



Evaluation of antibody to double stranded DNA and antibody to single stranded DNA levels in relation to biochemical markers in cardiovascular disease patients

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Abstract

Cardiovascular diseases are major public health issues, with very high mortality rates. The evaluation of anti-DNA antibody levels in patients with cardiovascular diseases aims to explore potential links between these antibodies and biochemical markers associated with cardiovascular diseases. This study aims to evaluate the levels of anti-DNA antibodies and their relationship with biochemical parameters in patients with cardiovascular diseases. Relatively healthy donors (30) and patients with cardiovascular diseases (60) were selected to determine the levels of anti-DNA antibodies in plasma using the ELISA method. Biochemical indicators such as cholesterol levels, triglycerides, glucose, apolipoproteins (apoB), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and atherogenic index were measured using the automated biochemical analyzer. The results showed a dependency relationship between cardiovascular diseases, autoimmunity, and biochemical markers. The level of anti-DNA antibodies (ranging from 0.03 to 0.17 U) varied according to the different clinical forms of cardiovascular disease and exhibited correlations with certain biochemical markers. A relatively weak and negative linear relationship was observed between the atherogenic index and anti-DNA antibody levels in all patient groups. A direct dependency relationship was also recorded between anti-DNA antibody levels and high-density lipoprotein (HDL) levels ($R_s = 0.13$). The results showed a dependency relationship between anti- dsDNA antibody levels and glucose levels ($R_s = 0.12$). The correlation between anti-DNA antibody levels and these biochemical markers could provide a better understanding of the role of immune responses in cardiovascular diseases and pave the way for new diagnostic and therapeutic strategies.

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Introduction

Cardiovascular diseases (CVDs) have been the leading cause of mortality worldwide for the past two decades, with over 17 million deaths annually (World Health Organization, 2020). They are the source of disastrous social and economic consequences, particularly in countries with limited income, and encompass a wide range of pathologies, often affecting the major organs of the circulatory system (Baigent *et al.*, 2010; Nadjioroum *et al.*, 2022). CVDs can largely be prevented through effective and efficient interventions targeting the main modifiable risk factors. Their primary prevention is possible through simple and accessible measures (Houehanou Sonou, 2015). Several risk factors, such as biochemical and immunological markers, contribute to the development of these diseases (Nadjioroum *et al.*, 2022). That's why, in clinical practice, the diagnosis and monitoring of cardiovascular diseases primarily rely on the the research and determination of biochemical markers, such as apolipoprotein B (ApoB) to estimate cardiovascular risk in individuals with metabolic syndrome, and C-Reactive Protein (CRP) to evaluate initial risk (Couderc *et al.*, 2012).

In recent years, several studies have highlighted the role of the immune system in the development of cardiovascular diseases (Mattina *et al.*, 2019). Indeed, changes in the expression of inflammatory biomarkers such as interleukin-6 (IL-6), C-reactive protein, and TNF α , as well as classical cell surface receptors like Pattern Recognition Receptors (PRRs), Toll-Like Receptors (TLRs), and more recent ones such as nucleotide-binding oligomerization domain-like receptors (NLRs), have been found to be involved in the progression of several cardiovascular diseases (Ferrario and Strawn, 2006; Kaptoge *et al.*, 2014; Held *et al.*, 2017; DuBrock *et al.*, 2018; Jaén *et al.*, 2020).

Anti-DNA antibodies (Ab) represent a specific immune entity that selectively targets DNA. They are known to be important diagnostic markers in autoimmune diseases such as systemic lupus erythematosus (Dong *et al.*, 2017). Their presence in

the serum of patients is often associated with severe clinical manifestations of the disease (Wang and Xia, 2019). Although many studies have focused on the phenomenological and fundamental characteristics of anti-double-stranded DNA (anti-dsDNA) antibodies, much remains to be discovered regarding the precise mechanisms that promote their production *in vivo* (Rekvig, 2022). Thus, the factors that stimulate the production of anti-dsDNA Ab *in vivo* are not yet fully understood. Several hypotheses have been proposed to explain this abnormal production of antibodies directed against DNA. These hypotheses include immune dysregulations, alterations in immune tolerance, and complex interactions between immune cells, cytokines, and antigen-presenting cells. However, their role in the development of atherosclerosis and cardiovascular diseases remains poorly understood.

Nevertheless, variations in the serum concentrations of these antibodies, when combined with appropriate biochemical markers, could serve as an effective tool for diagnosing the different clinical forms of cardiovascular diseases (Vuilleumier *et al.*, 2014). Therefore, identifying the link between the expression of anti-DNA antibodies and biochemical biomarkers of CVDs could provide a better understanding of the role of immune responses in cardiovascular diseases and pave the way for new diagnostic and therapeutic strategies. This study aims to determine the relationship between biochemical markers and the levels of anti-ds DNA Ab and anti-ss DNA Ab in the serum of patients suffering from cardiovascular disease.

Materials and methods

Study area

The study was carried out in the Kazan Federal University in the laboratory of the Department of Biochemistry, Institute of Basic Medicine and Biology, from September 12, 2020, to February 14, 2024.

Sampling and ethical considerations

The purpose of our research is to study immunological markers in the blood serum of Sixty

(60) patients suffering from various forms of cardiovascular disease (CVD) and thirty (30) relatively healthy donors (RHD) who provided their consent. The patient group included forty-two (42) patients with *angina pectoris* and fifteen (15) patients with myocardial infarction. The average age of donors ranged from (35+/-2) years to (60+/- 2) years. The clinical diagnosis of the different forms of CVD was established based on data analyses from the Interregional Clinic and Diagnostic Center (MKDTS) and according to the criteria recommended by the World Health Organization. The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and approved by the local ethics committees of the Republican Oncology Clinical Hospital and Kazan Federal University (protocol N°. 8 of February 13, 2018).

Sample collection

Blood samples were collected in the morning using heparinized tubes at the Clinical Immunology Laboratory of RKB. The samples were immediately centrifuged at +4°C for 10 minutes at 3000g to obtain plasma. The plasma was then aliquoted ($V = 1$ mL) and stored at -80°C (Vodounon, 2017). During each analysis, the plasma samples were kept on ice.

Detection of anti-DNA auto-antibodies by enzyme immunoassay

The determination of the level of anti-DNA Ab was carried out by enzyme immunoassay (ELISA) (Sedkaoui and Akli, 2017), following the method used by Vodounon *et al.* (2014) (Vodounon *et al.*, 2014). Sea urchin genomic DNA was used as an antigen in both its native and denatured form. The blood serum samples were incubated for 40 minutes at 56 degrees to inactivate proteins from the complement system and dissociation of immune complexes (Goldsby and Kindt, 2003). For the detection of anti-DNA Ab in ELISA plate wells, peroxidase conjugated to the human anti-IgG antibodies was used. The response of the ELISA reaction color was detected by the "Multiskan" nanodrop spectrophotometer (2000 c) in optical density units at a wavelength of 450 nm. The anti-DNA Ab content in blood serum was estimated in

relative units, as the ratio of experimental optical density to standard optical density

Determination of biochemical indicators in relatively healthy donors and patient groups

Biochemical indicators, including cholesterol, triglycerides, glucose, apolipoproteins (ApoB), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and the atherogenic index, were measured using the automated biochemical analyzer Architect ci8200, following the manufacturer's recommendations.

Statistical analysis

The data analysis was performed using Statistics 5.0 software. The non-parametric Mann-Whitney-Wilcoxon test was used to compare the medians of quantitative variables. For qualitative variables, the χ^2 test and/or Fisher's exact test were applied depending on the sample size. Differences were considered statistically significant when the probability (p) under the null hypothesis was ≤ 0.05 ($p \leq 0.05$).

Results

Characteristics of Anti-DNA antibody levels in the serum of patients with cardiovascular diseases

The ELISA method was used to determine the levels of anti-dsDNA Ab and anti-ssDNA Ab in the blood serum of patients with cardiovascular diseases and relatively healthy donors. The concentration of anti-DNA Ab in donor serum samples was expressed in relative units (U). Fig. 1 presents the data on the levels of anti-dsDNA Ab and anti-ssDNA Ab in the analyzed samples.

The range of optical density values in patients with cardiovascular disease (CVD) was higher, varying between 0.30 to 0.7 U. The anti-DNA Ab levels varied depending on the different forms of CVD. As for the optical density range in the samples from the relatively healthy donors (RHD), it ranged from 0.03 to 0.17 U.

Twenty-nine patients (50%) had a low level of anti-ssDNA Ab, ranging from 0.3 to 0.4 OD/U, and 25% of

patients had anti-ssDNA Ab levels between 0.5 and 0.6 OD/U. These data show that the levels of anti-dsDNA Ab in patients with angina pectoris were found across three ranges. They were 58.3%, 73.2%, and 100% of patients, respectively, with anti-dsDNA Ab levels between 0.3-0.4, 0.4-0.5, and 0.5-0.6.

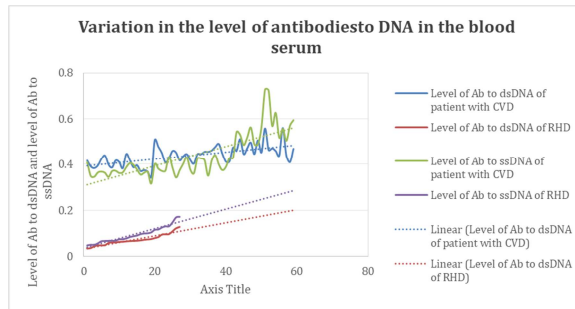


Fig. 1. Variation in the level of antibodies to double stranded DNA and antibody to single stranded DNA in the blood serum of relatively healthy donors and patients with cardiovascular disease: Ab- Antibody; dsDNA- double stranded DNA; ssDNA- single stranded DNA; CVD- cardiovascular disease; RHD- relatively healthy donors

Patients with Myocardial Infarction had anti-dsDNA Ab levels ranging from 0.3-0.4 (41.7%) and 0.4-0.5 (26.8%). Those suffering from both Myocardial Infarction (MI) and angina pectoris had anti-ssDNA Ab levels within the three identified ranges. 62.5% of patients with MI had anti-ssDNA Ab levels between 0.3-0.4, compared to 45.2% of patients with angina pectoris.

Determination of biochemical indicators in relatively healthy donors and patient groups

The biochemical analyzer (Architect ci8200) was used to determine blood biochemical parameters in relatively healthy donors and patient groups. Figures 2 and 3 present the correlations between the levels of anti-dsDNA Ab and anti-ssDNA Ab and the various determined blood biochemical parameters.

A normal cholesterol level in the blood allowed for sufficient production of anti-dsDNA Ab and anti-ssDNA Ab. However, an elevated or reduced cholesterol level led to a decrease in the production of these antibodies. The level of anti-ssDNA Ab

became more dispersed as their production increased (Fig. 2).

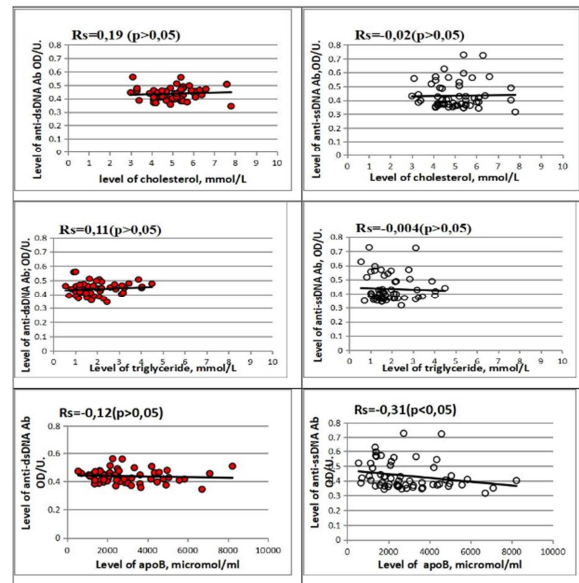


Fig. 2. Correlation between anti-dsDNA antibodies and anti-ssDNA antibodies levels and blood biochemical parameters (cholesterol, triglycerides, and ApoB)

High triglyceride levels (1 to 2 mmol/L) lead to an increased production of anti-dsDNA Ab, forming a cluster. An increase in triglyceride concentrations (0.3 to 0.5 mmol/L) causes a notable dispersion of anti-ssDNA Ab. A normalized triglyceride level (Fig. 2) in the blood promotes substantial production of both anti-dsDNA Ab and anti-ssDNA Ab, whereas abnormal triglyceride levels cause a decrease in these antibodies. As production increases, the denatured anti-DNA become Ab more dispersed.

For an apolipoprotein B level below 4000 mmol/L, the production of anti-dsDNA Ab and anti-ssDNA Ab increased. However, when this level exceeded 4000 mmol/L, their production gradually declined to 0.3 OD/U. Thus, the production of a significant amount of anti-dsDNA Ab and anti-ssDNA Ab appears to be dependent on normal apolipoprotein B levels in the blood.

When the LDL (low-density lipoproteins) and glucose levels were between 0.5 and 1.5 mmol/L and between 4 and 6 mmol/L, respectively, a high level of anti-

dsDNA Ab was observed, forming a block between 0.3 and 0.5 OD/U (optical density per unit). Similarly, a high quantity of anti-ssDNA Ab was present, with a concentration ranging from 0.3 to 0.4 OD/U. However, beyond 1.5 mmol/L of LDL and 6 mmol/L of glucose, the production of both anti-dsDNA Ab and anti-ssDNA Ab gradually decreased until reaching a null level (Fig. 3).

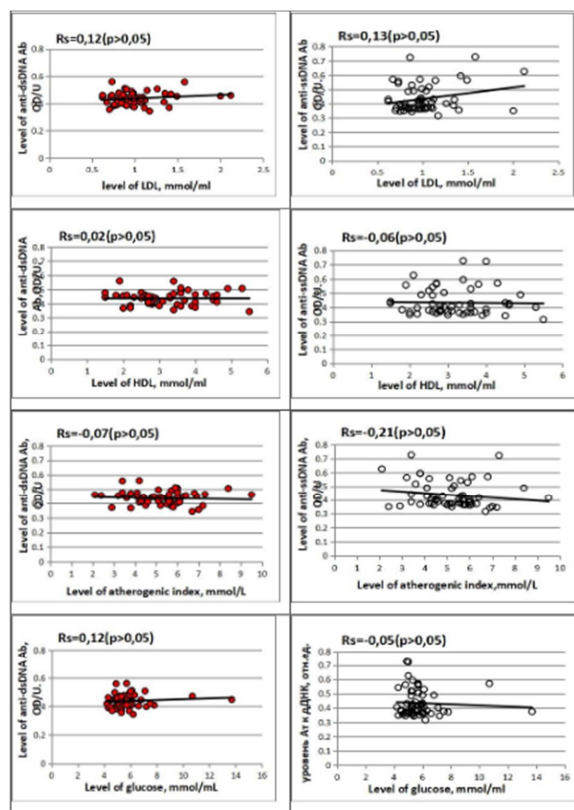


Fig. 3. Correlation between the levels of anti-dsDNA antibodies and anti-ssDNA antibodies and the biochemical blood parameters (LDL, HDL, atherogenic index, glucose).

Thus, a sufficient quantity of anti-dsDNA Ab and anti-ssDNA Ab would be produced when the levels of LDL and glucose are normal in the individual's blood. Moreover, as their production increased, the anti-ssDNA Ab began to disperse. When the levels of HDL (high-density lipoproteins) and the atherogenic index ranged from 1.5 to 4.5 mmol/L and 3 to 7 mmol/L, respectively, a high quantity of both anti-dsDNA Ab and anti-ssDNA Ab was observed, initially forming a slight cluster, followed by significant dispersion on either side.

However, this quantity of anti-dsDNA Ab and anti-ssDNA Ab gradually decreased when the levels of HDL and the atherogenic index exceeded 4.5 mmol/L and 7 mmol/L, respectively.

Thus, it seems that the production of anti-dsDNA Ab and anti-ssDNA Ab is linked to normal levels of HDL and the atherogenic index. When the levels of LDL, HDL, the atherogenic index, and glucose are within normal ranges in the blood, the body produces a substantial amount of anti-dsDNA Ab and anti-ssDNA Ab.

Correlation coefficients of the dependence between the levels of anti-dsDNA antibodies and anti-ssDNA antibodies in patient groups and certain biochemical parameters of the blood

A relatively strong positive relationship was noted between cholesterol levels and anti-dsDNA Ab levels (Table 2) in patients with MI and AP, with significance rates of 0.185 and 0.176, respectively. However, this relationship is relatively weak between cholesterol levels and anti-ssDNA Ab levels in patients with MI (0.007) and AP (-0.042) (Table 2). Similarly, a strong correlation exists between triglyceride levels and both anti-dsDNA Ab and anti-ssDNA Ab levels in patients with MI (0.246; 0.207). We observed a relatively weak linear relationship between triglyceride levels (Table 1) and both anti-dsDNA Ab and anti-ssDNA Ab levels in patients with AP (0.056; -0.079). A relatively negative linear relationship was also observed between Apolipoprotein B levels and both anti-dsDNA Ab and anti-ssDNA Ab levels in patients with MI and AP. Only patients with MI showed a significantly substantial negative correlation between ApoB levels and anti-ssDNA Ab levels.

A relatively weak and negative linear relationship was observed between the atherogenic index and the anti-dsDNA Ab levels in all patient groups. Moreover, a direct dependence relationship was also recorded between the levels of anti-dsDNA Ab and the levels of high-density lipoproteins (HDL) ($R_s = 0.13$). The analysis of the results also showed a dependence relationship between the levels of anti-dsDNA Ab and the glucose levels ($R_s = 0.12$) (Table 2).

Table 1. Correlation coefficients between the levels of anti-dsDNA Ab and anti-ssDNA Ab in MI and AP patient groups and blood biochemical parameters (cholesterol, triglycerides, apolipoprotein B, atherogenic index)

		Cholesterol (mmol/L)	Triglycerides (mmol/L)	Atherogenic index	Apo B (µg/ml)
Anti-dsDNA Ab	MI	0,185*	0,246*	0,084	-0,152*
	AP	0,176*	0,056	-0,093	-0,078
Anti-ssDNA Ab	MI	0,007	0,207*	-0,12	-0,014
	AP	-0,042	-0,079	-0,202*	-0,4*

Table 2. Correlation coefficients between the levels of anti-dsDNA Ab and anti-ssDNA Ab in patient groups with myocardial infarction (MI) and angina pectoris (AP) and blood biochemical parameters (LDL, HDL, Glucose)

		LDL (mmol/L)	HDL (mmol/L)	Glucose (mmol/L)
Anti-dsDNA Ab	MI	0,181*	-0,007	0,227*
	AP	0,144*	-0,002	0,096
Anti-ssDNA Ab	MI	0,052	-0,199*	0,061
	AP	0,139	-0,049	-0,08

Discussion

This current study examined the correlation between biochemical markers and the levels of anti-DNA Ab in patients with cardiovascular diseases. The results obtained suggest the existence of a significant relationship between these two variables. The levels of anti-ssDNA Ab and anti-dsDNA Ab in patients suffering from cardiovascular diseases were higher, ranging from 0.30 to 0.7 U. These anti-DNA levels vary depending on the different forms of cardiovascular diseases. In a study conducted by Narang *et al.* (2022) (Narang *et al.*, 2022), cardiovascular diseases are present in 50% of cases of systemic lupus erythematosus (SLE) (Narang *et al.*, 2022).

Furthermore, many patients with SLE have elevated levels of VDRL and LDL, and reduced levels of HDL, which are considered the "lupic lipoprotein profile" (Kim *et al.*, 2020). The elevated levels of anti-DNA antibodies observed in this study could therefore be explained by this relationship between SLE and cardiovascular diseases. Moreover, several authors have reported elevated serum levels of anti-DNA Ab in chronic cases of CVD (Dudas *et al.*, 2010; Soni *et al.*, 2012).

Among the biochemical markers analyzed, a direct correlation was observed between the levels of anti-DNA Ab and HDL levels. On the other hand, an inverse correlation was highlighted between the atherogenic index and apolipoprotein B, which is a

protein associated with low-density lipoproteins (LDL) involved in the development of atherosclerosis. Svenungsson *et al.* (2003) (Svenungsson *et al.*, 2003) demonstrated in a group of adult patients with SLE that increased triglyceride levels and low HDL levels are associated with the synthesis of anti-DNA antibodies (Svenungsson *et al.*, 2003). High levels of total cholesterol and low-density lipoproteins (LDL), combined with low levels of high-density lipoproteins (HDL), are associated with an increased risk of cardiovascular diseases in SLE (El-Magadmi *et al.*, 2004; Kostopoulou *et al.*, 2020). The presence and increase in anti-DNA antibody levels could therefore be associated with several parameters related to the increased cardiovascular risk, including carotid intima-media thickness, microvascular endothelial dysfunction, and the atherogenic risk index. This reinforces the idea that positivity for anti-DNA Ab could directly influence the development of cardiovascular diseases and indicate or predict a relapse of the disease (Yaniv *et al.*, 2015). Furthermore, previous studies have also suggested that anti-DNA Ab could play a protective role in the dysregulation of apoptosis in cardiovascular diseases.

A higher level of anti-DNA Ab may therefore correspond to a mild severity of the disease, such as angina pectoris, and potentially exert a protective function (Blatt and Glick, 1999; Lv *et al.*, 2005; Bertsias *et al.*, 2012). Indeed, the presence of a significant amount of anti-DNA Ab may be explained by their protective role during the dysregulation of

apoptosis in cardiovascular diseases (Wylie and Malemud, 2013). Similarly, studies by Pisetsky *et al.* (2020) (Pisetsky and Lipsky, 2020) also demonstrated that these antibodies are markers of a significant form of cardiovascular risk, aligning with those conducted by Dima *et al.* (2015) (Dima *et al.*, 2015). These results seem to validate the relevant role of anti-DNA Ab as modulators of the increased cardiovascular risk in patients with cardiovascular diseases. However, further studies are needed to better understand the underlying mechanisms of this correlation and assess their potential clinical value in the diagnosis and monitoring of cardiovascular diseases.

Conclusion

This study showed that there is a dependence relationship between cardiovascular diseases and autoimmunity. The level of anti-DNA Ab, considered as a biomarker, varies depending on the different clinical forms of cardiovascular disease and presents correlations with certain biochemical indicators. These data require further exploration through additional studies aimed at better understanding the factors underlying this interesting variability in anti-DNA Ab levels during the pathophysiology of cardiovascular diseases.

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