CHAPTER 142

Diabetic Ketoacidosis in COVID New Onset Patients

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INTRODUCTION

Globally only 5% of known diabetes is diagnosed to be type 1 diabetes but the incidence is increasing at about 3% every year.[1] The studies have correlated that the severity of developing COVID-19 and related complications amongst the obese and diabetes is high.[2] Even the reports had documented COVID-19-induced severe metabolic decompensation as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), of which SARS-CoV-2 is characteristically linked with new onset of type 1 diabetes.[3] The past experience from severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have taught the fact Coronavirus-mediated islet cell damage is not a novel phenomenon, may be because *Coronaviridae* family to inherited a genetic predisposition for islets cell damage.[4]

DIABETIC KETOACIDOSIS AND COVID

An important finding was high levels of inflammatory markers, same can be seen in DKA. Interleukin 6 (IL-6) has been highlighted as the main culprit for maladaptive immune response to the SARS-CoV-2 virus.[5] IL-6 is also elevated in DKA which hypothesized to be the driver of ketosis, but it is still a matter of debate.[6] The hormonal system responsible for maintaining blood pressure is called renin–angiotensin–aldosterone system (RAAS), which exerts its effect on vascular tone and aldosterone secretion. The RAAS is also found in the pancreas. The pancreatic cells express both angiotensin I and II receptor and prorenin genes.[7] **Figure 1** explains the role of amplification of angiotensin-converting enzyme 2 (ACE-2) at pancreatic islets and the kidney.[8]

Etiology and Pathogenesis of Type 1 Diabetes

Type 1 diabetes is an autoimmune condition executed through autoreactive $CD4^+$ and $CD8^+$ T cells lysis of β-cells. The regional differences are quite evident with known North–South gradient, having higher figures in northern latitudes showing the influence of environmental factors, hence seasonality in the new-onset type 1 diabetes mellitus (T1DM) has been linked with viral etiology.[9] The association of viral infections and T1DM is complex. The Mouse models reveal that while certain viruses could be harmful to the β-cells and begin autoimmunity, others could prove to be having both protective and preventive effects. Although one needs to stay cautious while extrapolating these findings to human subjects.[10]

Pathogenesis of β-cells Damage

Evidence of fulminant T1DM from Japan predominantly in adults had shown that to be preceded by minor upper respiratory or gastrointestinal infections mainly of viral etiology as mumps, human herpesvirus 6 (HHV6), Coxsackie B3, B4, herpes simplex virus (HSV), hepatitis A, influenza-B, and parainfluenza. This fulminant T1DM called as type 1 B diabetes, characterized by acute onset of ketoacidosis with very short (1 week) duration of osmotic symptoms, absence of islet-related autoantibodies, extremely low C-peptide levels, elevated serum pancreatic enzyme levels, and a HbA1c <8.5% on the first visit.[11,12]

Hence, it was stated that β-cell damage due to viral infection can be due to either:

- Direct lytic effects of viral replication
- Host inflammatory response-mediated damage by autoreactive CD^+ T cells, leading to autoimmunity **(Fig. 2)**.

The pathological processes for chronic β-cell damage are varied as:

- Molecular mimicry
- T-cell activation
- Chronic β-cell infection leading to major histocompatibility complex 1 (MHC-1) overexpression.

The Associated Viruses which may Cause β-cell Damage

The enterovirus infection has shown significant association with type 1 diabetes and related autoimmunity.[13] The TEDDY study (The Epidemiological Determinants of Diabetes

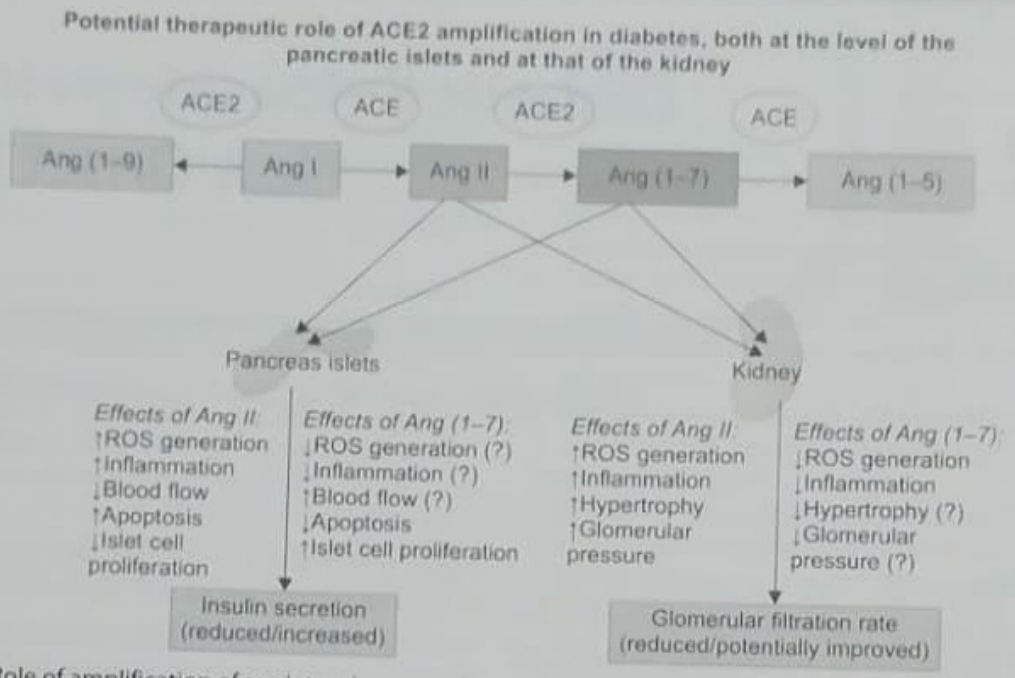

Fig. 1: Role of amplification of angiotensin-converting enzyme 2 (ACE-2) at pancreatic islets and the kidney.

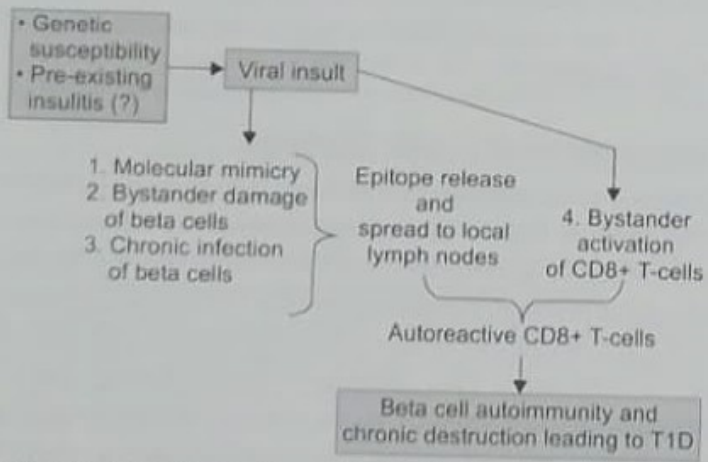

Fig. 2: Host inflammatory response-mediated damage by autoreactive CD+ T cells, leading to autoimmunity.
(Adapted from Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr. 2020;14(6):2211-7)

in Young) confounded that several respiratory infection occurring till 9-month postnatal period is associated with subsequent risk of type 1 diabetes autoimmunity, and interestingly coronavirus was one of the identified pathogens. With due time and research, many viruses came to be associated with T1DM, especially listed as, *Enteroviruses* (especially Coxsackie B1, B4), mumps, cytomegalovirus (CMV), rubella, etc. Even studies had substantial data to contradict the relationship between β-cell autoimmunity due to viral origin.

EPIDEMIOLOGY OF DIABETIC KETOACIDOSIS: AN UPDATE

The data from US and the UK has reported that hospitalization from DKA had increased in the last decade.[14,15]

From 2000, two subtypes being identified are as follows:

1. *Ketosis-prone diabetes*: Recognized from early 2000 amongst type 2 diabetes mellitus (T2DM) with obesity presented in DKA, they had impaired insulin levels bu still negative for T1DM autoimmune markers.[16]
2. *Euglycemic diabetic ketoacidosis (euDKA)*: This group accounts for up to 10% of DKA. It is characterized by metabolic acidosis along with increased total body ketone level, but having glucose levels ≤250 mg/dL.[17,18] It was first described by Munro et al. in 1972.

SARS CoV-1 and Diabetes

The studies had shown that ACE-2 is the functional receptor for both SARS-CoV-1 and SARS-CoV-2.[19] ACE-2 is mainly found abundantly in the lung and small intestine, hence becomes the routes of entry for the SARS-CoV-1 and SARS-CoV-2.[20] Studies during 2003 SARS-CoV-1 epidemic had documented that those who did not receive glucocorticoid medications for milder SARS symptoms even had raised fasting blood sugar (FBS) which in turn was an independent predictor of higher mortality and morbidity.[21] During the follow-up in 2010 for investigating any pancreatic lesions, they were found to be strongly immune positive for ACE-2 in pancreatic islets but only weakly positive for exocrine pancreases. Insulin-dependent diabetes was observed in 20 of the 39 patients (age: 47.2 ± 2.2 years) during hospitalization. At 3 years of follow-up, two still persisted with diabetes, hypothesizing that the damage on β-cells can only be acute and transient in nature.

COVID-19 and Pancreatitis

There is no report or documented case of acute pancreatitis with the SARS-CoV-1 in 2003. However, during COVID-19,

TABLE 1: Classification of hyperglycemic crisis severity and insulin treatment options.

	Mild DKA	*Moderate DKA*	*Severe DKA*	*HHS*	*HONK*
Blood glucose mg/dL (mmol/L)	>250 (>13.8)	>250 (>13.8)	>250 (>13.8)	>600 (>33.3)	>600 (>33.3)
pH	7.25–7.30	7.00–7.24	<7.00	>7.30	
HCO_3 (mmol/L)	15–18	10–14	<10	>18	
Urine/serum ketones	+	+	±	±	+
Serum osmolality (Osm_{eff})				320	320
Anion gap	Elevated	Elevated	Elevated	Elevated	Elevated
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma	Stupor/coma
Insulin therapy	SC/IV	SC/IV	IV	IV	IV
Frequency of glucose monitoring	every 1–2 hours	every 1–2 hours	every 1 hour	every 1 hour	every 1 hour
Location of care	Intermediate care unit	Intermediate care unit/ICU	ICU	ICU	ICU

(DKA: diabetic ketoacidosis; HCO_3: bicarbonate; ICU: intensive care unit; IV: intravenous; Na^+, sodium; SC: subcutaneous ; HHS: hyperglycemic hyperosmolar syndrome; HONK: hyperosmolar nonketotic coma)

Role of Subcutaneous Insulin Use in Diabetic Ketoacidosis

In context of pandemic along with available evidence, SC insulin therapy proves to be useful for mild/moderate uncomplicated DKA. From the Cochrane review (2016) assessing IV insulin versus SC rapid-acting insulin protocol found that the effects of SC versus IV insulin (rapid-acting insulin analogues) are comparable for treating mild or moderate DKA.[34]

Summary of SC insulin randomized controlled trials (RCTs) in DKA and potential strategies in COVID-19 is given in **Table 2**.

One study was assessing the impact of adding early basal insulin within the first 12 hours at the dose of 0.25 unit/kg. The authors observed reduction in rebound hyperglycemia [33.3% in the intervention group versus 93.5% in the control ($P < .001$)].

Even though SC protocol is useful but still not recommended for:

- Severe DKA
- Other complicated illness (end-stage renal disease, severe AKI, pregnancy, concomitant myocardial infarction, or stroke)
- Any patients requiring intensive care unit (ICU) care for mechanical ventilation and/or vasopressor support.

Management of Severe and/or Complicated Diabetic Ketoacidosis in Patients with COVID-19

Any patients presented with severe DKA should be managed in an ICU with IV access for fluid resuscitation along with SCII along with frequent monitoring of either venous blood or capillary glucose (e.g., every 1–2 hours). Also frequent monitoring for potassium and electrolytes to be done. The respiratory support and cardiac monitoring may be needed. The insulin requirement may be as high as needs 4 units/kg/day with critically ill patients with COVID-19.[35] The concomitant usage of corticosteroids and/or vasopressors also had an impact insulin requirement.[17]

The resolution from DKA leads to rapid increase in insulin sensitivity, mainly in severe DKA. Hence, insulin rate should adjust hourly.

PREVENTION OF DIABETIC KETOACIDOSIS DURING COVID-19

It is been observed that majority of people with diabetes and COVID-19 infection may not require hospitalization. The self-care of these categories of patient includes continuing insulin at home insulin and to reassess their oral hypoglycemic agent (OHA), especially those taking SGLT2i.

Most of the professional societies are doing advocacy to follow "sick day rules" which include at least 3-month supply of medications, all necessary supplies for insulin therapy and point-of-care ketones bodies (blood or urine) testing kit.[36]

Telemedicine is useful modality for adolescents in preventing DKA.[37]

Lastly, insulin initiation and proper behavioral change communication program should not be postponed during the pandemic. BCC can be achieved by either face to face counseling or, via video teleconferencing.

CONCLUSION

In this regard, the establishment of the CoviDiab Registry (covidiab.e-dendrite.com) 2 is timely and should provide valuable insights into issues regarding COVID-19-related diabetes. These pandemics provide us a classic example of a lethal intersection about the burden of a noncommunicable disease on communicable disease. Most of the DKA in T1DM is precipitated by omission of insulin, hence rationalization of insulin therapy is of paramount importance for which clinicians, clinical programs; along with insurers as well as manufacturers should come together with program for sustainable insulin regimens at an affordable cost.

SARS-CoV-2 had many cases documented of acute pancreatitis.[22] A researcher at Liverpool, UK observed that 10 out of 35 patients with acute pancreatitis during the period March/April 2020 were positive for SARS-CoV-2. 3 of the 10 had new-onset diabetes managed with insulin.[23]

COVID-19 and New-onset Diabetes

According to data from Hoffmann et al.[24] and Zhou et al.,[25] SARS-CoV-2 and SARS-CoV-1 use the same ACE-2 receptor. More intriguingly, recent reports show that newly diagnosed diabetes is commonly observed in COVID-19 patients.

The association between COVID-19 infections with new-onset hyperglycemia amongst people with no history of diabetes is increasing along with raised risk of mortality and morbidity. The phenomenon of infection leading to inflammation and cytokine storm resulting to insulin resistance and stress hyperglycemia is well known and that maybe a phenomenon resulting in hyperglycemia following COVID-19 infections.

During the recent pandemic of COVID-19 in Italy, those presented with more severe DKA was 44.3% in 2020 in compared with 36% in 2019 which was higher than 23% of annual cases of new childhood diabetes.[26] A similar observation was reported from Germany, i.e., twofold increase in DKA and severe ketoacidosis amongst children and adolescents during the pandemic of COVID-19 when diagnosis of diabetes was made, hence new-onset diabetes.[27]

A multicenter study had reported an increase in new-onset T1DM in children from UK, during COVID-19 pandemic. 21 out of 30 children presented with DKA of which 52% with severe DKA. Amongst them 2 of 21 tested positive for SARS-CoV-2 and 3 of 16 tested positive for SARS-CoV-2 antibody [immunoglobulin G (IgG)].[3]

The conclusion from meta-analysis by Sathish et al. where >3,700 patients from eight studies had shown a pooled proportion of 14.4% for newly diagnosed diabetes amongst patients hospitalized for COVID-19.

Euglycemic Diabetic Ketoacidosis

During the COVID-19 pandemic, a cluster of cases and reports of euglycemic DKA was reported across the globe. Especially in those presenting were mainly on sodium-glucose cotransporter 2 inhibitors (SGLT2i) where presenting blood glucose level <300 mg/dL, later they were managed with intravenous (IV) insulin infusion to treat DKA.

A case was reported by Oriot and Hermans about euDKA n T1DM patient with SARS-CoV-2 pneumonia.[28] Li et al. suggest that COVID-19 might accelerate fat breakdown and nduce ketosis, with further development of ketoacidosis.[29] Overall, the mechanisms linking COVID-19 with ketosis, ketoacidosis, or DKA need further research.

IMPACT OF COVID-19 AMONGST YOUTH AND PEDIATRICS

The impact of COVID-19 on diabetes is mainly adult centric, but impact of the same on pediatric diabetes still remains an ambiguous area. According to Chao et al., as quoted *"Spike in Diabetic Ketoacidosis Rates in Pediatric Type 2 Diabetes during the COVID-19 Pandemic."* They observed persistently increase in trend of new-onset type 2 diabetes cases for three consecutive years during the same 6 months of the year. During the same pandemic period, a spike in DKA is noted mainly among new-onset diabetes. Interestingly none had active SARS-CoV-2 infection, of which two new-onset diabetes were serology positive (IgG) for SARS-CoV-2.[30]

CONSIDERATIONS IN THE GENERAL MANAGEMENT OF DIABETIC KETOACIDOSIS

The main tenets of DKA management have not changed in decades and include the triad of *fluid resuscitation*, *potassium repletion*, and *insulin replacement*.

For fluid resuscitation, isotonic saline (0.9% NaCl) is often the preferred along with close monitoring and potassium repletion may be needed.

The major pitfalls of DKA treatment are as follows:[31]

- Inadequate potassium supplementation
- Failure to prevent hypoglycemia
- Recurrence of ketoacidosis due to ineffective transitioning from IV route to subcutaneous (SC) insulin therapy.

Management of euDKA is similar to classical DKA, but only difference is that dextrose-containing fluids may be required as an *initial step* during fluid resuscitation rather than adding later during when level of glucose declines. The other point is that glycosuria may last for days if DKA is due to SGLT2i use,[32] hence there may be extended phase of fluid resuscitation.

Assessing Diabetic Ketoacidosis Severity

The American Diabetes Association (ADA) classification is shown in **Table 1**.

Management of Uncomplicated Diabetic Ketoacidosis in Patient with COVID-19

Diabetic Ketoacidosis Management at Home

The point-of-care ketones testing kit is imprecise,[33] hence any patient having raised ketones should be looked for other signs of DKA. If clinically stable and taking oral fluids, should consult their care team. However, any patient with rapid decline in clinical parameter be urgently referred to nearby health facilities.

TABLE 2: Summary of subcutaneous insulin randomized controlled trials (RCTs) in DKA and potential strategies in COVID-19.

	Population	Intervention versus conventional IVI protocol	Outcomes measured	Key findings	Notes for use in COVID-19
Della Manna et al. (2005)	Pediatric and adolescent patients with DKA (n = 60)	SC lispro 0.15 units/kg every 2 hours until BG <13.8 mmol/L (250 mg/dL) then interval increased to every 4 hours until resolution of DKA	Time to resolution of DKA	Both groups reached BG <13.8 mmol/L (<250 mg/dL) within 6 hours Metabolic acidosis and ketosis resolved faster in control group (IVI) 95% (57/60) patients were treated in ED and did not require admission	Every 2–4 hours insulin dosing outside of ICU was effective but slightly slower to resolution
Ersöz et al. (2006)	Patients with mild/moderate DKA (n = 20)	Single bolus injection of 0.15 U/kg IV regular insulin then 0.075 units/kg every 1 hour until resolution of DKA	Time to resolution of DKA, amount of insulin used, mortality, hypoglycemia rate	No differences between groups with respect to time of resolution of DKA, amount of insulin use, rate of hypoglycemia or mortality	Every 1 hour monitoring used in both groups
Hsia et al. (2012)	Patients with DM1 or DM2 (n = 61)	Glargine 0.25 units/kg within 12 hours of initiation of IV insulin	Rates of rebound hyperglycemia (BG >180 mg/dL) within 12 hours of discontinuation of IVI	• Rebound hyperglycemia 33.3% in intervention group versus 93.5% in control (P <0.001) • Average lower glucose levels in intervention group (P <0.01)	SC basal insulin during IVI can improve overall glucose control post-DKA; may reduce rebound DKA
Karoli et al. (2011)	Patients with mild/moderate DKA (n = 50)	SC lispro initially 0.3 units/kg, followed by 0.2 units/kg 1 hour later then subsequently treated with 0.2 unit/kg every 2 hours until BG <250 mg/dL, then dose reduced to 0.1 unit/kg every 1 hour	Duration of treatment and resolution of hyperglycemia and ketoacidosis *Other endpoints*: Total length of hospitalization, amount of insulin administration, hypoglycemia rate	• No difference in the mean duration of treatment and amount of insulin required for correction of hyperglycemia and ketoacidosis • No differences in mortality or LOS	Could be adapted to allow every 2 hour monitoring and dosing until DKA resolution
Umpierrez et al. (2004)	Patients with mild/moderate DKA (n = 45)	SC aspart every 1 hour or every 2 hours 1-hour group: Initial dose of 0.3 units/kg followed by 0.1 units/kg every 1 hour until BG <250 mg/dL dose reduced to 0.05 units/kg 2-hour group: Initial dose of 0.3 units/kg followed by 0.2 units/kg every 2 hours until BG <250 mg/dL dose reduced to 0.1 units/kg	Duration of treatment and resolution of hyperglycemia and ketoacidosis *Other endpoints*: Total length of hospitalization, amount of insulin administration, hypoglycemia rate	No difference in mean duration of treatment until resolution of hyperglycemia or ketoacidosis or rate of hypoglycemia between group	Every 2 hours dosing was safe and effective
Umpierrez et al. (2004)	Patients with uncomplicated DKA (n = 40)	SC lispro, managed on medicine ward (n = 10) or an intermediate care unit (n = 10) initial dose of 0.3 units/kg followed by 0.1 units/kg every 1 hour until BG <250 mg/dL dose reduced to 0.05 units/kg	Duration of treatment and resolution of hyperglycemia and ketoacidosis *Other endpoints*: Total length of hospitalization, amount of insulin administration, hypoglycemia rate	• No difference in mean duration of treatment until resolution of hyperglycemia or ketoacidosis or rate of hypoglycemia between group • Treatment in ICU was associated with 39% higher hospitalization charges than was treatment with subcutaneous lispro in a nonintensive care setting ($14,429 ± $5,243 vs. $8,801 ± $5,549, P <.01)	Medical ward can be a safe environment for intensive SC protocol though every 1 hour monitoring used in all groups

(DM1: diabetes mellitus type 1; DM2: diabetes mellitus type 2; DKA: diabetic ketoacidosis; LOS: length of stay IV: intravenous; IVI: intravenous insulin; SC: subcutaneous)

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