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## Elevated beta-hydroxybutyric acid with no ketoacidosis in type 2 diabetic patients using sodium-glucose cotransporter-2 inhibitors

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Letter to the Editor

## Elevated $\beta$ -hydroxybutyric acid with no ketoacidosis in type 2 diabetic patients using sodium-glucose cotransporter-2 inhibitors

### KEYWORDS

Euglycemic-diabetic ketoacidosis;  
SGLT2;  
Cardiovascular;  
Ketonemia

*To the Editor,*

SGLT2 inhibitor (SGLT2i) class of medications are known to cause to euglycemic diabetic ketoacidosis (euDKA) as reported in the article by Lin et al. in your esteemed publication about this entity being reported for the first time in Taiwanese population.<sup>1</sup> We wish to share the findings from our center to further expand the spectrum of findings associated with SGLT2i therapy. SGLT2i treatment in patients with preexisting atherosclerotic heart disease and those with high risk of cardiovascular events is associated with a reduction in cardiovascular (CV) mortality, heart failure hospitalizations, and death from any cause.<sup>2</sup> Although the mechanism of the CV benefit from SGLT2i is likely to be multifactorial with a low level of ketonemia being one of the potential mechanisms.<sup>3</sup> In our study population, we measured serum  $\beta$ -hydroxybutyric acid (BHA) to assess the occurrence of asymptomatic ketogenesis in patients with type 2 diabetes mellitus after initiation of SGLT2i therapy. Between June 2015 and March 2016, we measured serum BHA before and after

starting an SGLT2 inhibitor in 28 patients at our outpatient endocrinology and metabolic medicine clinic. BHA levels  $>2.8$  mg/dL was considered elevated. We also analyzed changes in serum HbA1c and body mass index (BMI) before and after starting SGLT2i. Baseline population characteristics and results are detailed in [Table 1](#).

In our study, we found 14% ( $n = 4$ ) of the patients had elevated BHA without any acidosis (normal serum bicarbonate). To the best of our knowledge this very interesting finding has not been previously reported. Elevation in BHA levels was not associated with patient's age, duration of SGLT2i use, serum creatinine, change in BMI or change in HbA1c. Interestingly all 4 patients with increased in BHA levels were male. SGLT2 inhibitors' proven CV benefits could be potentially related to asymptomatic low grade ketonemia.<sup>3</sup> SGLT2 inhibition induces a rapid increase in urinary glucose excretion, the resultant decrease in circulating insulin levels lead to increased lipolysis, which in turn would increase the rate of ketone body formation in the liver.<sup>4</sup> In addition, patients treated with SGLT2i have higher circulating glucagon levels. Phlorizin, a nonselective inhibitor of the SGLT family transporters has shown to decrease urinary excretion of ketone bodies such as BHA.<sup>5</sup> In the absence of metabolic acidosis, these patients were managed conservatively. Our study provides another point of education for the treating physicians including endocrinologists, emergency physicians and a wider pool of internists that elevated BHA in patients with SGLT2 therapy should not be blindly considered as a surrogate marker for euDKA. Clinical and biochemical correlation with elevated anion gap and acidosis (indicated by low serum bicarbonate levels or pH) should be present to label these patients as euDKA.

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**Table 1** General demographics and results.

Total number of patients (n)	28	
Males (n)	75% (21)	
Mean Age (years) $\pm$ SD	56 $\pm$ 6 years	
Mean Duration of Diabetes Mellitus	8.26 $\pm$ 4.91	
Mean Duration of SGLT2 use (days) $\pm$ SD	207 $\pm$ 103 days	
Mean Creatinine $\pm$ SD	0.83 $\pm$ 0.25 mg/dL	0.5–1.5 mg/dL
Mean Serum Bicarbonate $\pm$ SD	21.7 $\pm$ 2.06 mEq/L	Normal 20–32 mEq/L
<b>HbA1c</b>		
Before SGLT2 use (% $\pm$ SD)	8.2 $\pm$ 1.3	
After SGLT2 use (% $\pm$ SD)	7.3 $\pm$ 0.9	P = <0.001
<b>BMI</b>		
Before SGLT2 use (kg/m <sup>2</sup> $\pm$ SD)	35.0 $\pm$ 6.1	
After SGLT2 use (kg/m <sup>2</sup> $\pm$ SD)	33.1 $\pm$ 6.0	P = <0.001

## Conflict of interest

The authors have no conflicts of interest relevant to this article.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jfma.2019.04.021>.

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