PLATELET RECEPTOR GENE POLYMORPHISMS AND ALTERED PLATELET AGGREGATION IN PATIENTS WITH COVID-19 AND TYPE 2 DIABETES MELLITUS

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COVID-19 is characterized by diffuse alveolar damage (COVID-19-DAD). The COVID-19-associated hemostatic alterations manifested by venous and arterial thrombosis deserve special attention. The issue is especially urgent for patients with diabetes mellitus. An observational study aimed to assess the role of polymorphisms of the genes *ITGB3*, *ITGA2*, and *GP1BA* in aggregation alteration in patients having COVID-19-DAD combined with type 2 diabetes mellitus (T2D). The control group included healthy volunteers (group 1; $n = 22$). Patients with COVID-19-DAD were divided into two groups based on the fact of having or not having T2D: group 2 with no T2D ($n = 52$) and group 3 with T2D ($n = 56$). Platelet aggregation was assessed with the ALAT-2 laser platelet aggregation analyzer; adenosine diphosphate (ADP) at a concentration of 2.5 μg/mL, collagen 2.0 μg/mL, adrenaline 5 μg/mL, and ristomycin 7.5 mg/mL were used as aggregation inducers. In patients with COVID-19-DAD and T2D, the rate of aggregate formation with the ADP induction was higher in carriers of the T/C and C/C variants compared to carriers of the T/T variant — by 14 and 23% based on the median ($p < 0.05$). Polymorphisms were determined by polymerase chain reaction in buccal epithelial scrapings. In the group of patients with COVID-19-DAD having no T2D, depending on the *ITGA2* gene rs1126643 polymorphism the collagen-induced platelet aggregation is accelerated with the C/T and T/T variants compared to the C/C variant — by 55 and 49%, respectively ($p < 0.05$); among individuals with COVID-19-DAD and T2D, carriers of the T/T variant show the rate of the collagen-induced platelet aggregation 30% higher compared to carriers of the C/C variant ($p < 0.05$). Conclusion: in patients with COVID-19-DAD and T2D, the presence of the mutant allele T of the *ITGA2* gene rs1126643 polymorphism and allele C of the *ITGB3* gene rs5918 polymorphism increases the rate of the collagen- and ADP-induced platelet aggregation.

Keywords: COVID-19, platelets, aggregation, polymorphisms, genotype, alleles

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ПОЛИМОРФИЗМЫ ГЕНОВ ТРОМБОЦИТАРНЫХ РЕЦЕПТОРОВ И ИЗМЕНЕНИЕ АГРЕГАЦИИ ТРОМБОЦИТОВ У БОЛЬНЫХ COVID-19 И САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

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COVID-19 характеризуется диффузным альвеолярным повреждением легких (COVID-19-АПЛ). Особого внимания заслуживают изменения гемостаза при COVID-19, проявлениями которых выступают венозные и артериальные тромбозы. Проблема особенно актуальна у больных с сахарным диабетом. Цель наблюдательного исследования — оценить роль полиморфизмов генов *ITGB3*, *ITGA2* и *GP1BA* в изменении агрегации тромбоцитов у больных с COVID-19-АПЛ в сочетании с сахарным диабетом второго типа (СД 2). В контрольную группу вошли клинически здоровые добровольцы (группа 1; $n = 22$). В зависимости от наличия СД 2 больные с COVID-19-АПЛ поделены на группы: группа 2 без СД 2 ($n = 52$) и группа 3 с СД 2 ($n = 56$). Агрегацию тромбоцитов оценивали на лазерном анализаторе агрегации тромбоцитов «АЛАТ-2», в качестве индукторов агрегации использовали аденозиндифосфат (АДФ) в концентрации 2,5 мкг/мл, коллаген 2,0 мкг/мл, адреналин 5 мкг/мл и ристомицин 7,5 мг/мл. Скорость формирования агрегатов при индукции АДФ у больных с COVID-19-АПЛ и СД 2 выше у носителей T/C- и C/C-вариантов по сравнению с T/T-вариантом на 14 и 23% по медиане ($p < 0,05$). Полиморфизмы определяли методом полимеразной цепной реакции в буккальном соскобе эпителия. В группе больных COVID-19-АПЛ без СД 2 в зависимости от полиморфизма rs1126643 гена *ITGA2* при вариантах C/T и T/T по сравнению с C/C ускоряется коллаген-индуцированная агрегация тромбоцитов — на 55 и 49% соответственно ($p < 0,05$); при COVID-19-АПЛ с СД 2 у носителей T/T-варианта скорость коллаген-индуцированной агрегации выше на 30% по сравнению с носителями C/C-варианта ($p < 0,05$). Вывод: у больных COVID-19-АПЛ и СД 2 наличие мутантного аллеля T полиморфизма rs1126643 гена *ITGA2* и аллеля C полиморфизма rs5918 гена *ITGB3* увеличивает скорость коллаген- и АДФ-индуцированной агрегации тромбоцитов.

Ключевые слова: COVID-19, тромбоциты, агрегация, полиморфизмы, генотип, аллели

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The COVID-19-DAD manifestation severity is determined inter alia by the genetic diversity of patients. The active search for markers of genetic determination of the COVID-19 course severity and outcomes is currently in progress. Most studies are focused on polymporphisms of the genes encoding angiotensin-converting enzymes and the membrane-anchored serine protease (*TMPRSS2*). There are data on the influence of polymorphisms of the genes encoding endothelial cell adhesion molecules, vitamin K epoxide reductase complex, interferon system components, cytokines and transcription factors, oxidative stress, metabolic molecules, and some other factors on the COVID-19 course [1–4].

At the same time, COVID-19-DAD can occur with the hemostasis system-associated complications and without any complications; some patients are sensitive to anticoagulant therapy and some are not. To determine the platelet function, it is feasible to explore its molecular genetic basis and the contribution to complications associated with thrombosis in COVID-19. High prevalence of thrombotic complications in individuals with severe COVID-19-DAD forms is associated with platelet hyperreactivity in the context of alteration of such genes, as *GP1BA* (glycoprotein Ib-alpha), *ITGB3* (integrin beta 3), and *ITGA2* (integrin alpha 2) [5].

A number of earlier studies revealed no differences in the effect on platelets in polymorbid individuals with *ITGA2* and *ITGB3* polymorphisms; conflicting information about the contribution of the genes *F2*, *NLRP3*, *TLR4*, *CX3CR*, *IL1RN*, and *IL1B* to the course of COVID-19 was obtained [6]. Polymorphisms of the genes regulating the homeostasis system can help identify the differences in susceptibility and severity in different patients. However, specific genetic factors and the extent, to which these can explain the susceptibility and COVID-19-DAD severity variation, are still unclear.

In patients with type 2 diabetes mellitus (T2D), hyperglycemia and insulin resistance cause the increased platelet production and activation, qualitative and quantitative changes in coagulation and fibrinolysis factors, thereby aggravating the hemostatic dysfunction [7]. However, alterations in hemostasis are observed in patients with COVID-19-DAD and T2D, along with the considerable functional variability of distinct hemostasis components, which can be associated inter alia with polymorphisms of factor genes.

The clinical and pathogenetic aspects of hemostasis in COVID-19, especially combined with T2D, are poorly understood, but it is well known that genetic factors have an effect on changes in the function of hemostatic links. The COVID-19 thrombohemorrhagic complications represent a pressing medical and social issue, despite the fact that the pandemic is over, due to their significant effect on the patients' quality of life, development of complications, and delayed mortality. To understand the mechanisms underlying the severe course and the emergence of thrombohemorrhagic complications in COVID-19 with T2D, clinical and laboratory, instrumental, and mathematical methods should be used to explore the role of genetic factors in alteration of hemostatic indicators.

The study aimed to assess the role of *ITGB3*, *ITGA2*, and GP1BA polymorphisms in platelet aggregation alteration in patients with COVID-19-associated pulmonary lesions combined with T2D.

METHODS

A total of 108 patients with COVID-19 admitted to the Regional Clinical Hospital No. 3 in Chelyabinsk (50 females and 58 males aged 45–74 years) took part in the study; they used no anticoagulants or other pharmaceuticals affecting hemostasis. The chest multispiral computed tomography performed using the Siemens SOMATOM Definition AS 64 scanner (Siemens AG, Germany) revealed bilateral diffuse lung tissue compaction (ground-glass opacity and consolidation) in combination with the reticular pattern (pulmonary involvement 11–64%) in all patients. The diagnosis of COVID-19 was confirmed by the detection of the SARS-CoV-2 viral RNA on the mucous membranes of the pharynx and nasal cavity by polymerase chain reaction (RealBest RNA SARS-CoV-2; Vector Best, Russia); the patients met the criteria of moderate-to-severe disease in accordance with the current version of the guidelines [8]. The control group consisted of 22 clinically healthy volunteers (group 1), who were matched for gender and age with COVID-19 patients. Patients with COVID-19-DAD were divided into two groups based on the fact of having or not having T2D: group 2 without T2D (n = 52) and group 3 with T2D (n = 56). Inclusion criteria for group 3: clinical diagnosis of T2D with the disease duration of 1–5 years (to rule out angiopathies, the T2D complications), achieved blood glucose and glycated hemoglobin targets. Exclusion criteria: cancer, autoimmune disorders, chronic diseases of the cardiovascular, respiratory, nervous systems, organs of the gastrointestinal tract and the kidney; extremely severe COVID-19-DAD course demanding the patient's admission to the ICU; development of the bacterial and/or other viral infection, fact of having stage 3 or more advanced stage arterial hypertension, body mass index (BMI) over 35 kg/m^2, anemia (hemoglobin levels below 119 g/L).

Blood sampling was performed on day 7 of hospital stay. The standard thromboprophylaxis provided to all subjects was the same. It consisted of the subcutaneous administration of low molecular weight heparin (enoxaparin sodium 4000 anti-Xa IU (40 mg) twice a day throughout the period of hospital stay). In addition to anticoagulant therapy, the patients received standard therapy with favibirin and glucocorticoids, antibacterial therapy.

To assess the inflammation severity in COVID-19-DAD, the serum C-reactive protein concentration was determined with the ChemWell 2910 EIA analyzer (Awareness Technology Inc., USA) using the test system manufactured by Vector-Best (Novosibirsk, Russia); blood lactate was assessed using the Medica Corp EasyLyte Plus acid-base state analyzer (Medica Corporation, USA). Blood platelet counts and morphological characteristics of platelets were determined using the Mindray BC 5800 analyzer (Mindray Co. Ltd., China). Plasma levels of fibrinogen (g/L), D-dimer (mg/L) were determined using the APG4-02P coagulometer (EMKO LLC, Russia) and test systems (Tehnologia-Standart, Russia).

Polymorphisms of the genes, the products of which are involved in platelet aggregation and plasma hemostasis, were studied. Testing of single polymorphisms was performed by real-time PCR (Roche LightCycler 96; Roche Molecular Systems, USA); buccal epithelial scrapes were used as biomaterial. The SNP-Express-Cardiogenetics reagent kits for identification of gene polymorphisms (Litech, Russia) were used. Polymorphisms rs6065 of the gene *GP1BA*, rs1126643 of the gene *ITGA2*, and rs5918 of the gene *ITGB3* were determined; mutant homozygous and heterozygous polymorphisms of these genes increase the risk of platelet aggregation and, therefore, the likelihood of thrombosis. Selection of polymorphisms was determined by their ability to take part in regulation of the function of appropriate key cellular hemostasis elements (in particular, components of major platelet receptors) and their clinical significance.

Table 1. Main clinical, laboratory, and instrumental indicators of the studied groups at admission

Indicator	Group 2 COVID-19-DAD, *n* = 52	Group 3 COVID-19-DAD + T2D, *n* = 56	p_{1-2}
Age, years [Me (Q_{25}; Q_{75})]	59.3 (55.8; 67.2)	61.1 (55.4; 68.6)	0.48
Male, *n* (%)	28 (53.8)	30 (53.6)	0.872
Female, *n* (%)	24 (46.2)	26 (46.4)	0.87
Number of patients with RD, *n* (%)	43 (82.7)	48 (85.7)	0.67
Grade I, *n* (%)	35 (67.3)	34 (60.7)	0.26
Grade II, *n* (%)	8 (15.4)	14 (25.0)	0.33
BMI, kg/m^2 [Me (Q_{25}; Q_{75})]	26.7 (21.5; 30.4)	31.2 (28.5; 33.4)	0.040 *
SpO_2, % [Me (Q_{25}; Q_{75})]	93.2 (89.4; 96.1)	91.0 (86.3; 93.6)	0.74
Lactate, mmol/L [Me (Q_{25}; Q_{75})]	1.86 (1.21; 2.26)	2.47 (2.01; 3.12)	0.003 *
CRP, mg/L [Me (Q_{25}; Q_{75})]	97.7 (71.2; 120.8)	123.4 (101.5; 162.5)	0.010 *
D-dimer, mg/L [Me (Q_{25}; Q_{75})]	1.39 (0.81; 2.11)	2.65 (1.87; 3.13)	0.040 *
Platelets, × 10^9/L	346.00 (245.00; 422.00)	275.00 (204.00; 316.50)	0.010 *
Fibrinogen, g/L	3.31 (2.88; 5.07)	5.84 (4.34; 7.19)	0.016 *

Note: * — significant ($p < 0.05$) differences from group 1.

Platelet aggregation was assessed with the ALAT-2 laser platelet aggregation analyzer (BIOLA, Russia). To obtain platelet-rich plasma (PRP), whole venous blood was centrifuged at 1500 rpm for 5 min. To obtain platelet-poor plasma (PPP), the residue was centrifuged for 15 min at 4500 rpm. The induced aggregation was assessed using the aggregation inducer kits by Tehnologia-Standart LLC (Russia): ADP at a final concentration of 2.5 μg/mL, collagen at a concentration of 2.0 μg/mL, adrenalin at a concentration of 5 μg/mL, and ristomycin at a concentration of 7.5 mg/mL. The intense two-wave (biphasic) aggregation with minimal disaggregation was observed with the ADP concentration of 2.5 μg/mL. Therefore, this ADP concentration was selected for the study.

Based on the light transmission curve the following were recorded by the Born method: aggregation amplitude or extent (%), aggregation time (min), aggregation rate (%/min); the extent of PRP aggregation was taken as 0 %, the extent of PPP aggregation was taken as 100 %. In addition, aggregation parameters were determined based on the average aggregate size curve [9]. After the system calibration the single platelet size was taken as 1 relative unit; the maximum aggregate size (hereinafter, aggregate size) was determined after adding the inducer. The rate of aggregate formation was determined as the maximum slope of the average curve and measured in relative units per minute (relative units/min).

Statistical processing was performed using IBM SPSS Statistics v. 23 (SPSS: An IBM Company; USA). Characteristics of samples are presented in the Me (Q_{25}; Q_{75}) format, where Me is the median, Q_{25}, Q_{75} are the lower and upper quartile values, respectively. The Hardy–Weinberg Carrier Frequency software tool (Focus Information Technology; USA) was used to test for the Hardy–Weinberg equilibrium. The Shapiro–Wilk test was used to assess the distribution of continuous variables. Testing statistical hypotheses in groups was performed using the nonparametric Mann–Whitney *U*-test with the calculation of the exact test *p*. The differences were considered significant at $p \leq 0.05$.

RESULTS

General characteristics of the surveyed patients are provided in Table 1. According to the data obtained, patients with COVID-19-DAD in combination with T2D show higher BMI, higher plasma levels of CRP, lactate, D-dimer, and fibrinogen, decreased platelet counts compared to patients having no T2D.

To determine the role of genetic factors in alteration of the platelet hemostatic link, the abundance of polymorphisms rs5918 of the gene *ITGB3*, rs1126643 of the gene *ITGA2*, and rs6065 of the gene *GP1BA* was assessed in patients with COVID-19-DAD and T2D. The above polymorphisms were selected due to their role in expression and realization of the function of platelet receptors involved in aggregation with ADP, collagen, and ristomycin. Considering the Shapiro–Wilk test results ($p \leq 0.05$) for the studied variables, further analysis was conducted using nonparametric methods for all comparisons. The distribution of *ITGB3*, *ITGA2*, *GP1BA* genotype frequencies was compliant with the expected equilibrium according to the Hardy–Weinberg exact test in the control group ($p = 0.77$; $p = 0.18$; $p = 0.31$, respectively), in the group of patients with COVID-19-DAD ($p = 0.50$; $p = 0.87$; $p = 0.82$, respectively), and in the group of patients with COVID-19-DAD and T2D ($p = 0.47$; $p = 0.82$; $p = 0.71$). A combination of two mutations was identified in five individuals (22.7%) in the control group; in 13 (25%) individuals with COVID-19-DAD without T2D; in six individuals (10.7%) with COVID-19-DAD and T2D. A combination of three mutations at once was identified in one patient (4.4%) in the control group; in four patients (7.7%) in the group of COVID-19-DAD without T2D; in three patients (5.4%) with COVID-19-DAD and T2D.

The *ITGB3* gene regulates the synthesis of the integrin β-3 membrane protein, the component of glycoprotein IIb/IIIa involved in the interplay between platelets. The rs5918 polymorphism of the gene *ITGB3* results from the nucleotide thymine (T) replacement with cytosine (C) in a certain DNA region, due to which the amino acid leucine (33rd in the protein chain) is replaced with proline, and the receptor 3D structure is disrupted [10]. The receptor structure disruption, in turn, results in the increased platelet reactivity and contributes to the platelet aggregation enhancement [11]. Individuals with the C/C variant of this polymorphism become more prone to platelet aggregation and, therefore, the risk of thrombosis increases [10]. In the group of patients with COVID-19-DAD having no T2D, there are no significant differences in the abundance of T/T, T/C, C/C genotypes in the gene *ITGB3* compared to controls ($p > 0.05$); the C allele of the *ITGB3* gene rs5918 polymorphism is more abundant ($p = 0.045$) (Table 2).

Table 2. Genotype abundance when analyzing polymorphisms of the genes *ITGB3*, *GP1BA* and *ITGA2* in individuals with COVID-19-DAD and T2D

Polymorphism	Genotypes/alleles		Genotype abundance, *n* (%)		
			Group 1 Healthy, *n* = 22	Group 2 COVID-19-DAD, *n* = 52	Group 3 COVID-19-DAD + T2D, *n* = 56
rs5918 of the gene *ITGB3*	Genotypes	0 (T/T)	17 (77.3)	34 (65.4)	29 (51.9) *
		I (T/C)	4 (18.2)	15 (28.8)	16 (29.6)
		II (C/C)	1 (4.5)	3 (5.8)	11 (18.5) * #
	Alleles	T	38 (86.4)	83 (79.8)	74 (64.8)
		C	6 (13.6)	21 (20.2) *	38 (35.2) * #
rs1126643 of the gene *ITGA2*	Genotypes	0 (C/C)	16 (72.7)	31 (59.6)	34 (60.7)
		I (C/T)	4 (18.2)	13 (25.0)	13 (23.2)
		II (T/T)	2 (9.1)	8 (15.4) *	9 (16.1)
	Alleles	C	36 (81.8)	75 (72.2)	81 (72.3)
		T	8 (18.2)	29 (27.8) *	31 (27.7) *
rs6065 of the gene *GP1BA*	Genotypes	0 (C/C)	19 (83.4)	42 (79.1)	46 (81.4)
		I (C/T)	3 (16.6)	9 (18.8)	10 (18.6)
		II (T/T)	0	1 (2.1)	0
	Alleles	C	40 (90.9)	93 (89.4)	102 (91.1)
		T	4 (9.1)	11 (10.6)	10 (8.9)

Note: * — significant ($p < 0.05$) differences from group 1; # — from group 2; 0 — wild type genotype; I — heterozygote; II — mutant homozygote.

In patients with COVID-19-DAD and T2D, the T/T genotype of the polymorphism considered is less abundant compared to controls, the T/C variant abundance is the same ($p > 0.05$), the C/C variant is more abundant ($p = 0.03$), and the C allele is 1.82 times more abundant ($p = 0.049$). In patients with COVID-19-DAD and T2D, the abundance of the T/T and T/C genotypes of the polymorphism considered is the same as in patients with COVID-19-DAD having no T2D, the C/C variant is 3.86 times more abundant ($p = 0.01$), and the C allele is 2.43 times more abundant ($p = 0.04$).

The *ITGA2* gene encodes the integrin alpha-2 protein, the membrane glycoprotein GPIa found on the membranes of various cells, including platelets. GPIa forms a complex with GPIIa being one of the collagen receptors on the platelet membrane. The *ITGA2* gene rs1126643 polymorphism results from the nucleotide cytosine (C) replacement with thymine (T) [12]. This mutation does not change the amino acid sequence, but determines the correlation between this polymorphism and the GPIa expression on the platelet membrane. When there is a T/T variant of the rs1126643 polymorphism, binding of platelets and collagen is faster; heterozygous individuals having the C/T variant demonstrate intermediate receptor expression levels [13].

In the group of patients with COVID-19-DAD having no T2D, there were no differences in the C/C, C/T, and T/T genotype abundance from controls ($p > 0.05$); the T allele of the *ITGA2* gene rs1126643 polymorphism was 1.82 times more abundant ($p = 0.007$). In patients with COVID-19-DAD and T2D, there were no differences in the C/C, C/T, T/T genotype abundance from controls ($p > 0.05$); the T allele of the *ITGA2* gene rs1126643 polymorphism was more abundant ($p = 0.03$). In patients with COVID-19-DAD and T2D, there were no differences in the C/C, C/T, T/T genotype and T allele abundance from patients with COVID-19-DAD having no T2D ($p > 0.05$).

The *GP1BA* gene encodes the α-subunit of the glycoprotein Ib involved in the GpIb/IX/V platelet receptor formation. vWF linking platelets to the damaged blood vessel site is the main receptor ligand [14]. The strength of the resulting link between the above depends largely on the receptor configuration,

Table 3. Characteristics of patients with COVID-19-DAD and T2D based on the abundance of *ITGB3*, *GP1BA*, and *ITGA2* polymorphisms

Polymorphism	Genotype/ alleles	COVID-19-DAD relative to control		COVID-19-DAD + T2D relative to control		COVID-19-DAD + T2D relative to COVID-19-DAD	
		χ^2 (*p*)	OR (95% CI)	χ^2 (*p*)	OR (95 % CI)	χ^2 (*p*)	ОШ (95 % CI)
rs5918 of the gene *ITGB3*	I (T/C)	0.99 (0.32)	1.86 (0.54–6.53)	1.85 (0.181)	2.34 (0.67–8.17)	1.19 (0.28)	1.25 (0.68–2.31)
	II (C/C)	0.12 (0.73)	1.50 (0.16–15.52)	1.53 (0.25)	1.80 (0.43–7.51)	6.55 (0.011) *	3.89 (1.07–14.12) *
	C	3.86 (0.045) *	1.61 (1.32–4.29)	7.60 (0.02) *	1.82 (1.15–2.86) *	9.35 (0.002) *	2.43 (1.54–3.83) *
rs6065 of the gene *GP1BA*	I (C/T)	1.465 (0.226)	1.36 (0.33–5.58)	1.77 (0.18)	0.65 (0.21–2.08)	0.04 (0.84)	1.02 (0.38–2.74)
	II (T/T)	–	–	–	–	–	–
	T	0.12 (0.73)	0.83 (0.47–3.90)	0.75 (0.39)	0.69 (0.37–1.28)	0.16 (0.69)	0.83 (0.44–1.58)
rs1126643 of the gene *ITGA2*	I (C/T)	0.1 (0.093)	0.96 (0.32–2.77)	0.16 (0.69)	1.15 (0.38–3.50)	0.08 (0.78)	0.91 (0.47–1.77)
	II (T/T)	3.68 (0.060)	2.11 (0.98–4.61)	0.40 (0.80)	1.07 (0.23–4.91)	0.12 (0.73)	1.08 (0.44–2.69)
	T	1.33 (0.04) *	1.71 (1.23–3.90) *	1.78 (0.013) *	1.84 (1.11–3.26) *	0.42 (0.52)	0.24 (0.11–0.52)

Note: * — significant ($p < 0.05$) differences; I — heterozygote; II — mutant homozygote.

Table 4. Induced platelet aggregation in individuals with COVID-19-DAD and T2D depending on the *ITGB3*, *ITGA2*, and *GP1BA* polymorphisms on day 7, Me(Q_{25}; Q_{75})

Polymorphism	Genotypes	Group 2 COVID-19-DAD, *n* = 52	Group 3 COVID-19-DAD + T2D, *n* = 56
rs1126643 of the gene *ITGB3*	Rate of ADP-induced aggregation, %/min		
	0 (T/T)	7.70 (5.07; 9.44)	8.53 (7.89; 12.35)
	I (T/C)	8.98 (5.78; 13.81)	11.44 (9.61; 15.24) *
	II (C/C)	8.28 (6.51; 9.57)	16.53 (7.89; 18.35) * #
	Rate of aggregate formation, ADP-induced aggregation, relative units/min		
	0 (T/T)	17.22 (12.38; 22.11)	20.19 (17.11; 23.17)
	I (T/C)	17.38 (11.26; 24.75)	23.19 (17.31; 25.72) *
	II (C/C)	18.04 (13.26; 21.82)	24.74 (16.91; 28.12) *
rs6065 of the gene *ITGA2*	Rate of collagen-induced aggregation, %/min		
	0 (C/C)	7.80 (6.97; 10.01)	9.39 (7.78; 11.55)
	I (C/T)	12.09 (10.37; 18.22) *	11.11 (9.51; 13.05)
	II (T/T)	11.59 (10.24; 13.39) *	12.24 (10.98; 14.45) *
	Rate of aggregate formation, collagen-induced aggregation, relative units/min		
	0 (C/C)	13.17 (7.31; 19.63)	17.17 (12.60; 24.11)
	I (C/T)	14.02 (8.67; 24.15)	18.24 (13.41; 22.58)
	II (T/T)	17.25 (9.42; 22.14) * #	16.22 (13.01; 19.28)
rs6065 of the gene *GP1BA*	Rate of ristomycin-induced aggregation, %/min		
	0 (C/C)	8.34 (5.02; 10.24)	9.34 (4.54; 12.06)
	I (C/T)	10.41 (8.67; 12.34)	10.32 (7.66; 14.43)
	II (T/T)	7.92	–
	Rate of aggregate formation, ristomycin-induced aggregation, relative units/min		
	0 (C/C)	12.72 (6.17; 19.03)	21.59 (11.24; 25.74)
	I (C/T)	13.06 (8.44; 17.28)	22.44 (12.78; 26.67)
	II (T/T)	13.68	–

Note: * — significant ($p < 0.05$) differences from the homozygous non-mutant variant within the group based on the Kruskal–Wallis test with the Dunn's test; # — from the heterozygous variant within the group; 0 — wild type genotype; I — heterozygote; II — mutant homozygote.

vWF structure, and blood flow rate. The *GP1BA* gene rs6065 polymorphism is associated with the cytosine (C) replacement with thymine (T) near the gene transcription start, resulting in the threonine replacement with methionine in the receptor fragment responsible for binding to vWF, so that carriers of the T/T genotype have a higher concentration of glycoprotein Ib on the platelet membrane compared to individuals with other genotype variants. With the mutant homozygous T/T form (frequency in the population about 1.5%), the risk of thrombosis is dramatically increased [15]. With the heterozygous C/T variant, the GpIb/IX/V receptor expression on platelets is less pronounced, but some studies have revealed the increased risk of thrombosis in carriers of this gene variant [16]. The study revealed no differences in the abundance of the studied genotypes of the *GP1BA* gene rs6065 polymorphism between patients with COVID-19-DAD and controls ($p > 0.05$); in patients with COVID-19-DAD and T2D, there were no differences in genotype frequency from both the control group and the group with COVID-19-DAD and no T2D.

Assessment of the abundance of polymorphisms considered based on the Pearson's test with calculation of the odds ratio (OR) was conducted (Table 3).

In patients with COVID-19-DAD, the T allele of the *ITGA2* gene rs1126643 polymorphism is 1.71 times more abundant compared to controls (95% CI: 1.23–3.90); in patients with COVID-19-DAD and T2D, mutant C and T alleles of the *ITGB3* gene rs5918 polymorphism and *ITGA2* gene rs1126643 polymorphism are 1.82 times (95% CI: 1.15–2.86) and 1.84 times (95% CI: 1.11–3.26) more abundant, respectively. In patients with COVID-19-DAD and T2D, the C/C variant and C allele of the *ITGB3* gene rs5918 polymorphism are 3.89 times (95% CI: 1.07–14.12) and 2.43 times (95% CI: 1.54–3.83) more abundant compared to patients having no T2D.

To determine the role of genetic factors in changes of indicators of the cellular hemostatic link in patients with COVID-19-DAD and T2D, the rate of the ADP-, collagen-, and ristomycin-induced platelet aggregation was assessed in individuals with variants of polymorphisms rs5918 of the gene *ITGB3*, rs1126643 of the gene *ITGA2*, and rs6065 of the gene *GP1BA* (Table 4, Fig.).

The analysis of platelet aggregation in patients with COVID-19-DAD having no T2D has shown that the *ITGB3* gene rs5918 polymorphism has no effect on the rate of the ADP-induced platelet aggregation; among patients with COVID-19-DAD and T2D, carriers of the T/C variants show the rate of the ADP-induced platelet aggregation 34% higher compared to carriers of the T/T variant; in carriers of C/C, it is 92% higher compared to T/T and 44% higher compared to T/C. In patients with COVID-19-DAD having no T2D, the rate of aggregate formation with the ADP induction does not change depending on the presence of the mutant allele; in patients with T2D, it is higher in carriers of T/C and C/C variants compared to carriers of the T/T variant — by 14 and 23 % based on the median, respectively.

To determine the role of *ITGB3* gene rs5918 polymorphism in changing the rate of the ADP-induced platelet aggregation in patients with COVID-19-DAD and T2D, the Kruskal–Wallis

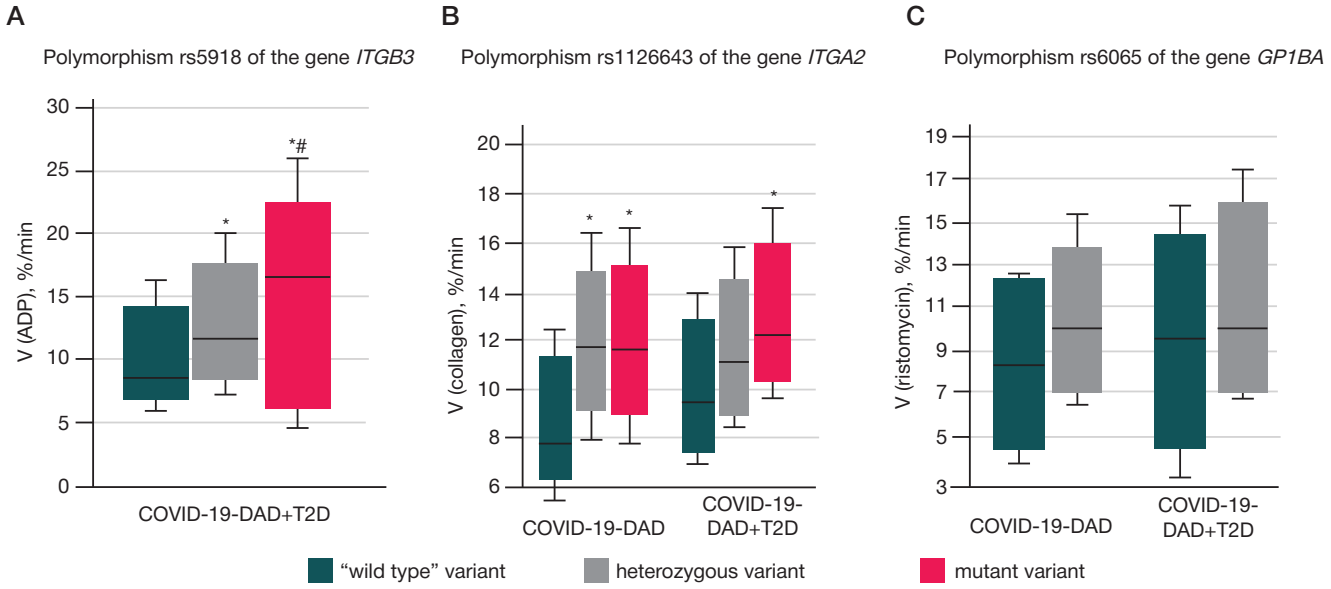

Fig. Hemostasis indicators in patients with COVID-19-DAD and T2D, carriers of the hemostasis factor gene mutant polymorphisms: rs5918 of the gene ITGB3 **(A)**; rs1126643 of the gene ITGA2 **(B)**; rs6065 of the gene GP1BA **(C)**. V (inducer) — rate of induced platelet aggregation; * — significant differences ($p < 0.05$) from carriers of the "wild type" genotype; # — from carriers of heterozygote

test with the Dunn's test was used; it was found that the presence of the mutant allele explained a large proportion of the overall variability of the ADP-induced platelet aggregation rate in patients with COVID-19-DAD having T2D ($p = 0.0045$). The increase in the average platelet volume in carriers of the increased amount of glycoprotein IIb/IIIa on the platelet membrane and, therefore, the increased platelet reactivity can be a possible explanation of the data obtained. However, the exact mechanisms causing platelet aggregation when there is a C/C variant of the rs5918 polymorphism are poorly understood and require further research.

When analyzing platelet aggregation in the group of patients with COVID-19-DAD having no T2D depending on the ITGA2 gene rs1126643 polymorphism, it was noted that the collagen-induced platelet aggregation is accelerated with the C/T and T/T variants compared to the C/C variant — by 55 and 49%, respectively ($p = 0.003$, $p = 0.005$); among individuals with COVID-19-DAD and T2D, carriers of the T/T variant show the collagen-induced platelet aggregation rate 30% higher compared to carriers of the C/C variant ($p = 0.014$).

DISCUSSION

Platelets of patients with T2D demonstrate a stronger response to agonists and the more apparent membrane expression of adhesion molecules, such as thrombospondin, P-selectin, GPIIb-IIIa, GPVI, and CD40L [17]. The T2D-associated hyperglycemia affects the expression of the key receptor and the activity of platelet enzymes: the expression of prostacyclin receptors is decreased in individuals with T2D, which enhances the platelet aggregation; the activity of the insulin-like growth factor 1 receptor (IGF1R) is increased, which makes platelets of such patients more sensitive to IGF1, being a regulator of the signal transmission and platelet responses, and causes platelet hyperactivity [18]. In T2D, the expression of integrin β3, the component of glycoprotein IIb/IIIa ensuring platelet aggregation, on platelets is increased, which results in the increased platelet activation and explains the platelet aggregation indicators obtained [19].

The findings of the study, i.e. the collagen-induced platelet aggregation acceleration, are consistent with the known information about the function of integrin alpha-2 and can indicate the role of the *ITGA2* gene rs1126643 polymorphism in the COVID-19 pathogenesis, despite the fact that the mechanism is poorly understood. The observed results demonstrate the polymorphism lower impact on the collagen-induced platelet aggregation rate in patients with T2D, which can be explained by predominance of other platelet activators in this group: oxidative stress or chronic inflammation.

The reported study has yielded no data suggesting the influence of the *GP1BA* gene rs6065 polymorphism on the acceleration of the ristomycin-induced platelet aggregation reflecting the vWF interaction with the GPIb receptor. The lack of the large number of the T/T homozygous mutant gene variant carriers in the population can be a possible explanation. Furthermore, there is a cooperativity effect in binding between vWF and platelet GpIb: glycoproteins IX and V, the structure of which can remain intact, are involved in the formation of a complex with collagen [20]. Moreover, the GpIb/IX/V receptor serves mostly for platelet adhesion; its role in aggregation is less pronounced [21]. Thus, the *GP1BA* gene rs6065 polymorphism is not the leading factor in acceleration of the ristomycin-induced platelet aggregation in patients with COVID-19-DAD; the finding can be explained by the predominant effect of other platelet activators: oxidative stress or hyperergic inflammation.

The data obtained suggest a possible role of genetic predisposition, particularly polymorphisms rs5918 of the gene *ITGB3* and rs1126643 of the gene *ITGA2*, in platelet hyperactivation in patients with COVID-19-DAD due to strengthening the binding of IIb/IIIa receptors to ADP and the GPIa/IIa collagen receptor expression increase [22].

The differences in hemostatic indicators in patients with COVID-19-DAD and that combined with T2D is a matter of scientific debate; one of the key issues is a controversial nature of the data on the contribution of genetic factors. On the one hand, modern research suggests that polymorphisms of the genes involved in hemostatic regulation can determine the individual's predisposition to thrombosis activated in the context of the T2D-associated metabolic disorder; on the other hand, there is credible evidence confirming that the inflammatory response and COVID-19 course severity are so dominant in the pathophysiological process that completely mask any genetic differences, making hemostatic

indicators merely a reflection of the acute systemic damage, and not the patient's constitutional characteristics [7, 17–19].

Despite the fact that the study was conducted in the context of using pharmaceuticals altering aggregation, is can be assumed that the effect of therapeutic doses of low molecular weight heparin and short courses of glucocorticoids on the aggregation indicators was minimal, which is in line with the earlier research results [23, 24].

Limitations of the study

The reported study limitations include the small sample size limiting the use of corrections for multiple comparisons, genetic models of inheritance, and other statistical methods, specifically the logistic regression method, and hampering the Hardy–Weinberg test interpretation. Furthermore, in addition to genetic factors, the platelet function in COVID-19-DAD is affected by the features of the patients' immune response and redox status, which should also be taken into account when interpreting the results.

CONCLUSIONS

Among individuals with COVID-19-DAD, the mutant allele T of the *ITGA2* gene rs1126643 polymorphism is 1.71 times more often found in patients having no T2D and 1.84 times more often in those having T2D, the rate of the collagen-induced platelet aggregation is increased in polymorphism carriers (by 30–55%, $p < 0.05$); in individuals with COVID-19-DAD and T2D, the *ITGB3* gene rs5918 polymorphism mutant variant C/C is 3.89 times more abundant and the C allele is 2.43 times more abundant, the ADP-induced platelet aggregation is increased in the carriers (by 14–23%, $p < 0.05$). The findings are a precondition for further research focused on exploring the pathogenesis of hemostasis alteration, developing personalized approaches to the diagnosis, treatment, and prevention of thrombotic complications of COVID-19-DAD in the context of T2D and other comorbidities, including the role of epigenetic factors and the studied polymorphisms' multicollinearity in shaping the platelet hyperreactivity as one of the key pathogenetic links.

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