

Re: Lovastatin for Reduction of Leptin in Nondialysis Patients With Type 2 Diabetic Nephropathy

IJKD 2014;8:344-9
www.ijkd.org

Dear Editor,

We read with interest the article in the Iranian Journal of Kidney Diseases, by Gholamin and colleagues, "Lovastatin for Reduction of Leptin in Nondialysis Patients With Type 2 Diabetic Nephropathy."¹ There is controversy regarding leptin and vascular endothelial function. Leptin induces endothelium-dependent vascular relaxation by stimulating nitric oxide (NO). However, some believe that the leptin-induced vasodilatation is independent on NO and other vasoactive agents such as endothelium-derived hyperpolarizing factor (EDHF) or prostacyclins are possibly involved.^{2,3} Data indicate a direct vasodilator effect of leptin on endothelium through endothelial NO or other factors. Leptin also stimulates upregulation of endothelin-1 and accumulation of reactive oxygen species.

The effect of leptin on proliferation of vascular smooth muscle cells (VSMCs) is also controversial. A few studies have reported that leptin inhibits cell growth of VSMCs and inhibits proliferation of VSMCs by angiotensin II.⁴ However, more animal studies have shown that leptin induces proliferation and hypertrophy of VSMCs. Leptin increases oxidative stress in vascular cells and promotes VSMC migration and proliferation.⁵ In addition, angiotensin II increases leptin synthesis in rat adipocytes, but the effect of angiotensin II on leptin expression in VSMCs is poorly understood.

Data suggest a close interaction between leptin and insulin signaling, also between hyperleptinemia and hyperinsulinemia. These data indicate that leptin plays a major role in islet cell growth and insulin secretion.⁶ On the other hand, leptin has a key role in controlling and reversing diabetes mellitus, which is also associated with weight loss. Further studies have shown the effect of leptin on glucose homeostasis, which can improve glucose metabolism.⁷ Leptin has direct and indirect effects on peripheral target tissues that contribute to glucose homeostasis. Leptin inhibits insulin and

glucagon secretion from pancreatic β -cells and α -cells respectively. Additionally, leptin affects adipocytes and suppresses insulin signaling and action. Leptin also directly antagonizes hepatic insulin sensitivity.

Direct action of leptin on skeletal muscle is to increase or decrease glucose uptake and insulin stimulated glucose metabolism. Another action of leptin on skeletal muscle is to stimulate skeletal muscle adenosine monophosphate protein kinase, which enhances insulin sensitivity.

Leptin decreases insulin signaling and metabolism in brown and white adipose tissue. Thus, it may have a role in pathogenesis of diabetes and its complications. Diabetic nephropathy is one of the major complications of diabetes and leptin has a role in glomerulopathy and glomerulosclerosis. There are several mechanisms for this complication. Leptin level has positive correlation with insulin resistance; leptin induces expression of tumor growth factor- β and finally it contributes to endothelial cell proliferation and mesangial expansion.⁸

Recent studies suggest that statins might be effective in diabetic patients with nephropathy. Statins have beneficial effects on kidney diseases including diabetic nephropathy. Previous studies have shown anti-inflammatory and antioxidant effects of statins. Al-Azzam and colleagues suggest that atorvastatin has multiple effects on interaction between leptin, adiponectin, and other clinical parameters in patients with type 2 diabetes mellitus. The results of the study, however, are controversial.⁹ Simvastatin significantly increases insulin and leptin levels in patients with hypercholesterolemia, but the study of Koh and coworkers on patients with coronary heart disease suggest simvastatin therapy significantly reduces leptin serum level.¹⁰

Statins are potent inhibitors of 3-hydroxy-3-methyl-CoA reductase and reduce blood leptin level in hypercholesterolemic rabbits and in patients with coronary artery disease. Statins also

suppress leptin expression in adipose cells through mitogen-activated protein kinase.

Angiotensin II induces leptin expression in human VSMCs and atorvastatin can inhibit the leptin expression induced by angiotensin II. The inhibitory effect of atorvastatin on angiotensin II-induced leptin expression is mediated by c-Jun N-terminal kinases, Rac, and reactive oxygen species signaling pathways.¹¹ Statin therapy does not deteriorate insulin sensitivity but significantly reduces adiponectin. In the study by Gholamin and colleagues, lovastatin, 20 mg/d for 3 months, reduced leptin level in nondiabetic nephropathy type 2 compared with placebo, but there were not significant changes in proteinuria and glomerular filtration rate as diabetic glomerulopathy.¹² One important question is what dose of statin and duration of therapy is effective? Do all statins have similar effects? And most importantly, does leptin level reduction leads to improvement of diabetic nephropathy? Previous studies have used atorvastatin, pravastatin, and simvastatin, and in this study, lovastatin was used. Chu and colleagues showed that atorvastatin (10 mg/d, 20 mg/d, and 40 mg/d) did not effectively reduce leptin level in hyperlipidemic patients with type 2 diabetes mellitus.¹² Also, Gannage and associates suggested that pravastatin, 40 mg/d, did not change leptin and adiponectin levels in healthy volunteers.¹³ Therefore, the effect of statins on leptin level is controversial in patients with diabetes mellitus and whether this reduction can influence diabetic nephropathy is uncertain. There is no study that has evaluated the effect of statins through the leptin level in diabetic nephropathy. However, statins with pleiotropic effects, including decreasing oxidative stress and vascular inflammation, can improve endothelial function, decrease the plasma concentration of tumor necrosis factor- α , and might reduce progression of nephropathy apart from serum leptin level. We need a large cohort study on different stages of diabetic nephropathy to address this essential issue.

Farrokhlagha Ahmadi,^{1,2*} Azin Mohebi-Nejad²

¹Division of Nephrology, Tehran University of Medical Sciences, Tehran, Iran

²Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran

*E-mail: ahmadifa@tums.ac.ir

REFERENCES

- Gholamin S, Razavi SM, Taghavi-Garmestani SM, et al. Lovastatin for reduction of leptin in nondialysis patients with type 2 diabetic nephropathy. *Iran J Kidney Dis.* 2014;8:201-6.
- Nakagawa K, Higashi Y, Sasaki S, Oshima T, Matsuura H, Chayama K. Leptin causes vasodilation in humans. *Hypertens Res.* 2002;25:161-5.
- Matsuda K, Teragawa H, Fukuda Y, Nakagawa K, Higashi Y, Chayama K. Leptin causes nitric-oxide independent coronary artery vasodilation in humans. *Hypertens Res.* 2003;26:147-52.
- Rodriguez A, Gomez-Ambrosi J, Catalan V, Fortuno A, Fruhbeck G. Leptin inhibits the proliferation of vascular smooth muscle cells induced by angiotensin II through nitric oxide-dependent mechanisms. *Mediators Inflamm.* 2010;2010:105489.
- Zeidan A, Purdham DM, Rajapurohitam V, Javadov S, Chakrabarti S, Karmazyn M. Leptin induces vascular smooth muscle cell hypertrophy through angiotensin II- and endothelin-1-dependent mechanisms and mediates stretch-induced hypertrophy. *J Pharmacol Exp Ther.* 2005;315:1075-84.
- Ookuma M, Ookuma K, York DA. Effects of leptin on insulin secretion from isolated rat pancreatic islets. *Diabetes.* 1998;47:219-23.
- Shimomura I, Hammer RE, Ikemoto S, Brown MS, Goldstein JL. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature.* 1999;401:73-6.
- Suganami T, Mukoyama M, Mori K, et al. Prevention and reversal of renal injury by leptin in a new mouse model of diabetic nephropathy. *FASEB J.* 2005;19:127-9.
- Al-Azzam SI, Alkhateeb AM, Alzoubi KH, Alzayadeen RN, Ababneh MA, Khabour OF. Atorvastatin treatment modulates the interaction between leptin and adiponectin, and the clinical parameters in patients with type II diabetes. *Exp Ther Med.* 2013;6:1565-9.
- Koh KK, Quon MJ, Han SH, et al. Differential metabolic effects of pravastatin and simvastatin in hypercholesterolemic patients. *Atherosclerosis.* 2009;204:483-90.
- Shyu KG, Chen SC, Wang BW, Cheng WP, Hung HF. Mechanism of the inhibitory effect of atorvastatin on leptin expression induced by angiotensin II in cultured human coronary artery smooth muscle cells. *Clin Sci (Lond).* 2012;122:33-42.
- Chu CH, Lee JK, Lam HC, et al. Atorvastatin does not affect insulin sensitivity and the adiponectin or leptin levels in hyperlipidemic Type 2 diabetes. *J Endocrinol Invest.* 2008;31:42-7.
- Gannage-Yared MH, Azar RR, Amm-Azar M, et al. Pravastatin does not affect insulin sensitivity and adipocytokines levels in healthy nondiabetic patients. *Metabolism.* 2005;54:947-51.