Does nebivolol improve endothelial dysfunction and will it rescue the reputation of the beta-blockers in the future?

Nebivolol endotelyal disfonksiyonu iyileştiriyor mu ve gelecekte beta-blokerlerin şöhretini kurtarır mı?

We have greatly enjoyed reading the article entitled 'Effect Of Nebivolol And Metoprolol Treatments On Serum Asymmetric Dimethylarginine Levels In Hypertensive Patients With Type 2 Diabetes Mellitus' published in current issue of the journal (1). In that clinical study, effects of nebivolol and metoprolol on serum asymmetrical dimethylarginine (ADMA) levels, an indicator of endothelial dysfunction, were compared. A total of 54 patients with type 2 diabetes and hypertension were included into the study. Patients were randomized to receive either nebivolol 5 mg/day (n=28) or metoprolol 100 mg/day (n=26) for 12 weeks. Similar reductions in systolic and diastolic blood pressure were observed in both groups. In nebivolol group, there were no significant changes in serum ADMA levels compared to baseline, whereas in metoprolol group a significant increase in serum ADMA levels was observed.

Normal vascular tonus depends on the equilibrium between the vasoconstrictor and vasodilator molecules released from the endothelium. In healthy endothelium, the balance is shifted towards vasodilatation due to nitric oxide (NO). Endothelial dysfunction is synonymous with the insufficiency of endothelium dependent vasodilatation and results in the failure of vasoactive, anticoagulant and anti-inflammatory effects of healthy endothelium. The most important mechanism for endothelial dysfunction is the decrease in NO availability. The insufficiency of substrate like L-arginine and its the decrease in endothelial cells or any defect in the transport of L-arginine into the cell, the existence of nitric oxide synthetase (NOS) inhibitors like ADMA and NG-monomethyl-L arginine (L-NMMA), increase in the reactive oxygen molecules, the decrease in the diffusion of NO due to intimal thickening, mutations in the eNOS gene expression, increase in the catabolism of NO, cofactor insufficiency and increase in the vasoconstrictor molecules released from endothelium are the other mechanisms that must be considered in endothelial dysfunction (2). Endothelial dysfunction coexists with many disease states in cardiovascular system and is known as the first step of atherosclerosis, which is probably the most important disease of the age. In cardiovascular system, other clinical conditions, related with endothelial dysfunction are hypertension, hyperglycemia- insulin resistance, dyslipidemia, menopause, heart failure, variant angina, cardiac syndrome X, and hyperhomocysteinemia (2).

There is a growing clinical evidence to support the hypothesis ADMA, an endogenous inhibitor of nitric oxide synthase is a new independent cardiovascular risk factor. Endothelial dysfunction due to the reduced bioavailability of nitric oxide is involved in the course of atherosclerotic cardiovascular disease as well as chronic kidney disease (CKD). Nitric oxide is synthesized from L-arginine via the action of NOS, which is blocked by endogenous L-arginine analogues such as ADMA. The ADMA is a naturally occurring amino acid found in plasma and various types of tissues. The plasma level of ADMA is reported to be associated with cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, and chronic kidney disease, and is a strong predictor for cardiovascular disease and the progression of chronic kidney disease (3, 4).

Elevated ADMA levels have been found in animal models of type 1 and type 2 diabetes and in patients with overt type 2 diabetes or insulin resistance (5). Indeed, there seems to be a strikingly close correlation between indices of insulin resistance and ADMA levels (6). Glucose itself may suppress dimethylarginine dimethylaminohydrolases activity (7) and increase ADMA, but the mechanisms by which diabetes or insulin resistance may increase ADMA have yet to be elucidated (8).

Treatment with both selective and non-selective beta-adrenergic blockers significantly increases insulin resistance and basal plasma insulin, despite lowering blood pressure (9). Nebivolol is a new cardioselective beta-blocking agent that has been shown to control blood pressure over 24 hours with a single daily dose (10). Nebivolol has novel cardiovascular properties such as endothelium dependent arterial and venous dilation via L-arginine nitric oxide pathway (9, 11). According to the hemodynamic theory of insulin resistance, these hemodynamic properties could favorably modify insulin sensitivity (12). We have recently showed that, nebivolol, differently from metoprolol, improved oxidative stress, insulin sensitivity, decreased plasma sP-selectin and increased adiponectin levels in hypertensive patients (13). From that standpoint of view, we conclude that nebivolol may improve endothelial dysfunction in hypertensive patients. In the current study, the authors demonstrated that nebivolol did not increase ADMA levels in diabetic hypertensive patients compared to those of the patients taking metoprolol. On the contrary, they found that metoprolol greatly increased serum

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ADMA levels compared to baseline. However, we believe that effect of nebivolol on serum ADMA levels would have been more impressive if the sample size of the study had been large enough. Besides, 3-month treatment period may be relatively short to assess the potentially beneficial effects of nebivolol on serum ADMA levels in that patient group.

In conclusion, although standard beta-blockers seem to having a hard time at present perhaps the new generation beta-blockers such as nebivolol might yet 'rescue' the reputation of the beta blockers in the future. We believe that further large-scale randomized studies are needed to clarify the beneficial effects of nebivolol on endothelial function in patients with cardiovascular disease.

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