possibly associated with vaccines raised questions about the benefits of application and even the acceptance among the general population. What is observed is that the numbers of cases seem to be insignificant in the face of the benefit of it, whereas Covid-19 is a disease with a very significant mortality rate (Bozkurt et al., 2021; Muthukumar et al., 2021; Pepe et al., 2021).

In this context, the purpose of the study is to investigate the temporal relationship between the vaccine against COVID-19 and the occurrence of myocarditis.

2. Methods

2.1 Study design

This is a systematic review research that seeks to evaluate scientific evidence from secondary data (scientific articles).

2.2 Search strategy

Data collection was performed in the database of National Library of Medicine (PubMed). The descriptors used were Myocarditis; COVID 19; SARS CoV 2; Vaccine; Adverse Effects. The search was made between February and March of 2022.

2.3 Inclusion and exclusion criteria

The inclusion criteria were scientific articles published from January 2020 to March of 2022; without language restriction; available in entirety; that involve human beings; with case report design, observational studies and clinical trials. Were excluded articles of bibliography review, systematic review and meta-analysis; studies that related side effects of the vaccine that was not myocarditis and did not relate vaccine and myocarditis specifically.

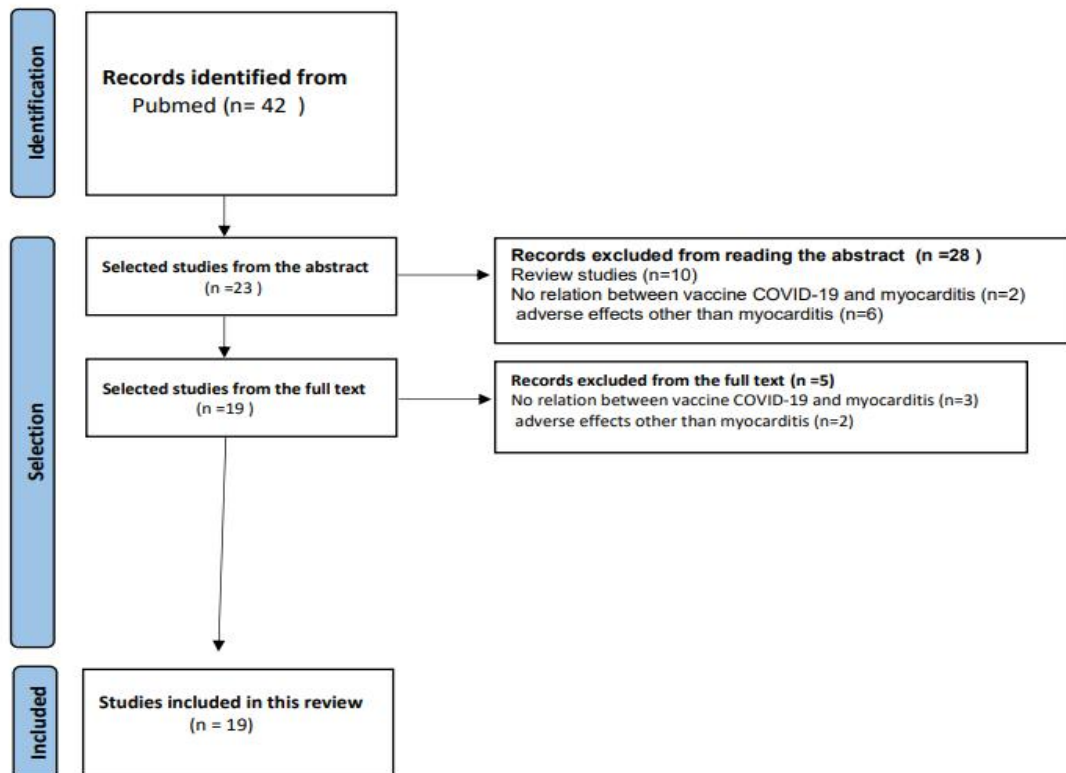
2.4 Data analysis

For the analysis, the articles were selected by their title and the abstract, and then read in full to assess their eligibility. This selection was performed by two reviewers independently who applied the inclusion and exclusion criteria. The sample consisted of these selected articles, tabulated with the following categories: author, year; sample; type of vaccine; diagnostic method; PCR-SARS-CoV-2 result; development of disease; Subsequently, the data underwent analysis seeking convergent and divergent points, according to the initial objective. The study followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) recommendations for performance and writing.

3. Results

Were identified 42 articles according to the defined descriptors, and 19 studies were selected according to the eligibility criteria as illustrated in the Flowchart (Figure 1).

Figure 1 – Flowchart of the articles that were selected to make up the sample.



Source: Authors (2022).

The articles that composed that review were published between the Years 2020 and march 2022. With samples that varies of 1 to 13 patients, and total of 63 people, of which 60 were men and 3 women, aged between 12 and 60 years. 62 of 63 patients, had previously been vaccinated with SARS-CoV-2 mRNA, with 50 participants receiving the BNT162b2 vaccine (Pfizer-BioNTech COVID-19) (King et al., 2021; Rosner et al., 2021; Singh et al., 2021; Patrignani et al., 2021; Patel et al., 2021), 12 receiving the mRNA-1273 (Moderna) (King et al., 2021; Muthukumar et al., 2021; Dickey et al., 2021; Larson et al., 2021; Patel et al., 2021; Habedank et al., 2022) and, in one study, the patient was vaccinated with adenovirus (Johnson & Johnson COVID-19) (Rosner et al., 2021).

The onset of symptoms occurred 2 to 3 days after vaccination in 54 of 63 patients (more than 85% of cases). In seven patients, symptoms appeared for 2 to 7 days (King et al., 2021; Rosner et al., 2021; Patrignani et al., 2021; Patel et al., 2021; Murakami et al., 2022; Dickey et al., 2021; Abatte et al., 2021; Shauer et al., 2021; Tailor et al., 2021), one patient occurred after 9 days of vaccination (Murakami et al., 2022), and in another patient the symptoms appeared 16 days after taking the vaccine Against COVID-19 (Abu Mouch et al., 2021).

Among all participants, 55 patients manifested symptoms after application of the 2nd dose of the SARS-CoV-2 mRNA vaccine (King et al., 2021; Rosner et al., 2021; Singh et al., 2021; Patrignani et al., 2021; Patel et al., 2021; Tailor et al., 2021; Habedank et al., 2022; Murakami et al., 2022), and eight patients showed the symptoms after taking the 1 dose (Abbate et al., 2021; Abu Mouch et al., 2021; Hasnei et al., 2021; Patel et al., 2021; Rosner et al., 2021; Patrignani et al., 2021; Larson et al., 2021; Tailor et al., 2021; Habedank et al., 2022; Murakami et al., 2022), and in only one case the Johnson & Johnson vaccine for Covid-19 was applied (Rosner et al., 2021).

Regarding the symptoms reported by the participants, 60 patients reported acute chest pain as the main complaint, one patient had palpitations followed by fainting, one reported epigastric pain and one had nausea and vomiting and progressed to cardiogenic shock. In 61 patients, the diagnostic technique used to confirm myocarditis was Cardiac Magnetic Resonance (CMR) with contrast, with compatible findings of the disease, such as late gadolinium enhancement. In two cases, there was fulminant myocarditis, and in these cases it was not possible to perform CMR, due to the poor hemodynamic status of the patients (Abbate et al., 2021).

The SARS-CoV-2 RT-PCR (Reverse Transcription Polymerase Chain Reaction) test was performed at patient admission in 47 cases and the result was negative (King et al., 2021; Rosner et al., 2021; Singh et al., 2021; Patrignani et al., 2021; Tailor et al., 2021), in 16 cases were not reported (Muhukumar et al., 2021; Azir et al., 2021; Singh et al., 2021; Patrignani et al., 2021; Tailor et al., 2021; Shauer et al., 2021; Habedank et al., 2022).

In most cases the clinical course of myocarditis was mild and symptomatic resolution was rapid, 30 patients were discharged within 1 to 3 days (King et al., 2021; Rosner et al., 2021). 13 patients were discharged between 4 a 10 days (Minocha et al., 2021; Muhukumar et al., 2021; Azir et al., 2021; Patel et al., 2021; Tailor et al., 2021; Habedank et al., 2022). 18 patients had improvement in symptoms and length of stay was not reported (Patrignani et al., 2021; Dickey et al., 2021; Larson et al., 2021; Azir et al., 2021; Schimitt et al., 2021; Hasnie et al., 2021; Watkins et al., 2021). However, one male patient, with Down syndrome, died 21 hours after admission, the cause was cardiogenic shock and worsening of the disease (Abbate et al., 2021). One patient, a 34-year-old woman, developed cardiogenic shock and was hospitalized for 73 days, and after that her condition improved (Abbate et al., 2021).

4. Discussion

As described in the literature and based in clinical studies, it is known that acute myocarditis, with a worse prognosis, occurs more in men than in women.²⁴⁻²⁷ However, there is no concrete explanation for the male predilection. Some studies point to a difference in the immune response, which is more exacerbated or dysregulated in men, and as a consequence, inflammation in general will be more pronounced (Tschöpe et al., 2021; Frisancho-Kiss et al., 2007).

The Cardiovascular magnetic resonance (CMR) is a non-invasive diagnostic method in cases of suspected myocarditis. MRI findings consistent with myocardial inflammation are based on the Lake Louise Criteria. It is necessary that two of the three patterns be observed in resonance; they are: Regional or global increase in myocardial S1 on T2-weighted images; increased global myocardial gadolinium-enhanced early-enhancement ratio between myocardium and skeletal muscle on gadolinium-enhancing T1-weighted images; at least one focal lesion with a non-ischemic regional distribution on T1-weighted images with delayed gadolinium enhancement (Friederich et al., 2009).

Vaccines cause the immune system to produce antibodies against a particular pathogen, providing preventive protection against infections. Therefore, throughout the spread of SARS-COV-2, different forms of vaccines were created to combat the virus, including BNT162b2 (Pfizer-BioNTech COVID-19) and mRNA-1273 (Moderna) from viral RNA. Following administration of the COVID-19 vaccine, local or systemic side effects may arise. The adverse effect of immunizations is usually the induction of exacerbated production of autoantibodies, so there is a high possibility that the damage to the myocardium of patients is caused due to the triggering of the post-vaccination immune response. Through the inoculation strategy and vaccination of recombinant mRNA encapsulated in lipomas, the encoding of the SARS-CoV-2 spike protein occurs (Muthukumar et al., 2021; Singh et al., 2021).

Based on this, the relationship between the development of myocarditis after mRNA vaccine administration is likely due to molecular mimicry between the Spike protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and

autoantigens, which activate immune pathways overly and activates the expression of cytokines related to myocardium inflammation (Bozkurt et al., 2021; King et al., 2021).

5. Conclusion

From the case reports reviewed in this work, we conclude that there is a temporal relationship between the administration of mRNA vaccines against COVID-19 and the manifestation of acute myocarditis, mainly in male patients, between 20 and 50 years old, who received the second dose of Pfizer and Moderna vaccines, some studies carried out tests for other possible etiologies of the disease and all were discarded. However, there is still no evidence supporting the pathophysiological mechanism that explains myocarditis as an adverse reaction to vaccination.

Therefore, considering the global impact of the COVID 19 pandemic and the wide demand and a need for the use of vaccine to control the disease, more studies are needed to understand the possible adverse reactions to the vaccine and possibilities of preventing or reversing them.

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