Objective: We have shown that local hyperinsulinemia causes vasoconstriction in the microcirculation of healthy humans via endothelin (ET-1) type-B- (ET-B) receptors. We now investigated the role of ET-1-receptors for insulin-mediated vasoconstriction in diabetic patients.

Design and methods: 11 type-II diabetic patients and 13 controls (63±8 vs. 53±5 years) were studied. We used a Laser-Doppler-Imager (moor LDI-V5.0) to measure changes in skin blood flow. $10^{-7}$ IU insulin (INS) were injected intradermally alone or following the ET-A-antagonist BQ123 $10^{-9}$ mol, the ET-B-antagonist BQ788 $10^{-10}$ mol and BQ123 $10^{-9}$+BQ788 $10^{-10}$ mol in combination. Data were analyzed with two-way ANOVA, are presented as arbitrary perfusion units (PU, mean ± SD).

Results: INS produced greater vasoconstriction in diabetics ($P<0.0001$ vs. controls). In controls, BQ123 as well as BQ788 abolished INS-mediated vasoconstriction ($P<0.0001$), with no difference between the antagonists. However, in controls vasodilation to BQ123 vanished in the presence of INS, whereas INS did not influence vasodilation to BQ788. In the presence of BQ123+BQ788, the application of INS in controls resulted in net vasodilation ($P<0.0001$ vs. baseline), which did not differ from vasodilation to BQ123 alone. In diabetics, BQ123 abolished insulin-mediated vasoconstriction ($P<0.0001$). BQ788 reduced but did not abolish INS-effects (BQ788+INS $P<0.0001$ vs. INS and vs. baseline). Neither BQ123 nor BQ788 changed perfusion from baseline in diabetics. BQ123+BQ788 caused vasodilation ($P<0.0001$ vs. baseline) that was slightly reduced by INS ($P=0.043$).

Conclusion: Insulin-mediated vasoconstriction in the microcirculation of diabetics is entirely attributable to enhanced ET-1-activity. While in healthy controls ET-B-receptors seem to be responsible for INS-vasoconstriction, in diabetics ET-A-receptors are also involved.