Reviewer 1:

The authors wrote a good article on the HHS-DKA relationship and diagnosis and management. However, the authors did not provide information apart from known information regarding HHS-DKA. When I scanned the literature, I saw sufficient and detailed articles o subject in the last 3 years. I do not think that this article contributes to the literature in its current form.

Response: We appreciate the reviewer candid response. We appreciate the reviewer positive feedback on liking our article. We did this manuscript for wide audience in a succinct and easy to follow knowledge base on this important though confusing clinical diseas

Reviewer 2:

1.Title. The title is about HHS DKA overlap. However, the manuscript does not cover the overlap 2 Abstract. “there is a lack of large-s studies that help define how hyperglycemic crises should be managed” the above statement in abstract should be removed. If autho 3 Key words. Do the key words reflect the focus of the manuscript? Yes 4 Background The manuscript does not define the backgroun present status and significance of the study. “ diabetes mortality is rising” is a controversial statement in introduction 5 Methods. Me not describes 6 Results. Not aplcable 7 Discussion. Discussion is incoherent with regard to aim of manuscript 8 Illustrations and table 1pplicable 9 Biostatistics. No statistics done 10 References. Are adequate. 12 Quality of manuscript organization and presentation. Language and grammar OK. 13 Research methods and reporting. PRISMA checklist for systematic reviews not followed 14 Ethics statements. NA Recommendation to authors: Kindly define the DKA Overlap and then do a systematic review. The manuscript needs rewritten

Response: We appreciate the reviewer comment, which sure help us in improving our manuscript. The statement in the abstract has removed as suggested. More keywords have been added. Since this is mini-review and not systematic review the methodological literature search and PRISMA guidelines are not applicable, neither the stats are applicable as this is not a research study nor meta-analysis. We have added several references and details to the manuscript to make it easier to read and cover the gaps. Language an grammar have been polished. We sincerely thank the reviewer for their time and feedback.

Reviewer 3:

Review Report I would like to thank the authors to write this mini-review and the editorial team to send it over to me for a critical pe review. Please find my suggestions on this manuscript as below: - Type 1 diabetes patients are more likely to experience DKA than ty from noncompliance to therapy, but infection, trauma, or acute coronary syndrome can also trigger it. Although this statement is tru incomplete. T2DM is much more prevalent than T1DM (8.5% compared to 0.5% prevalence of T1D), and due to this fact although T1 a stronger association with DKA, T2D patients are more commonly encountered with DKA in emergency and medical wards. It would nice to shed light on this fact. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, et al. Prevalence of diagnosed type 1 and type 2 diabetes among adults in 2016 and 2017: population based study. BMJ. 2018;362:k1497. doi: 10.1136/bmj.k1497 - Contrary to what authors suggest, donot agree that EuDKA is a diagnosis of exclusion. Excluding what exactly. I believe a working definition has been used multiple time studies. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015 Sep;38(9):1687-93. doi: 10.2337/dc15-0843. Epub 2 Jun 15. PMID: 26078479; PMCID: PMC4542270. - The definition of HHS as mentiond in the review by authors is incomplete. Authors s The mainstay for diagnosis of HHS is profound hyperglycemia with glucose greater than 600 mg per dL as per American Diabetes Association. This is incomplete, as mainstay is not only hyperglycemia but other characteristic and diagnostically important features. Complete definition as follows (from ADA): The hyperosmolar hyperglycemic state (HHS) is a syndrome characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of ketoacidosis. The exact incidence of HHS is not known, but it is estimated to account for <1% of hospital admissions in patients with diabetes Francisco J. Pasquel, Guillermo E. Umpierrez; Hyperosm Hyperglycemic State: A Historic Review of the Clinical Presentation, Diagnosis, and Treatment. Diabetes Care 1 November 2014; 37 (1 3124–3131. https://doi.org/10.2337/dc14-0984 - DM that presents with DKA after Immune checkpoint inhibitor is referred to as Fulmniant type 1 DM. WHO has recognized it as a separate entity. Better to enlighten the readership with the subcategory. WHO .

Classification of diabetes mellitus. Geneva: WHO; 2019. p. p14. [Google Scholar] - Although less common than SGLT2i, DKA has been observed wih GLP-1 agonsits and DPP-4 I as well, worth mentioning. - English language needs revision. Would recommend a review b native English speaker.

Response:
We thank the reviewer for their positive and detailed feedback. The manuscript has been reviewed by the native English-speaking authors. The manuscript has been extensively revised as per reviewer suggestions. The other responses are below

1# Type 1 diabetes patients are more likely to experience DKA than type 2 from noncompliance to therapy, but infection, trauma, or coronary syndrome can also trigger it

Response: A recent analysis from a safety net hospital in Atlanta found that insulin cessation was the main cause of DKA in 78% of pa and 56% of patients with multiple DKA episodes. Infections accounted for 14% and 4% were non-infectious causes such as acute myocardial infarction, neurovascular accidents, alcohol usage, and pancreatitis. (1)
REFERENCE
1.Fayfman M, Pasquel FJ, Umpierrez GE. Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmo State. Med Clin North Am. 2017 May;101(3):587-606. doi: 10.1016/j.mcna.2016.12.011. PMID: 28372715; PMCID: PMC6535398

#2 T2DM is much more prevalent than T1DM (8.5% compared to 0.5% prevalence of T1D), and due to this fact although T1DM has a stronger association with DKA, T2D patients are more commonly encountered with DKA in emergency and medical wards. It would b to shed light on this fact. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, et al.
Response: Type 2 diabetes had a 30-day death rate of 11.9% compared to type 1 diabetes's 2.4%. This might be because type 2 patie present at an older age and have more comorbid conditions. (1) T2DM is much more prevalent than T1DM (8.5% compared to 0.5% prevalence of T1D)
REFERENCE
1. Puttanna A, Padinjakara R. Diabetic ketoacidosis in type 2 diabetes mellitus. Practical Diabetes. 2014;31(4):155-8.

#3 Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population-based study. BMJ. 2018;362:k doi: 10.1136/bmj.k1497 - Contrary to what authors suggest, I don't agree that EuDKA is a diagnosis of exclusion. Excluding what exac believe a working definition has been used multiple times in studies. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment with Sodium-Glucose Cotransporter 2 Inhibition. Diabetes C 2015 Sep;38(9):1687-93. doi: 10.2337/dc15-0843. Epub 2015 Jun 15. PMID: 26078479; PMCID: PMC4542270. –

Response: A combination of hyperglycemia (serum glucose more than 250 mg/dL), acidosis (arterial pH 7.3 and bicarbonate 15 mEq/ and ketosis is referred to as DKA (moderate ketonuria or ketonemia) (1) The term "euglycemic DKA" (euDKA), which is used to descri DKA without significant hyperglycemia, is thought to be rare, but this may be due to underreporting. It is believed that elements inclu food restriction, alcohol consumption, partial therapy of DKA, and suppression of gluconeogenesis all contribute to the development euDKA.(2)
REFERENCES
1.Rawla P, Vellipuram AR, Bandaru SS, Pradeep Raj J. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. Endocr Diabetes Metab Case Rep. 2017 Sep 4;2017:17-0081. doi: 10.1530/EDM-17-0081. PMID: 28924481; PMCID: PMC5592704.
2. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatm with Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015 Sep;38(9):1687-93. doi: 10.2337/dc15-0843. Epub 2015 Jun 15. PMID: 26078479; PMCID: PMC4542270.

#4 The definition of HHS as mentioned in the review by authors is incomplete. Authors state: The mainstay for diagnosis of HHS is profound hyperglycemia with glucose greater than 600 mg per dL as per American Diabetes Association. This is incomplete, as mains not only hyperglycemia but other characteristic and diagnostically important features. Complete definition as follows (from ADA): Th hyperosmolar hyperglycemic state (HHS) is a syndrome characterized by severe hyperglycemia, hyperosmolality, and dehydration in absence of ketoacidosis. The exact incidence of HHS is not known, but it is estimated to account for <1% of hospital admissions in pat with diabetes Francisco J. Pasquel, Guillermo E. Umpierrez; Hyperosmolar Hyperglycemic State: A Historic Review of the Clinical

Presentation, Diagnosis, and Treatment. Diabetes Care 1 November 2014; 37 (11): 3124–3131.
Response: HHS is defined by extreme hyperglycemia more than 600 mg per dL, hyperosmolality, and dehydration, in the absence of ketoacidosis, Although the actual prevalence of HHS is unknown, it is likely to represent less than 1% of hospital admissions in diabet patients. (1) most cases are seen in elderly patients with type 2 diabetes; however, it has been reported in young adults and children
REFERENCE
1.Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatmer Diabetes Care. 2014 Nov;37(11):3124-31. doi: 10.2337/dc14-0984. PMID: 25342831; PMCID: PMC4207202.

#5 DM that presents with DKA after Immune checkpoint inhibitor is referred to as Fulminant type 1 DM. WHO has recognized it as a separate entity. Better to enlighten the readership with the subcategory. WHO. Classification of diabetes mellitus. Geneva: WHO; 20 p14. [Google Scholar] - Although less common than SGLT2i, DKA has been observed with GLP-1 agonists and DPP-4 I as well, worth mentioning. - English language needs revision. Would recommend a review by a native English speaker.
Response: The potential of Type 1 diabetes mellitus (T1DM) as a side effect of these drugs (Immune checkpoint inhibitors) has only recently been acknowledged, and current guidelines are still following behind this uncommon but potentially fatal condition. (1)
A spontaneous condition known as fulminant type 1 diabetes mellitus (FT1DM) is characterized by markedly elevated hyperglycemia, normal glycated hemoglobin (HbA1c) that is not consistent with the marked hyperglycemia, ketoacidosis, negative autoantibodies, se insulin deficiency, and elevated pancreatic enzyme levels. Several cases of FT1DM have been documented since the introduction of immune checkpoint medications. (2)
REFERNCES
1. Kyriacou A, Melson E, Chen W, Kempegowda P. Is immune checkpoint inhibitor-associated diabetes the same as fulminant type 1 diabetes mellitus? Clin Med (Lond). 2020 Jul;20(4):417-423. doi: 10.7861/clinmed.2020-0054. PMID: 32675150; PMCID: PMC738577
2. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and absence of diabetes-related antibodies. Osaka IDDM Study Group. N Engl J Med. 2000 Feb 3;342(5):301-7. doi: 10.1056/NEJM200002033420501. PMID: 10655528.

Reviewer 4:

very nice

Response: We thank the reviewer for their very positive response