Physical Exercise Training and Chagas Disease: Potential Role of MicroRNAs

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Abstract
Chagas disease (CD) is caused by Trypanosoma Cruzi. This parasite can infect several organs of the human body, mainly the heart, causing inflammation, fibrosis, arrhythmias, and cardiac remodeling, promoting long-term Chronic Chagas Cardiomyopathy (CCC). However, little scientific evidence has elucidated the molecular mechanisms that govern the pathophysiological processes in this disease. MicroRNAs (miRNAs) are regulators of post-transcriptional gene expression that modulate signaling pathways, participating in pathophysiological mechanisms in CD, but the understanding of miRNAs in this disease is limited. On the other hand, a wide range of scientific evidence shows that physical exercise training (PET) modulates the expression of miRNAs by modifying different signaling pathways in healthy individuals. Some studies also show that PET is beneficial for individuals with CD; however, these did not evaluate the miRNA expressions. Thus, there is no evidence showing the role of PET in the expression of miRNAs in CD. Therefore, this review aimed to identify miRNAs expressed in CD that could potentially be modified by PET.

Introduction
Chagas Disease (CD) is a complex disease caused by Trypanosoma Cruzi (T. cruzi), a flagellated protozoan parasite, infection at the intracellular level.1 In the acute phase, the T. cruzi infection generates great tissue inflammation, and there is an initial response of the innate immune system in an attempt to fight parasitemia.2

However, the infection persists and the adaptive immune system activates the T lymphocytes, as well as the auxiliary and cytotoxic T cells, which produce cytokines, such as gamma interferon (IFN-γ), which can in turn lead to intracellular parasitic death by inducing an increase in the reactive oxygen species and nitrogen, which are microbicids. This infection also increases the expression of the tumor necrosis factor (TNF-α) and specific antibodies to combat T. cruzi, which control parasitism, with a low-grade infection being established.1

Keywords
Exercise; Chagas Disease; MicroRNAs.

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Still in the acute phase of the disease, there is an increase in the expression of the vasoactive peptide endothelin-1 (ET-1) and cardiotrophin-1 (CT-1), both inducing cardiac hypertrophy, as well as an increase in the expression of interleukin-1 beta (IL-1β), inducing an inflammatory and pro-hypertrophic response of the myocardium, which may initiate cardiac hypertrophy even at this stage.3,5

Over the years, parasitemia is reduced; however, parasitic antigens persist, generating a diffuse inflammatory infiltrate and myocarditis, with the presence of CD4+ and CD8+ T lymphocytes and macrophages that continue to express TNF-α and IFN-γ.3 IFN-γ has an essential function to control and fight against parasites, but it also contributes to cardiac pathogenesis, as it damages the myocardium through several molecular mechanisms generating myocardial dysfunction.6

Thus, the disease evolves and passes to the chronic phase, which can be subdivided into two forms: indeterminate and symptomatic. In the indeterminate form, individuals can go for years without manifesting any type of more serious symptom, where there is a balance between parasitemia and the host’s immune system. However, about 30% of these patients develop a symptomatic or determined form, which can trigger dysfunctions in different organs, including the heart, developing Chronic Chagas Cardiomyopathy (CCC) associated with myocarditis and cardiac myofibrillary fibrosis, thereby reducing cardiac electrical conductivity and generating myocardial remodeling.7

CCC generates inflammation of the cardiac tissue, causing focal or diffuse myocarditis, hypertrophy, or dilation of the left ventricle and progressive death of some cardiomyocytes, necrosis, and collagen deposit,8 thereby increasing the fibrotic tissue, leading to a reduction in its contractile capacity. This outcome is mostly associated with arrhythmias and heart failure,9 but microRNAs (miRNAs) may also participate in these mechanisms. In general, the molecular mechanisms that govern these processes are poorly understood.

MiRNAs are small RNAs, with only 18 to 25 nucleotides in length,10 non-coding proteins; and regulators of post-transcriptional gene expression with the function of inhibiting or degrading its target genes.11,12 It has been shown that several types of physical exercise training (PET) modulate the expression of miRNAs.13 Nevertheless, articles that analyze the effects of PET on the expression of miRNAs in CD are still scarce in the literature. Thus, our literature review sought to analyze the miRNAs expressed in CD and to compare this finding with the miRNAs expressed during or after PET.

Chagas Disease and miRNAs
Few studies in the literature have analyzed the expression profile of miRNAs in CD, either in the acute or in the chronic...
phase, as well as the signaling pathways that are regulated by miRNAs in this neglected disease. Therefore, this study included all of the studies that evaluated the expression pattern of miRNAs in CD (Table 1).

Chagas Disease (acute phase) and miRNAs

During the acute phase of CD, the researchers evaluated the expression of miRNAs at 15, 30, and 45 days post-infection, and identified that miRNAs were differentially expressed during parasitemia and that changes in the QT interval were upregulated: miR-20, miR-20b, miR-21, miR-142, miR-146a, miR-146b, miR-155, miR-182, miR-203, and miR-222, and downregulated: miR-139, miR-145, miR-149, miR-322, and miR-503.14

Another study performed an in silico analysis to identify the differential expression of miRNAs and their target genes in several biological processes during the acute phase of T. Cruzi infection, demonstrating that some miRNAs may be associated with the pathological process, such as miR-238-3p, miR-149-5p, miR-143-3p, miR-145-5p, and miR-486-5p. Other miRNAs may be associated with cardiovascular immunity and function, for example: miR-10a-5p, miR-16-5p, miR-30c-5p, miR-34a-5p, miR-138-5p, miR-146a-5p, miR-149, miR-191-5p, miR-204-5p, miR-320b and miR-653-3p, as well as miRNAs related to the tissue fibrosis process: miR-34a-5p, miR-142-3p, miR-200b-3p, and 203a-3p.15

Chagas Disease (chronic phase) and miRNAs

The expression of miRNAs from the cardiac tissue of patients with CCC after heart transplantation was analyzed and compared with the expression of miRNAs from the cardiac tissue of healthy donor individuals. Of all miRNAs analyzed, five miRNAs had their expression reduced (miR-1, miR-133a, miR-133b, miR-208a, and miR-208b) in patients with CCC when compared to the control group.16 By contrast, the circulating miR-208a in a plasma sample was overexpressed in patients with CD; however, these were in the undetermined chronic phase.17

The overexpression of MiR-19a, miR-21, and miR-29b has been described in patients with CCC when compared to healthy individuals. In fact, in the histological analysis of the cardiac tissue of patients in the final stage of CCC, it was identified that, in addition to the miRNAs mentioned above, the miR-30a and miR-199b are also overexpressed in the CD.16

These studies demonstrate that many miRNAs participate in several processes in the CD both in the acute and chronic phase; however, further studies are needed to elucidate the role of these miRNAs and the signaling pathways they are regulating in the CD, including the importance of therapies or treatments that can modulate the pattern of expression shown in the disease.

Chagas Disease and Physical Exercise Training: miRNAs as potential modulators

Several types of PET have been described as modulators of the expression of many miRNAs,13 in experimental and clinical studies, such as swimming PET,19 marathon,20 running on a treadmill,21 and resistance training (RT)22 (Table 2).

Some studies have also reported the importance of PET modulating the expression of miRNAs in pathological situations, as well as in diabetics,24,25 in obesity,26 after myocardial infarction,27 and with heart failure;22 however, the role of PET-modulating miRNAs in CD has not yet been illustrated. The literature presents only studies that have shown beneficial effects of PET on CD, but they did not analyze the miRNA profile.

Performing only aerobic PET with moderate intensity (50% to 70% of maximum heart rate), three days a week, for 30 minutes, in 12 weeks, obtained a significant increase in maximum cardiorespiratory and metabolic capacity (VO2), increased time in exercise, distance covered, and improvement in emotional aspects,28 as well as association with an RT program, obtained similar beneficial results.29

In another study, with a similar PET protocol, an improvement in functional capacity was also evidenced, with an improvement in ejection fraction and respiratory strength, improvement in diastolic pressure in the left ventricle and in the quality of life of Chagas patients after 8 months of training.10

A cardiac rehabilitation program consisting of the same PET protocol mentioned above, with RT and stretches, adding nutritional guidance and pharmacological counseling

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<tr>
<th>MicroRNAs</th>
<th>Source</th>
<th>Findings</th>
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<tr>
<td>↓ miR-1, miR-133a, miR-133b, miR-208a, miR-208b</td>
<td>Heart samples</td>
<td>Association with connective tissue disorders and fibrosis</td>
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<tr>
<td>↑ miR-208b</td>
<td>Plasma samples</td>
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<tr>
<td>↓ miR-20, miR-20b, miR-21, miR-142, miR-146a, miR-146b, miR-155, miR-182, miR-203, miR-222</td>
<td>Heart samples</td>
<td>Association with heart rate-corrected QT (QTC) interval. Ventricular depolarization and repolarization.</td>
</tr>
<tr>
<td>↓ miR-19a, miR-145, miR-149, miR-322, miR-503,</td>
<td>Heart samples and cell model</td>
<td>Association with fibrosis and cardiac remodeling</td>
</tr>
<tr>
<td>↑ miR-16, miR-26b, miR-190b, miR-3586, let-7i-2, miR-190b</td>
<td>H9c2 cells, infected with T. Cruzi</td>
<td>Association with cell growth, hypertrophy, and cell survival</td>
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</table>

Table 1 – MicroRNAs in Chagas Disease
### Table 2 – MicroRNAs in Physical Exercise Training (pre-clinical and clinical studies)

<table>
<thead>
<tr>
<th>MicroRNAs</th>
<th>Target (Source)</th>
<th>Types of Exercises</th>
<th>Reference</th>
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<td><strong>In vivo experimental models</strong></td>
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<tr>
<td>↑ miR-27a, miR-155↓ miR-143</td>
<td>ACE, AT1R Heart samples</td>
<td>Wistar-Kyoto rats Exercise training on treadmill</td>
<td>39</td>
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<tr>
<td>↑ miR-17-3p</td>
<td>TIMP-3 PTEN Heart samples</td>
<td>C57Bl/6 mice Ramp swimming training model Voluntary wheel training</td>
<td>40</td>
</tr>
<tr>
<td>↑ miR-222</td>
<td>HIPK1 Heart samples</td>
<td>Ramp swimming model Voluntary wheel training</td>
<td>41</td>
</tr>
<tr>
<td>↑ miR-19b, miR-30e, miR-133b, miR-208a↓ miR-99b, miR-100, miR-191a, miR-22, miR-181a</td>
<td>IGF-1 PI3K/PIKT/mTOR MAPK Heart samples Plasma</td>
<td>Wistar albino rats Swimming training</td>
<td>42</td>
</tr>
<tr>
<td>↑ miR-29a, miR-101a</td>
<td>TG-β fos COL1A1 Heart samples</td>
<td>Intermittent run exercise</td>
<td>43</td>
</tr>
<tr>
<td>↑ miR-27a, miR-27b↓ miR-143</td>
<td>ACE ACE2 Heart samples</td>
<td>Wistar rats Swimming training</td>
<td>44</td>
</tr>
<tr>
<td>↑ miR-126</td>
<td>PI3KR2 Heart samples Plasma</td>
<td>Zucker rats Swimming training</td>
<td>26</td>
</tr>
<tr>
<td>↓ miR-214</td>
<td>SERCA2A Heart samples</td>
<td>Wistar rats Resistance training</td>
<td>23</td>
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<tr>
<td>↑ miR-1, ↑ miR-214</td>
<td>NCX COL1A2 Heart samples</td>
<td>Wistar rats Swimming training</td>
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<tr>
<td>↑ miR-29c, ↓ miR-1, miR-133a, miR-133b</td>
<td>COL1A1 COL3A1 Heart samples</td>
<td>Wistar rats Swimming training</td>
<td>45</td>
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<tr>
<td>↑ miR-126</td>
<td>SPRED1 PI3KR2 Heart samples</td>
<td>Wistar rats Swimming training</td>
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<tr>
<td>↑ miR-21, miR-144, miR-145↓ miR-124</td>
<td>PTEN PI3K/3A TSC2 Heart samples</td>
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<tr>
<td>↑ miR-336-5p, miR-130b-5p, let7d-3p, miR-466c-5p, miR-324-3p, miR-148b-5p, miR-132-3p, miR-21-5p, miR-187-3p, miR-29b-5p, miR-324-5p, miR-214-5p, miR-140-5p, miR-152-5p, miR-99b-5p, miR-130a-5p, miR-455-5p, miR-27b-3p, miR-23b-3p, miR-652-5p, miR-199a-3p, miR-223-5p, miR-421-3p, miR-27a-5p, miR-24-5p, miR-34a-3p, miR-140-3p, miR-125b-5p, miR-145a-5p, miR-192-5p, miR-139-5p, miR-199a-5p, miR-674-3p, miR-191-5p, miR-28-3p, miR-195-5p, miR-508, miR-452, miR-429, miR-224, miR-425, miR-221</td>
<td>TNF-α COL1A1 MMP9 PTEN AKT1 AMPK BCL2 Heart samples</td>
<td>Wistar rats Aerobic run training</td>
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<td>↑ miR-503, miR-465b-5p, miR-542-3p↓ miR-652</td>
<td>IGF1R GATA-4 NFAT1C GSK3B Heart samples</td>
<td>C57Bl6 mice Swimming training</td>
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<td>↓ miR-26b, miR-143</td>
<td>Heart samples</td>
<td>Baltic mice Aerobic metal wheels training</td>
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<td>↑ miR-21, miR-30b↓ miR-1</td>
<td>BCL-2 p53 PDCD4 Heart samples</td>
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<tr>
<td>↑ miR-126, miR-133</td>
<td>CPK</td>
<td>Plasma</td>
<td>Single symptom-limited spiroergometry test</td>
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<td>↓ miR-486</td>
<td>PTEN</td>
<td>Serum</td>
<td>Systematic-cycling at 70% VO2max</td>
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<tr>
<td>↑ miR-1, miR-126, miR-133a, miR-134, miR-146a, miR-208a, miR-499-5p</td>
<td>CPK, NT-proBNP, hsCRP</td>
<td>Plasma</td>
<td>Marathon run Immediately after run</td>
</tr>
<tr>
<td>↑ miR-1, miR-133a, miR-206, miR-208b, miR-499</td>
<td>Plasma</td>
<td>Marathon run Immediately after run</td>
<td>54</td>
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<tr>
<td>↑ miR-1, miR-133a, miR-206</td>
<td>Plasma</td>
<td>Marathon run Immediately after run</td>
<td>55</td>
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<tr>
<td>↑ miR-1, miR-133a, miR-133b, miR-206</td>
<td>Plasma</td>
<td>Marathon run Immediately after run</td>
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<td>↑ miR-181b, miR-214</td>
<td>Plasma</td>
<td>Uphill treadmill test (concentric) Immediately after Downhill treadmill test (eccentric) 2-6 hs after exercise</td>
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<td>↑ miR-194, ↑ miR-133a, miR-133b, miR-208b</td>
<td>Plasma</td>
<td>Systematic endurance cycle ergometry training</td>
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<td>↑ miR-1, miR-133a, miR-133b, miR-206, miR-485-5p, miR-509-5p, miR-517a, miR-518f, miR-620f, miR-622, miR-522, miR-553, miR-888</td>
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<td>↑ miR-181a</td>
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<td>Resistance exercise 3 days after exercise</td>
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<tr>
<td>↑ miR-1, miR-133a, miR-133b, miR-206, miR-208b, miR-499</td>
<td>Plasma</td>
<td>Systematic resistance training 36-72 hs after training</td>
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<td>↑ miR-8, ↑ miR-9, ↑ miR-23a, ↑ miR-23b, ↑ miR-31, ↑ miR-1, miR-29b</td>
<td>HDAC4, NRF1</td>
<td>Skeletal muscle samples</td>
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<td>↑ miR-23a, miR-27a</td>
<td>PTEN, Casp7, FoxO1</td>
<td>Skeletal muscle samples</td>
<td>Resistance exercise</td>
</tr>
<tr>
<td>↑ miR-29c</td>
<td>COL1A1, COL3A1</td>
<td>Heart samples</td>
<td>Swimming training</td>
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<td>↑ miR-382</td>
<td>Serum, tissues, and cell samples</td>
<td>IR mice</td>
<td>Aerobic exercise</td>
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Continuação

↑ miR-23a, miR-27a | PTEN, Casp7, FoxO1 | Skeletal muscle samples | Resistance exercise | 50 |
| ↑ miR-29c | COL1A1, COL3A1 | Heart samples | Swimming training | 51 |
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<p>| ↓ miR-486 | PTEN | Serum | Systematic-cycling at 70% VO2max | 53 |
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| ↑ miR-1, miR-133a, miR-206, miR-208b, miR-499 | Plasma | Marathon run Immediately after run | 54 |
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| ↑ miR-194, ↑ miR-133a, miR-133b, miR-208b | Plasma | Systematic endurance cycle ergometry training | 59 |
| ↑ miR-1, miR-133a, miR-133b, miR-206, miR-485-5p, miR-509-5p, miR-517a, miR-518f, miR-620f, miR-622, miR-522, miR-553, miR-888 | Plasma | High intensity interval exercise Immediately after | 60 |
| ↑ miR-181a | Plasma | Resistance exercise 3 days after exercise | 62 |
| ↑ miR-1, miR-133a, miR-133b, miR-206, miR-208b, miR-499 | Plasma | Systematic resistance training 36-72 hs after training | 63 |
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<td>miR-128, miR-204, miR-330, miR-345, miR-375, miR-446c, miR-483, miR-509, miR-520a, miR-548a, miR-628, miR-653, miR-670, miR-889, miR-1245a, miR-1270, miR-1280, miR-1322, miR-3180</td>
<td>Skeletal muscle samples</td>
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<td>↓ miR-125a, miR-145, miR-181b, miR-193a, miR-197, miR-212, miR-223, miR-340, miR-365, miR-485, miR-505, miR-520d, miR-629, miR-633, miR-939, miR-940, miR-1225, miR-1238</td>
<td>Serum</td>
<td>Cycle ergometer exercise</td>
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<td>↓ miR-17-1, miR-17a, miR-18a, miR-18b, miR-20a, miR-20b, miR-22, miR-93, miR-96, miR-106a, miR-107, miR-126, miR-130a, miR-130b, miR-151, miR-185, miR-194, miR-363, miR-660</td>
<td>PBMC</td>
<td>Cycle ergometer exercise</td>
<td>68</td>
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<tr>
<td>↓ miR-7, miR-15a, miR-21, miR-26b, miR-132, miR-140, miR-181a, miR-181b, miR-181c, miR-338, miR-363, miR-939, miR-940, miR-1225</td>
<td>PBMC</td>
<td>Running exercise</td>
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<td>↓ miR-7, miR-23b, miR-31, miR-99a, miR-125a, miR-125b, miR-126, miR-130a, miR-145, miR-151, miR-199a, miR-199b, miR-221, miR-320, miR-451, miR-486, miR-564, miR-652</td>
<td>PBMC</td>
<td>Cycle ergometer exercise</td>
<td>70</td>
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<tr>
<td>↓ let-7i, let-7f, miR-29c, miR-223</td>
<td>Serum</td>
<td>Cycle ergometer exercise</td>
<td>71</td>
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<tr>
<td>↓ let-7i, let-7f, miR-21, miR-29c, miR-223</td>
<td>(Endurance athletes, runners, cyclists, and triathletes)</td>
<td>Cardiopulmonary exercise test</td>
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<td>↓ miR-7, miR-29a, miR-29b, miR-29c, miR-30e, miR-142, miR-192, miR-338, miR-363, miR-590</td>
<td>Serum</td>
<td>Rowing training, 5Km, 1-3 h per session, 20-24 strokes/min</td>
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<td>↓ let-7e, let-7e, miR-126, miR-130a, miR-151, miR-199a, miR-221, miR-223, miR-326, miR-328, miR-652</td>
<td>Plasma</td>
<td>Aerobic run exercise training (4 days/week)</td>
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<tr>
<td>↓ miR-15a, miR-29b, miR-29c, miR-30a, miR-140, miR-324, miR-338, miR-362, miR-532, miR-660</td>
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<td>↓ miR-23b, miR-130a, miR-151, miR-199a, miR-221</td>
<td>Plasma</td>
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<td>↑ miR-15a, miR-29b, miR-29c, miR-30a, miR-140, miR-146a, miR-324, miR-338, miR-362, miR-532, miR-660</td>
<td>p-AKT</td>
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<td>p-S6K1</td>
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<td>↑ miR-19a, miR-19b, miR-20a, miR-26b, miR-143, miR-195</td>
<td>p-AKT</td>
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<tr>
<td>↑ miR-222</td>
<td>HIPK1</td>
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<td>↑ miR-221</td>
<td>Plasma</td>
<td>Basketball Exercise</td>
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for patients with CD, demonstrated an increase in the physical and functional capacity, improving the quality of life of Chagas patients.  

In another important study, researchers performed PET three times a week for six months on Chagas patients. They demonstrated that the exercise group increased peak exercise oxygen consumption and maximum minute ventilation, improving the functional capacity of these patients.  

However, even demonstrating that PET has beneficial effects for patients with CD, it is difficult to analyze the effects of this type of training at the tissue, cell, and molecular levels, given that these studies were performed in humans, where biopsies would be necessary. Therefore, to investigate the possible mechanisms associated with these beneficial effects of PET on CD, some studies have been carried out on experimental models of CD in vivo.  

Balb/c mice performed PET on a treadmill before being infected by T. Cruzi. It was observed that PET reduced the peak of parasitemia, concluding that PET can promote beneficial changes in the immune system and obtain better responses to infections.  

In other studies, the same finding as in the previous study was reported; however, they also observed that trained mice obtained greater protection from the metabolic activity of NADH in myenteric neurons and greater synthesis of TNF-α and TGF-β. This contributed to the survival and/or protection of 10.3% of myenteric neurons and their immunoreactive production of nitric oxide neuronal synthase, in fact, the trained group obtained a greater expression of TNF-α during the acute phase of T. Cruzi infection, providing benefits to the host and improving the immune system to preserve nitrergic neurons.  

In this context, in another study, researchers observed that the PET group obtained a greater expression of TNF-α, IFNγ, IL-6, and chemokines MCP-1 and CX3CL1 during acute infection, and also obtained better physical capacity, increased anaerobic threshold, increased activity of catalase and superoxide dismutase and reduced lipid and protein oxidation in cardiac tissue, demonstrating that PET can be an interesting strategy to increase the efficiency of endogenous antioxidant mechanisms, reducing oxidative damage in these animals.

Another study showed that PET before infection in Wistar rats, increased the time to reach fatigae and anaerobic threshold, reduced the expression of TNF-α, CCL-2, MCP-1, and CX3CL1, as well as lipid and protein oxidation, and increased the expression of IL-10, catalase, and superoxide dismutase, indicating that PET induces a protective phenotype, increasing the host’s defenses against the parasite agent, including the attenuation of the pathological remodeling process associated with musculoskeletal myositis.  

Finally, in another study, Swiss mice were infected by T. Cruzi after PET with moderate intensity on a treadmill, being carried out for 9 weeks. Researchers identified that PET was able to reduce the latent parasitemia of the infected animals they trained, corroborating with previous studies, and even obtained less production of pro-inflammatory cytokines (TNF-α, INFγ, IL-12) and type-1 monocyte chemotactic protein (MCP-1) during the first days of infection.  

Thus, it is suggested that PET has a therapeutic potential for the prevention and complementary treatment of CD and CCC through the modulation of the immune system. However, clinical studies lack morphometric, cellular, and molecular analyzes, mainly through the analysis of miRNAs for a better understanding of the beneficial effects of PET on signaling pathways in humans with CD, while preclinical studies, in vivo, need studies that evaluate the effects of PET with CD and CCC already installed and not only in the pre-infection stage.

**Overlaps between miRNAs in CD and PET**

Additionally, this study also performed an analysis using the Venn diagram to identify miRNAs that were modulated by PET in both clinical and pre-clinical studies that can possibly modulate miRNAs in CD.  

There were only 7 miRNAs expressed in CD, 95 miRNAs expressed in PET clinical studies, and 36 miRNAs expressed in PET pre-clinical studies. Interestingly, the present study identified 7 miRNAs that had modulations in both CD and PET clinical studies, 3 common miRNAs modulated in CD and PET pre-clinical studies and, mainly, 12 common miRNAs modulated in CD, PET clinical studies, and PET pre-clinical studies (Figure 1). These 12 miRNAs are: miR-1, miR-21, miR-26b, miR-29b, miR-133a, miR-133b, miR-139, miR-145, miR-146a, miR-208a, miR-208b, and miR-222.

Nevertheless, of these 12 common miRNAs, only miR-133b, miR-139, and miR-208a were identified with a different expression pattern in CD and PET; all 3 miRNAs are downregulated in CD and upregulated in PET (Figure 2).  

MiR-133b controls the connective tissue growth factor (CTGF) and can suppress cardiac remodeling; therefore, PET can be an excellent alternative to control cardiac remodeling, possibly through the modulation of miR-133b and the modification of some signaling pathways.

MiR-139 is associated with hypertrophic cardiomyopathy, regulating the expression of c-Jun, a transcriptional factor that binds in the promoter region of some genes to induce cardiac hypertrophy; thus, the overexpression of this miRNA reduces the expression of c-Jun, and consequently attenuates the pathological cardiac hypertrophy, which may be a signaling pathway by which PET suppresses the pathological hypertrophy in CD, since PET also increases the expression of this miRNA.  

In this context, miR-208a regulates the expression of some transcriptional factors, such as GATA-4, which is associated with the activation of pro-hypertrophic cardiac genes. In CD, this miRNA is downregulated, while PET can increase its expression, thus demonstrating that it may possibly be a molecular mechanism by which PET attenuates cardiac hypertrophy in this disease.

**Conclusions**

miRNAs participate in several processes in the pathogenesis of CD. Much evidence shows the beneficial effects of PET on CD; however, there still are no articles in the literature that demonstrate the changes in the molecular mechanisms of miRNAs that PET induces in CD. Therefore, further studies are necessary to elucidate these mechanisms.
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Review Article

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Author Contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Improta-Caria AC; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Improta-Caria AC, Aras Júnior R.

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**Figure 1** – Venn diagram shows overlaps between miRNAs: miRNAs (miRs) in Chagas Disease (blue), miRs PET clin: clinical studies (pink) and miRs PET pre-clin: pre-clinical studies (green).

**Figure 2** – miRNAs expressed in CD that can likely be modulated by PET.
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