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# HYPERGLYCEMIA AND COVID-19 – TWO SIDES OF ONE COIN

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## ABSTRACT

The coronavirus pandemic, which has spread with monstrous rapidity, placed a huge "burden" on humanity. In the attempt to deal with the disease many efforts were directed in the course of unraveling the pathogenetic mechanisms contributing to its adverse complications.

The increased frequency of new-onset hyperglycemia during COVID-19 illness gave reason to assume that the SARS-CoV-2 virus could damage the insulin-producing pancreatic beta (β) cells. This fact set a new a focus of research interest related to studying potential mechanisms, leading to hyperglycemia or diabetes mellitus (DM). Literature data indicate that Corona viruses can damage pancreatic β-cells by a direct or indirect mechanism and cause changes in insulin synthesis, secretion and sensitivity. Assessment of the metabolic status of pancreatic β-cells infected with the SARS-CoV-2 virus showed a predominance of the glycolytic metabolic pathway, which further contributed to the worsening of β-cell dysfunction. All these observations give reason to assume that SARS-CoV-2 induces specific morphological and functional changes in pancreatic β-cells, which in long term, would have an impact on the metabolic homeostasis of the individual with a potential risk of future development of DM.

In this review, the possible mechanisms of pancreatic β-cell damage are discussed in details, searching the answer to the question of whether SARS-CoV-2 can cause diabetes.

**Keywords**: pancreas, beta-cell, COVID-19, diabetes mellitus, insulin resistance, beta-cell dysfunction

## INTRODUCTION

The coronavirus pandemic, caused by the Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2), gave rise to an avalanche of global morbidity and mortality, posing a serious challenge to public health, in result of the devastating damage on a number of vitally important organs and systems, as well as on the immune, endocrine and homeostatic regulation of the body.

To date, it is already well known that COVID-19 is a multi-organ disease with an acute and prolonged course, and metabolically active tissues including adipose tissue, liver, pancreas and others, are being especially vulnerable. Changes in them influence on their functional activity, both during the acute active phase of infection and afterwards - the so-called post-covid-syndrome or long-COVID.

The increased incidence of new-onset hyperglycemia during COVID-19 illness was a reason to suggest that the SARS-CoV-2 virus may cause damage to the insulin-producing pancreatic beta (β) cells. This fact has placed a new focus of research interest related to studying the potential mechanisms leading to hyperglycemia or diabetes mellitus (DM) occurrence. Literature data indicate that Corona viruses can damage pancreatic β-cells by direct or indirect mechanism and cause changes in insulin synthesis, secretion and sensitivity. Assessment of the metabolic status of pancreatic β-cells infected with the SARS-CoV2 virus showed a predominance of the glycolytic metabolic pathway, which further contributed to the worsening of

β-cell dysfunction. All these observations give reason to assume that SARS-CoV-2 induces specific morphological and functional changes in pancreatic β-cells, which, in the long term, would have an impact on the metabolic homeostasis of the individual with a potential risk of future development of DM.

This review examines in details the possible mechanisms of pancreatic β-cell injury, in attempt to find an answer to the question of whether SARS-CoV-2 can trigger diabetes mellitus.

## SARS-COV-2 - ENTRY RECEPTOR MODULATIONS AND ENZYME PROTEASES

The process of viral attachment and entry is multi-step, with each step being critical. Factors relevant to viral invasion have been extensively studied over the past few years. In addition to the obligate receptor expressed on target cells - angiotensin-converting enzyme -2 (ACE2) and transmembrane serine protease -2 (TMPRSS2), several molecules involved in the viral entry process**,** designated as co-factors, have been identified.

Some of them function as receptors, participating in the process of viral attachment - neuropilin-1 (NRP-1), transferrin receptor (TFRC), heparan sulfate (HS), and others - performing the role of proteases - furin, transmembrane serine protease type 11 (TMPRSS11D), adam metalloproteinase domain 17 (ADAM 17), lysosomal cathepsins (CTSL), transmembrane serine protease 4 (TMPRSS4). [42,52,6,9,34,27,19,7,17,25]

The intracellular concentration of the virus, its half-life and its direct intracellular cytotoxicity is modulated by various additional factors. However, they are all non-specific and do not support efficient SARS-CoV infection or SARS-CoV-2 in the absence of ACE2 [17;25], so they are designated as additional factors.

*Table 1: Expression of major and accessory factors in the pancreas*

| Expression | Endocrine cells | Exocrine cells | Endothelial cells and pericytes |
|---|---|---|---|
| **ACE -2** | Low [31,19,52] | High [40,19] | High [31, 19] |
| **TMPRSS2** | Low [31,42,] | Moderate [19;7] Low [31] | Low [19;7] |
| **NRP - 1** | High [42;52] | | |
| **FURIN** | High [42;52] | | |
| **ADAM – 17** | High [42;52] | | |
| **TFRC** | High [42;52] | | |
| **TMPRSS4** | Low [19,52] | | |
| **TMPRSS11D** | Low [19,52] | Low [19,52] | |
| **HS** | High [52] | | |

*Angiotensin-Converting Enzyme -2 (ACE2), Transmembrane Serine Protease -2 (TMPRSS2), Neuropilin-1 (NRP-1), Transferrin Receptor (TFRC), Heparan Sulfate (HS), Transmembrane Serine Protease Type 11 (TMPRSS11D), ADAM metalloproteinase domain 17 (ADAM 17), Lysosomal Cathepsins (CTSL), Transmembrane Serine Protease 4 (TMPRSS4).*

## PANCREATIC BETA CELLS ARE PREFERENTIALLY ATTACKED BY SARS-COV-2

Viral invasion is strictly dependent on the presence of the ACE2 receptor [41], as ACE2 expression has been demonstrated in both the endocrine and exocrine part of the pancreas. [42,52,8, 46, 31,53]

Furthermore, all possible ACE2 isoforms have been found to be expressed in all pancreatic (endocrine and exocrine) cell types. [31]

However, the expression of ACE2 in endocrine cells is low, only below 1.5%. [42;52,19;7;53]

Similar to ACE-2, expression of TMPRSS2 among endocrine cells is low, and it has even been suggested that

TMPRSS2 expression alone is not sufficient to predict infection. [42,52, 19,7].

In fact, less than 1.3% of β-cells were found to co-express the ACE2-receptor with any of the other input factors.[7]

However, data suggest that β-cells are more susceptible to SARS-CoV-2 infection. [52, 46]

When examining the expression levels of the various input factors within the two main populations of pancreatic islet cells: insulin-secreting β-cells and glucagon-secreting α-cells, no major differences in ACE2 and TMPRSS2 expression were observed between β-cells and α-cells, suggesting that the expression levels of these receptors are unlikely to be solely responsible for the propensity of SARS-CoV-2 to infect β-cells.

Selectively high expression of NRP1 and TFRC was found in β-, compared to α-cells, suggesting that NRP1 facilitates SARS-CoV-2 infection. [42,52]

Neuropilin-1 (NRP1) is a multifunctional membrane receptor involved in cell signaling of many important processes – such as angiogenesis, tumor growth, viral entry, axonal guidance and immune function [34].

Moreover, the expression of NRP1, but not that of ACE2, is increased in β-cells in individuals infected with SARS-CoV-2. [**52**]

Treatment with the small molecule EG00229, a selective NRP1 antagonist, has been shown to reduce the efficiency of SARS-CoV-2 infection in vitro and ex vivo.

Moreover, the results showed that the percentage of cells showing viral presence (the presence of viral protein (SARS-N)) was significantly higher for those expressing both markers mediating viral invasion – ACE2 and neuropilin-1 (NRP1) than those expressing only one or none of the markers. [52]

## EPIDEMIOLOGICAL DATA FROM THE SHARED LINK OF COVID-19 AND HYPERGLYCEMIA

Several of the first studies since the onset of the disease have shown a link between the COVID-19 infection and the new onset of hyperglycemia in the course of the disease. Rubino and co-authors reported that during COVID-19 illness three forms of hyperglycemia were observed:

1. acute hyperglycemia without diabetes,
2. new-onset hyperglycemia non-insulin-dependent diabetes and
3. acutely occurring high-grade hyperglycemia with diabetic ketoacidosis, in pre-existing diabetes. [38]

A team of Bode et al reported stress elevation of blood glucose, defined as newly diagnosed hyperglycemia with normal glycated hemoglobin levels [(HbA1c)<6.5%], in 38% of hospitalized patients with COVID-19. [5]

In a study by Li et al, among 453 individuals with COVID-19, 94 (4.3%) individuals were reported to have newly diagnosed T2DM as evidenced by fasting blood glucose (FBG) ≥7mmol/l and HbA1c ≥6.5% , measured at the time of hospitalization. [20]

Montefusco and co-authors followed long-term disturbances of glucose homeostasis assessed as glucometabolic control, insulin resistance and β-cell function in patients with COVID-19 and found that among 551 hospitalized Italian patients with acute COVID-19, 46% were with new-onset hyperglycemia without a previous history of diabetes. [29]

## POTENTIAL MECHANISMS OF B-CELL INJURY

Different models of interaction between SARS-CoV-2 and islet β-cells have been proposed. SARS-CoV-2 is thought to be able to act on β-cells by three different mechanisms.[12]

1. Direct: virus entry through several viral receptors in β-cells and their subsequent damage as a result of direct acute viral damage or long-term persistent presence of uncleared SARS-CoV-2. In both scenarios, SARS-CoV-2 directly induces β-cell dysfunction, virus-induced cell death (necroptosis), or acts as an initiator of β-cell autoimmunity.
2. Indirect damage: SARS-CoV-2 infects neighboring pancreatic cells expressing viral receptors - such as ductal or endothelial cells and pericytes in the microvasculature, leading to their structural and functional transformation. Local inflammation is induced, release of cytokines and chemokines, and generation of a prodiabetic milieu that can act on neighboring uninfected β-cells in a paracrine manner and potentially lead to β-cell loss or β-cell dysfunction.
3. Systemic: SARS-CoV-2 attacks target cells expressing viral receptors in metabolic organs such as

liver, adipose tissue, and kidneys, causing impairment and/or loss of their metabolic, protective, and adaptive functions. Systemic subclinical or active inflammation occurs, followed by generation of inflammatory cytokines and accumulation of multiple prodiabetic metabolites, causing β-cell damage or new-onset insulin resistance and lipid metabolic dysregulation. [15]

There is still scant and conflicting evidence on the potential effects of the virus on β-cells. Most of the results are based on studies performed under in vitro conditions or on cell cultures of human pancreatic cells (ex vivo). Data based on in vivo studies have also been reported, which have their limitations due to existing methodological difficulties that affect the results. Some of them refer to the invasive way of obtaining pancreatic tissue /biopsy/, storage and processing of the samples and the difficult examination due to the tendency of pancreatic tissue to autolysis.

Yet in the past two years, a significant body of data has accumulated indicating that the virus leads to changes in β-cell function, induces increased levels of cellular stress and cell death, and β-cell dedifferentiation and transdifferentiation.

## SARS-COV-2 AND BETA-CELL DYSFUNCTION

To determine whether SARS-CoV-2 infection affects insulin production and secretion, Wu and colleagues quantified insulin content and Glucose stimulating Insulin Secretion (GSIS) as a functional test to assess insulin secretion from a pancreatic β-cell line of human pancreatic islets of Langerhans. They observed a dramatic decrease in insulin and GSIS content in SARS-CoV-2-infected humans compared to uninfected ones. What is interesting is that this effect was partially reversed by treatment with the NRP1 antagonist EG00229. [52]

Similar results were reported by Müller and colleagues, who also found a reduced magnitude of GSIS in infected islets, supporting the proposition that SARS-CoV-2 infection may affect glucose-dependent insulin secretion in pancreatic islets.[31]

A new publication presents evidence for β-cell dysfunction in vivo. The authors found reduced numbers of mature, insulin-containing granules and increased numbers of immature, proinsulin-containing granules in the β-cells of patients with COVID-19 and new-onset hyperglycemia. [4]

An interesting hypothesis has been proposed based on the results of studies in rodents (rats) which found that hypoxia impairs pancreatic β-cell function. The authors demonstrate that intermittent exposure to hypoxia leads to an imbalance between chlorine transporters (importers and exporters) on the β-cell membrane, with a predominance in the expression of chlorine exporters and in particular the KCC1-exporter. This in turn is followed by a decrease in intracellular chlorine (Cl-) concentrations and this imbalance in the homeostasis of chloride anions in the β-cell causes a decrease in insulin secretion due to an inability to depolarize the plasma membrane. [33]

Previous studies by other authors have also established that chloride ion homeostasis and its maintenance are essential for β-cell membrane depolarization, which in turn is important for adequate insulin secretion. The beta-cell membrane is depolarized by increasing the transport of chloride ions across the membrane, along with maintaining intracellular chloride concentrations within a certain range. [10;40]

The change in intracellular chlorine concentrations, due to altered transmembrane transport, also leads to a decrease in insulin secretion. This mechanism is proposed to function independently of the well-known Na+/K+/ATPase. [33;10]. A similar mechanism has not yet been demonstrated in humans, although expression of the chlorine exporter in human β-cells has been established. [18] Further studies are needed to elucidate the effects of chlorine transporters in SARS-CoV-2-infected human β-cells and to confirm or reject the above hypothesis.[33]

## SARS-COV-2 INDUCED B-CELL DEATH

The role of many viruses in the etiology of DM and in inducing β-cell apoptosis is known.

In type 1 diabetes mellitus (T1DM), virus-induced β-cell damage can result from either virus-induced cell death (necroptosis) or immune-mediated loss of the infected pancreatic β-cell mass. Previous reports of SARS-CoV-1/2-induced apoptosis in ACE2-expressing cell lines (A549 and Vero E6 cells) [11;21;57] suggested a similar mechanism of virus-mediated pancreatic β-cell death ex vivo.

A specific method was used for in situ detection of apoptosis - TUNEL (Terminal deoxynucleotidyl transferase dUTP nick-end labeling) among human islet cells infected with SARS-CoV-2. The TUNEL method allows detection of DNA fragmentation as a result of apoptosis under the action of endonucleases. [30] TUNEL-signal was found to be significantly increased in infected β-cells compared to uninfected ones.

Because SARS-CoV-2 has been shown to infect a small number of other cells, the authors next investigated

and confirmed that α-cells, the second largest population of cells in the islets of Langerhans, also underwent apoptosis, confirmed by increased TUNEL signal. This leads to the conclusion that virus-induced cell death (necroptosis) is not cell-type specific, although the percentage of β-cells undergoing apoptosis is greater due to their higher viral susceptibility.

Also, there is evidence that treatment with SARS-CoV-2 spike proteins (SARS-CoV-2-SP) is sufficient to induce apoptosis in β-cells, which was confirmed by an increase in TUNEL signal. [52]

Overall, these results support a model in which SARS-CoV-2 induces β-cell apoptosis and causes dysregulation in insulin production and secretion.[52]

Detailed study of the most subtle pathophysiological mechanisms proves the central role of regulatory kinases in the control of virus-induced apoptosis. Further studies established that binding of SARS-CoV-2 to its respective receptors is sufficient to trigger apoptosis-related signaling pathways independent of virus-induced additional cellular stress resulting from viral invasion and replication.

Through a large-scale phosphoproteome analysis, an increased up-regulation of some of the most important apoptotic kinaseswas found , among them - mitogen-activated protein kinases (MAPKs), including c-Jun-N-terminal kinase (JNK/p38 or also known as MAPK8/11) [49] and p21-activated kinases (PAK) [23], which are involved in the two classical pathways of apoptosis. Furthermore, multiple members of the protein kinase C (PKC) family show down-regulation in response to SARS-CoV-2 infection, suggesting an unlocking of virus-induced necroptosis because PKC is associated with cell survival. Subsequently, an increase in the activity of JNK and PAK was also observed in islet cells infected with SARS-CoV-2, confirming that the infection induces their activation. [52]

Recent studies provide data on in vitro and in vivo β-cell death in individuals with COVID-19. Elevated levels of unmethylated regions in insulin DNA have been found in the serum of patients with active COVID-19 infection, which are considered an indicator of β-cell death. Also, pancreatic islets incubated ex vivo with sera from these patients also showed signs of apoptosis and a drastic decrease in insulin secretion. [4]

## SUBCELLULAR CHANGES IN INFECTED BETA CELLS

Among SARS-CoV-2-infected beta cells, interesting changes indicative of cellular stress—dilation and vacuolization of the endoplasmic reticulum (ER) and Golgi apparatus—data for ER stress and swelling of the Golgi apparatus were observed. [31] β-cells are known to be vulnerable to ER stress due to increased insulin levels above normal synthesized in response to glucose stimulation. Changes were found in EP stress granules in terms of their intensity and number, which were increased in infected β-cells. Expression of genes related to cellular stress was also increased. [42]

Interesting transcriptional changes were also observed in infected islets and β-cells. Increased expression of multiple cytokines (TNF-α, IL-13, IL-1β and IL-6) and chemokines (CCL2, CXCL2, CXCL1, CCL4, CCL3, CXCL5, CCL8, IL1RN), activation of classical biochemical pathways [42], up-regulation of interferon (IFN)-stimulated genes as well as other genes associated with cellular stress [46], and also down-regulation of genes related to β-cell physiology. [31]

## SARS-COV-2 AS A CAUSE OF BETA-CELL TRANSDIFFERENTIATION

Another remarkable discovery was made by Tang and colleagues, who found that during infection with SARS-CoV-2, β-cells undergo a process of transdifferentiation. Among ex vivo infected β-cells, lower levels of insulin expression (β-cell marker) were observed, along with higher expression levels of glucagon and trypsin-1 (α-cell and acinar-cell marker, respectively). Moreover, the authors also reported increased expression of ALDH1A3, a marker of dedifferentiated human β-cells, among those infected ex vivo. This was subsequently confirmed in autopsy samples of COVID-19 positive subjects. Interestingly, no significant difference in insulin concentration was found among the corresponding receptor-expressing double-positive (+) ACE2+NRP1+ cells, ACE2+ NRP1-negative (-) cells, ACE2 negative-NRP1+ cells, and double-negative ACE2-NRP1- cells.

Using transcriptome (trajectory) analysis, the pathway regulating the transdifferentiation process was also identified, namely the signaling pathway of eukaryotic translation factor 2alpha (eIF2α), which is part of the so-called integrated cellular response to stress [Integrated stress response (ISR)]. [42]

Eukaryotic translation factor 2α is required for translation initiation and is regulated by a mechanism involving both guanine nucleotide exchange and phosphorylation.[1] Phosphorylation occurs in the α-subunit of eIF2 by a number of stress-activated serine kinases activated by various stimuli – amino acid deficiency (GCN2 kinase) [51], by EP stress (PERK-kinase) [44], double-stranded RNA - dsRNA (PKR-kinase) [48], or heavy metals (HRI-kinase). [26]

In the course of ex vivo infection with SARS-CoV-2, the levels of β-cell markers decrease, while the levels of α- and acinar cell markers increase, and the transcript levels of SARS-CoV-2 genes also increase. In parallel,

the levels of the two phosphorylated forms – PKR-kinase and eIF2a were found to be higher in SARS-CoV-2-infected β-cells than in uninfected ones. This, together with data on increased levels of cellular stress, confirms that the eIF2 pathway plays a causal role in β-cell transdifferentiation upon SARS-CoV-2 infection.

A pharmacological molecule was developed - Trans-ISRIB, which has been proven to block β-cell transdifferentiation during SARS-CoV-2 infection. Trans-ISRIB (Trans-Integrated stress response inhibitor) works by reversing the phosphorylation process and reducing the activation of eIF2a.

In Trans-ISRIB - treated infected β-cells, increased intracellular insulin concentration has been observed, among with decreased expression of α- and acinar cell markers, and decreased number and intensity of stress granules, as well as decreased expression of ALDHA3 [42]

## HYPERGLYCEMIA AND COVID – BIDIRECTIONAL RELATIONSHIP

A relationship has been established between hyperglycemia on admission [54] as well as between fluctuations in glucose levels during hospitalization [56] and disease severity, course and outcome.

An increased frequency of abnormal glucose and lipid metabolism has been reported among patients with COVID-19, including those without preexisting metabolic diseases. [15;8;29]

So far, whether SARS-CoV-2 is a diabetes-inducing or a diabetes-predisposing virus is still difficult to determine. The internal environment of the individual and his genetic predisposition to the development of DM are of essential importance for its risk manifestation.

What has been confirmed so far is that the processes taking place in the conditions of the COVID-19 infection are complex and mutually potentiating. On the other hand, the pathophysiological mechanisms underlying the new-onset hyperglycemia among patients with COVID-19 are diverse and in a large percentage of cases mutually complementary.

They maintain a constant continuum of progressive pancreatic β-cell damage caused by induced viral-toxic cytolysis or by hyperimmune inflammation induced by proinflammatory cytokines and/or autoimmunity. Gradually over time, β-cell dedifferentiation and transdifferentiation develop, with subsequent programmed cell death. [32]

## COVID-19 AND ACUTE PANCREATITIS

Another very well-accepted hypothesis for the potential diabetogenic effect of the virus is based on the fact that the virus, exhibiting organotropism, can also attack the pancreas, due to the increased expression of ACE2 by the islet capillaries. This leads to acute pancreatitis, due to virus-induced micro-occlusion in the capillaries of the islets of Langerhans, with subsequent ischaemia, necrosis and insulinopenia. [14]

Indeed, some observational studies have reported insulinitis, acute hyperglycemia, insulinopenia, decreased basal and stimulated C-peptide concentration in combination with negative antibodies, making this hypothesis highly probable.

Autopsy reports of patients with COVID-19 also describe acute-onset inflammation, necrosis, and hemorrhage in the pancreas, but primarily involving the exocrine part of the pancreas and partially the endocrine part. [22]

Qadir et al reported an association between pancreatic thrombofibrosis and new-onset DM in patients with COVID-19. Pancreatic sections of non-human primates infected with SARS-CoV-2 showed numerous microthrombi in small veins throughout the pancreas, increased fibrosis and the presence of endothelium, together with increased serum lipase enzyme levels compared to uninfected controls [35].

Remarkably, these primates developed diabetes in the time interval of 9-24 days after inoculation, suggesting that the long-term consequences of fibrotic/thrombotic pancreatitis may manifest themselves over a different time horizon. This finding in humans allows speculation that even mild micro-thrombo-fibrotic pancreatic changes could cause hyperglycemia due to incipient β-cell dysfunction, with a progressive course and, at a later stage, clinically apparent symptomatic postpancreatic diabetes mellitus in patients in convalescent stages of COVID-19.

Other observational studies have found elevated plasma levels of pancreatic enzymes (amylase and lipase) in up to 31% of patients with COVID-19, with autopsy evidence of pancreatic necrosis and hemorrhage in some patients. [14,15]

So far, there is still no clear answer as to whether COVID-19 with its effects on

pancreas induces insulin-dependent diabetes mellitus. [2]

However, as a general opinion of the authors, it is necessary to state that the reported cases of acute

pancreatitis in the course of COVID-19 are not so many to accept this etiological cause as the leading one. However, the possibility that changes in the pancreas cause DM at a later time period remains.

## COVID-19 AND NEW-ONSET TYPE 1 DM

On the other hand, there is the possibility of autoimmune-mediated damage to the pancreas. Reports from the first wave of COVID-19 infection in 2020 indicate increased incidence of new-onset GAD-65-positive TDT1 among children and adolescents after recovery from the infection. [24]

The positivity of anti-GAD-65 antibodies was observed at the earliest after the 30th day from the onset of the disease. An increased frequency of GAD-65 positive T1DM diagnosed several months after a relapse from COVID-19 was first reported in the UK [45] Soon after, a report from Romania also confirmed an increased frequency of new-onset T1DM. [47] According to the Centers for Disease Control and Prevention in the United States, the incidence of diabetes among individuals aged <18 years infected with COVID-19 compared with the group without COVID-19 was increased (HR = 2.66, 95% CI = 1, 98-3.56). [3] Cases of COVID-19-induced T1DM presenting with hyperglycemia, DKA, low C-peptide levels, and negative antibodies have also been reported. [16]

Based on data from other studies of an increased incidence of new onset hyperglycemia, in the acute phase of COVID-19, either early or late convalescent period, gives reason to assume that SARS-CoV-2 may be included in the group of so-called "diabetogenic" viruses.

## COVID-19 AND EMERGING INSULIN RESISTANCE

Insulin resistance (IR) is a condition in which there is a deficiency in the biological action of insulin in insulin-sensitive tissues - muscle, fatty and hepatic. In the conditions of IR, at the central level it cannot be suppressed hepatic gluconeogenesis, and peripherally impaired insulin-stimulated glucose uptake, which is due to a defect in the expression of the glucose transporters, GLUT-4, on the surface of smooth muscle cells and adipose tissue. Already in the first scientific reports related to COVID-19, hyperglycemia and hyperinsulinemia were reported, with elevated insulin indices taken as markers of IR.

Montefusco et al. reported hyperinsulinemia evidenced by high C-peptide levels in COVID-positive patients. [29,26,52]

In the context of COVID-19 infection, β-cell injury and IR have been associated with RAAS dysfunction. Depletion of the viral receptor ACE2, impairs the balance between ACE-2 and ACE with a preponderance of ACE, angiotensin II and aldosterone and their effects become predominant. RAAS hyperactivity potentiates hypoxia, islet oxidative stress, changes in islet blood flow and subsequent β-cell damage, and aldosterone-induced hypokalemia contribute to IR.

Although the exact mechanisms of the onset of IR in COVID-19 are still not fully elucidated, the existence of a complex of mechanisms is assumed, associated with viral-toxic damage to all insulin-sensitive tissues.

Through metabolomic analysis, a team of He and collaborators demonstrate changes in metabolic factors that modulate both glucose and lipid levels metabolism, in the conditions of Corona virus inflammation. They found increased levels of metalloproteinases and decreased levels of the organokines apelin and myostatin in SARS-CoV-2 infection, which is potentially related to the onset of insulin resistance. [15]

MPO could induce insulin resistance in adipocytes, pre-adipocytes and myocytes, while the action of apelin and myostatin is expressed in improving insulin sensitivity in adipocytes and preadipocytes.

Their concept is that viral infection increases the expression of a specific transcription factor, RE1-silencing transcription factor (REST), which in physiological conditions transcriptionally regulates the above three metabolic factors, and in conditions of COVID-19 infection alters glucose and lipid metabolism, causing metabolic dysregulation with subsequent hyperglycemia, insulin resistance, and hypertriglyceridemia.

Moreover, they found new-onset hyperglycemia, IR, and dysregulation in lipid metabolism, among patients with no prior abnormalities in lipid metabolism.

The authors observed significant changes in serum lipids that were present in both the acute and convalescent phases of non-severely ill and severely ill patients with COVID-19. Some lipids (5 NETE, 12 NETE and 14 (S) HDHA, propionic, isobutyric acid) even show significant correlations with metabolic parameters (HOMA-IR, HDL-C, plasma glucose, triglycerides), which could serve as potential biomarkers for dysregulation in lipid metabolism in COVID-19. [15]

Obesity and ectopic deposition of visceral adipose tissue is a major pathophysiological circuit for the occurrence of IR and altered adipocyte metabolism. Processes of increased production of hormonally active substances, adipokines, inflammatory cytokines and free fatty acids take place in adipocytes of adipose tissue. As a result of their unfavorable complex interaction, a constant low-grade inflammation is

maintained, which alone or in complex with numerous adipokines, myokines and others organokines, triggers and deepens IR.

Not surprisingly, in individuals with active infection, the SARS-CoV-2 genome was identified only in mature secretory active adipocytes but not in functionally inactive preadipocytes.

Adipokines, the hormones of adipose tissue, are the determinant of the onset of IR and in COVID-induced inflammation. A key regulator of metabolic homeostasis is leptin. Leptin resistance in obesity impairs glucose and lipid regulation with complex effects on overall metabolism.

Increased expression of ACE2 in adipocytes contributes to increased production of leptin and decreased production of adiponectin, which is well known to improve insulin sensitivity. SARS-CoV-2-induced insulin and leptin resistance and associated hyperglycemia and hyperlipidemia. Together they activate the nuclear factor kappa beta (NF-κB) inflammatory pathway and trigger a cascade of proinflammatory reactions involving interleukin-1β (IL)-1β, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), etc. [37]

In abdominal adipose tissue, IL-6 stimulates neutrophil production, hyperactivates proinflammatory CD4+Th1 lymphocyte subpopulation cells, and suppresses differentiation of immunosuppressive regulatory cells (T regs), thereby contributing to cytokine storms. [43]

In adipose tissue, in addition to adipocytes, immune cells are also found - mainly macrophages (normally up to 10% of the cell composition). Their number significantly increases with obesity (up to 40%), and the so-called a phenotypic switch between anti-inflammatory (M2-) and pro-inflammatory (M1-) macrophages, leading to a predominance of the pro-inflammatory M1-phenotype, with all the ensuing consequences. [13;55]

Changes in the metabolic profile of T-lymphocyte subpopulations have been observed in individuals with obesity and SARS-CoV-2 induced infection, which also contribute to changes in the adaptive immune response, amplifying the magnitude of immune inflammation, sustaining progressively increasing IR and the gradual decline of β-cell function [28]

Adiposity-associated metabolically active adipocytokines progressively reduce insulin sensitivity in metabolically active tissues and exacerbate the effects of immune inflammation. Chronic exposure to IL-6 reduces insulin sensitivity and induces hepatic IR in obese and COVID patients, which may lead to new-onset hyperglycemia with a permanent course. [39]

Chronic immune dysregulation, persistent subclinical inflammation in adipose tissue, increased dysregulated adipokines and proinflammatory cytokines influence the fluctuation of insulin levels and contribute to the occurrence of IR and stress-induced hyperglycemia in pre-sickened COVID-19 patients.

## IMPACT OF THE COVID-19 SECRETOME ON BETA CELL FUNCTION

Recent evidence suggests that the COVID-19 secretome may alter β-cell function and survival. Human pancreatic cells have been found to express multiple cytokine receptors, including receptors for TNF-α, the interleukins (IL) IL-13, IL-1β, and IL-6. [3]

Montefusco et al. determine the specificity of the cytokine profile (secretome), characteristic of SARS-CoV-2 induced inflammatory status and found that certain cytokines and other secreted proteins are significantly increased (IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, G-CSF, MIP-1β and TNF-α) and they definitely contribute to the occurrence of hyperglycemia, disturbances in insulin signaling and β-cell function [29]

The demonstrated hyperglycemia, insulin resistance, and β-cell hyperstimulation is a result of the SARS-CoV-2-associated secretome, which induces an inflammatory state similar to that which induces insulin resistance and β-cell dysfunction in DMT2.

The authors suggest that it is the high levels of IL-1β and IL-6 in patients with COVID-19 that play a crucial role in β-cell dysfunction, which may be permanent, as the altered secretome persists. Interestingly, cytokine damage to pancreatic β-cells can be reversed after treatment with specific antibodies targeting the respective interleukins (anti-IL-1β and anti-IL-6), opening a new therapeutic horizon. [3]

Last but not least, the cause of hyperglycemia and hyperinsulinemia in COVID-19 is the effects of certain medications, such as the antiviral lopinavir-ritonavir or glucocorticoids, which cause drug-induced hyperglycemia and hyperinsulinemia, but which are not the subject of this presentation.

The big challenge – figuring out the mechanism for the onset of diabetes remains.

Despite the accumulated data to date, it is still difficult to elucidate the mechanism of new onset diabetes. The underlying processes cannot be fully covered by a single clinical, immunological, genetic or biomolecular test. Therefore, experimental studies must encompass this complexity as a whole to help unravel the

mechanisms underlying new-onset diabetes.

Great hope is placed on the data obtained from the so-called omic systems, including the study of the genome, epigenome, transcriptome, proteome, metabolome, lipidome and microbiome, which are of high fidelity and can contribute to a better understanding of the biomolecular processes related to the onset of diabetes and its progression.

Currently, three clinical trials are underway to monitor and analyze patients with COVID-19 regarding the onset of DM.

## CONCLUSION

Many hypothetical scenarios are possible for the occurrence of DM associated with SARS-CoV-2, which involve a combination of different pathological processes such as β-cell stress, programmed cell death, hyperimmune inflammation, central and/or peripheral insulin resistance. So far, the most advanced hypothesis is that of virus-induced β-cell damage and the indirect consequences of hypoxia and immune inflammation, but to be accepted, convincing evidence from more numerous histological analyzes of direct viral toxicity needs to be provided. The fundamental role of SARS-CoV-2 in the induction of DM is much more complex and not limited to whether pancreatic β-cells express ACE2 and whether β-cell destruction triggers autoimmunity. Of importance are individual metabolic changes, obesity, IR and subclinical inflammation in abdominal adipose tissue with their synergistic effects of pancreatic gluco- and lipotoxicity, β-cell stress and progressive insulin dysregulation. In-depth study of this virus-metabolite pathophysiological relationship will contribute to a better understanding of the molecular and pathogenetic mechanisms associated with the onset of DM after recovery from COVID-19 infection.

## CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

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