Review Article DOI: http://doi.org/10.4038/sjdem.v12i1.7449

New-onset diabetes in COVID-19: A literature review

Nugroho N.P [1,4], Novida H [2,4], Hapsari S.P [3]

[1] Department of Pulmonology & Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Indonesia
[2] Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Indonesia
[3] Emergency Department, Simpang Lima Gumul Hospital, Kediri, Indonesia
[4] Dr Soetomo General Teaching Hospital, Indonesia

Abstract

COVID-19 has become a major global health problem. COVID-19 teaches us many things, one of which is the relationship between COVID-19 and diabetes. Recent evidence suggests that the coronavirus may cause diabetes. In addition, the term new-onset diabetes in COVID-19 was introduced in 2020, and evidence has been reported. It poses a new challenge to the clinical management of COVID-19 patients. The pathophysiology of this disease is still not fully known. However, hypotheses have been proposed. Therefore, we write this literature review to add insight into new-on set diabetes in COVID-19 patients.

Keywords: ACE-2, COVID-19, Insulin resistance, New-onset diabetes, SARS-CoV-2

Correspondence email: mazpraz.keren@gmail.com

https://orcid.org/0000-0003-2197-355X

Introduction

At the end of 2019, the world was shocked by a new type of coronavirus that causes pneumonia in Wuhan Province, China. The virus is known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) named the disease caused by SARS-CoV-2 as a Coronavirus Disease-19 (COVID-19) and designated it as a global pandemic on March 11, 2020 (1).

The primary receptor for this virus in the human body is the Angiotensin-Converting Enzyme-2 (ACE-2) receptor. More than 150 human body cells are reported to express ACE-2, including organs with endocrine functions such as the hypothalamus, thyroid, gonads, and pancreatic islet cells (2,3). In COVID-19 patients, it is reported that blood sugar dysregulation can occur even in patients who do not have a history of diabetes. The ACE-2 receptor on the pancreas may cause SARS-CoV-2 to bind directly(4). In addition, the cytokine storm and hyper inflammation that occur in COVID-19 patients can also cause insulin resistance (5).

COVID-19 teaches us many things, one of which is the relationship between COVID-19 and diabetes. Recent evidence suggests that the coronavirus may cause new-onset diabetes (6). Rubino introduced the term new-onset diabetes in COVID-19 in 2020 (7). Several case reports of new-onset diabetes in COVID-19 patients have also been reported (Table 1). This condition poses new challenges to the clinical management of COVID-19 patients. The pathophysiology of new-onset diabetes in COVID-19 patients is still not fully understood. However, hypotheses have been developed. Therefore, we write this literature review to gain insight and open up the curiosity of doctors and health workers about the incidence of new-onset diabetes in COVID-19 patients.

Epidemiology of new-onset diabetes in covid-19

Currently, the prevalence of new-onset diabetes in COVID-19 is not fully known. 47% of the 4102 COVID-19 patients hospitalized in the US had hyperglycemia (8). In Italy, during the pandemic, 23% of new cases of type 1 diabetes were reported in children. A 2-fold increase in ketoacidosis diabetic (KAD) incidence in children and adults was reported in Germany. A study in the UK reported 30 incidences of new diabetes in COVID-19, where 70% of them had KAD, and 52% had severe KAD with a pH of 6.82-7.05 (9). Another study in China reported that out of 39 COVID-19 patients in hospitals with no history of diabetes, 20 of them developed diabetes when they were hospitalized (10).

There have been several published case reports of new-onset diabetes in COVID-19 (Table 1). In Germany, a young man developed type 1 diabetes after a history of being infected with SARS-CoV-2 a few weeks earlier. The C-peptide level was low in this patient, negative diabetes-typical autoantibody values, and positive human leukocyte antigen (HLA) results (11). A case series in the United States reported new-onset diabetes in 3 adult patients infected with SARS-CoV-2, of which 2 had the infection a few weeks earlier (12). In addition, in the United States, a Hispanic woman experienced an episode of KAD when diagnosed with COVID-19. The patient had decreased levels of C-peptide and positive insulin antibodies (13). In China, it was also reported that a man with COVID-19 without a history of diabetes had KAD and many other case reports (14). We summarize case reports of adult patients with new-onset diabetes in COVID-19 in table 1.

Pathophysiology of new-onset diabetes in covid-19

The pathophysiology of developing new-onset diabetes in COVID-19 is still not fully known. New-onset diabetes in COVID-19 can occur due to 2 main mechanisms: damage to pancreatic beta cells or insulin resistance. Hypotheses about the pathophysiology of this disease have been proposed, including impaired function of the renin-angiotensin-aldosterone system (RAAS), a direct viral infection of beta cells, auto-immunity, and increased insulin resistance due to cytokine storms. (8).

ACE-2 dysfunction and RAAS hyperactivity

The renin-angiotensin-aldosterone system (RAAS) is a critical pathophysiological pathway of COVID-19. Renin causes angiotensinogen change to the angiotensin-I. Furthermore, angiotensin-I will be converted into angiotensin-II by the ACE enzyme. Angiotensin-II will signal to its receptors, namely AT1R and AT2R. Activation of AT1R will increase inflammation, proliferation, fibrotic, and vasoconstrictive cytokines through activation of NF-kB, NADH/NADPH oxidase, and toll-like receptor 4 (TLR-4). ACE-2, a homolog of ACE, acts to break down Angiotensin-II into Ang 1-7, which has an anti-inflammatory effect by binding and activating the G-protein coupled Mas receptor. ACE-2 regulates blood pressure, reduces oxidative stress, and decreases insulin resistance through GLUT4 activation (5).

ACE-2 in the pancreas plays a vital role in regulating sugar and beta-cell function. RAAS activated locally can cause oxidative stress in the pancreas. Therefore the presence of ACE-2 / Angiotensin 1-7 can counteract the effects of RAAS on the pancreas (20). Decreased action of ACE-2 is caused by the competition with SARS-CoV-2 on binding the ACE-2 receptor. ACE-2 dysfunction will increase several pro-inflammatory cytokines such as IL-1B, IL-4, IL-10, monocyte chemoattractant protein-1 (MCP-1), interferon-gamma, and IFP-10. These cytokine storms will cause a hyper coagulopathy response and endothelial damage in all body including pancreatic vessels (5). Combining oxidative stress, hypercoagulopathy, and inflammation in the pancreas will make apoptosis, reduce blood flow in islet cells, and reduce insulin secretion (21).

Direct damage of pancreatic beta cells due to virus

ACE-2 is widely expressed in all eukaryotic cell membranes, including pancreatic beta islet cells (22). RNA sequence examination also showed that human ACE-2 expression was present in endocrine and exocrine islet cells (23). However, ACE-2 expression was higher in endocrine than exocrine tissue (22). Like its predecessor, SARS-CoV, the SARS-CoV-2 virus can also bind to the ACE-2 receptor in the pancreas (23). This binding will cause cytolytic damage in pancreatic beta cells and cause decreased beta-cell function. The process is similar to the pathophysiology of insulin-dependent diabetes in the absence of autoimmune antibodies (11).

Previous research has shown a strong link between hyperglycemia and the severity of COVID-19. Recent studies have shown that glycosylation of the ACE-2receptor in humans substantially contributes to SARS-CoV-2 binding. The study of the

Table 1 : Case reports of new-onset diabetes in COVID-19 patient

Citation	Gender/Age	COVID Status	HbA1c	C-Peptide	Insulin antibody	HOMA-IR/B	Outcome
Omotosho et al., 2021 (13)	F/45 YO.	PCR positive	13,7%	0,49 ng/mL	GAD dan IA2A positive	N/A	Discharged with insulin
Hollstein et al., 2020 (11)	M/19 YO.	IgG positive. IgM negative	16,8%	0,62 ng/mL	HLA positive GAD, IA2A, ZnT8 negative	N/A	Discharged and treated as insulin-dependent diabetes
Otair et al., 2020 (15)	M/48 YO.	PCR positive	6,2%	0,5 ng/mL	N/A	N/A	Discharged on the 16th day with Gliclazide, Metformin, and Linagliptin
Eskandarani and Sawan, 2020 (16)	M/36 YO.	PCR positive	14,9%	N/A	N/A	N/A	Discharged with insulin on the 13th day
Rabizadeh et al., 2020 (1)	M/16 YO.	PCR positive	12,9%	0,25 ng/mL	N/A	N/A	Discharged with basal-bolus insulin
Marwa Saleem, Tasneem Zahra, Vidya Menon, Julia Vargas-Jerez, 2021 (17)	Case series of 5 M /patients with median age 54YO.	IgG positive	Median 11,5%	N/A	GAD and IA2A has been examined in 2 patient, and the result was negative	N/A	3 patients were treated with insulin and improved(HbA1C 7.1% s 2nd month), (5.85% 4th month).1 patient lost-to-follow-up patient improved 2nd-month (11.4% to 5.4%)
Suwanwongse and Shabarek, 2021 (12)	1. M/18 YO.	PCR positive	10,4%	N/A	GAD, IA2A, ICA, anti-CCP negative	N/A	Discharged with subcutaneous insulin and metformin
	2. M/51 YO.	2 months post PCR was positive	12,4%	N/A	N/A	N/A	Discharged with subcutaneous insulin
	3. F/64 YO.	10 weeks post PCR was positive	N/A	N/A	N/A	N/A	Discharged with metformin
Marchand, Pecquet and Luyton, 2020 (18)	F/29 YO.	1 month post PCR was positive	11.8%	0,07 ng/mL	GAD positive IA2A dan ZnT8A negative	N/A	N/A
Al-naami et al., 2020 (19)	M/46 YO.	PCR positive	10,1%	N/A	N/A	N/A	Died on day five due to complications of ARDS

structure and function of the virus also showed that the S protein from SARS-CoV-2 was highly glycosylated, which allow protein S to bind to ACE-2 and alter the immune response to the virus (20).

Virus-induced autoimmunity in beta cells

SARS-CoV-2 may also trigger autoimmunity and autoinflammatory mechanisms in the pancreas. Autoimmune mechanisms due to viral infection are molecular mimicry and bystander mechanisms (24). Molecular mimicry makes beta cells easily recognized by CD8+ T cells. T cells will be activated due to exposure to the virus presented by antigen-presenting cells (APC). Some viruses, such as Coxsackievirus B (CVB), have the P2-C protein similar to glutamic acid decarboxylase (GAD), a protein excreted by islet cells. The formed memory cells will mistake GAD as an antigen because the structure is similar to a viral protein, resulting in autoimmune and auto-inflammatory mechanisms that cause islet cell damage (25).

Another mechanism is the bystander, where pro-inflammatory mediators play an essential role. The antigen from the virus will be bound by APC to be presented and activate autoreactive T cells (24). APC will increase the release of the inflammatory mediator, and it maintains immune response in islet cells. Thus, the activation of autoreactive T cells will cause inflammation and the appearance of islet antigens (25).

Insulin resistance in COVID-19

The excess increase in inflammatory mediators in COVID-19 can contribute to insulin resistance and increase the patient's blood glucose levels. In cytokine storms, the accumulation of innate immune cells in the tissue will cause the release of inflammatory mediators, especially IL-1β and TNF-α. In addition, inflammation also causes an increase in cytokines such as Jun kinase (JNK), kappa B kinase β inhibitor (IKKβ), and nuclear factor-ϰB (NF-ϰB). These cytokines directly suppress insulin action by phosphorylation of serine from insulin receptor substrates 1 and 2 (IRS-1 and IRS-2). Then there will be interference with tyrosine phosphorylation activation of IRS-1 and IRS-2 for degradation (23).

In addition, in COVID-19, there may also be a stress response at the cellular level by an integrated stress response (ISR). ISR is influenced by various factors such as hypoxia, viral infection, and intrinsic factor. As a result, several kinases will be activated, such as the PKR family-like ER kinase (PEKR) and double-stranded RNA-dependent protein kinase (PKR). PEKR and PKR will interfere with insulin receptor signalling pathways through elF2a serine phosphorylation. Typically there will be a response to serine dephosphorylation, which normalizes the synthesis of PKR gs2. However, if this response does not work, then the phosphorylation of the receptors still occurs, thus inhibiting the action of insulin. Specifically, in COVID-19, viral RNA can activate PKR, which induces serine phosphorylation on IRS-1 and leads to insulin resistance. Furthermore, cytokine storms can also activate kinases via the Angiotensin-II and cortisol pathways (21).

Insulin resistance in adipose tissue

Beta-cell function and insulin sensitivity depend on stimuli between endocrine tissues. In the last few decades, adipose tissue has been known to act as a significant endocrine stimulus on beta cells and insulin receptors. In experiments with mice infected with SARS-CoV-2, the viral RNA was found in adipose tissue. It shows that adipose tissue can be a site of infection and virus replication (8). Adipose tissue secretes proteins called adipokines. In patients with severe COVID-19, serum adipokine levels decreased by 50-60% compared to patients without severe symptoms. Adipokines function as antidiabetic, anti-inflammatory, and anti-atherogenic. Adipsin is an adipokine derivative, and leptin is an adipokine regulator. The adipsin-leptin ratio is known to decrease in COVID-19 patients (21).

Insulin resistance in adipose tissue causes macrophage infiltration and increased inflammatory status. This mechanism occurs through AKT activation by a protein kinase complex called m-TORC2, which plays an essential role as an insulin mediator in glucose metabolism. An important gene that m-TORC2 in adipose tissue suppresses is monocyte chemoattractant protein-1 (MCP-1). Loss of suppression in MCP-1 will cause macrophages to attract the adipose tissue and cause inflammation and adipose damage (21).

Ketoacidosis diabetic in COVID-19

COVID-19 infection can cause stress-induced hyperglycemia. This hyperglycemia is usually temporary and resolved when the critical condition is improved.However, in some COVID-19 patients, hyperglycemia still occurs after a critical condition has been treated. In addition, some patients continue to experiencehyperglycemia even without steroid therapy (8). The increased KAD incidence in type 2

diabetes mellitus with COVID-19 may be related to the damage of pancreatic islet cells and the change in glucagon and insulin ratio (26). Beta-cell damage may also result from cytokine storms that cause thrombosis throughout the body, including the pancreas.

The recent hypothesis states that pro-inflammatory cytokines, especially IL-6, may manifest maladaptive immune responses (27). IL-6 level is also increased in patients with KAD and is suspected to be one of the causes of ketosis. IL-6 as a leader of inflammation, will suppress insulin synthesis and increase counter-insulin hormones activity such as glucagon, growth hormone, and catecholamine. It will cause a degradation of free fatty acids to ketone bodies, gluconeogenesis, and acidosis that lead to KAD (28). Many COVID-19 patients present with a catabolic status, ketosis, and a compensatory reduction in metabolic acidosis. Patients are often in low intake and dehydration, causing volume deficiency and electrolyte disturbances (26).

According to Rubino et al., SARS-CoV-2 causes ketoacidosis by binding to ACE-2 receptors in pancreatic beta cells and adipose tissue. In addition, autoimmune disorders caused by SARS-CoV-2 can damage pancreatic cells and mimic the pathogenesis of insulin-dependent diabetes. However, elevated HbA1C and risk factors for diabetes in some patients may indicate that newly diagnosed diabetes results from COVID-19 uncover existing diabetes. However, the unusually high incidence of KAD in type 2 diabetes raises the suspicion of pancreatic cell damage due to SARS-CoV-2. Therefore, more research is needed to investigate the causal relationship between DM, KAD, and COVID-19 (12).

Diagnosis of new-onset diabetes in covid-19

There has been no definite diagnosis of new-onset diabetes in COVID-19. New-onset diabetes is usually found incidentally while a patient is being treated for COVID-19. Patients with new-onset diabetes also experience clinical symptoms of diabetes such as 4T, namely toilets, thirsty, tiredness, and thinners. Examination of blood glucose, urine glucose and urine ketones should also be done (29).

The main processes in the pathophysiology of new-onset diabetes mellitus are insulin resistance and beta-cell dysfunction. Several examinations can assess both processes, such as the homoeostasis model of assessment (HOMA). HOMA-IR serves to assess insulin resistance and HOMA-B to assess beta-cell dysfunction. The standard value of HOMA-IR is less than two, and the standard value of HOMA-B is more than 107 (30). Therefore, both must be examined simultaneously to determine the location of the abnormality. An increase in HOMA-B often compensates for an increase in HOMA-IR, and a decrease in HOMA-B can sometimes occur due to an improvement in insulin resistance (31).

An important role is examining C-peptide, an insulin peptide residue that connects the A-chain of insulin to the B-chain of insulin. The amount of C-peptide is proportional to the insulin produced by pancreatic beta cells. Therefore, the C-peptide value will not be affected by exogenous insulin administration. In two case reports of COVID-19 patients with new-onset diabetes with a beta cell damage phenotype, C-peptide levels were decreased indicates that there is damage to the beta cells of the pancreas (11). Meanwhile, increased C-Peptide values accompanied by hyperglycemia in COVID-19 patients indicates insulin resistance (8).

Another essential test following the proposed new-onset diabetes pathogenesis in COVID-19 and excludes the diagnosis of type 1 diabetes or LADA is autoantibody testing. Autoimmune antibodies associated with type 1 diabetes include GAD-65, islet cell antibodies (ICA), insulinoma-associated antigen (IA-2A), and insulin antibodies (IAA). GAD-65 and ICA are common in latent autoimmune diabetes in adults (LADA), whereas IA-2A and IAA are more common in children with type 1 diabetes and less common in adult-onset type 1 diabetes. Recently, antibodies to zinc transporter-8 were significantly associated with the onset of type 1 diabetes and may be positive when other antibodies are negative (32).

Diagnosis of new-onset diabetes in COVID-19 should still follow the guidelines for the diagnosis of diabetes by the American Diabetes Association (ADA). The criteria of diabetes are fasting blood sugar levels (GDP) ≥126 mg/dL or blood sugar levels after an oral glucose tolerance test ≥200 mg/dL or HbA1C levels ≥6.5%, or patients with classic symptoms of diabetes with random blood sugar ≥ 200 mg/dL (33).

Management of new-onset diabetes in covid-19

COVID-19 patients with diabetes problems are complex patients, so patient management must be carried out as well as possible (26). The principles of managing new-onset diabetes in COVID-19 are the same as diabetes in general. Classifying the new-onset diabetes phenotype resulting from beta-cell damage

insulin resistance in COVID-19 patients through testing for C-peptides, HOMA-B, HOMA-IR, and insulin antibodies can help determine the therapy for patients. In patients with newly onset diabetes on COVID-19 with an insulin resistance phenotype, administration of drugs that can increase insulin sensitivity may have benefits, such as metformin or thiazolidinedione. Conversely, the primary therapy uses insulin in patients with new-onset diabetes on COVID-19 who have a beta cell damage phenotype. Avoid drugs that increase insulin sensitivity because of their potential side effects (8).

Several diabetes medications benefit COVID-19, such as insulin and DPP-4 inhibitor. In addition to having a role in controlling glucose, insulin also acts as an anti-inflammatory in critical illnesses. Insulin receptor signalling plays a vital role in T cell function during inflammation. Glucagon-like peptide-1 (GLP-1) receptor agonists reduce inflammation in diabetes and obesity, but the use of COVID-19 should be used with caution. The therapeutic effect of GLP-1 agonists is to reduce food intake and body weight which can negatively affect COVID-19 patients (20,34).

Table 2 : The recommendation of diabetes drugs in COVID-19 [38]

Metformin	Not recommended for patients with severe symptoms, gastrointestinal disturbances or hypoxia. It can be continued on an outpatient basis if there are no complaints
Sulfonylurea	It can be continued on an outpatient basis if symptoms are mild. Risk of hypoglycaemia if food intake is not good or in combination with hydroxychloroquine.
Alpha-glucosidase inhibitors	It can be used to control blood sugar after eating. However, it is not recommended in patients with a severe degree or gastrointestinal symptoms.
Thiazolidinedione (TZD)	It can be used during treatment with glucocorticoids on an outpatient basis. Risk of fluid retention and not recommended in hemodynamic compromise.
DPP-4i	It can be continued if symptoms are mild
SGLT-2i	Not recommended for COVID-19 patients with moderate to severe symptoms due to the risk of dehydration and ketosis
GLP-1 RA	Continue on an outpatient basis with no gastrointestinal symptoms.
Insulin	Generally used in hospitalization with moderate to severe symptoms. Beware of hypoglycemia

DPP-4 inhibitor may improve outcomes in COVID-19 and type 2 diabetes. DPP-4 inhibitor is a relatively new drug on type 2 diabetes treatment as FDA first approved it in 2006 (34). DPP-4 has a role in the entry of SARS-CoV and MERS-CoV and may have a protective effect on COVID-19. DPP-4 has been suggested to excess the inflammatory responses in various diseases by promoting CD86 expression, NF-$\varkappa$B, and pro-inflammation cytokines. DPP-4 inhibitor, Sitagliptin, has proven efficacy in ARDS by inhibiting IL-6, IL-1, and TNF in lung injury (35).The benefit of DPP-4 inhibitor in COVID-19 has blocked virus entry, reduced cytokine storm, and improved glucose control and cardiorenal effects (36). DPP-4 inhibitor is associated with lower mortality in COVID-19 (37).

The management of new-onset diabetes in COVID-19 is the same as common diabetes, depending on its phenotype (type 1 or type 2). The recommendation of diabetes drugs in COVID-19 are summarized in table 2.

Conclusion

New-onset diabetes in COVID-19 patients poses new challenges to the clinical management of patients. Diagnosis of diabetes follows the guidelines of the American Diabetes Association (ADA). Determining the diabetes phenotype

resulting from beta-cell damage or insulin resistance in COVID-19 patients through testing for C-peptides, HOMA-B, HOMA-IR, and insulin antibodies can help patient management. The use of an antidiabetic drug such as DPP-4 inhibitors may benefit COVID-19. However, it is still unknown whether new-onset diabetes is temporary or permanent. Until this literature review was done, the international diabetes research group was still collecting data in a CoviDIAB registry for new-onset diabetes in COVID-19.

References

1. Rabizadeh S, Hajmiri M, Rajab A, Kouchak HE, Nakhjavani M. Severe diabetic ketoacidosis and coronavirus disease 2019 (COVID-19) infection in a teenage patient with newly diagnosed diabetes. *J Pediatr Endocrinol Metab* 2020;**33**(9):1241–1243. https://doi.org/10.1515/jpem-2020-0296 PMid:32809963

2. Atkinson MA, Powers AC. Distinguishing the real from the hyperglycaemia: does COVID-19 induce diabetes? *Lancet Diabetes Endocrinol [Internet]* 2021;**9**(6):328–329. Available from: http://dx.doi.org/10.1016/S2213-8587(21)00087-5

3. Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine Significance of SARS-CoV-2's Reliance on ACE2. *Endocrinol (United States)* 2020;**161**(9):1–7.https://doi.org/10.1210/endocr/bqaa108 PMid:32652001 PMCid:PMC74544994.

4. Ilias I, Diamantopoulos A, Pratikaki M, et al. Glycemia, beta-cell function and sensitivity to insulin in mildly to critically ill covid-19 patients. *Med* 2021;**57**(1):1-6.https://doi.org/10.3390/medicina57010068 PMid:33466617 PMCid:PMC7828687

5. Sonja A. Rasmussen, MD, MS JCS. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. *Ann Oncol* 2020;(January):19–21.

6. Balasubramanyam M. Does COVID-19 Warn Us to Revisit Virus-Induced Diabetes? *Explor Res Hypothesis Med* 2020;000(000):1–5. https://doi.org/10.14218/ERHM.2020.00046

7. Rubino F, Amiel SA, Zimmet P, et al. New-Onset Diabetes in Covid-19. *N Engl J Med* 2020;**383**(8):789–790. https://doi.org/10.1056/NEJMc2018688 PMid:32530585 PMCid:PMC7304415

8. Reiterer M, Rajan M, Gómez-Banoy N, et al. Hyperglycemia in Acute COVID-19 is Characterized by Adipose Tissue Dysfunction and Insulin Resistance. *medRxiv [Internet]* 2021;2021.03.21.21254072. Available from: http://medrxiv.org/content/early/2021/03/26/2021.03.21.21254072.abstract

9. Kusuma S, Aurangabadkar G, Sha M. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company' s public news and information . 2020;(January).

10. Sadera R, Youssef J, Ramadan A, Ahmed MH. What are the changes and burden associated with covid-19 in diabetes management and delivery of the diabetes services? *J Endocrinol Metab* 2020;**10**(6):155–161. https://doi.org/10.14740/jem699

11. Hollstein T, Schulte DM, Schulz J, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. *Nat Metab [Internet]* 2020;**2**(10):1021–1024. Available from:http://dx.doi.org/10.1038/s42255-020-00281-8 Available from: https://doi.org/10.1038/s42255-020-00281-8 PMid:32879473

12. Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: Causality or coincidence? A report of three cases. *J Med Virol [Internet]* 2021;**93**(2):1150–1153. Available from: http://dx.doi.org/10.1002/jmv.26339 Available from: https://doi.org/10.1002/jmv.26339 PMid:32706395 PMCid:PMC7404645

13. Omotosho YB, Ying GW, Stolar M, Mallari AJP. COVID-19-Induced Diabetic Ketoacidosis in an Adult with Latent Autoimmune Diabetes. *Cureus* 2021;**13**(1):10–13. https://doi.org/10.7759/cureus.12690

14. Jie Y, Jia S, Ng H, Yeoh E. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company' s public news and information . 2020; (January).

15. Otair HA Al, Sheshah E, Zuhair B, Shirah A, Jammah A. Diabetic Ketoacidosis and New Onset Diabetes Mellitus Precipitated by COVID-19 Infection. 2020;**11**(3):69–71.

16. Eskandarani RM, Sawan S. Diabetic Ketoacidosis on Hospitalization with COVID-19 in a Previously Nondiabetic Patient: A Review of Pathophysiology. *Clin Med Insights Endocrinol Diabetes* 2020;**13**:0–5. https://doi.org/10.1177/1179551420984125 PMid:33488135 PMCid:PMC7768872

17. Marwa Saleem, Tasneem Zahra, Vidya Menon, Julia Vargas-Jerez AS. Covid-19 and New Onset Diabetes: A Case Series. *J Endocr Soc [Internet]* 2021;Supplement. Available from: https://academic.oup.com/jes/article-abstract/4/Supplement_1/SUN-047/5832719 Available from: https://academic.oup.com/jes/article-abstract/4/Supplement_1/SUN-047/5832719 https://doi.org/10.1210/jendso/bvab048.690 PMCid:PMC8135410

18. Marchand L, Pecquet M, Luyton C. Type 1 diabetes onset triggered by COVID-19. 2020;19–22.

19. Al-naami AQ, Khan LA, Zaidan FI, et al. Hyperglycemic Hyperosmolar State (HHS) with New-onset Diabetes Mellitus in a Patient with SARS CoV-2 Infection . 2020;2:5–8. Available from https://doi.org/10.21203/rs.3.rs-38116/v1

20. Liao Y, Zheng J, Zheng C, Lu K. Novel Molecular Evidence Related to COVID-19 in Patients with Diabetes Mellitus. 2020; https://doi.org/10.3390/jcm9123962 PMid:33297431 PMCid:PMC7762278

21. Santos A, Magro DO, Evangelista-Poderoso R, Saad MJA. Diabetes, obesity, and insulin resistance in COVID-19: molecular interrelationship and therapeutic implications. *Diabetol Metab Syndr [Internet]* 2021;**13**(1). Available from: https://doi.org/10.1186/s13098-021-00639-2.

22. Agarwal S, Agarwal SK. Endocrine changes in SARS-CoV-2 patients and lessons from SARS-CoV. *Postgrad Med J* 2020;**96**(1137):412–416. https://doi.org/10.1136/postgradmedj-2020-137934 PMid:32527756 PMCid:PMC7306278

23. Li G, Chen Z, Lv Z, Li H, Chang D, Lu J. Diabetes Mellitus and COVID-19: Associations and Possible Mechanisms. *Int J Endocrinol* 2021;2021:1–10. https://doi.org/10.1155/2021/7394378 PMid:33859687 PMCid:PMC8025139

24. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company' s public news and information . 2020; (January). https://doi.org/10.1016/j.autrev.2020.102597 PMid:32535093 PMCid:PMC7289100

25. Filippi CM, Herrath MG Von. Viral trigger for type 1 diabetes: *Pros and cons. Diabetes* 2008;**57**(11):2863–2871.

26. Accili D. Can COVID-19 cause diabetes? *Nat Metab [Internet]* 2021;**19**. Available from: http://dx.doi.org/10.1038/s42255-020-00339-7 PMid:33432203

27. Sathish T, Tapp RJ, Cooper ME, Zimmet P. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. *Diabetes Metab [Internet]* 2020;101204. Available from: https://doi.org/10.1016/j.diabet.2020.10.002. PMid:33129968 PMCid:PMC7591867

28. Palermo NE, Sadhu AR, McDonnell ME. Diabetic Ketoacidosis in COVID-19: Unique Concerns and Considerations. *J Clin Endocrinol Metab* 2020;**105**(8):1–11. https://doi.org/10.1210/clinem/dgaa360 PMid:32556147 PMCid:PMC7337869

29. Clare Hambling Chair, Dipesh Patel Chair BT. COVID-19 and diabetes: Update for primary care in response to the ongoing

coronavirus pandemic. Diabetes Prim Care 2021;**23**(1):1–4.

30. Decroli E, Efendi Y, Kam A, Manaf A, Syahbuddin S. Description of Insulin Resistance and Beta-Cell Pancreas Dysfunction in Prediabetic Patients. 2019;14–17. https://doi.org/10.4108/eai.13-11-2018.2283632

31. Caumo A, Perseghin G, Brunani A, Luzi L. New insights on the simultaneous assessment of insulin sensitivity and β-cell function with the HOMA2 method. *Diabetes Care* 2006;**29**(12):2733–2734. https://doi.org/10.2337/dc06-0070 PMid:17130216

32. Largay J. Case study: New-onset diabetes: How to tell the difference between type 1 and type 2 diabetes. *Clin Diabetes* 2012;**30**(1):25–26. https://doi.org/10.2337/diaclin.30.1.25

33. American Diabetes Association. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;**43**(January):S14–S31. https://doi.org/10.2337/dc20-S002 PMid:31862745

34. Krejner-Bienias A, Grzela K, Grzela T. DPP4 Inhibitors and COVID-19–Holy Grail or An other Dead End? A*rch Immunol Ther Exp (Warsz) [Internet]* 2021;**69**(1):2–9. Available from: https://doi.org/10.1007/s00005-020-00602-5

35. Yang Y, Cai Z, Zhang J. DPP-4 inhibitors may improve the mortality of coronavirus disease 2019: *A meta-analysis. PLoS One [Internet]* 2021;**16**(5 May):1–10. Available from: http://dx.doi.org/10.1371/journal.pone.0251916

36. Scheen AJ. DPP-4 inhibition and COVID-19: From initial concerns to recent expectations. *Diabetes Metab* 2021;**47**(2).

37. Iis Inayati Rakhmat a, Yudith Yunia Kusmala b, *, Dewi Ratih Handayani a, Henny Juliastuti a, Eka Noneng Nawangsih c, Arief Wibowo d, Michael Anthonius Lim e R. Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19) e A systematic review, meta-analysis, and meta-regression, and meta-regression. *Diabetes Metab Syndr Clin Res* Rev 2021;**15**(January).

38. Burhan E, Dwi Susanto A, Isbaniah F, et al. PEDOMAN TATALAKSANA COVID-19 Edisi 3. 3rd ed. Jakarta: 2020.