S28-2 Insulin signaling defect in endothelial cells causes skeletal muscle insulin resistance

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Close coexistence of insulin resistance and endothelial dysfunction throughout the natural history of diabetes and obesity has been reported. Here, we demonstrate that endothelial function mediated by insulin signaling in the endothelial cells participates in the regulation of skeletal muscle insulin sensitivity. Endothelial cell-specific insulin receptor substrate (Irs)2-knockout (ETIrs2KO) and high-fat (HF) diet-fed mice showed endothelial dysfunction, accompanied by impaired insulin-induced endothelium-dependent vascular relaxation, reduced insulin-induced increase of blood flow and decrease in the interstitial concentrations of insulin in the skeletal muscle, and consequently skeletal muscle insulin resistance. Moreover, improvement of endothelial dysfunction ameliorated the aforementioned reduction of insulin-induced blood flow and increased the interstitial concentrations of insulin in the skeletal muscle, resulting in alleviation of the skeletal muscle insulin resistance in these mice. Taken together, it is postulated that endothelial dysfunction caused by a genetically and/or environmentally induced insulin signaling defect in the endothelial cells decreased insulin-induced increase of blood flow and decreased the interstitial insulin concentrations in the skeletal muscle, consequently resulting in skeletal muscle insulin resistance, a novel paradigm of insulin resistance.