ISSN No:-2456-2165

Inflammatory Autoimmunity Caused by Lymphoid Cells, Related to Chronic Cardiomyopathy in Patients with Chagas Disease

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Abstract:- Chagas disease causes the death of over 12,000 people annually worldwide. Discovered in 1909, it had been infecting humans since 7000 BC. Chagas disease progresses through different stages, with the parasite residing intracellularly in the human body, multiplying and causing cellular damage in cardiac structures, leading to heart-related pathologies such as arrhythmias or heart failure.

The objective of this research is to provide the scientific community with a historical overview of the various studies conducted on Chagas disease. Articles were reviewed in databases like Pubmed and Scielo, considering titles such as "chagas chronic cardiomyopathy" and "autoimmunity in chagas disease." Initially, a total of 2421 articles were gathered, with 2008 excluded for being over five years old. An additional 340 were discarded for not being classified as review articles, and 50 more were rejected as their abstracts did not contain relevant information. Ultimately, 23 reference documents, published between 2019 and 2024, were included, meeting the inclusion criteria set by the researcher.

The research began with the historical foundations of the disease, exploring the scientific and biological study of its discoverer. Subsequent stages detail the long-term consequences of Chagas, such as chronic cardiomyopathy, and the studies on the disease's pathophysiology, understanding its impact on cardiac structures. Advances in treatment approval were described, highlighting their limited effectiveness in managing cardiomyopathy. Various diagnostic methods were also discussed, demonstrating how technology has enabled the diagnosis and management of the disease's progression in patients. This comprehensive review was achieved through a historical-logical approach to the literature.

Keywords:- *Cardiomyopathy, Trypanosoma Cruzi, Inflammatory Autoimmunity, Cardiomyocyte Damage.*

I. INTRODUCTION

Chagas disease, also known as American trypanosomiasis, is characterized by the indirect interaction between humans and an insect. “There are several ways to transmit the protozoan Trypanosoma cruzi (T. cruzi) to humans, including through the feces of a kissing bug, congenitally, through blood transfusion, orally, by laboratory contamination, and through organ transplantation” (1). The disease is transmitted by a vector called the kissing bug, scientifically known as Triatoma infestans.

Chagas disease is named after its discoverer, Dr. Carlos Chagas, who identified it in 1909. “He first observed the domestic and peridomestic cycles during the discovery phase and then the wild cycle of the disease” (2). Additionally, it is the only example in the history of medicine where the causal agent was discovered before the disease. “Chagas disease is divided into two phases. The acute phase begins 6 to 10 days after infection and lasts approximately 4 to 8 weeks” (3).

The causes of mortality from Chagas disease until the last century were attributed to the direct damage of the parasite to the heart tissue. However, more recent studies have shown that the autoimmune-inflammatory response is the most direct cause. This is due to the release of multiple cytokines by cytotoxic cells that pursue any intracellular foreign agent, promoting intoxication by toxins and waste during the process of cell division and replication of the parasite in heart cells. “Reinfections influence the genetic and regional diversity of T. cruzi, tissue tropism, modulation of the host immune response, clinical manifestations, and the risk of congenital infections” (4). Likewise, the immune response of the parasite is another crucial factor in parasitemia since T. cruzi has developed ways to evade the oxidative processes of macrophage cells, which in turn creates an ideal scenario for inflammation in heart tissue. “Chronic inflammation and oxidative stress are characteristics of chronic cardiomyopathy in Chagas disease” (5).

Advances in the detection and control of Chagas disease have been beneficial for patients, as there are now direct diagnostic methods that allow the parasite to be observed at the genetic level, studied, and understood in order to find ways to counteract it on a molecular or genetic basis. There have been no advances in treatments that eradicate Chagas disease itself; it has only been possible to delay death from arrhythmias or heart failure caused by cardiac damage. Treatments have only been implemented to reduce parasitemia, such as antiparasitics that are mainly effective in the acute stages, and for the control of heart diseases, surgeries for pacemaker implantation, and heart transplants—none of which completely eradicate the parasite.

These scenarios allow us to propose a comprehensive theoretical framework where we can mention various aspects surrounding Chagas disease, including limitations, lack of information, and theoretical scientific gaps.

- Limitations in Bolivia regarding studies and research related to chronic heart diseases.
- Increase in risk factors according to the age group considered in South America, lifestyle, and precarious health system.
- Reduced interest from the international community in determining a treatment for both the eradication of 100% parasitemia and the total modulation of heart disorders.
- Limited efforts to control triatomine vectors that carry the causal agent (T. cruzi).

Theoretically, different factors promoting chronic cardiomyopathy have been proposed. In its pathophysiology, direct damage to cardiomyocytes is described, as well as an immediate pro-inflammatory immune response attributed to human cells. This atmosphere of limitations and scientific gaps does not deter the researcher from taking action in an unfavorable scenario for the population. Thus, the foundations for future research have been laid, generating a problem with the intention of providing a prompt solution.

What is the relationship between inflammatory autoimmunity caused by lymphoid cells and chronic cardiomyopathy in patients with Chagas disease? This study describes the damage caused directly by the causal agent, as well as the direct damage to lymphoid cells, which occurs as a result of the attempt to eliminate T. cruzi from the system. The significance of this study arises because infectious diseases progress very quickly and can become highly detrimental to the patient's life. Cardiomyopathy is a disease indirectly caused by Chagas disease, attributed to a patient with a high parasitic load.

➢ *Hypothesis*

There is a relationship between inflammatory autoimmunity caused by lymphoid cells and chronic cardiomyopathy in patients with Chagas disease. With this hypothesis, the researcher suggests that lymphoid cells cause damage to heart tissue through constant inflammation caused by the action of attempting to eradicate the causal agent, which leads to dysfunction and alteration of the heart's motor functions.

II. METHODOLOGY

This research distinguished itself by applying various data collection techniques, such as reviewing, synthesizing, and analyzing different sources with information supported by years of study in the health field. Articles were reviewed in databases like Pubmed and Scielo, considering titles such as "chagas chronic cardiomyopathy" and "autoimmunity in chagas disease." Initially, a total of 2421 articles were gathered. Of these, 2008 were excluded for being over five years old. An additional 340 were discarded for not meeting the requirement of being classified as review articles, and another 50 documents were rejected as their abstracts did not contain information of interest to the researcher. Ultimately, 23 reference documents, published between 2019 and 2024, were included, meeting the inclusion criteria set by the researcher.

The theoretical method employed was the historical-logical approach, as the aim was to provide data and knowledge on the evolution of Chagas disease within a timeline, particularly its association with mortality in chronic cardiomyopathy. The research was based on an inductive-deductive approach, intending to offer both general and specific details about the pathophysiological, cellular, and biochemical aspects surrounding this disease.

III. RESULTS AND DISCUSSION

Chagas disease, like any other infectious disease, involves several factors to study, from the vector, the life cycle of the causal agent, the indirect damage caused by lymphoid cells, and also a broad knowledge that must be considered, such as pharmacological, pathophysiological, and diagnostic aspects. All of these factors can be evaluated from a more objective standpoint by conducting a stage-based periodization in which the evolution of Chagas disease throughout history can be observed.

A. Stage I. From 1909 - 1925. Discovery of Chagas Disease: Description of the Biological Cycle and Resistance to Oxidative Stress

The medical researcher who discovered Chagas disease was Dr. Carlos Ribeiro Justiniano das Chagas, a Brazilian physician. In 1909, Dr. Carlos Ribeiro Chagas, who is credited with contributing to the eradication of malaria, discovered Chagas disease through the story of a railway worker in Brazil who spoke of an insect called "chupoes." Chagas focused his attention on these vector insects, and Dr. Carlos decided to study the biology of this insect with the aim of discovering whether it functioned as a vector, meaning it could carry a parasite that causes diseases in that region of Brazil. The biological cycle of T. cruzi is detailed in Figure 1.

ISSN No:-2456-2165

However, Chagas disease is much older, even dating back to 7000 B.C. In a study where mummies were exhumed from archaeological sites in both Peru and Chile, "carbon dating of their tissues revealed an approximate date of 7000 B.C., and the presence of T. cruzi kinetoplast DNA was confirmed through polymerase chain reaction (PCR)" (6).

History also tells of a young Charles Darwin, who, before the invention of the railroad, traveled to South America with his crew, who fell ill, and it was understood that they had contracted typhoid fever, a disease characterized as "infectious, acute, and potentially fatal. Socioeconomic conditions are determinants in its transmission" (7).

At night, he suffered an attack by a "Benchuca," a Reduviid insect, which he described as: "The most repulsive thing is feeling soft, wingless insects about an inch long crawling on your body; before sucking, they are quite thin, but then they become round and swollen with blood, and in this state, they are easily crushed."

In this first stage of the study, we understand that Chagas disease was first scientifically recorded in the 20th century. However, some studies have revealed that cases in humans existed as early as 7000 B.C. Chagas disease is as old as, or even older than, mankind.

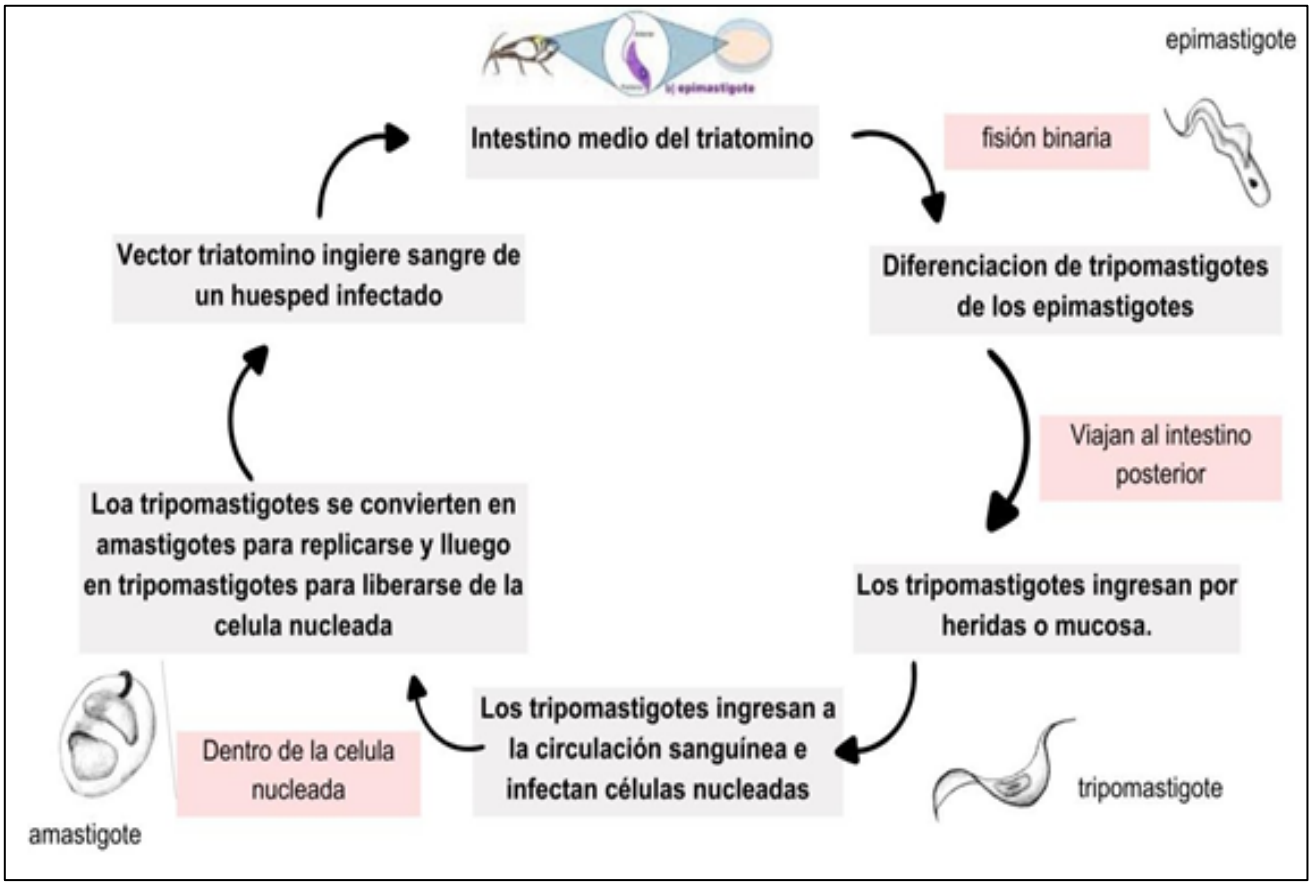

Fig 1: Biological Cycle of Trypanosoma Cruzi
Source: Self-Made

This figure details the processes that T. cruzi undergoes for its survival, helping us understand how the trypomastigotes follow a complex infection pathway, both intracellularly and extracellularly. They have to differentiate in order to replicate and then differentiate again to continue infecting. It provides an explanation of the importance of eradicating the parasite in its acute phase, as the parasite tends to replicate uncontrollably in the host, attacking and using nuclear cells as intermediaries, which it then destroys, causing cellular, tissue, and consequently organ damage. "Within the host, trypomastigotes invade cells near the site of inoculation, where they differentiate into intracellular amastigotes that multiply and differentiate into trypomastigotes with no replication capacity" (8).

The oxidative stress characteristic of cells involved in macrophage-like activities aims to eliminate and degrade the chemical properties of foreign agents. "There is an immune-suppressive nitric oxide-dependent mechanism that involves the appearance of Gr1/Cd11b+ cells producing NO in response to TNF and IFN-gamma in the spleen" (9).

T. cruzi has evolved to such an extent that it uses a line of peroxidases to degrade reactive oxygen and nitrogen species released by the host's defense system. "T. cruzi has

ISSN No:-2456-2165

adapted several antioxidant mechanisms to inactivate reactive oxygen and nitrogen species released by the host during the early stage of infection" (10).

The enzymes responsible for degrading these oxidative components act and "are strongly correlated with the parasite's life cycle" (11), as shown in Figure 2.

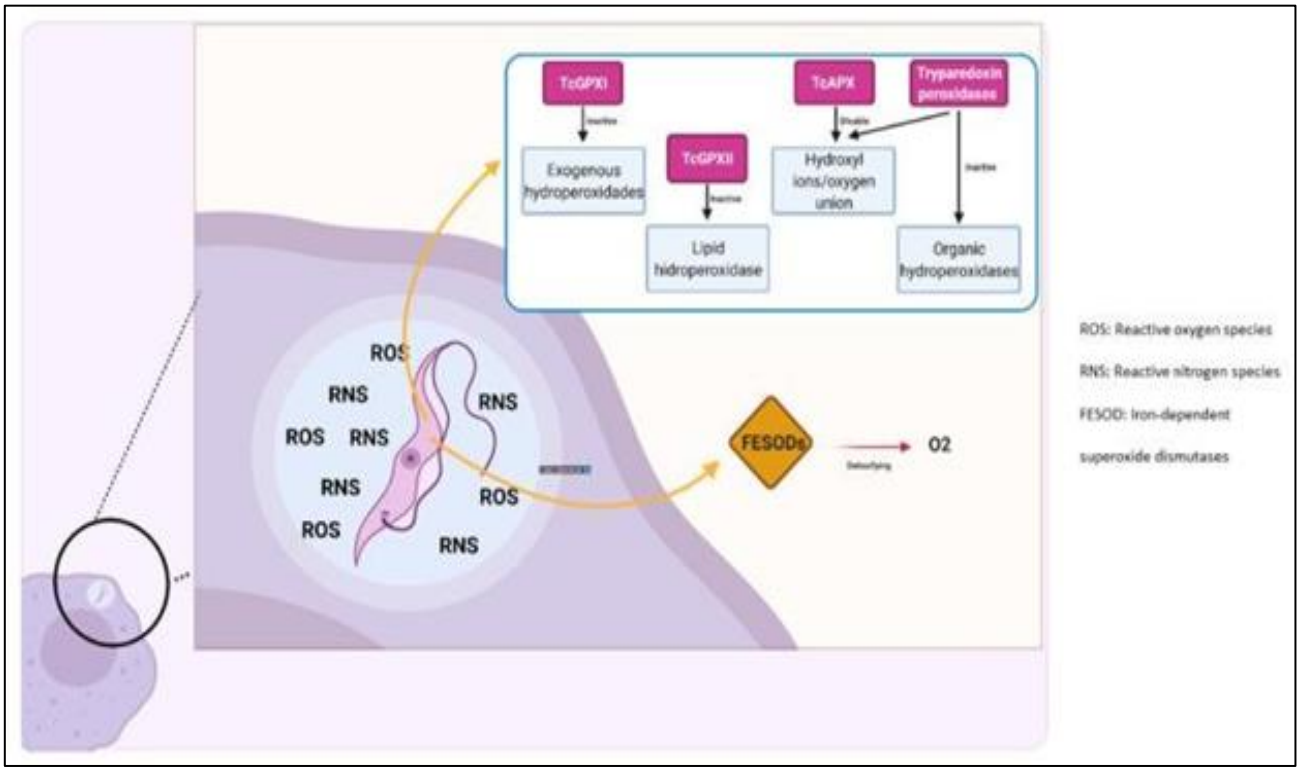

Fig 2: Resistance to Oxidative Species
Source: Maldonado E., Rojas D. y otros, The Oxidative Stress and Chronic Inflammatory Process in Chagas Disease: Role of Exosomes and Contributing Genetic Factors

In this stage, it is detailed that understanding the biological cycle of *T. Cruzi* is essential for various aspects related to its control and eradication. Additionally, this characteristic parasite stands out due to its mechanism of resistance to the different cellular oxidation responses of the host organism.

B. Stage II. 1926 - 1964. Identification of the First Cases of Chronic Chagasic Myocarditis, Scenarios of Cardiac Tissue Damage by Lymphoid Cells

Much later after the registration of Chagas' disease, the first cases of Chagasic myocarditis were described. This was thanks to Dr. Salvador Mazza, an excellent professional who worked in fields like bacteriology and psychology. He took a deeper look at the effects of Chagas' disease, and as a result, certain investigations related to Dr. Chagas' work were re-evaluated. This is why the disease is also referred to as Chagas-Mazza disease.

Regarding the first cases of Chagasic myocarditis, history describes that in Argentina: "The historians - Sierra Iglesias, Rubén Storino, and Daniel Rigan, the researchers who most stood out in the study of Chagas-Mazza disease, were Cecilio Romana and Miguel Jorg. The former had the merit of describing in 1932 in the Argentine Chaco the first cases of chronic Chagasic myocarditis." (12)

In 1957, Dr. Julio Rodriguez Rivas, a physician, published the first cases of Chagasic myocarditis in Bolivia in *Prensa Médica*, La Paz, Bolivia. In 1961, a special publication on *Chagas Disease and Chagasic Cardiomyopathy in Bolivia* was released by the Universidad Mayor de San Simón, Cochabamba, Bolivia. Regarding Paraguay, "the first cases were discovered in 1939, and in Ecuador, acute and chronic cases were published in 1950 and 1959" (12).

Chronic Chagasic myocarditis is a disease characterized by the enlargement of the heart. "The macroscopic study of the heart usually shows enlargement of the four cardiac chambers (hypertrophy and dilation), sometimes with a predominance of the right chambers" (13). Through various studies, it has been demonstrated that the damage is not only attributed to the direct action of the parasite on the cardiomyocytes, but other factors involved are a result of our own body's response. "During the last century, cardiac damage was attributed to the direct action of the parasite on the cardiomyocytes, and the parasite was considered the sole cause of myocardial injury. Now, other mechanisms involved in the pathophysiology are known" (14).

ISSN No:-2456-2165

The direct damage to the cardiomyocytes is caused by intracellular amastigotes during cellular division. This, along with the waste and toxins released during the process, results in damage to the cardiac tissue because the parasite has an affinity for it. "During the acute phase, cardiac damage is related to the presence of the parasite and is caused by the mechanical rupture of the infected cell due to intracellular amastigotes dividing" (14).

The damage caused by immune-inflammatory response "which may be related to a myocarditis rich in Th1-T cells with abundant interferon (IFN)-γ and tumor necrosis factor (TNF)-α" (15), occurs once the parasite divides and breaks through cardiac cells, fostering the immune response of the body through NK cells, neutrophils, basophils, until eventually activating CD4+ and CD8+ T cells, which are cytotoxic cells specific to *Trypanosoma cruzi*. These cells release Th1 cytokines such as interferon (IFN)-γ, interleukins, and tumor necrosis factor alpha (TNF)-α. Over time, the amount of cytokines secreted by these cells in their attempt to eradicate the parasite becomes exaggerated, which in turn promotes inflammation. This favors microvascular damage and cardiac muscle, degrading muscle fibers such as actin, which are responsible for the cellular electrical response in the heart's pumping action. This scenario is detailed more clearly in Figure 3.

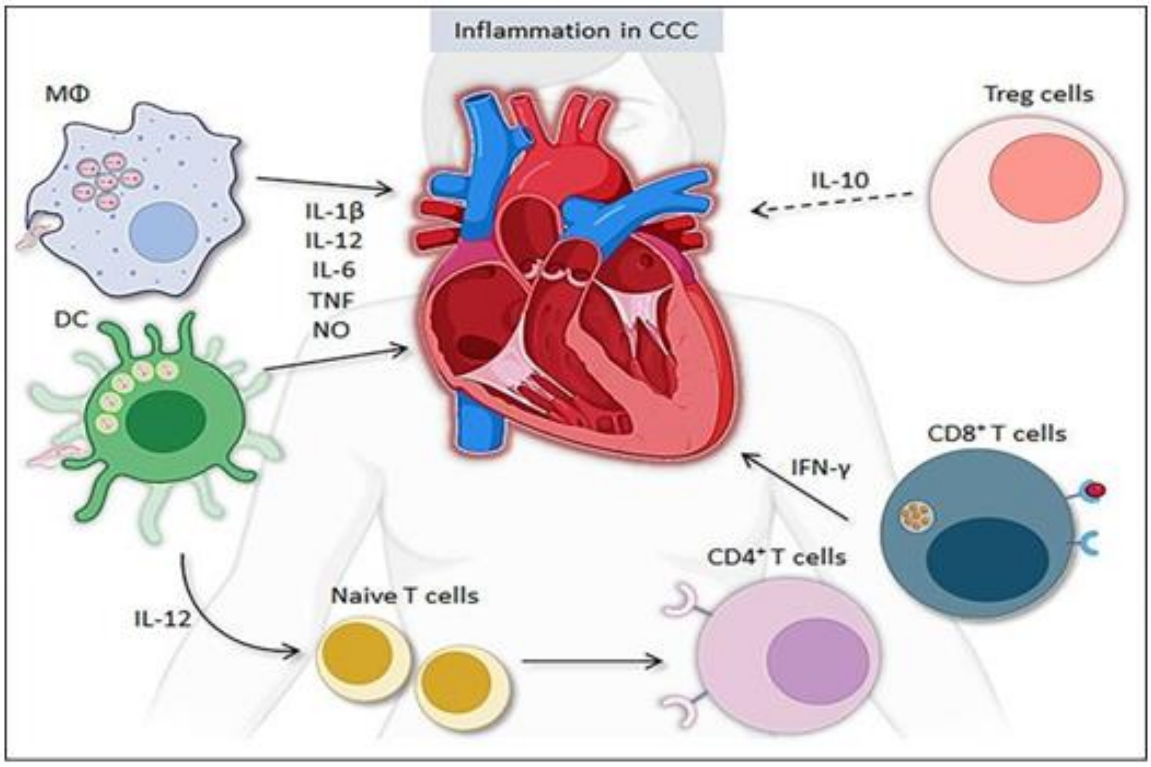

Fig 3: Pro-Inflammatory Chemical Processes in Cardiac Muscle
Source: adapted from Souza Santos E, D. Carvalho Silva y otros, Immunomodulation for the Treatment of Chronic Chagas Disease Cardiomyopathy: A New Approach to an Old Enemy

"The thymus undergoes an atrophy process that begins in the first year of life and accelerates due to hormonal changes during puberty" (16). When this factor is added, the direct threat of *T. Cruzi* attacking the thymus causes alterations in the production of T-type cells, creating an unstable situation in the patient during the first few weeks, where the body is left with little chance of counteracting the parasitemia.

C. Stage III. 1965 - 2011. Approval of a Pharmacological Treatment

Despite the approval of a treatment with nifurtimox in 1965, 30% of positive Chagas cases become chronic and suffer from the disease until their death due to arrhythmias or heart failure. It has been proven that pharmacological support with anti-trypanosomal treatment has not yielded any significant results or changes in preventing death caused by cardiomyopathy and its consequences. This was demonstrated in a study where antiparasitic treatment was administered to a random group through a controlled, international, multicenter clinical trial called "Evaluation of Benznidazole to Interrupt Trypanosomiasis" between 2004 and 2011. This trial randomized 2,854 patients to be treated with either a placebo or benznidazole. The benznidazole group showed a significant reduction in parasitemia, but no difference in clinical outcomes such as sudden cardiac death (SCD), pacemaker requirements, mortality, insertion of implantable defibrillators, heart transplants, heart failure, and stroke.

Similarly, a meta-analysis from Cochrane-Chile found no significant data to counteract chronic Chagas with antiparasitic treatment. "A Cochrane meta-analysis found insufficient evidence in favor of using NFX and BNZ in the treatment of severe Chagas cardiomyopathy." (17)

ISSN No:-2456-2165

Chagas disease predisposes the body to provide an immediate innate response: "The humoral response against *Trypanosoma cruzi* is characterized by a response to a complex mixture of antigens." (18)

As a result, multiple mechanisms are triggered, leading to inflammation in the cardiac muscle, and over time, dysfunction in various areas, including electrical function: "Chronic Chagas cardiomyopathy causes alterations in the electrical conduction of the heart, ventricular dilation, ventricular arrhythmias, and sudden death." (19) The use of immunomodulatory drugs has proven effective in modulating certain chemical and enzymatic factors: "Immunomodulatory drugs and cellular/genetic therapies are capable of modulating systemic inflammation and myocarditis through different pathways in CCC models." (20)

"Cevey et al. reported that treatment with fenofibrate, a PPARα agonist, was able to induce mitochondrial fatty acid beta-oxidation, restore left ventricular function, and reduce myocarditis and fibrosis in a mouse model of CCC." (15)

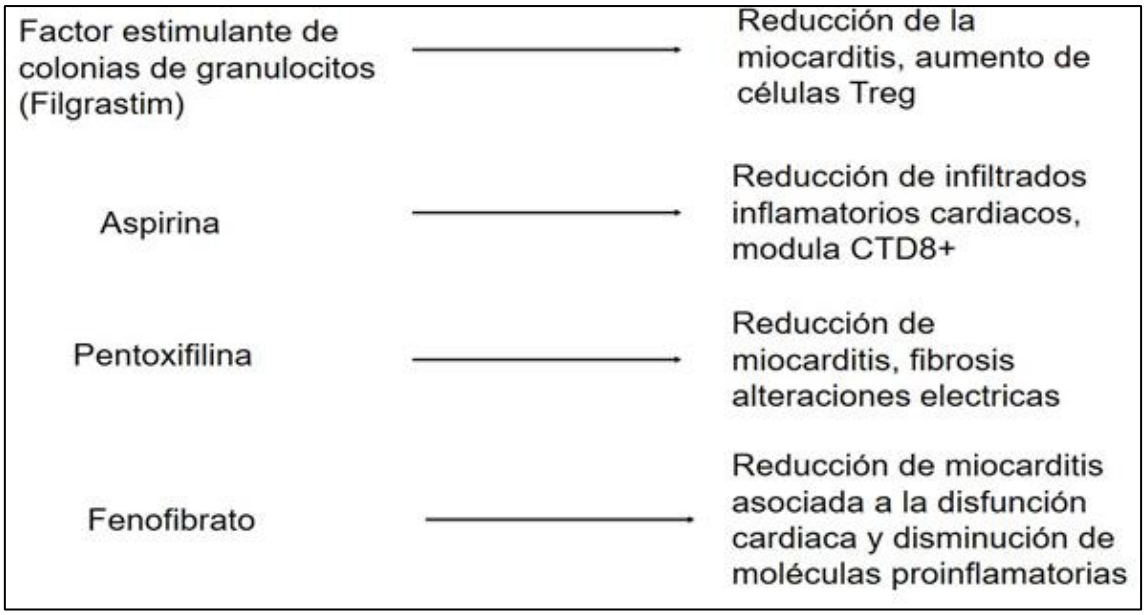

Fig 4: Immunomodulatory Drugs and their Effect
Source: self-made

D. Stage IV: From 2012 to the Present. Improvements in Diagnostic Tests

Regarding the diagnosis of Chagas disease, different methods have been described, and they vary depending on the stage of the disease, whether in the acute, chronic, or indeterminate phase. Two types of techniques are described for correct diagnosis:

Indirect parasitological diagnosis includes methods such as fresh microscopy observation, thick blood smear, "thick blood smears are particularly useful in malaria-endemic countries due to the high level of expertise in microscopic evaluation for this technique." (21), concentration methods, and xenodiagnosis.

Direct diagnostic studies include indirect agglutination, enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IFI), "when echocardiography does not provide conclusive results, cardiac magnetic resonance imaging is the next recommended step." (22)

"Some rapid diagnostic tests based on immunochromatographic techniques have been developed, which can be useful in areas with difficult access to the healthcare system or in mass screening situations. In recent decades, the detection of T. cruzi DNA in peripheral blood using polymerase chain reaction (PCR) has been increasingly used." (23)

PCR is becoming more widely used to monitor treatment efficacy and evaluate new treatments in clinical trials. A positive result after completing treatment would indicate treatment failure.

The next box provides a summarized and synthesized version of the stage-wise periodization based on data and information gathered in this study. See figure 4.

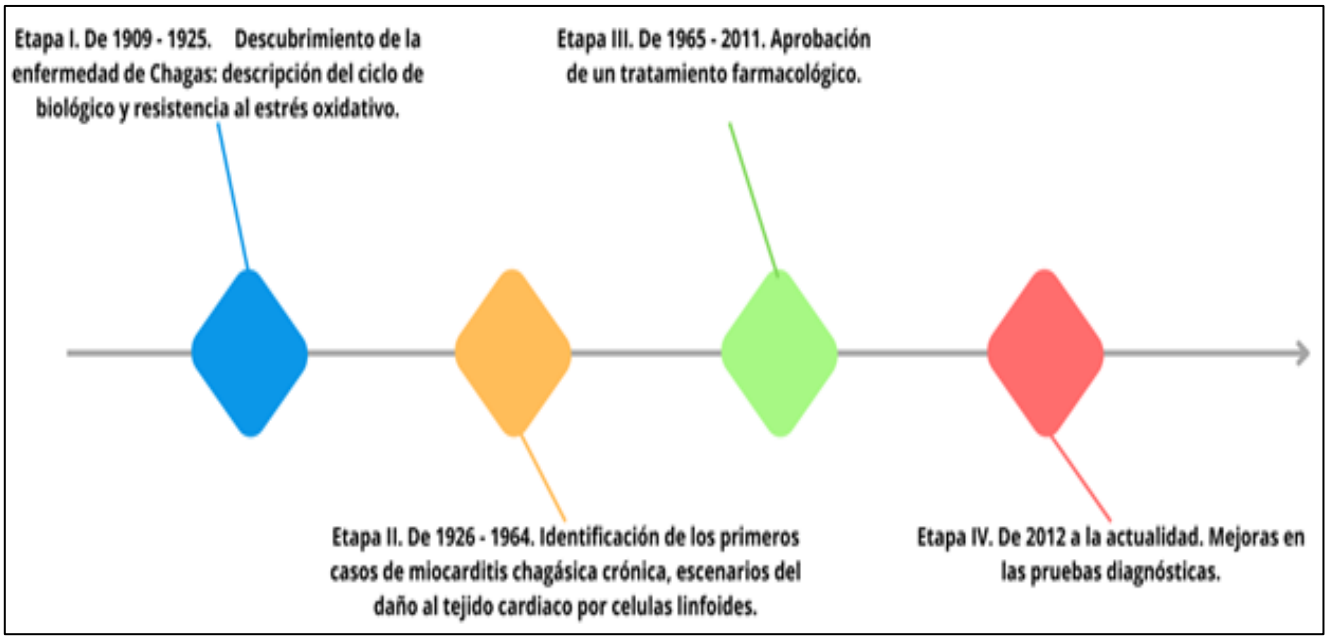

Fig 5: Periodization by stage.
Source: self-made

In this timeline, the stages established as the most representative according to this study are outlined. The first stage (1909 – 1925) emphasizes the discovery of Chagas disease and its description. It also takes into account the biological cycle of the causal agent, as well as its resistance to oxidative stress, covering a biochemical aspect from the mechanism of action in degrading various protective chemical products of our organism. The second stage (1926 – 1964) adopts a concept more focused on biochemistry and molecular biology, describing the cellular and chemical processes of the action mechanism of lymphoid cells in their attempt to eradicate the foreign agent and how it indirectly harms cardiac tissue. The third stage (1965 – 2011) details how humanity has fought pharmacologically against the parasite and the proposals for the use of immunomodulators for the stability of cardiac health. The fourth stage (2012 – Present) involves technological advances in diagnostics, reaching the study of the parasite at the genetic level.

IV. CONCLUSIONS

- The discovery of Chagas disease and its association with a causal agent like the parasite *T. Cruzi* has marked a turning point in history. Its description was key to controlling this pathology.
- The pathogenesis caused indirectly by the activation of the organism's innate immunity by the parasite creates a scenario in which lymphoid cells such as CD4+ and CD8+ cells, along with the secretion of pro-inflammatory interleukins, increase cytotoxicity and mitochondrial alterations in cardiac myocytes.
- The parasite *T. Cruzi* has shown good adaptability in the organism through its resistance to oxidative mechanisms by macrophages and Treg cells.
- Regarding the treatment of parasitemia and cardiac alterations, further studies are needed on the positive effects of immunomodulatory drugs combined with antiparasitics to modulate electrical dysfunctions.
- Diagnostic tests are continually improving with molecular approaches, including both DNA and RNA analysis, such as PCR and immunochromatography.

REFERENCES

[1]. Alcides Bocchi E, Bulgarelli Bestetti R, Ibrahim Scanavacca M, Cunha Neto, Sarli Issa V. Chronic Chagas Heart Disease Management: From Etiology to Cardiomyopathy Treatment. ElSevier. 2017; 70(12, 19): p. 1510-1524.
[2]. Rodrigues Coura J, Albajar Viñas P, Junqueira. Ecoepidemiology, short history and control of Chagas disease in. Scielo. 2014; 109(7): p. 856-860.
[3]. Steverding D. The history of Chagas disease. Biomed Central. 2014; 7(317).
[4]. Olivo Freites C, HenaoMartínez A. Chronic Chagas Disease—the Potential Role of Reinfections in Cardiomyopathy Pathogenesis. Springer Nature Link. 2022; 19: p. 279–289.
[5]. Maldonado E, Rojas D, Urbina F, Solari A. The Oxidative Stress and Chronic Inflammatory Process in Chagas Disease: Role of Exosomes and Contributing Genetic Factors. Pubmed. 2021.
[6]. Vigliano C, Chen C, Leone J. Chagas disease: Historic perspective. ElSevier. 2020; 1866(5).
[7]. Goldaraz J, Casuriaga A, Pardo L, Giachetto G. Fiebre tifoidea: una etiología poco frecuente de síndrome febril prolongado en pediatría. Scielo. 2022; 9(2).
[8]. Pino-Marín A, Medina-Rincón G, Gallo-Bernal, Duran-Crane A, Arango Duque Á, Rodríguez M, et al. Chagas Cardiomyopathy: From Romaña Sign to Heart Failure and Sudden Cardiac Death. 2021Pubmed; 505(5).

[9]. Alcaide Alonso P. Dialnet. [Online].; 2003. Acceso 28 de Diciembre de 2024. Disponible en: https://dialnet.unirioja.es/servlet/tesis?codigo=27798.
[10]. Medina-Rincón G, Gallo-Bernal S, Jiménez P, Cruz-Saavedra L, David Ramírez J, Juliana Rodríguez, et al. Molecular and Clinical Aspects of Chronic Manifestations in Chagas Disease: A State-of-the-Art Review. Pubmed. 2021; 1493(11).
[11]. De Castro Neto A, da Silveira J, Arruda Mortara R. Comparative Analysis of Virulence Mechanisms of Trypanosomatids Pathogenic to Humans. Pubmed. 2021; 16(11).
[12]. Ruiz Guzmán J. Historia de la enfermedad de chagas. Scielo. 2007; 30(2).
[13]. V. Elizari M. La miocardiopatia chagasica. Perspectiva histórica. 1999; 59(2).
[14]. Geovanny Pech-Aguilar A, Haro-Álvarez A, Rosado-Vallado M. Revisión actualizada sobre la fisiopatología de la cardiomiopatía chagásica. IMSS. 2020; 58(3).
[15]. Paulo Silva Nunes J, Moraes de Paiva Roda V, Andrieux P, Cunha-Neto, Chevillard C.
[16]. Inflammation and mitochondria in the pathogenesis of chronic Chagas disease cardiomyopathy. National Library of Medicina. 2024; 248(22).
[17]. Revista Española de Geriatria y Gerontología. 2013; 48(5).
[18]. Werner, Heitmann I, Leonor Jofré J, Sapunar J, Zulantay I, Torres. Guías clínicas de la enfermedad de Chagas 2006: Parte VI. Tratamiento antiparasitario de la enfermedad de Chagas. Revista Chilena de Infectología. 2008; 25(5).
[19]. Respuesta inmune de las células del hospedero a la infección por Trypanosoma cruzi. Revista Médica del Hospital Nacional de Niños Dr. Carlos Sáenz Herrera. 2002; 37(1-2).
[20]. Pardo Nancy, Condori Paxi M, Arnez Terrazas R. Miocardiopatía Chagásica con taquicardia ventricular: Hospital Obrero Nº 2 "Caja Nacional de Salud". Revista Científica Ciencia Médica. 2012; 15(1).
[21]. Souza Santos E, Carvalho Silva, Bruna CdR, Cardim Barreto B. Immunomodulation for the Treatment of Chronic Chagas Disease Cardiomyopathy: A New Approach to an Old Enemy. Front Cell Infect Microbiol. 2021; 12(11).
[22]. Giraldo Echavarría N, E. Echeverría L, Stewart, Gallego C, Saldarriaga C. Chagas Disease: Chronic Chagas Cardiomyopathy. Current Problems in Cardiology. 2021; 46(3).
[23]. Llerena-Velastegui J, Lopez-Usina A, Mantilla-Cisneros C. Advances in the Understanding and Treatment of Chronic Chagas Cardiomyopathy. Cardiol Res. 2024; 16(4): p. 340–349.
[24]. Molina I, Salvador, Sánchez-Montalvá A. Actualización en enfermedad de ChagasUpdate Chagas disease. Enfermedades Infecciosas y Microbiología Clínica. 2016; 34(2).