

Coagulation disorders and thrombophilia markers in a patient with SARS-CoV-2, type 2 diabetes, hypothyroidism and phlebitis of the left pelvic limb

Alteraciones de la coagulación y marcadores de trombofilia en un paciente con SARS-CoV-2, diabetes tipo 2, hipotiroidismo y flebitis de miembro pélvico izquierdo

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To the editor:

With great interest we pick up the work by Carrillo-Esper R et al.¹ in which a review of coagulation disorders in patients with SARS-CoV-2 is made. In the management of patients with type 2 diabetes, it becomes important due to insulin resistance, which leads to a pro-inflammatory and pro-thrombotic state, which in turn exacerbates the cytokine storm, as well as immunothrombosis, through multiple endocrine resistance². In this sense, we present the case of a 55-year-old male, normotensive, with an 8-year history of type 2 diabetes, native to the Sierra Sur region, Oaxaca, who developed SARS-CoV-2 pneumonia (confirmed by polymerase chain reaction and sequencing; variant ▲382 at ORF1a). He had grade I obesity and hypothyroidism due to dysmorphogenesis, and was hospitalized with type 1 clinical phenotype and 86% oxygen saturation. During his hospital stay, a superficial thrombus was detected on Doppler ultrasonography of the pelvic limb on left external saphenous vein lateral dorsal branch, with a patent deep venous system. Biomarkers for diabetes, inflammation and

thrombosis were determined (Table 1). Management was started with glycemic control with rapid-acting insulin until normalizing it at values of 70-100 mg/dL, and was subsequently maintained with insulin glargine (40 IU in the morning) and lispro (10 IU in the morning and evening). Hypothyroidism was controlled with levothyroxine (100 mg/24 h). Pneumonia was managed with ivermectin (6 mg/8 h) for the first 3 days and for 14 days additionally with dexamethasone (8 mg/24 h), azithromycin (500 mg/24 h), hydroxychloroquine (400 mg/12 h initially, for two doses, and subsequently 200 mg/12 h) and nitazoxanide (500 mg/12 h). Nephrocardioprotection and thromboprophylaxis were implemented with dapagliflozin (10 mg/24 h), acetylsalicylic acid (100 mg/24 h) and enoxaparin sodium (60 mg/24 h, subcutaneous). The patient was discharged at 18 days with 96% oxygen saturation, temperature of 36.5 °C and negative SARS-CoV-2 RNA. The patient certainly had a genetic makeup for type 2 diabetes and insulin resistance, with heterozygous genotypes for SNVs on *ELMO1* and *ATM* and VNTRs on *ATXN2* and *ATXN3*³, which lead to coagulopathy, vascular pro-inflammatory state, hyperfibrinolysis (Fig. 1)⁴, potentiated by

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Table 1. Genetic and biochemical markers at admission of the patient with SARS-CoV-2

Genetic markers	Genotype	Risk
Factor V Leiden mutation, F5 G1691A	G/G	Normal
Prothrombin polymorphism at 20210, F2 G20210A	A/A	Hypercoagulability risk
MTHFR C677T polymorphism	C/T	Normal
MTHFR A1298C polymorphism	A/A	Normal
Intron 16 ins/del polymorphism of the gene for angiotensin-converting enzyme I (ACE-1 I/D)	I/D	Secondary risk, vascular pro-inflammatory, hyperfibrinolysis-inducing, increases plasma ACE-1, ACE-2 and angiotensin II
Polymorphism (CAG) n at exon 1 of the gene for ataxin 2 (ATXN2).	22/25	Long (> 22) or short (< 22) alleles are linked to insulin resistance, type 2 diabetes, increased red blood cell count and mean corpuscular volume, as well as hypercoagulability
Polymorphism (CAG) n at exon 10 of the gene for ataxin 3 (ATXN3)	25/30	Ataxin 3 participates in the response to viral infections Long alleles (12-44) are associated with hyperinsulinemia, type 2 diabetes and insulin-like growth factor 1 elevated values
<i>ATM</i> gene T>G SNV rs11212617 polymorphism	T/G	Heterozygous status is associated with insulin resistance, development of type 2 diabetes, and inadequate vascular repair Homozygous T status is linked to response to metformin treatment
<i>ELMO1</i> gene G >A SNV rs1345365 del polymorphism	G/A	Heterozygous status is associated with metabolic syndrome traits and is vascular pro-inflammatory Homozygous AA status is protective against the development of type 2 diabetes
Laboratory and biochemical tests	Level	Interpretation
Protein C	109.42%	Normal (reference 102.4)
Antithrombin III	96.12%	Normal (reference 94.56)
Factor VII	144.60%	Normal (reference 132.6%)
Von Willebrand factor	189.74%	Increased (reference 125.6)
Tissue partial thromboplastin time	26/31.3s	Normal, ratio 0.89
Prothrombin time	11.8/11.8s	Normal, ratio 0.96
D-dimer	1001 mg/L	Increased, severity increase
Fibrinogen	1001 mg/dL	Increased
Ferritin	931 ng/mL	Increased
Interleukin 6	36 pg/mL	Normal
Basal total cholesterol after 8-h fasting	227 mg/dL	Increased (normal 100-240)
Total triglycerides after 8-h fasting	399 mg/dl	Increased (normal 35-160)
Basal serum glucose after 8-h fasting	270 mg/dL	Increased (normal < 100 mg/dL)
Glycated hemoglobin	10.5%	Good metabolic control 5.5-6.8%, intermediate 6.8-7.1%, and poor > 7.6%
Aspartate aminotransferase	72 IU/L	Increased
Alanine aminotransferase	98 IU/L	Increased
Lactate dehydrogenase	121 IU/L	Normal
Laboratory and biochemical tests	Level	Interpretation
Serum lactate	1.28 mg/dL	Normal
Total bilirubin	0.8 mg/dL	Normal

(Continues)

Table 1. Genetic and biochemical markers at admission of the patient with SARS-CoV-2 (continued)

Genetic markers	Genotype	Risk
Indirect bilirubin	0.2 mg/dL	Normal
Direct bilirubin	0.6 mg/dL	Normal
Blood count		
Leukocytes	6.68 million/mm ³	Normal
Erythrocytes	4.85 thousand/mL	Normal
Lymphocytes	8.7%	Slightly increased
Hemoglobin	13.4 mg/dL	Normal
Hematocrit	42.1%	Normal
Platelets	383,000 thousand/mL	Normal
Arterial blood gas analysis		
pH	7.47	Compensated respiratory alkalosis
pCO ₂	28.1 mmol/L	
pO ₂	60.9	
HCO ₃	20 mEq/L-3	
Base deficit		
Serum nitrogen compounds		
Urea	28.1 mg/dL	Normal
Ureic nitrogen	13 mg/dL	
Creatinine	0.8 mg/dL	
Serum electrolytes		
Sodium	136 mEq/L	Normal
Potassium	4.7 mEq/L	

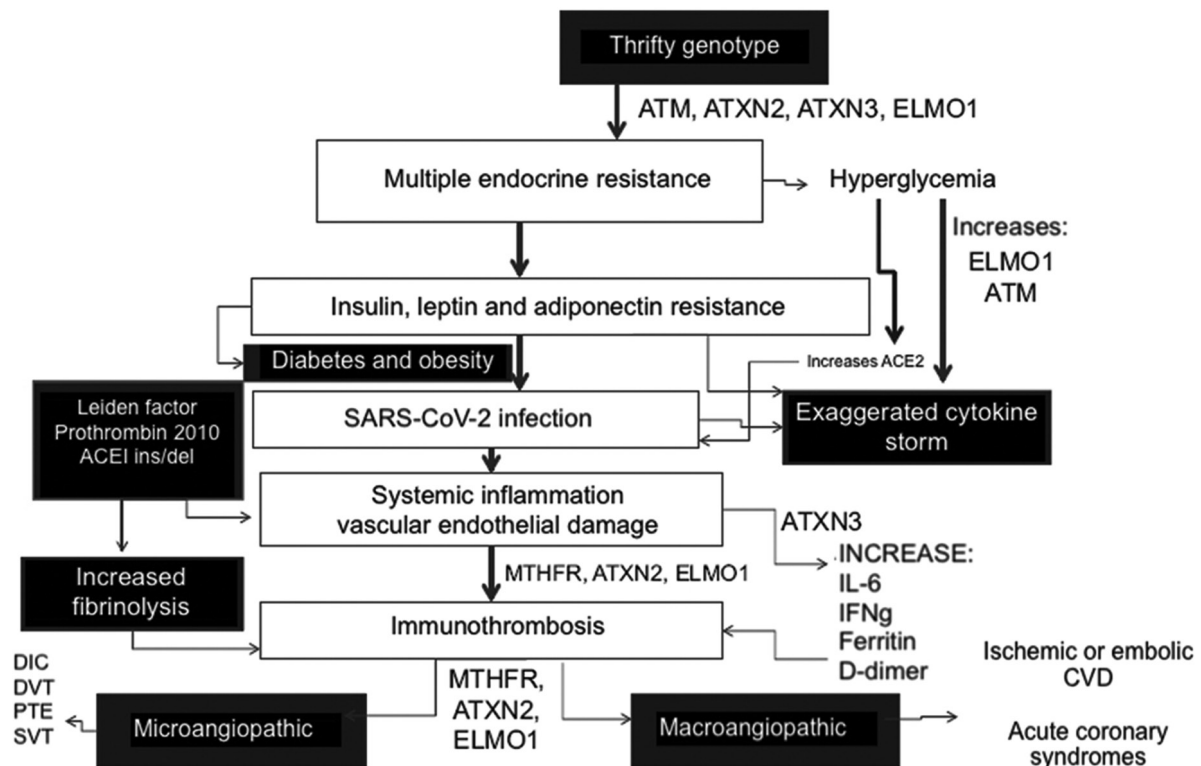


Figure 1. Participation of the genetic markers analyzed in SARS-CoV-2-related coagulopathy in patients with type 2 diabetes. ATM: ataxia telangiectasia gene; ATXN2: ataxin 2 gene; ATXN3: ataxin 3 gene; CVD: cerebrovascular disease; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; ELMO1: engulfment and cell motility type 1 gene; IFN-g: interferon gamma; IL: interleukin; MTHFR: methylenetetrahydrofolate reductase gene; PTE: pulmonary thromboembolism; SVT: superficial vein thrombosis.

angiotensin-converting enzyme I/D-genotype and prothrombin 20210 homozygous A-genotype, obesity, dyslipidemia, elevated values of von Willebrand factor and fibrinogen, which together explain the occurrence of superficial saphenous thrombosis, not described in patients with SARS-CoV-2. We consider that, in addition to the presence of D-dimer, interleukin 6 and ferritin (below the cutoff point in the patient) reported by Carrillo-Esper R et al¹ as biomarkers of coagulopathy, the analyzed genetic markers of thrombophilia and inflammation are complementary, as well as the variants in the *CBS*, *VKORC1* and *SERPINC1* genes, since by docking, they have high affinity for SARS-CoV-2 ORF7a^{4,5}. Patient response to treatment lied in glycemic control and hypothyroidism initial management, and in the fact that he is a carrier of a viral genotype with lower affinity for hemoglobin.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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Conflicts of interest

The authors declare not to have any conflicts of interest.

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