Effect of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors and their combination on markers of neurohumoral activation and left atrial strain

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Background: We investigated the effects of insulin, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and their combination on neurohumoral biomarkers, left ventricular and left atrial function in type 2 diabetes mellitus.

Patients and methods: A total of 200 patients (60.3±10.3 years old, 138 male) with type 2 diabetes mellitus treated with metformin were randomized to insulin (n=50 served as controls), liraglutide (n=50), empagliflozin (n=50) or their combination (GLP-1RA+SGLT-2i) (n=50) as add-on. We measured at baseline and 6 months posttreatment: (a) Left atrial reservoir strain (LASr) (b) serum biomarkers of cardiac function as Growth/Differentiation Factor-15 (GDF-15), NTproBNP, Placental Growth Factor (PLGF).

Results: In all patients, increasing GDF-15 levels at baseline were positively related with NTproBNP (r=0.230, p=0.017), PWV (r=0.357, p<0.001), GLS (r=0.425, p=0.005) and negatively related with LASr (r=-0.388, p=0.005).

Increasing NTproBNP concentration at baseline was positively related with GLS (r=0.454, p=0.002) and negatively related with LASr (r=-0.424, p=0.002).

Treatment with SGLT-2i improved GDF-15 and NTproBNP (2032±187 vs 1803±178 pg/mL, p=0.016, 215±67 vs 124±52 pg/mL, p=0.005, respectively), while treatment with GLP-1RA had a neutral effect on these biomarkers (p>0.05). However, the combined treatment of SGLT-2i with GLP-1RA also improved the examined biomarkers (p<0.05).

Compared to baseline, no significant change in GDF-15 and NTproBNP levels was observed in patients treated with insulin (1815±234 vs 1730±192 pg/mL, p=0.235, 245±43 vs 232±32 pg/mL, p=0.583, respectively).

After intervention, all patients treated with GLP1RA, SGLT2i and their combination improved left atrial reservoir strain (GLP1RA: 30.7±9.3 vs 33.9±9.7%, p=0.011, SGLT2i 30±8.3 vs 32.3±7.3%, p=0.04/ GLP1&SGLT2i:29.1±8.7 vs 31.3±8.2, p=0.007) in comparison with insulin (33±8.3% vs 32.8±7.4, p=0.829).

Conclusions: Treatment with GLP-1RA, SGLT-2i and their combination for 6 months showed a greater improvement of markers of neurohumoral activation and left atrial function compared to insulin, suggesting a role in heart failure prevention.