INSULIN GLARGINE INCREASES NITRIC OXIDE BIOAVAILABILITY AND REDUCES OXIDATIVE STRESS IN ENDOTHELium FROM DIABETIC RATS

ACC Poster Contributions
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Background: Endothelial cell (EC) dysfunction is a major contributor to vascular disease in diabetes and is characterized by reduced nitric oxide (NO) bioavailability and increased oxidative stress. In this study, we hypothesized that insulin glargine reverses EC dysfunction by restoring glucose control and improving NO synthase function.

Methods: Male rats were treated with streptozotocin (65 mg/kg/BW) to induce diabetes, followed by treatment with insulin glargine (4 U/kg/day) or vehicle for 30 days. Blood glucose levels were measured before and after inducing diabetes and at various intervals throughout the study. Following treatment, aortic and glomerular ECs were isolated, stimulated with calcium ionophore, and assayed for nitric oxide (NO) and peroxynitrite (ONOO-) release using amperometric nanosensor approaches. Changes in EC function were correlated with blood glucose levels.

Results: Glucose levels increased significantly in diabetic rats (483 ± 49 mg/dL) as compared to control animals (108 ± 3 mg/dL) and corresponded to a 56% decrease in body weight. In both aortic and glomerular ECs isolated from diabetic rats, NO bioavailability decreased by ~50% (p<0.001) while ONOO- levels increased by more than 200% ((p<0.001). Insulin glargine reduced glucose levels (129 ± 8 mg/dL), restored body weight and essentially reversed changes in EC function in diabetic animals. In animals treated with insulin glargine, NO release increased by 82% (p<0.001) and 112% (p<0.001) in aortic and glomerular ECs, respectively, as compared to diabetic controls; ONOO- levels decreased by nearly 200% (p<0.001) in both tissue groups. The NO/ONOO- ratio increased by four-fold with insulin glargine treatment in both aortic and glomerular ECs.

Conclusion: Vascular and renal EC function was reduced in diabetic rats in a manner that correlated with loss of glucose control. Insulin glargine reversed these effects and restored NO bioavailability while reducing nitroxidative stress in arterial and renal endothelium.