

Research Article

Atherogenic insulin resistance indices and immune disturbances in COVID-19

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Summary

Background: It is now proven that insulin resistance occurring during SARS-CoV-2 infection is the major cause for the hyperglycemia observed, and it can even persist long after recovery. The precise mechanisms of insulin resistance, whether new-onset or pre-existing, remain largely a mystery. Chronic immune dysregulation, persistent sub-clinical inflammation, adipose tissue dysfunction and pro-inflammatory cytokines are thought to be of fundamental importance. The current study aims to investigate the role of SARS-CoV-2 infection and the related inflammation in the pathogenesis of insulin resistance in different types of newly emerging disorders of carbohydrate metabolism following infection.

Methods and materials: The current study included 168 patients (59 males and 109 women; mean age 54.04 ± 8.08 years), divided into three groups: group 1 (patients with active COVID-19 infection; $n = 100$), group 2 (individuals with newly diagnosed carbohydrate disorders after proven COVID-19 or post-COVID group; $n = 35$) and group 3 (COVID-19 negative subjects with Metabolic Syndrome; $n = 33$). Standard biochemical and immunological parameters were measured, and atherogenic indices for IR (TyG index and TG/HDL-C ratio) were calculated using the corresponding formula.

Results: Patients with active coronavirus infection demonstrated the highest levels of TyG index and TG/HDL-C ratio, which differed significantly from both the reference COVID-negative group and from the Post-COVID group ($p < 0.05$). Among the individuals in the post-COVID group, we found a positive correlation between TyG index and IL-10 ($r = 0.481$; $p = 0.008$), IL-17A ($r = 0.384$; $p = 0.048$) and HCF-D ($r = 0.387$; $p = 0.038$). In the same group, the TG/HDL-C ratio positively correlated with CD8 ($r = 0.648$; $p < 0.001$), TNF- α ($r = 0.559$; $p < 0.001$), IL-10 ($r = 0.954$; $p < 0.001$), 8-Epi-PGF2 α ($r = 0.451$; $p = 0.006$) and HIF-1 α ($r = 0.863$; $p < 0.001$).

Conclusion: Immune dysregulation, along with oxidative stress and cellular hypoxia observed during and after infection, seems to be implicated in the genesis, maintenance and progression of the insulin resistance (IR). IR, as measured by widely used atherogenic indices, is present not only during the COVID-19 course but also in cases of newly emerging carbohydrate disorders following infection, including T2DM, prediabetes, and T1DM.

Key words: Atherogenic indices, COVID-19, immunological disturbances, insulin resistance, new-onset carbohydrate disorders



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Introduction

The coronavirus pandemic has posed a serious challenge to humanity, especially considering the consequences of infection, including the so-called Long COVID syndrome. It has been established that SARS-CoV-2 is associated with increased risk of developing diabetes mellitus (DM) (approximately by 60%), which is higher than that of respiratory infections caused by other viruses (Wong et al. 2023).

The glycemetic abnormalities caused by COVID-19 include both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) (Zhao et al. 2025), but also prediabetic conditions – impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Sosibo and Khathi 2021).

Literature data also indicate that COVID-19 may contribute to the development of new-onset insulin resistance (IR) and alterations in lipid profile parameters, even in patients without pre-existing disturbances (He et al. 2021).

Furthermore, IR appears to be a leading cause of hyperglycemia observed during and after illness, rather than beta cell dysfunction (Reiterer et al. 2021).

The precise mechanisms of IR, whether new-onset or pre-existing, remain largely a mystery. It is suggested that chronic immune dysregulation, persistent subclinical inflammation, and adipose tissue dysfunction, characterised by increased dysregulated adipokines and pro-inflammatory cytokines, influence the fluctuation of insulin levels and contribute to the occurrence of IR and stress-induced hyperglycemia in recovered COVID-19 patients.

On the other hand, it is widely known that COVID-19-related inflammation is associated with elevated plasma levels of pro-inflammatory cytokines, including interleukin (IL)-6, IL-17A, tumour-necrosis factor-alpha (TNF- α), interferon-gamma (IFN- γ), and IL-12, defining a characteristic feature of the disease known as a “cytokine storm.” This is the main reason leading to an increased incidence of complications and adverse outcomes of the disease (Ye et al. 2020; Hirano and Murakami 2020; Quirch et al. 2020).

It is also speculated that the specific COVID-19 secretome (specific cytokine profile) may induce both IR and beta cell dysfunction, which can be transient or permanent (Montefusco et al. 2021).

The extent to which these abnormalities in immune homeostasis are related to the emergence or worsening of pre-existing IR remains unclear and awaits further elucidation.

Aim of the study

The current study aims to investigate the role of SARS-CoV-2 infection and the related inflammation and immune dysfunction in the pathogenesis of insulin resistance in different types of newly emerging disorders of carbohydrate metabolism following infection, DM, and prediabetes.

Methods and materials

Study design

A prospective observational study was conducted on 168 hospitalised participants (59 men and 109 women) who were treated in the Clinic of Pulmonology

and Phthisiology and the Clinic of Endocrinology and Metabolic Diseases at Dr Georgi Stranski University Hospital – Pleven, Bulgaria. To investigate the role of basic and other poorly understood pathophysiological mechanisms in the development of carbohydrate disorders and insulin resistance, individuals were selected based on precise criteria and divided into three groups. Each group was studied for similar diagnostic, metabolic, biochemical, and hormonal aspects.

Studied population

The study population includes three groups of patients in the age range between 18 and 90 years:

- **Group 1** – unselected patients with active COVID-19 infection (100 individuals). A COVID-19 diagnosis was made using a polymerase chain reaction (PCR) test, which confirmed the presence of the virus's genetic material.
- **Group 2** – individuals with newly diagnosed carbohydrate disorders after proven COVID-19 (post-COVID group) (35 individuals). All individuals were non-vaccinated and had had a history of positive PCR tests for COVID-19 at least 6 months before they were newly diagnosed with carbohydrate disorders. They were diagnosed with T1DM, T2DM and prediabetic conditions – IFG and IGT, as well as patients with IR and/or hyperinsulinemia. Diagnosis DM was made according to the WHO criteria (2019). Prediabetic conditions (IFG, IGT) were diagnosed according to the WHO criteria (2015) (Bansal 2015). In order to study the early stages of metabolic disturbances, individuals with laboratory constellation for IR and/or hyperinsulinemia were also included.
- **Group 3** – persons who did not suffer from COVID-19 (COVID-19 negative), with the characteristic of Metabolic Syndrome (MS) (33 individuals). The diagnosis of MS was made according to the IDF criteria (2009) (Alberti et al. 2006, 2009).

Methods

All the individuals included in the study participated in a survey and underwent anthropometric measurements and basic clinical exams.

Laboratory tests were performed after venipuncture on the cubital vein of one arm. All invasive procedures were performed after the patients had signed informed consent.

Standard biochemical parameters were evaluated, including fasting plasma glucose, glycated haemoglobin (HbA1c), lipid profile parameters (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol), uric acid, and liver function tests (ASAT, ALAT). Hormonal parameters related to the regulation of glucose homeostasis were also evaluated, as well as some immunological markers as indicators of immune dysfunction, oxidative stress and hypoxia.

The hormonal samples were studied by electrochemiluminescent immunoassay (ECLIA), according to the methodology of the test, on an automatic analyser. All immunological samples, as well as the samples for some of the hormonal studies, were investigated by enzyme-linked immunosorbent assay (ELISA) using commercial kits.

Insulin resistance was determined with atherogenic insulin resistance indices, calculated according to the formula:

TG/HDL-C ratio:

This index was calculated from the ratio of fasting triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C), and reflects the balance between pro-atherogenic and anti-atherogenic lipoproteins. **Formula: $TG/HDL-C \text{ ratio} = TG \text{ (mmol/l)} / HDL-C \text{ (mmol/l)}$**

Triglyceride-Glucose (TyG) Index:

Derived from fasting triglycerides and glucose levels. **Formula: $TyG \text{ index} = \ln (\text{Fasting TG (mmol/l)} \times \text{Fasting Glucose (mmol/l)}) / 2$** (Simental-Mendía et al. 2008).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25. The data was presented in suitable tables and figures. The quantitative variables were assigned a mean value, standard deviation (SD) denoted as “mean \pm SD, median (Med) and interquartile range (IQR).

The first part of the analysis included checking the normality of the distributions of the quantitative variables (Kolmogorov-Smirnov and Shapiro-Wilk test). The tests results showed that for each variable, the distribution in at least one of the groups was not normal. This was the basis for choosing non-parametric methods for comparisons between groups. The first method is the Kruskal-Wallis test.

It is used to compare three or more quantitative variables. The test uses the ranks of the variables, comparing the mean values of the ranks for each group. When the Kruskal-Wallis test is statistically significant ($p \leq 0.05$) which means that there is a difference in the distribution of the groups, which are three or more. However, in order to determine exactly where the difference is, i.e. which groups are statistically significantly different, several additional post hoc Mann-Whitney tests must be performed, one for each pair of groups, using the Bonferroni-adjusted p-value for this purpose. This value for three groups is equal to $0.05/3 = 0.0167$, not 0.05. Therefore, when using the Mann-Whitney test as a post hoc test, only at $p \leq 0.0167$ is it assumed that the Mann-Whitney test is statistically significant.

A Spearman correlation analysis was performed to identify correlation coefficient (r) that shows an association between the evaluated variables. Only statistically significant correlations ($p < 0.05$) were considered. ROC curve analysis was also performed to study the risk role of the study's indices and cu-off value was determined for both indices.

Ethical principles

The study adhered to the ethical principles of the Declaration of Helsinki. Each person included in the study declared their voluntary willingness to participate in the study by signing and dating the consent form. The researcher also signed

the informed consent, declaring his obligation to comply with the ethical principles set out in the Declaration of Helsinki. No psychological pressure was allowed on the volunteers to sign the informed consent.

Results and discussion

The main demographic features of the studied population are presented in the table below (Table 1).

Table 1. Socio-demographics and clinical characteristics of the study population.

Socio-demographics and clinical characteristics	Group 1	Group 2	Group 3	Total
	(n = 100)	(n = 35)	(n = 33)	(n = 168)
Age, years (Mean \pm SD; Me, IQR)	68.6 \pm 14.750 (67, 24)	45.4 \pm 4.980 (45, 26.5)	48.2 \pm 4.510 (50, 14)	54.0 \pm 8.080 (53, 19.5)
Gender (n, %)				
Male	43 (43.0%)	13 (37.2%)	3 (9.1%)	59 (35.1%)
Female	57 (57.0%)	22 (62.9%)	30 (30.9%)	109 (64.9%)
Family history of DM (n, %)				
Yes	32 (32.0%)	14 (40.0%)	15 (45.5%)	61 (36.3%)
No	68 (68.0%)	21 (60.0%)	18 (54.6%)	107 (63.7%)
Diabetes Mellitus				
Pre-existing	21 (21.0%)	0 (0.0%)	9 (27.3%)	30 (17.7%)
New diagnosed	10 (10.0%)	19 (54.3%)	2 (6.1%)	31 (18.5%)
No	69 (69.0%)	16 (45.7%)	22 (66.7%)	107 (63.7%)

The mean age of the studied cohort is 54.04 \pm 8.08 years old. The oldest group consists of individuals with active COVID-19 (Group 1), followed by the COVID-19 negative group, which includes subjects with Metabolic Syndrome (Group 3). The youngest group comprises patients with new onset carbohydrate disorder following COVID-19 (Group 2), showing a significant difference between the three groups (Kruskal-Wallis $H(2) = 73.39$; $p < 0.01$).

Female predominance is most pronounced in the reference group (Group 3), whereas in the other two groups, the ratio between females and males is almost similar ($p = 0.150$; $\chi^2 = 2.076$).

As seen in the data below, the majority of subjects had no positive family history of diabetes (DM), whereas only 36.3% reported such a history.

A total of 61 (36.3%) subjects of the studied population had diabetes: half of them ($n = 30$) had pre-existing DM (17.9%), and the remaining 31 (18.4%) were newly diagnosed with DM.

Diabetes was newly diagnosed in 10% of the patients with active infection, and half of the subjects in the post-COVID group, who were preselected explicitly according to those criteria (being newly diagnosed with carbohydrate disorder after proven COVID-19). Only 2 subjects (6.1%) of the COVID-negative group were newly diagnosed, whereas 9 (27.3%) had pre-existing DM. The majority of the group (66.7%) were non-diabetics.

The distribution of the patients in the post-COVID group (Group 2) is as follows: a total of 19 individuals (54.3%) had newly diagnosed DM – 8 of them were diagnosed with T1DM, including LADA (22.9%), while the remaining 11

individuals (31.4%) were diagnosed with T2DM. Prediabetes, as IGT, was found in 3 individuals (8.6%), and as IFG in 4 subjects (11.4%). The remaining 9 individuals, who were normoglycaemic (25.7%), had data on basal and/or stimulated hyperinsulinemia and IR.

Insulin resistance was determined with atherogenic insulin resistance indices – TyG index and TG/HDL-C ratio. These indices are biochemical markers that combine lipid profile data with insulin resistance indicators, in order to assess overall cardiovascular risk and the severity of insulin resistance. Calculated from standard blood tests, they help predict the likelihood of atherosclerosis and associated conditions like type 2 diabetes and metabolic syndrome, with higher values generally indicating greater risk (Table 2).

Table 2. Estimated atherogenic insulin resistance indices among the studied population.

Variable		Group 1 (n = 68)	Group 2 (n = 29)	Group 3 (n = 33)	Significance (p < 0.05)
TyG index	<i>Mean ± SD</i>	4.89 ± 0.49	4.68 ± 0.61	4.46 ± 0.56	P < 0.05*
	<i>Median (IQR)</i>	4.90 (0.593)	4.53 (0.557)	4.42 (0.808)	
TG/HDL-C ratio	<i>Mean ± SD</i>	3.80 ± 2.69	1.93 ± 2.58	2.42 ± 1.51	P < 0.05**
	<i>Median (IQR)</i>	3.63 (2.485)	1.16 (1.592)	1.86 (1.363)	

NS – no significant difference; p < 0.05 – statistical significance difference:

P < 0.05* – Statistically significant difference between Group 1 and Group 2 (p = 0.015); between Group 1 and Group 3 (p < 0.001);

P < 0.05** – Statistically significant difference between Group 1 and Group 2 (p = 0.002), between Group 1 and Group 3 (p = 0.0166) and between Group 2 and 3 (p = 0.01).

To study the differences between distinct types of carbohydrate disorders in detail, mean values of the respective indices were compared among separate subgroups in subjects from group 2 (Table 3).

Table 3. Estimated atherogenic insulin resistance indices among the different subgroups from Group 2 according to the type of carbohydrate disorders.

Variable		T1DM (n = 8)	T2DM (n = 11)	IFG (n = 4)	IGT (n = 3)	IR (n = 9)	Sign. (P < 0.05)
TyG index	<i>Mean ± SD</i>	5.18 ± 0.81	4.7 ± 0.26	4.59 ± 0.6	4.5	4.27 ± 0.36	P < 0.05*
	<i>Median</i>	4.92	4.65	4.35	4.5	4.18	
	<i>(IQR)</i>	(1.1)	(0.371)	(0.551)	(-)	(0.499)	
TG/ HDL-C Ratio	<i>Mean ± SD</i>	2.62 ± 2.55	1.87 ± 0.75	0.67 ± 0.13	2.29	2.35 ± 1.4	NS
	<i>Median</i>	1.211	1.6	0.67	2.29	1.87	
	<i>(IQR)</i>	(2.687)	(0.817)	(0.094)	(-)	(0.91)	

NS – No statistical significant difference; P < 0.05* – Statistical significant difference between T1DM subgroup and IR subgroup (Mann Whitney U = 63.0; P = 0.0079).

Triglyceride-glucose index (TyG index)

The triglyceride-glucose index (TyG index) is a comprehensive statistical measure that serves as an effective alternative biomarker for insulin resistance due to its high sensitivity and specificity (Araújo et al. 2022).

Calculated using fasting serum triglycerides and fasting plasma glucose values, a high TyG index is a significant indicator of adverse prognosis in the general population, as well as in patients with various diseases.

Guerrero-Romero et al. demonstrated that the TyG index showed an excellent correlation with the HEC method, considered the gold standard in diagnosing insulin resistance (area under the curve (AUC) = 0.858), with a TyG index cut-off value of 4.68, a sensitivity of 96.5% and a specificity of 85% in assessing insulin resistance in the adult population (Guerrero-Romero et al. 2010).

The widely accepted cut-off values are around the one established in a study by Salazar et al. (2017). According to them, the so-called cut-off value of the TyG index suggesting insulin resistance is 4.49, with a sensitivity of 82.6% and a specificity of 82.1% (AUC = 0.889, 95% CI: 0.854–0.924). Thus, individuals with values > 4.49 are indicated as at risk for IR.

Using the validated, generally accepted formula, we calculated the index in individuals from the study population. Individuals with active coronavirus infection (Group 1) demonstrated the highest mean values of TyG, which differed significantly from the reference COVID-negative group (Mann Whitney U = 604.0; p < 0.001) and from the Post-COVID group (Mann Whitney U = 677.0; p = 0.015). We found similar TyG values among the other two groups (Mann Whitney U = 575.0; p = 0.176). However, higher levels were reported among the group of patients with newly occurring carbohydrate disorders following infection (Group 2), respectively (Table 2).

When comparing the mean values across patients with and without diabetes, people with diabetes from all three groups demonstrated higher levels as expected (Table 4). However, there was a significant difference between diabetics and non-diabetics from both group 2 (Mann Whitney U = 168.0; p = 0.005) and group 3 (Mann Whitney U = 205.0; p = 0.001).

Table 4. TyG index (Mean values ± SD; Median and IQR) among patients with (DM+) and without (DM-) diabetes in all three groups – Group 1 (active COVID-19); Group 2 (post-COVID with newly diagnosed carbohydrate disorders) and Group 3 (COVID-negative with MS).

	TyG index			Significance
		DM (+)	DM (-)	
Group 1 (n = 68)	Mean ± SD	5.18 ± 0.57	4.78 ± 0.4	NS
	Median	5.18	4.83	
	(IQR)	(0.547)	(0.521)	
Group 2 (n = 29)	Mean ± SD	4.94 ± 0.63	4.36 ± 0.41	P = 0.005
	Median	4.84	4.31	
	(IQR)	(0.499)	(0.389)	
Group 3 (n = 33)	Mean ± SD	4.89 ± 0.58	4.24 ± 0.41	P = 0.001
	Median	4.86	4.09	
	(IQR)	(0.395)	(0.614)	

NS – no statistical significant difference.

When examining differences in the separate subgroups within group 2, we identified several notable distinctions. Interestingly, individuals with T1DM demonstrated the highest levels of the indices, followed by those with T2DM and prediabetes (IFG and IGT). The lowest levels were recorded among patients with IR and hyperinsulinemia (Table 3).

However, statistically significant differences between the individual subgroups were observed only in terms of the TyG index values, and they were between the subgroups with T1DM and IR (Mann Whitney U = 63.0; P = 0.0079) (Fig. 1).

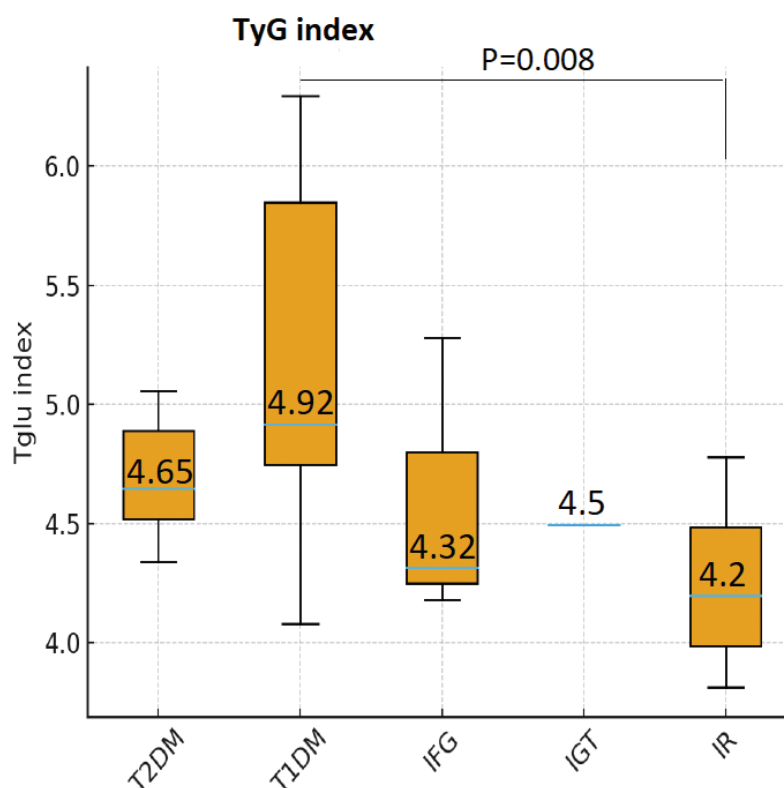


Figure 1. Levels of TyG index among individual subgroups in Group 2.

A correlation analysis was performed to study the relationship between the TyG index and some immunological parameters, along with other lipid and glucose homeostasis markers, among the individuals with newly diagnosed carbohydrate disorders from the post-COVID group (Group 2).

The results showed a positive week correlation between serum levels of IL-10, a potent anti-inflammatory cytokine, and TyG index ($r = 0.481$; $p = 0.008$). Also, a positive week correlation was found between TyG index and serum IL-17A levels ($r = 0.384$; $p = 0.048$), a potent pro-inflammatory cytokine and one of the significant components of the cytokine storm. In the same group, we found another positive week association with HCF-D ($r = 0.387$; $p = 0.038$), which is used as a marker of the complement system and immune reactions implicated.

All these findings indicate that in the pathogenesis of insulin resistance, following COVID-19, multiple complex immunological mechanisms are involved, including potent pro- and anti-inflammatory cytokines as well as the complement system.

Among individuals with new-onset carbohydrate disorders following COVID-19 (Group 2), a positive correlation was also found between TyG index and fasting plasma glucose ($r = 0.646$; $p < 0.001$), HbA1c ($r = 0.528$; $p = 0.012$), and serum triglycerides ($r = 0.551$; $p = 0.002$). A moderate negative correlation was found with HDL-C levels ($r = -0.597$; $p = 0.002$).

This correlation confirms once more that the TyG index is a helpful index for assessing glucometabolic homeostasis.

Triglyceride/HDL-cholesterol ratio (TG/HDL-C ratio)

Another widely used index of insulin resistance is the triglyceride/HDL-cholesterol ratio (TG/HDL-C ratio). A high TG/HDL-C ratio is associated with reduced insulin sensitivity, metabolic syndrome, and adverse cardiovascular events. The values considered ideal by health professionals are $TG/HDL-C \leq 2.0$, acceptable in the range of 4.0 to 6.0, and elevated ≥ 6.0 .

In another study, the optimal cut-off values for the TG/HDL-C ratio were 2.967 in men and 2.237 in women based on a ROC analysis of the relationship between the TG/HDL-C ratio and the influence of various cardiometabolic risk factors, including visceral obesity, hypertension, and diabetes (Wakabayashi and Daimon 2019).

We calculated the TG/HDL-C ratio among the studied population, and higher values were found among the reference group with MS (Group 3) while in the group of patients with newly occurring carbohydrate disorders (Group 2) the values were lower (Mann Whitney U = 284.0; $p = 0.01$). The patients with active coronavirus infection (Group 1) demonstrated the highest levels compared to the other two groups, and they were statistically different only from those in the COVID-negative group (Mann Whitney U = 187.0; $p = 0.00166$) as well as from the post-COVID group (Mann Whitney U = 122.0; $p = 0.002$) (Table 2).

Comparing the average values in diabetics and non-diabetics, the people with diabetes had higher values of the TG/HDL-C ratio, except for group 1 (active COVID-19 group), where non-diabetics demonstrated higher mean values of the ratio (Table 5). However, only in the COVID-negative group was a statistically significant difference found between diabetics and non-diabetics (Mann Whitney U = 191.0; $p = 0.007$).

A significant difference was also observed among diabetics in groups 2 and 3 (Mann Whitney U = 28.0; $p = 0.0127$) as well as between non-diabetics in groups 1 and 2 (Mann Whitney U = 28.0; $p = 0.006$) and groups 1 and 3 (Mann Whitney U = 61.0; $p = 0.003$).

All this confirms once more the hypothesis for the virus's influence on insulin sensitivity itself.

Table 5. TG/HDL-C ratio (Mean values \pm SD; Median and IQR) among patients with (DM+) and without (D-) diabetes in all three groups – Group 1 (active COVID-19); Group 2 (post-COVID with newly diagnosed carbohydrate disorders) and Group 3 (COVID-negative with MS).

	TG/HDL-C ratio			Significance
		DM (+)	DM (-)	
Group 1 (n = 68)	Mean \pm SD	2.51 \pm 1.14	4.26 \pm 2.96*	NS
	Median	2.28	3.7	
	(IQR)	(1.899)	(3.132)	
Group 2 (n = 29)	Mean \pm SD	4.03 \pm 7.45*	2.06 \pm 1.36*	NS
	Median	1.54	1.86	
	(IQR)	(1.421)	(1.321)	
Group 3 (n = 33)	Mean \pm SD	3.26 \pm 1.82*	1.99 \pm 1.15*	P = 0.007
	Median	2.96	1.74	
	(IQR)	(1.171)	(1.127)	

NS – no statistical significant difference; *Statistical difference found between diabetics from groups 2 and 3 ($p = 0.0127$) and non-diabetics from groups 1 and 2 ($p = 0.006$) and 1 and 3 ($p = 0.003$).

When examining differences in the separate subgroups in group 2, individuals with T1DM again demonstrated the highest mean levels of the indices, whereas the lowest levels were recorded among patients with IFG (Fig. 2). The other subgroups demonstrated similar values with no statistical difference found between the separate subgroups (Table 3).

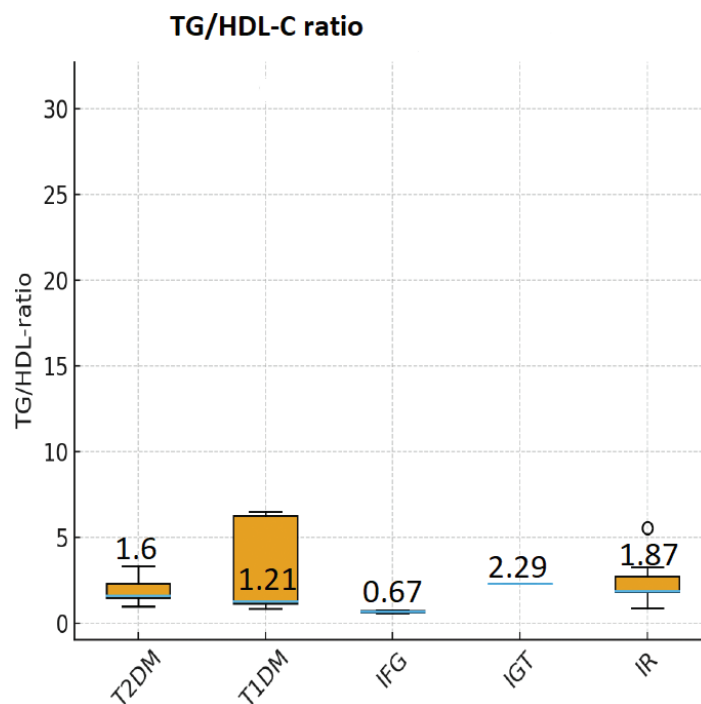


Figure 2. Levels of TG/HDL-C ratio among individual subgroups in Group 2.

To investigate the relationship between immune dysregulation observed during and after COVID-19 and the new onset carbohydrate disorders, a correlation analysis was conducted. The results showed a positive moderate correlation between the TG/HDL-C ratio, as an indicator of the IR, and CD8, a T-cytotoxic Ly cellular marker ($r = 0.648$; $p < 0.001$). On the other hand, the TG/HDL-C ratio correlates with TNF- α ($r = 0.559$; $p < 0.001$), a major component responsible for the cytokine storm.

Interestingly, we also found a strong positive correlation between the ratio and IL-10, a potent anti-inflammatory cytokine ($r = 0.954$; $p < 0.001$). TG/HDL-C ratio also positively correlates with 8-Epi-PGF2 α levels, an oxidative stress marker ($r = 0.451$; $p = 0.006$) and HIF-1 α , an indicator for cellular hypoxia ($r = 0.863$; $p < 0.001$), confirming the multifactorial genesis of the IR.

Based on these correlations, it can be concluded that in the pathogenesis of IR arising under COVID-19 conditions, cell-mediated immunity also participates, alongside oxidative stress and cellular hypoxia.

ROC-curve analysis was performed to evaluate the predictive value of the mentioned indices for determining the risk of COVID-19 disease and to identify the optimal cut-off value that maximises sensitivity and specificity.

The data analysis showed that the TyG index was associated with an increased risk of disease caused by SARS-CoV-2 infection, with cut-off values ≥ 4.296 (AUC = 0.731 (0.619–0.842); $p < 0.001$), with a sensitivity of 88.2% and a specificity of 48.5% (Fig. 3).

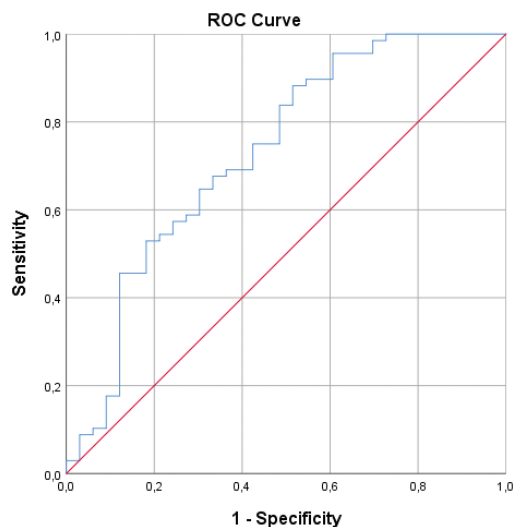


Figure 3. ROC curve analysis for determining the cut-off values of the TyG index for COVID-19 disease.

The other atherogenic index, TG/HDL-C ratio, was also proven to contribute to the risk for COVID-19 disease. The data from the analysis indicated that the cut-off values ≥ 3.619 were associated with an increased probability of disease from the infection (AUC = 0.702 (0.546–0.858); $p = 0.016$), with a sensitivity of 52.6% and a specificity of 90.9% (Fig. 4).

Based on the results from the ROC-curve analysis, it can be concluded that IR, measured by the atherogenic indices (TyG index and TG/HDL-C ratio), is both a risk factor and a consequence of the disease.

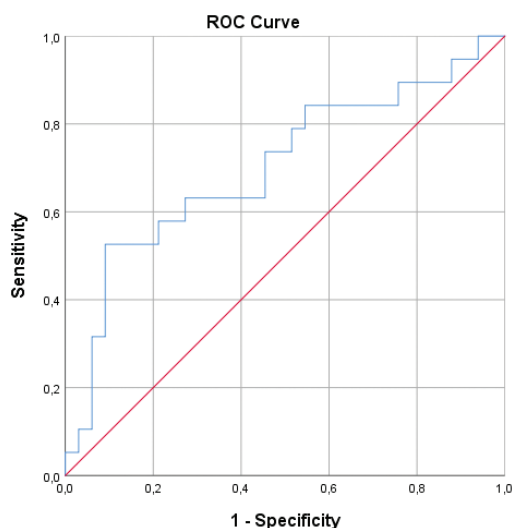


Figure 4. ROC curve analysis for determining the cut-off values of the TG/HDL-C ratio for COVID-19 disease.

Conclusion

Insulin resistance occurring during infection is the major cause for the hyperglycemia observed, and it can even persist long after recovery. It is also present in the cases of newly emerging carbohydrate disorders following infection, including not only T2DM and prediabetes, but also T1DM. Immune dysregulation,

along with oxidative stress and cellular hypoxia observed during and after infection, is implicated in the genesis, maintenance, and progression of the IR. To what extent is their role primary and leading, and does the genetic terrain on which all these processes develop have an influence, remains a question whose answer is yet to be actively sought.

Additional information

Conflict of interest

The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical statements

Clinical trials: The study is performed after received ethical approval from the Ethical commission of Medical University Pleven – Protocol №72/23.06.23.

The authors declared that experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: Clinic of Endocrinology and Metabolic Diseases, University Hospital "Georgi Stranski" – Pleven. Each person included in the study declared their voluntary willingness to participate in the study by signing and dating the informed consent form.

The study adhered to the ethical principles of the Declaration of Helsinki.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

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Author contributions

Conceptualization: KT, VTT. Formal analysis: MA, IG. Methodology: IG, VTT, MA. Resources: MST. Supervision: KT. Visualization: VTT. Writing – original draft: VTT. Writing – review and editing: VTT, KT.

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Data availability

The authors declare that data supporting the findings of this study are available within the article.

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