Does changes of dipeptidyl peptidase-4 and IGF binding protein 1 during cardiac rehabilitation can predict recurrent anginal pain – correlation with nitric oxide response – 3 years follow up

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Background: Dipeptidyl peptidase 4 (DPP4) is a proteolytic enzyme, and its expression and activity is increased in coronary artery disease (CAD). Insulin-like growth factor binding protein 1 (IGF BP1) can affect prognosis and mortality from cardiovascular diseases.

Purpose: To evaluate the effects of cardiac rehabilitation on DPP4 and circulating IGF BP1 levels, also on circulating blood marker of endothelial function, nitric oxide (NOx); to assess their relationship and prognostic significance on recurrent chest pain.

Methods: 51 subjects; 31 pts with stable CAD (CAD group; 58.4 ± 6.8 years) and 20 healthy controls (C group; 57.4 ± 8.1 years) were studied. All patients underwent a supervised 3 weeks exercise training. At baseline and after 3 weeks in all pts values of DPP4, IGF BP1 and NOx were determined and exercise test was performed. Clinical long-term follow-up (3 years) was performed. All medical therapy were documented, and for this analysis, we focused on recurrent anginal chest pain.

Results: After follow-up period there were no cardiovascular (CV) hard end points (CV death, MI, stroke), however 18 pts (58%) had episodes of typical anginal chest pain while 13 pts (42%) were without anginal chest pain. Baseline value of DPP4 and IGF BP1 was significantly higher in CAD than in C group ($P<0.01$ and $P<0.01$), while NOx was lower (58.61 ± 7.64 vs 77.28 ± 29.86 μmol/L $P=0.024$). After 3 weeks of exercise training DPP4 decreased significantly in CAD group (from 762.32 ± 185.76 to 604.88 ± 206.18 μg/L, $P<0.001$), as well as IGF BP1 ($P=0.018$) and NOx inreased ($P<0.01$). Those changes resulted in no significant difference in DPP4, IGF BP1 and NOx after three weeks between CAD and C group. Exercise capacity (METs) at baseline was significantly lower in CAD than in C group ($P<0.001$), and it significantly increase in CAD group after exercise period ($P<0.001$). A positive correlation during exercise period was found between IGF BP1 decrease and NOx increase ($r=0.790$, $P<0.001$), between IGF BP1 decrease and DPP 4 decrease ($r=0.880$, $P<0.001$), between IGF BP1 decrease and METs increase ($r=0.866$, $P<0.001$), between DPP 4 decrease and NOx increase ($r=0.975$, $P<0.001$), between DPP 4 decrease and METs increase ($r=0.718$, $P<0.001$), and between METs increase and NOx increase ($r=0.846$, $P<0.001$). Univaried logistic regression analyses were performed and showed that NOx increase (OR 0.842, CI 0.562–0.944, $p<0.01$), DPP4 decrease (OR 0.718, CI 0.644–0.826, $p=0.01$), IGF BP1 decrease (OR 0.695, CI 0.475–0.822, $p=0.002$) and METS increase (OR 0.924, CI 0.788–0.988, $p=0.015$) significantly predict a 3 years period without anginal chest pain.

Conclusion: Residential cardiovascular rehabilitation, in patients with stable CAD, improved endothelial function. Patients with higher increase of NOx and METs, and greater reduction in DPP4 and IGF BP1 after 3 weeks of specialized cardiac rehabilitation, during 3 years follow up, were without anginal chest pain and without any CV event.