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Betaine Potentials to Prevent Diabetes and Diabetic Complications: What Hindered the Favorable Clinical Trial Outcomes and What to do?

Mina T Kelleni[1,2]*

[1]Department of Pharmacology, College of Medicine, Jouf University, Sakaka, Kingdom of Saudi Arabia

[2]Department of Pharmacology, Faculty of medicine, Minia University, Minia, Egypt

***Corresponding author:** Mina T Kelleni, Department of Pharmacology, College of Medicine, Jouf University, Sakaka, Kingdom of Saudi Arabia, Tel: +966560407874; Email: drthabetpharm@yahoo.com

Editorial

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Editorial

Betaine, also known as trimethylglycine, is a major water-soluble component of Lyciumchinense and widely distributed in animals, plants, and microorganisms. It acts mainly as an important osmoprotectant as well as oxidative metabolite of choline by suppressing superoxide-induced free radicals through donation of methyl groups and was suggested to have beneficial actions in several human diseases, such as obesity, diabetes, cancer, and Alzheimer's disease [1,2]. In 2013, researchers have inversely associated serum choline indiabetic patients with the risks of diabetes and its microangiopathic complications ($p < 0.001$) and though serum betaine was not associated with the risk of diabetes, it had a significant inverse association with diabetic microangiopathy [3]. Other researchers have also shown betaine to reduce hypoxia induced increased relative quantification of leptin gene transcription, reduction of mRNA level of the pro-inflammatory markers IL-6 and TNF-alpha in human adipocytes as well as inhibition of nuclear factor-kappa B activity and NLRP3 inflammasome activation [2,4]. Further, a log-linear relation between baseline betaine excretion and the risk of developing new diabetes during follow-up as well as an association between urinary betaine excretion and glycated hemoglobin showing glycated hemoglobin as the strongest determinant of betaine excretion in patients with diabetes mellitus were also demonstrated [5]. In 2016, plasma betaine levels were shown to be reduced in insulin-resistant humans and correlated closely with insulin sensitivity. Moreover, betaine administration to mice with diet-induced obesity prevented the development of impaired glucose homeostasis, reduced hepatic lipid accumulation, increased white adipose oxidative capacity, and enhances whole-body energy expenditure [6]. Unlike the preclinical studies, in 2018, a small randomized clinical trial on 27 persons with obesity and prediabetes has shown betaine supplementation, 3300 mg orally twice daily for 10 days, then 4950 mg twice daily for 12 weeks, in prediabetes to have a little metabolic effect and further studies were suggested to elucidate the reason [7]. From my point of view, the administered dose of betaine may contribute to this lack of efficacy as betaine aldehyde at concentrations above 500 microMis known to behave as a non-competitive inhibitor against nicotinamide adenine dinucleotide (NAD^+) which is an essential pyridine nucleotide that serves as an essential cofactor and substrate for a number of critical cellular processes involved in oxidative phosphorylation and ATP production, DNA repair, epigenetically modulated gene expression, intracellular calcium signaling, and immunological functions and is depleted in response to either excessive DNA damage due to free radical or ultraviolet attack [8,9]. I also wish to try to look for or synthesize betaine aldehyde dehydrogenase inhibitor(s) to explore the potential of increasing the endogenous betaine concentrations rather than administering betaine supplementations.

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