

Prevalence and Clinical Outcomes of Patients with Diabetic Ketoacidosis/Hyperglycemic Hyperosmolar Syndrome and COVID-19: A Systematic Review

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ABSTRACT

BACKGROUND AND OBJECTIVES. Several reports have shown that coexistence of diabetes mellitus and COVID-19 is one of the risk factors for poor outcome and increased mortality. Rapid metabolic deterioration with development of diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS) may result due to the acute insulin secretory capacity loss, stress condition and the cytokine storm. In this review, we aim to describe the prevalence of hyperglycemic crises (DKA/HHS) in patients with COVID-19 infection as well as their clinical outcomes.

METHODS. An intensive search was done using the WebMD, PubMed, Medline and Google Scholar databases for articles published between December 2019 to October 2020 that identified the number of patients who developed DKA and/or HHS among those who were admitted for COVID-19. Their clinical outcomes were likewise described.

RESULTS. This review included 4 articles in which individual quality was assessed. A total of 1282 patients were admitted for COVID-19 and the prevalence of DKA was 1.32%. HHS was not reported in any of the studies. Five (29.4%) of the patients with DKA and COVID-19 died and 12 (70.6%) recovered.

CONCLUSIONS. A significant number of COVID-19 patients developed DKA and it is associated with a high mortality rate. This reimposes the need for an appropriate algorithm for the optimal management of concomitant COVID 19 and hyperglycemic crises to avoid morbidity and mortality. Additionally, there is paucity of large-scale studies describing the prevalence of DKA/HHS in patients with COVID-19.

Keywords: Diabetic ketoacidosis, Diabetic hyperosmolar syndrome, COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging illness that is spreading rapidly and is now a major health concern. Globally, there have been 39,596,858 confirmed cases of COVID-19, including 1,107,374, deaths reported to the World Health Organization (WHO) as of October 18, 2020.¹ COVID-19 is caused by the SARS-CoV-2 virus and it has affected people of various age, sex, ethnicities and comorbidities. Clinical presentations vary from asymptomatic to severe manifestations and worse prognosis has been associated with the presence of certain underlying conditions such as cancer, chronic kidney disease, lung diseases,

immunocompromised state, and diabetes mellitus.² Several studies have been conducted and they showed that coexistence of diabetes mellitus and COVID-19 is one of the risk factors for poor outcome and increased mortality.

The inhaled SARS-CoV-2 virus binds to epithelial cells in the nasal cavity and starts replicating. The main receptor for SARS-CoV-2 is Angiotensin-converting enzyme 2 (ACE2).³ Aside from the respiratory tract, ACE2 receptors are expressed in pancreatic tissue and β -cells in particular. The tropism of SARS-CoV-2 for the β -cell could cause acute impairment of secretion of insulin or β -cell destruction resulting in de novo development of diabetes. Rapid metabolic deterioration with development of diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS) may result due to the acute insulin secretory capacity loss, stress condition and the cytokine storm.⁴ Interleukin-6 (IL-6), an important cytokine of the hyper-inflammatory state in COVID-19 which serves as a driver of ketogenesis, has

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been found to be elevated in DKA and this contributes to the state of ketosis in patients with coexisting COVID-19 and diabetes mellitus. DKA is a life-threatening condition which is seen most commonly in patients with type 1 diabetes mellitus, but can also be seen in patients with type 2 diabetes mellitus in the presence of precipitating factors. Nearly half of DKA cases are triggered by infection and given the high-risk nature of both DKA and COVID-19, it is paramount that clinicians are able to promptly recognize DKA in patients with COVID-19.⁴

According to Apicella, et al. in the article "COVID-19 in people with diabetes: understanding the reasons for worse outcomes", people with diabetes with COVID-19 are at a greater risk of worse prognosis and mortality. Adequate glycemic control in patients with diabetes with COVID-19 must be ensured as therapies for COVID-19 have potential complications which may arise when used in patients with diabetes. Medical teams must then ensure good glycemic control in these patients at hospital admission and during the hospital stay to prevent worsening rapid and severe deterioration of metabolic control and development of DKA and HHS.

The significance of this systematic review is to know the real burden of hyperglycemic crises in patients with COVID-19 infection. To date, there is only one systematic review which only described the clinical profile and outcomes in COVID-19 patients with DKA.¹¹ However, there was no data on the prevalence of DKA and HHS and their mortality rate in patients with COVID-19.

Our objectives were to describe the prevalence of hyperglycemic emergencies (DKA and HHS) in patients

with COVID-19 and to determine the clinical outcomes of COVID-19 patients with concomitant hyperglycemic emergencies.

METHODS

Inclusion and Exclusion Criteria

We searched for articles meeting all of the inclusion criteria: they involved all adult (over 18 years old) patients admitted for COVID-19, they described the prevalence of DKA/HHS or reported results that permitted its computation, and they reported the clinical outcome of these patients. The studies reviewed were 2 retrospective cross-sectional and 2 retrospective cohort studies. Excluded were studies limited to pediatric population and case reports or case series.

Search strategy and Article Selection

An intensive substantial electronic search was conducted using the PRISMA guidelines on the WebMD, PubMed, Medline and Google Scholar databases. The bibliographies of the articles retrieved were also reviewed for additional references. The researcher formulated the strategies as seen below (Figure 1).

We used 7 Medical Subject Headings (MeSH): "COVID-19", SARS-CoV-2, diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hyperglycemic crises, hyperglycemic emergencies and prevalence, with interposition of Boolean operator "AND" and "OR". Literatures were limited to studies published in English on human subjects from December 2019 to October 2020. An electronic search was also conducted for relevant peer-reviewed journals. One author (S.V.) read the abstract to exclude articles that were not eligible. Full text of the retrieved papers was independently appraised by the two authors (S.V. and M.C.). Articles meeting all inclusion criteria were retained for quality assessment and data extraction. Inconsistencies between the two reviewers were resolved by team consensus.

Assessment of Study Quality

We assessed the quality of the studies using the National Institute of Health - National Heart, Lung, and Blood Institute (NIH-NHLBI) study quality assessment tool for observational cohort and cross-sectional studies. Quality rating was expressed as good, fair or poor. Each reviewer (S.V. and M.C.) independently assessed the quality of the studies. To be retained in our review, articles had to have a rating of good. (See Appendix A and B for reference)

Data Extraction and Calculations

The following data were extracted from the included studies: total number of patients admitted for confirmed COVID-19 infection, number of patients who developed DKA/HHS, and clinical outcomes of patients with COVID-

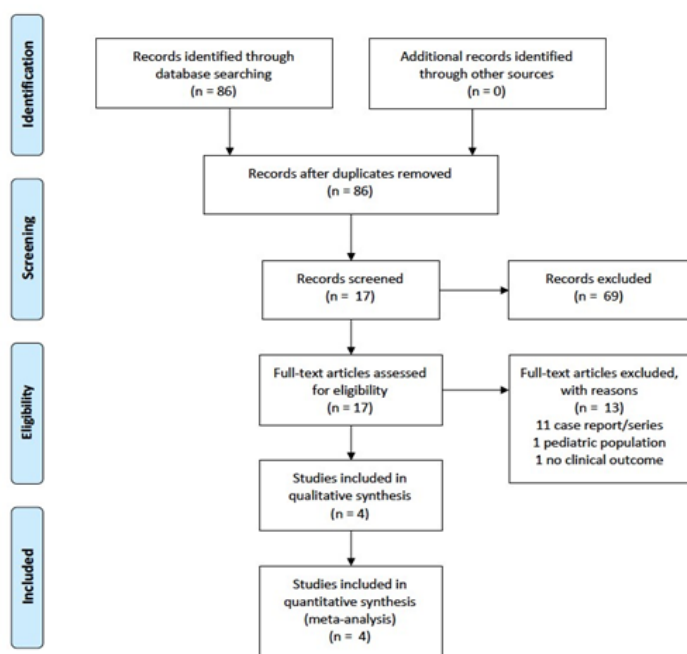


Figure 1. Flow Diagram showing the study selection process

19 and DKA/HHS. Clinical outcomes were described as either recovered or died. Statistical analysis was performed using the Stata software for statistics and data science.

Definition of terms

1. *COVID-19 infection* = laboratory-confirmed severe acute respiratory syndrome-2 (SARS-CoV-2) by RT-PCR)
2. *Diabetic ketoacidosis (DKA)* = a form of hyperglycemic crisis characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration.¹⁰
3. *Hyperglycemic Hyperosmolar Syndrome (HHS)* = characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.¹⁰

Outcomes

Primary outcome: Prevalence of DKA and/or HHS in confirmed COVID-19 patients

Secondary outcome: Mortality rate in patients with coexisting COVID-19 infection and DKA/HHS

RESULTS

Articles Included in the Review

Our process for determining the chosen articles is shown in Figure 1. The search strategies identified 86 references with the words "COVID-19", "SARS-CoV-2", "diabetic ketoacidosis", "hyperglycemic hyperosmolar syndrome", "hyperglycemic crises", "hyperglycemic emergencies and prevalence, of which 86 articles were collected after duplicates were removed. Thereafter, the records were screened for which sixty-nine (69) of the papers were excluded. The articles were then analyzed for eligibility after title, abstract, and full text reading, and a total of 4 studies were finally selected.

The quality of the articles was likewise assessed. Quality scores in the final list of articles were assessed as good. (See Appendix A)

Prevalence and Clinical Outcomes of COVID 19 patients with DKA/HHS

The total number of admitted COVID-19 patients and those with concomitant DKA as well as their clinical outcomes are summarized in Table I. Out of 1282 patients with confirmed COVID-19, 17/128 (1.32%) developed DKA. None of the studies included reported occurrence of HHS. Among those who developed DKA, 12/17 (70.6%) recovered while the remaining 5/17 (29.4%) died.

One of the 4 studies did not indicate the demographics of all the patients included in their study. All but one of the studies classified the total population based on the presence of type 1 or type 2 diabetes mellitus. However, only 1 study mentioned the presence and type of pre-existing diabetes among patients with DKA. Goldman, et al conducted a small retrospective review of 218

Table I. Prevalence of COVID-19 patients with DKA/HHS and their clinical outcome

Study	N	DKA (N)	HHS (N)	Recovered (N)	Died (N)
Alkundi et al (2020)	232	8	0	7	1
Li et al (2020)	658	3	0	2	1
Guo et al (2020)	174	2	0	1	1
Goldman et al (2020)	218	4	0	2	2
Total (%)	1282	17 (1.32)	0 (0)	12 (70.6)	5 (29.4)

DKA – Diabetic Ketoacidosis; HHS – Hyperosmolar Hyperglycemic Syndrome

Table II. Population of studies based on DM Classification

Study	N	With DM
Alkundi et al (2020)	232	87 (T1DM = 11; T2DM = 76)
Li et al (2020)	658	129 (T1DM = 1; T2DM = 128)
Guo et al (2020)	174	37
Goldman et al (2020)	218	67 (T1DM = 6; T2DM = 61)

T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus

admitted COVID-19 patients wherein one of four patients who developed DKA had no known diagnosis of DM but had elevated HbA1c (12.8%) on admission and the remaining 3 had a known diagnosis of type II DM. Their metabolic parameters upon admission were likewise indicated in the study.

Likewise, the demographic profile of patients who died from DKA was not mentioned in the 3 studies that presented patients' clinical profile. Two out of the 4 studies only stated the age and admission metabolic parameters of those who developed DKA however did not identify who among those patients died.

In the study by Alkundi, et al, out of the 232 patients, 145 were male and 87 were female with mean age of 70.5 years. Comorbid conditions such as asthma, chronic obstructive pulmonary disease, heart disease, hypertension, cancer, etc. are present in 194 patients. Eleven had type 1 diabetes while 76 had type 2 diabetes (Table II). Mean HbA1c was 15.5%.

In the first retrospective cross-sectional study in the UK by Goldman, et al which described prevalence and characteristics of DKA in patients admitted for COVID-19, 61 out of 218 patients had type 2 diabetes and 6 had pre-existing diagnosis of type 1 diabetes. The metabolic parameters of 4 patients who developed DKA were described. Admission metabolic parameters were: pH

7.1-7.27, bicarbonate 8-15.7 mmol/L, blood glucose 19-26 mmol/L, capillary ketones 4.2-6.2 mmol/L and HbA1c 9.5-12.8%. Three of them had a known diagnosis of type 2 diabetes and 1 had no pre-existing diagnosis of diabetes mellitus. Two patients with DKA required critical care: one for continuous veno-venous hemofiltration for refractory severe metabolic acidosis and one for mechanical invasive ventilation to manage hypoxemic respiratory failure. Guo, et al in the retrospective review of 174 patients admitted for COVID-19, the median age was 59 years and 76/174 were men. Fever was the most common symptom and the most common underlying comorbidities were hypertension and diabetes. Out of the 174 patients, 37 (21.2%) had diabetes. Of all the diabetic patients, 3 had diabetic complications wherein 2 had DKA and 1 had septic shock.

In the retrospective cohort of Li, et al, 658 hospitalized patients with confirmed COVID-19 were included. Median age was 57.5 years and 297/658 (45.1) were men. Fever was also the most common symptom at disease onset. A total of 129 (19.6%) patients had diabetes with only one case of type 1 diabetes. Median HbA1c of patients with diabetes was 9% (7.6-12.3) and their median glucose was 13.0 mmol/L (9.2-16.6%).

The most significant potential confounding variable is the presence of other comorbidities. Since patients included belong to the relatively elderly population, most of them had coexisting chronic comorbid conditions. In the study by Guo, et al, patients were first divided based on whether they had diabetes. In the second part, patients with comorbidities other than diabetes were excluded to avoid the impact of other comorbidities, and then the patients with diabetes and patients without diabetes were separated into two groups.

DISCUSSION

Diabetes mellitus is caused by either absolute insulin deficiency as seen in type 1 DM or insulin resistance in type 2 DM. Chronic hyperglycemia gives rise to glucotoxicity to body tissues with the formation of advanced glycation end products which are responsible for the chronic complications of diabetes.¹² Serious acute metabolic complications of diabetes include DKA and HHS. The triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration characterizes DKA. HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.¹⁰ The most common precipitating factor in DKA and HHS is infection causing uncontrolled hyperglycemia due to increase in body's insulin requirements.

It has been shown that SARS-CoV-2 virus binds to ACE2 in the pancreatic islets leading to islet damage and acute diabetes. This pathophysiology could lead to insulinopenia and increased risk of DKA, especially in patients with pre-existing DM.¹¹ Several studies have similarly shown that SARS-CoV-2 must be considered as a potential cause of metabolic decompensation in patients with DM and a possible precipitant of DKA.

However, up to date, only one retrospective study had specifically evaluated the high prevalence of COVID-19 associated diabetic ketoacidosis in the UK setting. In our systematic review, the prevalence of DKA in COVID-19 patients is 1.32%. There was no case of HHS recorded in any of the studies. There were no sufficient data from the studies reviewed as to whether these patients who developed DKA were newly diagnosed or already had a previous history of either Type 1 or Type 2 Diabetes Mellitus. However, the systematic review by R. Pal, et al (2020), elaborated that the majority of COVID-19 patients with DKA (77%) already had a past history of Type 2 Diabetes Mellitus, suggesting the higher prevalence of Type 2 Diabetes Mellitus worldwide.

COVID-19 infection may cause ketosis or ketoacidosis and induced diabetic ketoacidosis for those patients with diabetes. DKA is a potentially fatal metabolic complication which is more common in type 1 DM. In some cases, however, it can also occur in type 2 DM and viral infection.⁹ Current data on prevalence of DKA are only among the diabetic population. In the studies reviewed, occurrence of DKA/HHS was found even in patients with no known previous diagnosis of DKA/HHS, hence they are not comparable. However, it is important to note that in our review, the presence of DKA in patients with COVID-19 accounted for a mortality rate of 29.4%. In contrast to the findings of our systematic review, mortality rate among patients with COVID-19 and DKA/HHS (29.4%) is higher than those DKA/HHS patients who do not have COVID-19.

According to Umpierrez, et al (2002) in the article "Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome" published in the American Diabetes Association journal, mortality rates are 2-5% for DKA and 15% for HHS. Therefore, we should be vigilant in managing COVID-19 patients with ketoacidosis, especially those with diabetes to reduce associated mortality from complications of COVID-19.

STUDY LIMITATIONS

The main limitation of this systematic review is that studies describing prevalence of DKA/HHS in COVID-19 patients are scant. Another limitation, like any systematic review, is the potential omission of relevant articles. Exhaustive inclusion criteria was used and further articles were identified through reference lists.

All of the participants included in the 4 studies were confirmed COVID-19 cases. However, since the studies were only observational, the patients' comorbidities were just summarized by the 3 studies however, the individual profile of the patients who had DKA and those who died were not indicated.

CONCLUSION

Our systematic review features the increasing prevalence and the significance of the need to be on the lookout for diabetic ketoacidosis or hyperglycemic hyperosmolar state in patients with both type 1 and type 2 diabetes in patients diagnosed with COVID-19 infection. Lastly, it

reimposes the need for an appropriate algorithm for the optimal management of concomitant COVID 19 and hyperglycemic crises to avoid morbidity and mortality.

RECOMMENDATIONS

Since there is a paucity of large-scale studies describing the prevalence of DKA in patients with COVID-19 and the most frequently mentioned limitation of the studies included in this review was a small number of patients, future studies involving more patients must be carried out. Currently, there is also no available local data regarding the prevalence of coexisting COVID-19 infection and DKA. Classification of DKA patients based on presence or absence of pre-existing diagnosis of type 1 or 2 DM and their biochemical parameters on admission must also be included.

It was shown in our systematic review that there is a high mortality rate among patients with hyperglycemic emergencies and COVID-19. This serves as a reminder to the clinicians to promptly recognize DKA/HHS among patients who are admitted for COVID-19. Studies conducted in our local setting must also be done and the demographic profile as well as the metabolic parameters of these patients must be included.

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DECLARATION OF COMPETING INTEREST None.

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APPENDIX A

Summary of Results for Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Alkundi et al (2020)	Li et al (2020)	Guo et al (2020)	Goldman, et al (2020)
Was the research question or objective in this paper clearly stated?	YES	YES	YES	YES
Was the study population clearly specified and defined?	YES	YES	YES	YES
Was the participation rate of eligible persons at least 50%?	YES	YES	YES	YES
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	YES	YES	YES	YES
Was a sample size justification, power description, or variance and effect estimates provided?	N/A	N/A	N/A	N/A
For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome(s) being measured?	YES	YES	YES	YES
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	YES	YES	YES	YES
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?	N/A	N/A	N/A	N/A
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	YES	YES	YES	YES
Was the exposure(s) assessed more than once over time?	N/A	N/A	N/A	N/A
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	YES	YES	YES	YES
Were the outcome assessors blinded to the exposure status of participants?	N/A	N/A	N/A	N/A
Was loss to follow-up after baseline 20% or less?	YES	YES	YES	YES
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	YES	YES	YES	YES

*CD, cannot determine; NA, not applicable; NR, not reported