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News and Views

Sevelamer, a phosphate-binding resin with beneficial effect in diabetic kidney disease; a modern paradigm shift

Azar Baradaran[1], Saeed Mardani[2], Mohammad-Reza Tamadon[3], Heshmatollah Shahbazian[4], Seyed Seifollah Beladi Mousavi[4*]

Implication for health policy/practice/research/medical education

Recent clinical and preclinical investigations have detected glucose and lipid-lowering effects of sevelamer, which imply the role of this drug in the treatment of type II diabetic patients.

The proportion of individuals diagnosed with diabetes mellitus is increasing throughout the world, which sequentially drives upward the global frequency of diabetic kidney disease (1,2). Diabetes is a costly and deadly disease. Patients with diabetic kidney disease are at an increased risk for cardiovascular disease, premature death, and other severe diseases that ensue in increased health-care utilization and frequent hospitalizations (1,2). In fact, type II diabetes mellitus is an ongoing medical dilemma that clinicians deal with on a daily basis and the need for treating diabetes sufficiently is essential because of the many complications and comorbidities associated with uncontrolled diabetes (1,2).

Present modalities focus on controlling hyperglycemia and high blood pressure with the specific use of angiotensin receptor blockers or renin-angiotensin system inhibitors. Although such measures diminish the risk of progressive renal disease, diabetic kidney disease remains the leading cause of end-stage renal disease and the major risk amplifier for mortality in this group of patients (1-4). Hence, new therapeutic interventions based on new findings of the pathophysiology of this disease are necessary.

The preservation of normal metabolism and body defenses depends on the balance between cellular antioxidant and anti-inflammatory factors. This balance can be interrupted by agents and mechanisms in the extracellular milieu that induce additional reactive oxygen species and inflammation (2-5).

Advanced glycation end-products, are formed both inside and outside of the body. Specifically, they originate from glycation reaction, which mentions to the addition of a carbohydrate to a protein without the participation of an enzyme. Glucose is able to bind with proteins in a process named glycation, making less pliable, cells stiffer and more prone to damage and premature aging (3-6).

Advanced glycation end-products, are elements that can be a factor in the development or deteriorating of various diseases, likediabetes, chronic renal failure and atherosclerosis (2-5). In fact, the cytopathic effect of advanced glycation end-products, acts as a major environmental factor that causes excess reactive oxygen species or inflammationwhich induce chronic renal failure or type II diabetes. In diabetic patients, the raised advanced glycation end products levels can also contribute to the excessive cardiovascular disease in this population, by stimulating oxidant stress and chronic vascular inflammation. Various investigations, had revealed that sevelamer binds advanced glycation end products in vitro in a pH dependent manner (3-7).

Advanced glycation end products may be of significant importance in the development and progression of chronic renal failure in type II diabetes, while type 2 diabetes mellitus patients with increased levels of advanced glycation end products have a three-fold increased risk for renal disease and a seven-fold augmented risk for any complication (3-7).

Hence, a drug that blocks advanced glycation end product formation blunts the rise in serum creatinine in patients with type II diabetes mellitus and progressive chronic renal failure, approving the beneficial effects of advanced glycation end product reduction (4-8).

Sevelamer carbonate has shown to reduce HbA1c, advanced glycation end-products, lipids, and TNFα by reduced inflammation and oxidative stress in stage 2-4 diabetic chronic kidney disease (2-7).

Additionally, fibroblast growth factor 23 , serum phosphate and calcium reduced by sevelamer carbonate, in various studies, while fibroblast growth factor 23 is associated with cardiovascular disease and vascular calcification in dialysis and diabetic patients. Furthermore, sevelamer carbonate also diminishes LDL-C and improves insulin resistance. Sevelamer also reduces coronary artery calcification in patients on hemodialysis (2-7).

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[1]Department of Clinical Pathology, Isfahan University of Medical Sciences, Isfahan, Iran. [2]Department of Nephrology, Shahrekord University of Medical Sciences, Shahrekord, Iran. [3]Department of Nephrology, Semnan University of Medical Sciences, Semnan, Iran. [4]Chronic Renal Failure Research Center, Ahvaz Junishapur University of Medical Sciences, Ahvaz, Iran.

***Corresponding author:** Seyed Seifollah Beladi Mousavi, Email: beladimusavi@yahoo.com

Retinal vascular changes are associated with hypertension and diabetes and can predict clinical cardiovascular events consisting myocardial infarction in individuals with diabetes. Investigations had shown that microvascular disease in the retina, named as retinopathy signs, is accompanied with subclinical coronary macrovascular disease, encountered as increased coronary calcification, independently of age, gender, race or ethnicity, blood pressure, and other traditional and nontraditional risk factors (4-7). Likewise it was found that diabetic individuals with retinopathy had significantly higher coronary artery calcification intensity than diabetic subjects without retinopathy. Hence the association of retinopathy with coronary artery calcification supports the idea that, the same pathophysiological processes may relate to both macrovascular and microvascular diseases. Therefore, it has possible that sevelamer abolishes progression of vascular calcification, and affects inflammatory markers, LDL-C, and consequently decrease the incidence of retinopathy in diabetic patients who suffer from high blood pressure (4-7).

The rationale behind this hypothesis is, a direct influence of sevelamer on microvasculature via inflammatory markers, LDL-C and phosphorus reducing capability. An indirect influence on microvasculature as a result of large vessels calcification diminution and finally an indirect eefct influence through hypertension (3-8).

Many individuals with diabetes have concomitant nephropathy. In patients with chronic renal failure, sevelamer is administered in the management of hyperphosphatemia. In a recent study, sevelamer was detected to lower HbA_{1c}, triglycerides and total cholesterol. The mechanism behind of this effect of sevelamer on HbA_{1c} is ill-understood. Sevelamer is likewise a bile sequestrant in addition to being a phosphate binder. Hence, it is possible that, this effect of sevelamer on HbA_{1c} be related to its bile acid–binding ability (3-8).

Sevelamer augments the delivery of bile acids to the distal colon via its bile sequestration capability, thereby promoting glucagon-like peptide 1(GLP-1) release and modulating HbA_{1c} (3-6).

Recent clinical and preclinical investigations have detected glucose and lipid-lowering effects of sevelamer, which imply the role of this drug in the treatment of type II diabetic patients. These properties possibly derived from the bile acid-binding efficacy of sevelamer (4-9).

Authors' contributions

All authors wrote the manuscript equally.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

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References

1. Vejakama P, Ingsathit A, Attia J, Thakkinstian A. Epidemiological study of chronic kidney disease progression: a large-scale population-based cohort study. Medicine (Baltimore) 2015; 94(4): e475.
2. Maezawa Y, Takemoto M, Yokote K. Cell biology of diabetic nephropathy: Roles of endothelial cells, tubulointerstitial cells and podocytes. J Diabetes Investig 2015; 6(1): 3-15.
3. Brønden A, Hansen M, Sonne DP, Rohde U, Vilsbøll T, Knop FK. Sevelamer in a diabetologist's perspective: a phosphate-binding resin with glucose-lowering potential. Diabetes Obes Metab 2015; 17(2): 116-20.
4. Shantha GP, Kumar AA, Kahan S, Cheskin LJ. Association between glycosylated hemoglobin and intentional weight loss in overweight and obese patients with type 2 diabetes mellitus: a retrospective cohort study. Diabetes Educ 2012; 38: 417-26.
5. Vlassara H, Uribarri J, Cai W, Goodman S, Pyzik R, Post J, *et al.* Effects of sevelamer on HbA1c, inflammation, and advanced glycation end products in diabetic kidney disease. Clin J Am Soc Nephrol 2012; 7(6):934-42.
6. Draca N, Lazic R, Simic P, Dumic-Cule I, Luetic AT, Gabric N. Potential beneficial role of sevelamer hydrochloride in diabetic retinopathy. Med Hypotheses 2013; 80(4): 431-5.
7. Alicic RZ, Tuttle KR. Novel therapies for diabetic kidney disease. Adv Chronic Kidney Dis 2014; 21(2): 121-33.
8. Vlassara H, Cai W, Chen X, Serrano EJ, Shobha MS, Uribarri J, *et al.* Managing chronic inflammation in the aging diabetic patient with CKD by diet or sevelamer carbonate: a modern paradigm shift. J Gerontol A Biol Sci Med Sci 2012; 67(12): 1410-6.
9. Thet Z, Win AK, Pedagogos E, Beavis J, Crikis S, Nelson C. Differential effects of phosphate binders on pre-dialysis serum bicarbonate in end-stage kidney disease patients on maintenance haemodialysis. BMC Nephrol 2013; 14: 205.

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