Coagulopathy associated with COVID and thrombosis: an opportunity to change

Coagulopatía asociada con COVID y trombosis: oportunidad para cambiar

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The endothelium and blood are the only two disseminated organs in the human body, and it should come as no surprise that they are always side by side in an exquisitely regulated physiological pairing. Among a few other critical factors, human life depends on keeping blood in the liquid state; preservation of this state is the result of an optimal functioning of the coagulation system, contrary to general belief that its essential function is to form clots. Indeed, communication between the millions of cells of each human being, their feeding and oxygenation, immune surveillance and disposal of undesirable substances, among many other functions, entirely depend on the liquid state of blood.

On the other hand, vital effects depend on a healthy endothelium: vasodilator, anti-inflammatory, anticoagulant, antiangiogenic, anti-proliferative effects and an always appropriate vascular permeability regulation; in endothelial dysfunction states, vasoconstrictive, pro-thrombotic, pro-inflammatory, proangiogenic and pro-proliferative effects predominate, and adequate permeability is lost. A healthy endothelium largely regulates inflammatory mechanisms and is, therefore, the meeting point of two systems, which until very recently we considered separate: coagulation and inflammation. Today we know that activation of one of these two inevitably translates into activation of the other, since both are required for adequate tissue repair after injury. However, under pathological conditions, excessive and simultaneous activation of both systems can become dangerous. To highlight the

importance of this dual activation, which is increasingly recognized in critically-ill patients, the term "immunothrombosis" was recently coined.^{1,2}

Given that the endothelium is the basis for coagulation system proper functioning, it loses a large part of its regulatory mechanisms if there is endothelial dysfunction. Therefore, if an exquisite regulation of the coagulation system is required to maintain blood in the liquid form, and this depends on endothelial function, any state of endothelial dysfunction is associated with a pathological transformation of blood into a solid state, a phenomenon we call thrombus; its clinical manifestation, thrombosis, is the leading cause of death in humans.³ Indeed, the elderly and patients with chronic non-communicable diseases (obesity, smoking, diabetes mellitus, high blood pressure, among others) develop endothelial dysfunction (although the latter much earlier) and are more likely to die from thrombosis.

Infection with SARS-CoV-2 (which causes COVID-19), identified in December 2019 in China, has exponentially increased almost in the entire world. Its fatality rate is low and most infected patients are asymptomatic; however, a percentage of them suffer a type of single-organ failure (respiratory failure) and some progress to systemic disease with multiple-organ failure.⁴ In some cases, uncontrolled alveolar inflammatory reaction induces an activation of the coagulation system that is similar to classic disseminated intravascular coagulation. We do not know the immune, racial or personal variables that predispose

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to a more aggressive evolution of the infection or intimate details of the coagulopathy associated with COVID-19, but we do know that, as a consequence of the latter, disseminated microvascular thrombosis occurs and, consequently, organ failure and multiple organ damage, which are fundamental causes of death in these patients.⁴

The presence of vascular risk factors in the COVID-19 patient is associated with the appearance of more serious clinical manifestations. This is quite apparent in Mexico, since the prevalence of vascular risk factors is very high and, therefore, the occurrence of serious infections is observed in younger patients in comparison with that which occurs in Europe, for example.^{5,6} An explanation for this phenomenon is that endothelial dysfunction affects the Mexican population earlier. In addition to this, we know that COVID-19-associated coagulopathy initiation and maintenance are largely determined by the entry of the virus into the endothelium, an early phenomenon in the course of infection that translates into higher endothelial dysfunction. A clear example of the essential role of COVID-19-associated coagulopathy is D-dimer increase, which is a marker of fibrin generation and subsequent lysis by fibrinolysis; COVID-19-associated elevated D-dimer is a negative marker of coagulopathy, evolution and mortality.⁷

For all of the above reasons, since the description of COVID-19-associated coagulopathy in the first cases of infection, anticoagulant therapy became the foundation of treatment. Containing COVID-19 has been tried with various therapies, but most have been ruled out with the publication of controlled clinical trials; the only treatment that remains undisputed is anticoagulation.

For some years now, we have known that thrombosis is the leading cause of both death and disability in human beings.⁸ Indeed, if we add the cases of acute myocardial infarction, ischemic cerebrovascular disease, consumption coagulopathy or pulmonary thromboembolism, among others, the fact is clear that initially this seems dramatic in excess. COVID-19 has allowed something that was believed to be remote only a few months ago: drawing the attention of physicians and society towards thrombosis.

Why is it that thrombosis did not appear in collective consciousness until now? The causes are multiple. The coagulation system is not taught in medical school despite the weight it will have on the budding doctor's professional activity. Thrombosis is not considered of sufficient specific significance not only in

undergraduate education but even in postgraduate medical specialties and, even more, unfortunately, in the training of hematologists, who should be the experts in everything that concerns blood.

We have social, educational and training programs available for the public to develop awareness about diabetes mellitus, obesity or high blood pressure, but there are no mechanisms that allow the dissemination of information on thrombosis at these levels. There are no institutional programs in the health sector to attack the thrombotic problem head-on, designed with the intention of raising the level of awareness and basic knowledge in this regard, in order to, consequently, apply thromboprophylaxis or the best possible antithrombotic treatment. For example, we have concerns about cancer, but we evade the fact that more than 40 % of cases will complicate with or die from thrombosis. The problem is fundamental, but it is neglected. Today, we talk regularly about D-dimer and low molecular weight heparins; however, do we know what D-dimer really is? Do we know how anti-thrombotic drugs, including heparins, act? Or do we only repeat assimilated, but not understood, concepts?

The impact of thrombosis on current medical practice in almost all medical areas is undeniable, including some that were impossible to imagine of a few years ago, such as pediatrics or obstetrics & gynecology. Even when we have the coldness and objectivity of international epidemiological data regarding the impact of thrombosis at hand, in Mexico there is a divorce between published evidence and response to the problem at all medical and social levels. We are full of myths about antithrombotic treatment, among which hemorrhage secondary to its use is the most serious.

Why the resistance to change the thinking and attitude towards thrombosis despite the information we have available? Perhaps the answer is simple: we can see hemorrhage, it terrifies us, it is engraved in our evolutionary memory as part of our alert mechanisms, subtly modifying primary aspects of our life, such as, for example, some religious beliefs. We cannot see thrombosis; conceiving it requires a more advanced, more rational and less instinctive thinking. If I don't see it, I don't believe it... Certainly, in medical thought, hemorrhage is always present when the murderer is on the opposite side of the scale. COVID-19 has put us, for better or for worse, in perspective: Bleeding rarely complicates this disease, but thrombosis kills the majority of patients.

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