Association of GDF15, NTproBNP and PLGF with subclinical cardiac dysfunction in type 2 diabetes: effects of novel antidiabetic treatment

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Background: In type 2 diabetics, we investigated the effects of insulin, GLP-1Ra, SGLT-2i and their combination on blood biomarkers of cardiac function and their association with left ventricular and atrial function.

Patients and methods: A total of 200 diabetics (60.3±10.3-year-old) treated with metformin were randomized to insulin (n=50), liraglutide (n=50), empagliflozin (n=50) or their combination (GLP-1RA+SGLT-2i) (n=50) . We measured at baseline and 6 months post-treatment: (a) perfused boundary region of the sublingual arterial microvessels (marker of endothelial glycocalyx thickness), (b) pulse wave velocity (PWV), (c) Left Ventricular (LV) Global Longitudinal Strain (GLS) and Torsion, (d) LV Global Work Index (GWI), Global Constructive Work (GCW), Global Wasted Work (GWW), Global Work Efficiency (GWE), (e) Left atrial reservoir strain (LASr) and (f) Growth/Differentiation Factor-15 (GDF-15), NTproBNP, Placental Growth Factor (PLGF) as markers of cardiac dysfunction.

Results: Increasing GGDF-15 levels at baseline were related with increasing PWV (r=0.357, p<0.001). Moreover, increasing GDF-15 was related with reduced absolute GLS values (r=-0.425, p=0.005), increased LV Torsion (r=0.309, p=0.035), Twisting Velocity (r=0.345, p=0.018) and E/E' (r=0.307, p=0.041) as well as reduced Untwisting velocity (r=-0.383, p=0.008) and LASr (r=-0.388, p=0.005).

Increasing NTproBNP concentration at baseline was related with increasing PWV (r=0.445, p=0.001 and PBR5-25 (r=0.222, p=0.04) . Also, increasing NTproBNP was related with reduced absolute GLS (r=-0.454, p=0.002), LV GL strain rate (r=-0.360, p=0.008), increased LV Torsion (r=0.329, p=0.029) and E/E' (r=0.365, p=0.021). Increasing NTproBNP was also related with decreasing GWI (r=-0.471, p<0.001), GWE (r=-0.555, p<0.001), Untwisting velocity (r=-0.383, p=0.008) and LASr (r=-0.424, p=0.002).

PLGF concentration at baseline was related with reduced absolute GLS (r=-0.341, p=0.012), LV GL strain rate (r=-0.302, p=0.008) and LASr (r=-0.321, p=0.036).

At 6 months, the reduction of GDF-15 and NTproBNP levels was related with the respective reduction of PWV (p=0.022 and p=0.34).

Furthermore, the reduction of NTproBNP at 6 months was related with an increase of GWI and GWE (r=0.455, p=0.006/ r=0.631, p=0.001, respectively).

In patients treated with GLP-1RA, SGLT-2i and their combination, there was greater improvement of GLS, Torsion, Myocardial Work, LASr, NTproBNP, GDF-15 PLGF compared to patients treated with insulin (p<0.05) post-treatment.

In patients treated with insulin, NTproBNP, GDF-15 and PLGF changes post-treatment were not related with the respective changes of the examined cardiac and vascular markers.

Conclusion: Elevated levels of GDF15, PLGF and NTproBNP are associated with cardiac and vascular dysfunction in patients with type 2 diabetics and their improvement after 6 months of treatment with GLP-1RA and SGLT2i is associated with improved cardiovascular function.