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COMMENTARY

Serum amyloid A protein has been undervalued as a biomarker of COVID-19

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A commentary on:

Guo et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020. e3319. 10.1002/dmrr.3319.

We are currently experiencing a catastrophic pandemic caused by Sars-Coronavirus type 2 (Sars-Cov-2), which is undoubtedly more widespread and more lethal than other coronaviruses. Based on data from Wuhan in China, recently published in this journal,[1] we can already see that infected diabetics have a higher mortality, compared to non-diabetic patients, which can be attributed to a greater susceptibility to infections due to chronic inflammation and immune dysfunction in these patients.[2] A scenario of hyperinflammation has been reported in critically ill patients with COVID-19, caused by a cytokine storm, where IL-6 is highly elevated,[3] which is and accompanied by lymphocytopenia, coagulopathy (characterized by increased D-dimers) and hepatic overactivation (characterized by increased serum ferritin).[4]

Hepatocytes respond to circulating cytokines (mainly IL-6) by synthesizing and secreting specific proteins, described as acute-phase proteins (APP). C-reactive protein (CRP) is the prototype of these proteins and increases in inflammatory states, whether infectious or not.[5] However, this innate immune system protein is not very useful in differentiating bacterial from viral infections. Supporting a hyperinflammation scenario, mediated by IL-6, a meta-analysis highlighted a reduced lymphocyte/CRP ratio as a marker of severity in COVID19.[6] Ferritin is another APP, and is frequently used as clinical marker, particularly in very used and very appropriate for cases of viral infections,[7] including COVID-19. In fact, Guo and co-workers found elevated levels of serum ferritin in COVID-17, but no difference was found between diabetic and non-diabetic Sar-Cov-2 infected patients ($P = .15$, Table 2). However, when other comorbidities (such as hypertension and pulmonary disease) were excluded, both the CRP and ferritin markers were observed as significantly elevated ($P < .01$, Table 4) in the diabetic patients, compared to non-diabetic ones.

Nevertheless, we want, herein, to call attention to another APP, serum amyloid A (SAA). SAA, like CRP, is increased in chronic inflammatory processes, such as diabetes and obesity. A meta-analysis study indicated a strong correlation between elevated SAA and obesity, a major risk for diabetes mellitus type 2.[8] SAA is a pentraxin that

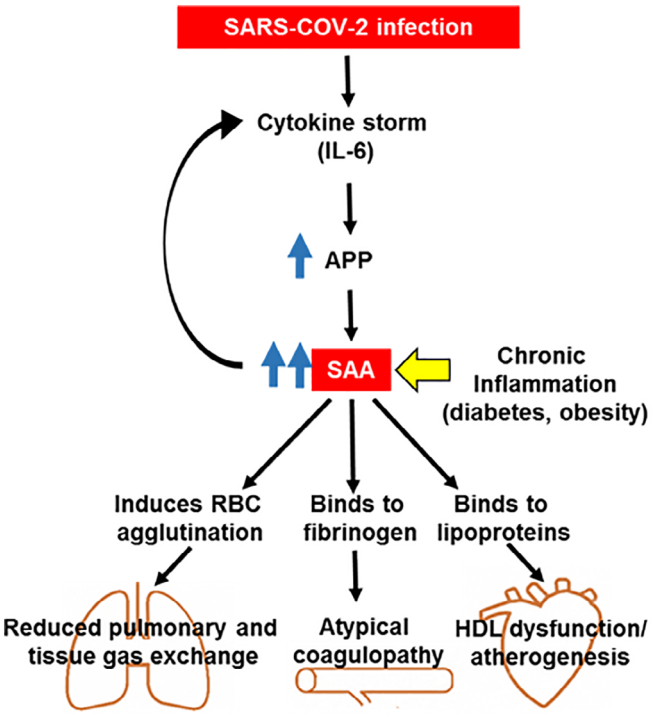

FIGURE 1 Serum amyloid A (SAA) may play a key role in the pathogenesis of COVID-19 in diabetic patients. Interleukin-6 (IL-6) induces the synthesis and release of acute-phase proteins (APP) in hepatocytes. Serum amyloid A (SAA), which is already elevated in chronic inflammatory conditions (eg, obesity and diabetes mellitus), is one of the APP generated. This APP reinforces primary cytokine production, contributing to a cytokine storm. SAA directly binds to fibrinogen leading to an atypical coagulopathy. Moreover, it binds to apoB-containing lipoproteins, leading to HDL dysfunction, and induces red blood cell (RBC) agglutination. Taken together, these changes contribute to embolic and multiinfarct events in COVID-19

activates the classic complement system via C1q and reinforces the production of the primary cytokines, IL-β1 and TNF, contributing to the cytokine storm.

Interestingly, other important actions have been described for this protein; SAA is able to induce an atypical coagulation, which is dependent on fibrinogen, and mediate red blood cell (RBC) agglutination.[9] Moreover, when SAA is elevated it is found in apoB-containing lipoproteins (LDL and HDL), potentially favouring vascular atherogenesis.[10,11]

It may be hypothesized that an acute increase in SAA (compared to the already high levels found in diabetics) occurs in COVID-19 (see Figure 1). This could contribute to the severity of the clinical condition by leading to coagulopathy (not always accompanied by a large increase in fibrinogen, another APP), a reduction in pulmonary and tissue gas exchange (due to RBC agglutination) and atherogenesis (accentuating cardiovascular dysfunction). Although SAA may be more useful than CRP as a marker of viral infections,[12] data on SAA have not been reported in COVID-19. In a very recent paper, also from the Wuhan dataset, authors suggested SAA as a severity marker for COVID-19.[13] However, there is no information available on comorbidities in these critically ill patients.

Guo and colleagues' data on the severity of COVID-19 in diabetic patients are very clear.[1] This commentary is to point out the need to investigate levels of SAA, particularly in obese and diabetic patients. This protein may play a key role in the pathogenesis of COVID-19, in addition to having a potential prognostic role. It would be of importance to include SAA measurement in ongoing protocols and further reports.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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