Immunothrombotic dysregulation in chagas disease and COVID-19: a comparative study of anticoagulation

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Abstract
Chagas and COVID-19 are diseases caused by Trypanosoma cruzi and SARS-CoV-2, respectively. These diseases present very different etiological agents despite showing similarities such as susceptibility/risk factors, pathogen-associated molecular patterns (PAMPs), recognition of glycosaminoglycans, inflammation, vascular leakage hypercoagulability, microthrombosis, and endotheliopathy; all of which suggest, in part, treatments with similar principles. Here, both diseases are compared, focusing mainly on the characteristics related to dysregulated immunothrombosis. Given the in-depth investigation of molecules and mechanisms related to microthrombosis in COVID-19, it is necessary to reconsider a prompt treatment of Chagas disease with oral anticoagulants.

Keywords COVID-19 · Hypercoagulability · Platelet · Hyperaggregability · Immunothrombosis · SARS-CoV-2

Introduction
Chagas disease (CD) and COVID-19 caused by Trypanosoma cruzi and SARS-CoV-2, respectively, have the common characteristic of dysregulated immunothrombosis. Here, we have integrated the reported evidence of both, which leads us to consider that the possibility of anticoagulant treatment in Chagas disease can prevent the immunothrombosis stage.

Although the prevalence of immunothrombotic dysregulation in Chagas disease and COVID-19 is not yet known, the proportion depends on the method of detection and the group studied. As an example, the chronic cardiac form of CD was inferred through echocardiography in a study of ischemic cerebrovascular events (ICE); the authors found cardioembolism as a factor associated with 20% of CD cases [1], however, could reach 44% [2]. Even though the reported evidence is extremely diverse, it currently indicates that the incidence of deep vein thrombosis (DVT) in COVID-19 patients ranges between 6 and 66% [3]. In mild/moderate COVID-19, deep venous thrombosis (DVT) was found in the lower extremities by duplex ultrasound, with a rate of around 25% [4], but it could reach as much as 82% by computed tomography venography (CTV) and doppler ultrasound [5]. In pulmonary vessels, it is 46% [6], while in arterial thromboses, it is 9.6% [7].

Immunothrombosis has been reported in COVID-19 [8] and Chagas disease [9, 10]. Immune-driven thrombosis,
immunothrombosis, or thrombo-inflammation [11] has the characteristics of upregulation of monocytes/macrophages and vessel wall-exposing podoplanin, activating C-type lectin-like receptor-2 (CLEC-2) in platelets on the microvasculature [12], which causes endotheliopathy and microthrombi [13]. The expression of podoplanin, known as gp38, T1α, D2-40, or Aggrus, is also upregulated during inflammation by cytokines and other compounds in different cells, such as T helper cells, fibroblasts, epithelial cells, and in fibroblastic reticular cells in secondary lymphoid organs [14].

In viral diseases such as dengue and H5N1 influenza, CLEC-2 binds fucoids in a similar way to a ligand [15, 16]. These glycans interact with viruses, such as the dengue virus, which binds to CLEC-2 on platelets [16]. In the dengue virus interaction, CLEC-2 on platelets releases exosomes and microvesicles that trigger the activation of CLEC5A and TLR2, and promote the release of neutrophil-derived extracellular traps (NETs) in addition to the release of proinflammatory cytokines in neutrophils and macrophages [12]. NETs, due to the content of DNA-histone complexes and high mobility group box 1 proteins (HMGB1), are cytotoxic and procoagulant [17, 18].

In SARS-CoV-2 infection, the spike protein induces platelet activation [19]. This is explained by the fact that platelets have ACE2-TMPRSS2 receptor-protease axis [20], and also, platelets favour increases in fibrinogen, von Willebrand factor, and factor XIII [21], this favours the prothrombotic state [22].

In COVID-19, activation of the complement through mannose-binding lectin (MBL) has been reported [23]. In SARS-CoV, MBL initiates the complement activation in a calcium-dependent and a mannann-inhibitable manner [24]. MBL circulates in a complex with mannose-associated serine protease (MASP)-1 and MASP-2. MASP-1 can activate coagulation through factor XIII (FXIII) and thrombin-activatable fibrinolysis inhibitor (TAFI) [25]. That is, MBL acts from a different route to that of heparin (thrombin and factor Xa), which could explain thromboembolic events in patients with thromboprophylaxis.

In the severe form of Chagas disease, a greater binding capacity of MBL was observed, which could facilitate the internalization of T. cruzi in cardiomyocytes [26]. Furthermore, MASP-2 deficiency does not represent an important mechanism against T. cruzi infection [27].

A disparity is assumed since the etiological agent is different, added to the large inter-individual and inter-population differences between Chagas disease and COVID-19. Nevertheless, when these illnesses are compared regarding susceptibility/risk, ethnicity, age, sex, and other co-morbidities, there are similarities in both diseases. For example, there are genetic polymorphisms associated with the protection or greater risk of damage, as in Chagas disease in which the genetic variant of CCL5 and CCR1 confers protection, while CCR5 deficiency is associated with cardiac damage [28]. On the other hand, depending on the population studied, a higher or lower risk may be related to variants CCL2, MBL, CCL5, AHSG, and IL4 in COVID-19 [29]. We compare and show a series of different factors in both infections (Table 1).

**Chagas disease**

Chagas disease (CD) is a neglected tropical disease, with an estimated 6 to 7 million people infected with *T. cruzi worldwide* [30]. In 2006, the number of cases recorded in Latin America was 7,544,500 [31]. Migration, blood transfusion, and organ transplantation have caused the spread of CD not only in Latin America but also in many other places around the world, e.g. the prevalence per in some European countries is 2.7–4.8 in Spain; 2.0–4.8 in Switzerland; 1.3–1.7 in France; and 1.3–2.4 in The United Kingdom [32].

In a post-mortem study in Sao Paulo Brazil with 1,345 studied cases of Chagas heart disease, a thromboembolic phenomenon was found in 44% of patients, and this included infarction at different phases of evolution and cardiac thrombosis in 27% of cases [2]. The protocol for treatment recommends just benznidazole and nifurtimox [33]; however, anticoagulants or antiplatelet agents should be considered in addition.

**Hypercoagulability and endotheliopathy in Chagas disease**

In Chagas disease, hypercoagulability is characterized by an increase in the prothrombin fragment 1 + 2 (F1 + 2), endogenous thrombin potential (ETP), D-dimer, and plasmin-antiplasmin complexes (PAP), before or after treatment [13, 34]. Thrombin activation causes a procoagulant and fibrinolysis pathway. Furthermore, platelet hyperactivity and endothelial damage occur, which are correlated with increases in circulating microparticles from endothelial cells, macrophages, and CDS + T cells [35], PAC-1 (GPIIb/IIIa), and CD62P (P-selectin) [36].

In the initial host-trypanosome interaction, the infective trypanastigote recognizes 2,3-sialyl residues [37] and releases neuraminidase, which can desialylate myocardial or human vascular endothelial cells, and mediate the development of Chagas heart disease [38]. Different mechanisms affect the invasion process of trypanastigote forms in cardiomyocytes by *T. cruzi*. One of the known mechanisms is through glycosaminoglycan-binding or heparin-binding proteins in the amastigote and trypanastigote forms of *T. cruzi*, which bind to cardiomyocyte heparan sulphate proteoglycans (HSPG) [39, 40].
### Table 1 Comparative factors between Chagas disease and COVID-19

|                                | Chagas disease (CD)                                                                                                                                                                                                 | COVID-19                                                                                                                                                                                                 |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Age and Gender**             | This varies in parallel with the pathology and the studied group, e.g. in a study of Chagasic megaesophagus in Brazil, men had a higher frequency (54%) and those under 31 years of age had a prevalence of 4.2% [88]. In a population from Venezuela, a 4.2% with heart disease in a four-year follow-up was found [89]. | Higher mortality has been observed in men than in women in the US and 10 European regions [90, 91]. In addition, no statistical differences had been found in viral load according to gender and age [92]. Still, other studies differ slightly in viral load; women present higher viral load than men [93]. |
| **Comorbidities**              | Among the most frequent concurrent diseases in CD in the elderly are hypertension, osteoporosis, osteoarthritis, and dyslipidaemia [94]                                                                                                                                          | The proportion of comorbidities depends on the population studied. Among the most frequent conditions experienced are hypertension, diabetes, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease [95]. |
| **Prevalence of asymptomatic infection** | The prevalence of CD in asymptomatic blood donors is 4.3% in Mexico [96]. In asymptomatic patients with chronic CD in Brazil, the prevalence of cardiovascular disorders ranges from 2 to 77% [97].                         | Incidence rates of asymptomatic infection range from 1.6 to 56.5% in China and the USA, respectively [98].                                                                                           |
| **Susceptibility/risk**        | Genetic susceptibility to CD depends on ethnic group, e.g. DRB1 *08 and DRB1 *01, DQB1 *05:01 in Venezuela. HLA-B39 b, HLA-B35 b, HLA-DR4, and HLA-DR16 in Mexico. A31, B39, and DR8 in Latin-American mestizos [99].                                    | HLA-A*25:01, HLA-B*46:01, and HLA-C*01:02 have a lower number of binding peptides in antigen presentation, which could be associated with greater severity of the disease [100]. |
| **Genetic polymorphisms**      | In Brazil, the microsatellite locus D6S291 of the major histocompatibility complex (MHC) and in the microsatellite of the IL-10, allelic differences were found in CD [101]. The genetic variant of L18 rs360719 causes the loss of the binding site of the octamer transcription factor (OCT)-1 [102]. In the Latin-American population, L18 rs360719 is related to susceptibility by T. cruzi infection [103]. The gene variant of IL17A rs2275913 binds to the nuclear factor-activated T cells (NFAT) [104]. In the Latin-American population, IL17A rs2275913 is related to T. cruzi susceptibility. [105]. In Brazil, the variants IL17A and IL17F are associated with the development of cardiomyopathy [106]. | In the African/African-American population, p.Arg514-Gly, a polymorphism of ACE2, is associated with cardiovascular and pulmonary conditions [107]. In Genome-wide Association Study (GWAS) in Italian and Spanish hospitals, a 3p21.31 gene cluster encompassed the SLC6A20, LZTFL1, CCR9, FYCO1, CXC6R, and XCR1 genes [108]. |
| **Genetic polymorphisms of Interferon-γ Production** | In Brazil, the microsatellite locus D6S291 of the major histocompatibility complex (MHC) and in the microsatellite of the IL-10, allelic differences were found in CD [101]. The genetic variant of L18 rs360719 causes the loss of the binding site of the octamer transcription factor (OCT)-1 [102]. In the Latin-American population, L18 rs360719 is related to susceptibility by T. cruzi infection [103]. The gene variant of IL17A rs2275913 binds to the nuclear factor-activated T cells (NFAT) [104]. In the Latin-American population, IL17A rs2275913 is related to T. cruzi susceptibility. [105]. In Brazil, the variants IL17A and IL17F are associated with the development of cardiomyopathy [106]. | The single nucleotide polymorphism (SNP) rs6598045 of the interferon-induced transmembrane protein 3 (IFITM3) gene correlates with COVID-19 fatality rates [111]. Populations with a low allele frequency of rs19076070 (T allele) in IFIH1 (InterFeron-Induced Helicase 1; MDA5) are associated with less IFN-beta expression and potential susceptibility to COVID-19 infection [112]. |
| **ABO blood group system**     | Inconclusive studies found an increase in blood group B patients dying suddenly from CD [113]. The histo-blood group system explored by GTA, GTB, FUT II, and FUT III glycosyltransferases found that B plus AB secretor phenotypes are related to megaesophagus and megacolon in CD [114]. | GWAS found blood group A is associated with COVID-19 and respiratory failure [111]. Type A blood is associated with the risk of in-hospital death [115]. |
Table 1 (continued)

| Ethnicity                                                                 | Chagas disease (CD)                                                                 | COVID-19                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
|                                                                            | CD with megacolon, calibre and length of the rectosigmoid depends on altitude,    | COVID-19 presents an increased risk depending on the population studied, | |
|                                                                            | ethnicity, and diet [116]                                                          | e.g. Black and Asian compared to white subjects had increased risk of   | |
|                                                                            |                                                                                   | COVID-19 [117]                                                          | |
|                                                                            |                                                                                   | In Mexico, native peoples have a higher risk of death due to COVID-19   | |
|                                                                            |                                                                                   | [118]                                                                  | |

*Dysregulated immunothrombosis*

Hypercoagulability

The activation of haemostasis is related to the activation and increase of various molecules, e.g. Lys-bradykinin is released by cruzipain, and this could activate contact factors and, therefore, the intrinsic pathway of coagulation [119, 120]. In addition, there is prothrombotic activation with an increase of endogenous thrombin potential (ETP) and F1 + 2 levels, plasmin-antiplasmin complexes (PAP) [9, 34], PAI-1, and fibrinogen [121].

In structural studies, it has been reported that platelets are not only related to microthrombi but also erythrocytes and amyloid microclots. [122]

A study of Post-acute COVID-19 syndrome in Bergamo, Italy, found hypercoagulation in 17% of patients with D-dimer values that increased more than two times above 500 ng/mL. [123]. In addition, ischemic cardiovascular events are increasing in COVID-19 [124], myocardial injury and elevated troponin levels are also reported. [125]

Inflammation and vascular leakage

Trypomastigotes boost their infectivity through activation of the mast cell/kallikrein-kinin system pathway, resulting in inflammatory oedema [126]. At the site of infection by *T. cruzi*, C5a, and bradykinin are released and modulate innate and adaptive immunity, inflammation, and plasma leakage [127].

The severity of COVID-19 is related to increased inflammation markers such as C-reactive protein (CRP), interleukin-6, nuclear factor kappa B (NFκB), and tumour necrosis factor-alpha (TNFα) as well as multiorgan failure [128].

Mid-Regional proAdrenomedullin (MR-proADM), a marker of endothelial integrity and vascular leakage, is also related to severity and mortality in COVID-19 [129].

During COVID-19, inflammation, vasodilation, hypotension, and plasma leakage may be due to the bradykinin system, in particular des-Arg9-BK, which acts on Bradykinin 1 (B1) receptor [130].
T. cruzi infection also causes generalized vasculitis with peculiar characteristics in the myocardium, such as vasospasm, myocardial ischaemia, myonecrosis, and platelet hyperaggregation. Therefore, activation of the extracellular signal-regulated kinase, activator-protein-1, endothelin-1, and cyclins release thromboxane (TX2) from T. cruzi [41, 42].

COVID-19, immunothrombosis and endotheliopathy

The COVID-19 pandemic caused by SARS-CoV-2 has resulted in more than 169 million confirmed infections and 3.5 million deaths worldwide as of May 29, 2021 [43].

SARS-CoV-2 entry depends on the ACE2 receptor and the serine protease TMPRSS2 for S protein priming [44], as well as other proteins such as endosomal cysteine proteases cathepsins B/L (CTSB, CTSL) [45]. These molecules are primarily co-expressed in the respiratory tract, kidneys, heart, and gastrointestinal system [34] and show higher levels of ACE2 gene expression in the testes, thyroid, and adipose tissue [46], as well as in arterial and venous endothelial cells, and arterial smooth muscle cells [47, 48].

The concept of dysregulation of immunothrombosis defines a vicious cycle of immune activation and formation of microthrombi [11]. Microthrombi have been reported in different tissues, in alveolar capillaries, kidneys, and glomerular capillaries; furthermore, they are accompanied by signs of disseminated intravascular coagulation despite anticoagulation [49] in pulmonary, hepatic, renal, and cardiac microvasculature [50], in addition to pulmonary arterial thrombi [51]. Microthrombosis is assumed to be found in larger series in different extrapulmonary tissues, depending on the expression of ACE2 and TMPRSS2 [52].

In COVID-19 immunothrombosis, monocytes and neutrophils activate platelets and coagulation through ACE2 receptors and TMPRSS2 pro tease from the entry of the virus into the body [53], particularly in pneumocytes and the endothelial cells. Microvascular dysfunction, apoptosis of endothelial cells, and mononuclear cells have been observed [54], which may explain endothelial damage and the elevation of circulating endothelial cells in the presence of SARS-CoV-2 infection [55].

Regarding endothelial damage in non-critical patients in the non-intensive care unit (non-ICU), pro-angiogenic factors such as VEGF-A, PDGF-AA, and PDGF-AB/BB increase significantly, while critical patients in the ICU have significantly increased levels of biomarkers related to endotheliopathy such as angiopoietin-2, FLT-3L, and PAI-1 [56]. This is consistent with the pathological findings of severe endothelial injury associated with the intracellular SARS-CoV-2 virus and alveolar-capillary microthrombi [57].

Hypercoagulability in COVID-19

COVID-19 is associated with hypercoagulability and thrombosis due to damaged endothelial cells through ACE2 receptors. Subsequently or simultaneously, when SARS-CoV-2 enters, its pathogen-associated molecular pattern (PAMP) can be recognized. This activates the innate and adaptive immune response, platelet activation, the release of neutrophil extracellular traps (NETs), the tissue factor release and contact pathway activation, the activation of the coagulation system and thrombin generation, complement activation, and the activation of the fibrinolytic and anticoagulant systems [58]. All these activation mechanisms are expressed to different degrees but integrate dysregulated immunothrombosis [59] and then thrombosis.

In COVID-19 infection, hypercoagulability mimics disseminated intravascular coagulopathy and are characterized by thrombocytopenia and platelet hyperreactivity [19, 60]. Results are heterogeneous, depending on the severity of the patient, e.g. in initial presentations, abnormalities in prothrombin time, partial thromboplastin time, and platelet counts show little change [61]. Nevertheless, in patients with severe pneumonia and a poor prognosis, an elevated D-dimer and higher prothrombin time (PT) are observed [62] in up to 50% of patients [63]. A state of hypercoagulation and aberrant hyperfibrinolysis [64] is characterized by an increase in the activated partial thromboplastin time (APTT) and fibrinogen, with lower platelet count [65] and an increase in fibrin degradation products (FDP) [66].

Anticoagulants in COVID-19 and Chagas disease

The use of low molecular weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for the treatment or reduction of an increased risk of venous thromboembolism (VTE) [67]; however, direct oral anticoagulants (DOAC) (dabigatran, apixaban and rivaroxaban) and viral medications (lopinavir, ritonavir, or darunavir) are commonly used in COVID-19 patients, although DOAC plasma levels increase significantly, as observed in the Cremona study. Therefore, they suggest the use of parental anticoagulants [68].

In general, prophylactic anticoagulation (including oral, subcutaneous, or intravenous forms) in COVID-19 patients results in lower mortality [69]. Moreover, derivatives of heparin have been proposed. Heparinoids constituted of heparan, dermanan, and chondroitin sulphate, are found in plants and animals, and are also of synthetic origin [70]. In the production of low molecular weight heparin, two waste heparinoids are obtained: Danaparoid and Sulodexide. Danaparoid is 84% heparan sulphate [71]; it inhibits activated factor X (Factor Xa) and activates factor II (Factor IIa) and has low cross-reactivity with antibodies associated with
heparin-induced thrombocytopenia [72]. Sulodexide constituted of 80% heparan sulphate [73], increases the effect of antithrombin III and heparin cofactor II [74], and releases an inhibitor of the endothelial tissue factor pathway [75].

Another sub-group of heparinoids are Fucoidans, which have 30–60% sulphated polysaccharides [55]. These also increase the interaction of thrombin with Antithrombin III (AT-III) and heparin cofactor II (HC-II) [76].

Heparan sulphate is a heparinoid constituted of repeating units of disaccharide N-acetylglucosamine and glucuronic acid (1 → 4 linked) with alternatively sulphated domain structures [77]. Heparan sulphate and heparin are related to cell adhesion, recognition, migration, modulation of enzymatic activities, and anticoagulant activity [55].

A ubiquitous molecular component on the cell surface is heparan sulphate proteoglycans (HSPG) which are constituted of heparan sulphate (HS) polysaccharides attached to core protein by the global negative charge from HSPG. This facilitates interaction with viral molecules such as the herpes simplex virus, dengue virus, and coronaviruses [78].

SARS-CoV-2 recognizes 9-O-acetyl-sialic acid [79] and sulphated polysaccharides [80]. Various studies have reported the participation of heparin or heparan sulphate in initial virus adherence [81], and heparin and enoxaparin also bind to the spike (S1) protein receptor-binding domain (S1 RBD) [82]. Low-molecular weight heparin is the best treatment for inhibiting microthrombosis in SARS-CoV-2 infections. In addition, heparin or its derivatives could be used to compete with the virus and reduce its entry into the organism, as has been shown [83].

It should be noted that in Chagas disease with hypercoagulability, with or without associated COVID-19, the incorporation of anticoagulants is important. Considering that heparan sulphate proteoglycans participate in Chagas cardiomypathy, the initial proposal may favour the use of heparin, heparinoids, or HS mimetics substituted carboxymethyl dextran sulphates or RGTA [84] in treatment. However, there are two important reasons not to use unfractionated heparin (UFH) or heparinoids: the first is the activation of bradykinin receptors through a papain-like enzyme called cruzipain, derived from infective forms of T. Cruzi (Trypanosoma cruzi) (Tripep­mastigotes), this enzyme enhances cell invasion; in addition, heparan sulphate enhances the interaction of molecules of the kinin system, such as high molecular weight kininogen (HK) and cruzipain, which would potentiate cell invasion [85]. Something similar has been reported in COVID-19, a critical imbalance in the renin-angiotensin system (RAS) in combination with decreased ACE expression, increases in ACE2, renin, and angiotensin, which causes the bradykinin cascade to accelerate [86]. The second reason for not using unfractionated heparin or heparinoids is that these molecules would be blocked in all patients with chronic Chagas disease because anti-sulphatide antibodies have been found. These antibodies are inhibited and compete with heparin, dextran sulphate, and chondroitin sulphate [87]. Therefore, it is necessary to consider whether thromboprophylaxis using DOAC is required in patients with Chagas disease and understand the mechanisms of activation and regulation of microthrombosis in COVID-19. More clinical trials are certainly required in these fields.

Conclusion

We have reviewed the mechanisms and found some similarities between SARS-CoV-2 and T. cruzi infections. In particular, both clinical entities present microthrombosis and endotheliopathy. Low-molecular weight heparin (LMWH) is commonly used in moderate to severe COVID-19, although some cases do not respond to this, which suggests MBL-MASP-2 pathway activation. On the other hand, in Chagas disease, it is important to carry out further clinical trials and consider thromboprophylaxis using DOAC.

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Declarations

Conflict of interest The authors have declared no competing interests in this study.

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