# Verapamil in Diabetes

Sir,

Loss of pancreatic β cells is a pathological hallmark of both type 1 and type 2 diabetes mellitus; however, no specific therapy targeting this defect is yet available. A paradigm shift with such a molecule has always been awaited. Verapamil – a nondihydropyridine calcium channel blocker used in the treatment of hypertension, angina, and tachyarrhythmias, particularly atrial fibrillation – has been observed to show some hope in preventing β cell loss in diabetics by inhibiting thioredoxin-interacting protein (TXNIP).

TXNIP was first cloned in 1994 and the relation with β cells was elucidated in 2002. Pancreatic β cells have a poor antioxidant system and are highly susceptible to oxidative stress. TXNIP inhibits thioredoxin – a redox protein/antioxidant system [Figure 1],[1] and thereby induces oxidative stress. β cells TXNIP expression is strongly induced by glucose and is increased in diabetes. The overexpression of TXNIP in β cells has been shown to promote β cell apoptosis and reduce insulin production,[2] as shown in Figure 1.[1] Genetic deletion or pharmacological inhibition of TXNIP seems to be protective against diabetes. In animal studies, the calcium channel blocker verapamil has been shown to prevent β cell apoptosis in streptozocin-induced diabetic mice; it supposedly promotes β cell survival and improves glucose homeostasis by inhibiting TXNIP expression.[2,3]

Recently, verapamil has also been shown to decrease fasting plasma glucose in diabetic patients in an observational study of 4978 patients – REasons for Geographic And Racial Differences in Stroke (REGARDS). Type 1 diabetics, and type 2 diabetics on insulin with or without oral drugs, who also received verapamil had fasting serum glucose levels that were 24 mg/dL lower than those who did not receive verapamil ($P = 0.039$),[4] correlating with approximately 1% reduction in glycated hemoglobin. In another study of patients with no prior diabetes, oral verapamil use was associated with a lower incidence of type 2 diabetes (6.41 vs. 8.07 per 1000 per year) compared with other calcium channel blockers.[5] Following REGARDS observation, a randomized controlled trial (NCT02372253) is ongoing to study the effect of verapamil in β cell survival in type 1 diabetics focusing on functional β cell mass, exogenous insulin requirements, glycemic control, and TXNIP expression in peripheral blood monocytes.[6] The future of clinical studies holds prospect for verapamil as well as other TXNIP inhibitors to come up as β cell saviors in preventing and treating diabetes. If it proves

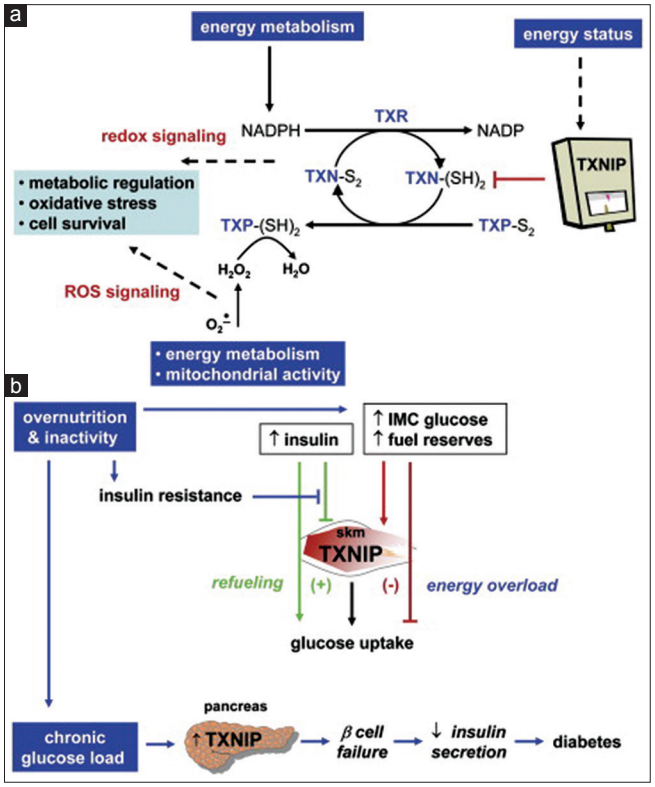


**Figure 1:** Models of thioredoxin-interacting protein action: (a) Role of thioredoxin-interacting protein in the thioredoxin system. Thioredoxin-interacting protein binds and inhibits the reduced form of thioredoxin, thereby functioning as a rheostat that modulates both redox status and reactive oxygen species-mediated signaling to regulate metabolism and other cellular processes. (b) Proposed role of thioredoxin-interacting protein in type 2 diabetes. Chronic glucose load on the pancreas, triggering thioredoxin-interacting protein-mediated β cell failure and overt diabetes. Adapted with permission from[1]

for clinical significance, the use of verapamil can hit two targets in diabetics – hyperglycemia and hypertension.

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## Conflicts of interest

There are no conflicts of interest.

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