**Name of Journal: *World Journal of Diabetes***

**Manuscript NO: 41841**

**Manuscript Type: EDITORIAL**

# Role of vitamin C in diabetic ketoacidosis: Is it ready for prime time?

Casillas S *et al*.Vitamin C in DKA

Sebastian Casillas, Alan Pomerantz, Salim Surani, Joseph Varon

**Sebastian Casillas, Alan Pomerantz,** Dorrington Medical Associates, Houston, TX 77054, United States

**Sebastian Casillas, Alan Pomerantz,** Universidad Autonoma de Baja California, Campus Otay, Tijuana 22440, Mexico

**Salim Surani,** Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Health Science Center, Texas A and M University, Corpus Christi, TX 78414, United States

**Joseph Varon,** Department of Medicine, Critical Care Services, Medical Branch at Galveston, Health Science Center at Houston, the University of Texas, Houston, TX 77030, United States

**ORCID number:** Sebastian Casillas (0000-0002-7465-1768); Alan Pomerantz (0000-0001-6609-1417); Salim Surani (0000-0001-7105-4266); Joseph Varon (0000-0002-7622-9974).

**Author contributions**: All authors have contributed to the preparation of manuscript, literature search and review for this editorial.

**Conflict-of-interest statement:** The authors have no conflict of interest to declare.

**Open-Access:** This is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

# Manuscript source: Invited manuscript

**Correspondence to: Joseph Varon, FACP, FCCP, MD, Professor**, Critical Care Services, Medical Branch at Galveston, Health Science Center at Houston, the University of Texas, 2219 Dorrington Street, Houston, TX 77030, United States.joseph.varon@uth.tmc.edu

# Telephone: +1-713-6691670

**Fax:** +1-713-6691671

**Received:** August 28, 2018

**Peer-review started:** August 28, 2018

**First decision:** October 16, 2018

**Revised:** October 20, 2018

**Accepted:** November 2, 2018

**Article in press:**

**Published online:**

# Abstract

Diabetic ketoacidosis (DKA) is life-threatening acute metabolic complication of diabetes mellitus (DM) that is characterized by acidosis, ketosis, and hyperglycemia, currently affecting mostly patients under 30 years of age with diabetes mellitus type 1. In both, DM and DKA, a pro-inflammatory state exists. This clinical entity occurs as a result of hyperglycemia-induced disturbances, resulting in an increased oxidative metabolism. For the latter reason, the use of vitamin C seems promising in DKA due to its antioxidant role in reducing the superoxide radicals that are consequence of the oxidative stress. This can decrease the pro-inflammatory state and avoids complications. Vitamin C, or also known as ascorbic acid, has been widely used in several illnesses, such as common cold, tissue healing, fertility, atherosclerosis, cancer prevention, immunity restoration, neuro-degenerative disease and also has been suggested to decrease the risk of DM, and this reason is giving place to believe that vitamin C can have an important role in treating diabetic complications such as DKA. In order to counteract these oxidative disturbances in DKA patients, we analyzed the current data regarding vitamin C and evaluate its role in any type treatment of this complication in the near future.

**Key words:** Vitamin C; Ascorbic acid; Diabetic ketoacidosis; Diabetes mellitus; Diabetes complications

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The use of vitamin C in diabetic ketoacidosis (DKA) has remained controversial due to insufficient clinical data. The lack of concrete evidence, and no randomized controlled trials available on the use of vitamin C for DKA has caused significant controversies and debate. Some preliminary data, however, has shown a decrease in lipid peroxidation and limitation of endothelial damage. There is a significant need for a large randomized clinical trial to evaluate the role of vitamin C in patients with diabetes mellitus and specifically in those with DKA.

Casillas S, Pomerantz A, Surani S, Varon J. Role of vitamin C in diabetic ketoacidosis: Is it ready for prime time? *World J Diabetes* 2018; In press

**INTRODUCTION**

Diabetes mellitus (DM) continues to present a global challenge, with a large number of individuals being diagnosed daily around the world. It is estimated that the number of patients with DM in the world will be 366 million, or approximately 4.4% of the population by the year 2030[1]. A life-threatening complication of DM is diabetic ketoacidosis (DKA), which is an acute metabolic complication marked by acidosis, ketosis, and hyperglycemia. It results from lack of insulin, or insulin resistance along with increased levels of cortisol, glucagon, catecholamine and growth hormone. In addition, this clinical entity may be precipitated by an inadequate insulin administration, infection or other comorbidities (such as acute myocardial infarction, hyperthyroidism, stress)[2].

 In the United States, most patients with DKA (54%-76%) are less than 30 years of age and have type 1 DM, with a mortality rate of less than 1% in hospitalized patients[3]. In these critically ill patients, an increase in the oxidative metabolism is commonly seen[4].

 Ascorbic acid, most commonly known as vitamin C, is a water-soluble antioxidant, which has a role in scavenging superoxide radicals, and has been reported to inhibit low-density lipoprotein oxidation and stabilize the endothelium[4,5]. Vitamin C is essential for the normal physiological function of the body by playing a role in the synthesis and metabolism of tyrosine, tryptophan and folic acid, in addition to hydroxylation of proline, glycine and catecholamine. This vitamin also helps in lowering the cholesterol level by conversion of cholesterol into bile acid[6,7]. Vitamin C has also been widely used in the treatment of common cold, tissue healing, fertility, atherosclerosis, cancer prevention, immunity restoration, and neurodegenerative disease and has been suggested to decrease the risk of developing DM[7]. Furthermore, vitamin C is known to participate in the regeneration of antioxidants molecules such as tocopherol, glutathione, carotenes and urate[8].

**DISCUSSION**

Diabetes is characterized by a pro-inflammatory state, which leads to oxidative stress that results in the production of free radicals[9]. This has been studied in the context of DKA. For example, Lee *et al*[4] studied the degree of oxidative stress by determining the levels of fatty acids in six patients before, during and after DKA, as well as, the levels of vitamin A, C and E during these periods. In this study, lipid peroxidation was noted 24 to 72 h after correction of DKA; In addition, the levels of vitamin C and E were also decreased 24 to 72 h post correction of DKA. These authors suggested that vitamin C and E may play and important role in the presence of oxidative stress in DKA[4].

 Recently, vitamin C has been shown to be beneficial in-patient with septic shock, opening a new era of interest in the role of vitamin C on many other diseases. There are several studies that have clearly documented vitamin C deficiency among patients who are critically ill with sepsis and septic shock[10-12]. To our knowledge, no randomized clinical trial analyzing the role of vitamin C in DM complications, such as DKA, is being done. Prior studies have shown that vitamin C ingestion interferes with testing devices that monitor glucose and ketones, giving false-positive results[13].

 Ceriotti *et al*[14] showed that vitamin C exhibited falsely elevated readings for glucose and beta-hydroxybutyrate in hospitalized patients. Moreover, the use of vitamin C in diabetic patients has remained questionable due to a prior study performed by Beckman *et al*[15] showing that oral intake of vitamin C achieved a low concentration of plasma level, being unlikely to scavenge extracellular superoxide anion.

# CONCLUSION

The use of vitamin C in DKA has remained controversial due to insufficient data collected in recent years. For the latter reason, it has not been applied in the clinical field. We believe that based on the data mentioned above vitamin C supplementation may have a role in patients with DKA. A large randomized controlled clinical trial aimed to identify if vitamin C supplementation in patients with DKA modifies their outcome is needed.

# REFERENCES

1 **Wild S**, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047-1053 [PMID: 15111519]

2 **Meas T**, Taboulet P, Sobngwi E, Gautier JF. Is capillary ketone determination useful in clinical practice? In which circumstances? *Diabetes Metab* 2005; **31**: 299-303 [PMID: 16142023 DOI: 10.1177/2042018816681706]

3 **Fazeli Farsani S**, Brodovicz K, Soleymanlou N, Marquard J, Wissinger E, Maiese BA. Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review. *BMJ Open* 2017; **7**: e016587 [PMID: 28765134 DOI: 10.1136/bmjopen-2017-016587]

4 **Lee DM**, Hoffman WH, Carl GF, Khichi M, Cornwell PE. Lipid peroxidation and antioxidant vitamins prior to, during, and after correction of diabetic ketoacidosis. *J Diabetes Complications* 2002; **16**: 294-300 [PMID: 12126788 DOI: 10.1016/S1056-8727(01)00215-X]

5 **Dalton RR**, Hoffman WH, Passmore GG, Martin SL. Plasma C-reactive protein levels in severe diabetic ketoacidosis. *Ann Clin Lab Sci* 2003; **33**: 435-442 [PMID: 14584758]

6 **Dunitz JD**. Linus Carl Pauling: 28 February 1901 - 19 August 1994. *Biogr Mem Fellows R Soc* 1996; **42**: 317-338 [PMID: 11619334 DOI: 10.1098/rsbm.1996.0020]

7 **Chambial S**, Dwivedi S, Shukla KK, John PJ, Sharma P. Vitamin C in disease prevention and cure: an overview. *Indian J Clin Biochem* 2013; **28**: 314-328 [PMID: 24426232 DOI: 10.1007/s12291-013-0375-3]

8 **Ashor AW**, Werner AD, Lara J, Willis ND, Mathers JC, Siervo M. Effects of vitamin C supplementation on glycaemic control: a systematic review and meta-analysis of randomised controlled trials. *Eur J Clin Nutr* 2017; **71**: 1371-1380 [PMID: 28294172 DOI: 10.1038/ejcn.2017.24]

9 **Gillani SW**, Sulaiman SAS, Abdul MIM, Baig MR. Combined effect of metformin with ascorbic acid versus acetyl salicylic acid on diabetes-related cardiovascular complication; a 12-month single blind multicenter randomized control trial. *Cardiovasc Diabetol* 2017; **16**: 103 [PMID: 28807030 DOI: 10.1186/s12933-017-0584-9]

10 **Marik PE**, Hooper MH. Doctor-your septic patients have scurvy! *Crit Care* 2018; **22**: 23 [PMID: 29378661 DOI: 10.1186/s13054-018-1950-z]

11 **Fowler AA 3rd**, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S; Medical Respiratory Intensive Care Unit Nursing, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014; **12**: 32 [PMID: 24484547 DOI: 10.1186/1479-5876-12-32]

12 **Reynolds PS**, Fisher BJ, McCarter J, Sweeney C, Martin EJ, Middleton P, Ellenberg M, Fowler E, Brophy DF, Fowler AA 3rd, Spiess BD, Natarajan R. Interventional vitamin C: A strategy for attenuation of coagulopathy and inflammation in a swine multiple injuries model. *J Trauma Acute Care Surg* 2018; **85**: S57-S67 [PMID: 29538225 DOI: 10.1097/TA.0000000000001844]

13 **Plüddemann A**, Heneghan C, Price CP, Wolstenholme J, Thompson M. Point-of-care blood test for ketones in patients with diabetes: primary care diagnostic technology update. *Br J Gen Pract* 2011; **61**: 530-531 [PMID: 21801574 DOI: 10.3399/ bjgp11X588600]

14 **Ceriotti F**, Kaczmarek E, Guerra E, Mastrantonio F, Lucarelli F, Valgimigli F, Mosca A. Comparative performance assessment of point-of-care testing devices for measuring glucose and ketones at the patient bedside. *J Diabetes Sci Technol* 2015; **9**: 268-277 [PMID: 25519295 DOI: 10.1177/1932296814563351]

15 **Beckman JA**, Goldfine AB, Gordon MB, Garrett LA, Keaney JF Jr, Creager MA. Oral antioxidant therapy improves endothelial function in Type 1 but not Type 2 diabetes mellitus. *Am J Physiol Heart Circ Physiol* 2003; **285**: H2392-H2398 [PMID: 12881209 DOI: 10.1152/ajpheart.00403.2003]

**P-Reviewer:** Dabla PK, Quintos JB

**S-Editor:** Ma RY **L-Editor:** **E-Editor:**

**Specialty type:** Endocrinology and metabolism

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0