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Alterations of matrix metalloproteinase-9, transforming growth factor-beta1, plasminogen activator inhibitor-1 and vasomotor responses in insulin resistant patients with diabetic polyneuropathy

P. Tretjakovs[1,2], A. Jurka[1,2], I. Bormane[1], D. Reihmane[1], I. Mikelsone[1], L. Balode[1], J.I. Aivars[1], V. Pirags[1,2] [1] University of Latvia, Riga, Latvia; [2] Pauls Stradins Clinical University Hospital, Riga, Latvia

Background and aims: Insulin resistance (IR) is associated with enhanced matrix metalloproteinase-9 (MMP-9) and plasminogen activator inhibitor 1 (PAI-1) expression, besides transforming growth factor (TGF)-beta1 is a potent inducer of PAI-1 synthesis. IR, PAI-1, MMP-9 and TGF-beta1 are associated with development of microvascular complications of diabetes mellitus (DM). The study aimed to evaluate relationships between IR, MMP-9, TGF-beta1, PAI-1 and cutaneous vasomotor responses (endothelial-dependent vasodilatation and peripheral sympathetic failure) in type 2 DM patients with diabetic polyneuropathy. **Patients and methods:** Type 2 DM patients with IR were divided into two groups: 22 patients with diabetic polyneuropathy (DP) and 22 patients without DP (wDP) (all patients without insulin therapy and without other pronounced diabetic complications or macroangiopathy). 22 healthy subjects were selected as controls (C). The study groups were matched for age and sex. IR was measured by HOMA-IR method (IMx Abbott analyzer), but MMP-9, TGF-beta1, and PAI-1 were measured by xMAP technology (Luminex-200 analyzer). In order to evaluate cutaneous vasomotor responses, we recorded changes in laser Doppler flux (LDF; PeriFlux 4001, Perimed) in the foot. The following variables were measured: basal LDF (b-LDF), post occlusive hyperemia (m1-LDF), vasoconstrictor response (v-LDF) to deep inspiration on the pulp of the toe; and heat (+44 oC; PeriTemp 4005) induced hyperemia (m2-LDF) on the dorsum of the foot. **Results:** b-LDF and local skin temperature were higher in DP group ($p<0.05$) in comparison with C group. Only DP group demonstrated a significant diminution in v-LDF ($p<0.05$), and also only in DP group the decrease of m1-LDF and m2-LDF was significant ($p<0.05$) in comparison with C group. Similarly, in DP group MMP-9, TGF-beta1, PAI-1 levels were elevated ($p<0.05$) in comparison with wDP and C groups. Only the PAI-1 concentrations correlated with HOMA-IR indexes ($p<0.01$). **Conclusion:** Our findings show that insulin resistant type 2 DM patients with DP have significant cutaneous vasomotor dysfunction and abnormal MMP-9, TGF-beta1 and PAI-1 levels, where PAI-1 correlates with IR.