Ketoacidosis in diabetic subjects treated with inhibitors of Na^+-glucose co-transporters type-2: New mechanisms?

Sir,

Ketoacidosis with mild or absent hyperglycemia has been reported in diabetic patients (both type-1 and 2), treated with inhibitors of Na^+-glucose co-transporters type-2 (SGLT-2).[1] SGLT-2 enhances sodium and glucose re-absorption against concentration gradient in the proximal renal tubule, whereas SGLT-2 inhibitors cause increased urinary glucose excretion, thus contributing to systemic glucose lowering.

As explanations for ketoacidosis, some hypotheses have been forwarded. The glucose-lowering effect of SGLT-2 inhibitors may lead to the (inappropriate) reduction of insulin dosage, resulting in enhanced lipolysis and ketone body production. In addition, increased tubular reabsorption and decreased renal clearance of acetoacetate,[2] increased glucagon/insulin ratio, depletion of body energy and carbohydrate stores favoring lipolysis, lipid oxidation[3] and ketogenesis, gastroenteritis-induced dehydration, and, finally, a low carbohydrate diet[2] have been proposed. Indeed, it is well known that ketogenesis can be inhibited by glucose.[4]

However, these hypotheses can be integrated by additional considerations involving the sites of both ketone body production and of the SGLT-2 inhibition effects.

The ketone bodies acetoacetate and 3-hydroxybutyrate are mainly produced by the liver, but also by skeletal muscle, particularly in uncontrolled diabetes.[5] While in muscle, the ketogenic capacity is low when expressed per gram of tissue, it may become quantitatively important given the large muscle mass. Conversely, although SGLT-2 expression/activity has been predominantly located in the kidney, they have also been detected in liver and skeletal muscle in human tissues.[6]

Therefore, I would propose the following integrative mechanism: Treatment with SGLT-2 inhibitors, by reducing glucose uptake (both oxidative and nonoxidative) in peripheral tissues,[3] possibly also in liver and muscle, may favor a switch from glucose to lipid utilization, resulting in increased ketogenesis in these tissues. The decrease of systemic glucose concentration is probably the major cause of reduced glucose utilization. However, a possible direct effect of SGLT-2 inhibitors on SGLT-2-mediated glucose uptake in tissues or organs other than the kidney cannot be excluded "a priori," and might be specifically investigated.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Paolo Tessari

Department of Medicine, Metabolism Unit, University of Padua, 35128 Padova, Italy

Corresponding Author: Prof. Paolo Tessari, Department of Medicine, Metabolism Unit, University of Padua, Via Giustiniani 2, 35128 Padova, Italy.
E-mail: paolo.tessari@unipd.it

References

1. Kalra S, Sahay R, Gupta Y. Sodium glucose transporter 2 (SGLT2) inhibition and ketogenesis. Indian J Endocrinol Metab 2015;19:524-8.
2. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100:2849-52.
3. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499-508.
4. Riou JP, Beylot M, Laville M, De Parscau L, Delinger J, Sautot G, *et al.* Antiketogenic effect of glucose *per se in vivo* in man and *in vitro* in isolated rat liver cells. Metabolism 1986;35:608-13.
5. Nosadini R, Avogaro A, Saccà L, Vigorito C, de Kreutzenberg S, Cobelli C, *et al.* Ketone body metabolism in normal and diabetic human skeletal muscle. Am J Physiol 1985;249 (2 Pt 1):E131-6.
6. Zhou L, Cryan EV, D'Andrea MR, Belkowski S, Conway BR, Demarest KT. Human cardiomyocytes express high level of Na+/glucose cotransporter 1 (SGLT1). J Cell Biochem 2003;90:339-46.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.183465

Cite this article as: Tessari P. Ketoacidosis in diabetic subjects treated with inhibitors of Na^+-glucose co-transporters type-2: New mechanisms?. Indian J Endocr Metab 2016;20:576.