

Understanding sex-based cardiometabolic responses to contemporary diabetes therapies

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Introduction. The impact of sex is often overlooked in presentation and treatment of cardiometabolic disease. We have demonstrated that contemporary therapies, such as sodium glucose co-transporter 2 inhibitors (SGLT2i), may exert sex- and comorbidity-specific cardioprotection in patients with type 2 diabetes (T2D) when compared to glucagon-like peptide 1 receptor agonists (GLP-1RAs) (Sharma et al., 2023), with the underlying mechanisms unknown.

Aims. To investigate sex differences in phenotype and the effects of SGLT2i and GLP-1RAs in mouse models of metabolic syndrome or type 2 diabetes (T2D).

Methods. The cardiometabolic effects of the SGLT2i, dapagliflozin (moderate dose: 2.5 mg/kg/day; high dose: 5 mg/kg/ day, s.c. osmotic mini-pumps), and the GLP-1RA, liraglutide (1 mg/kg, thrice-weekly s.c. injections), were assessed in male and female high fat diet (HFD) mice (n=8-12 per treatment group), or in female T2D *db/db* mice (n=5-9 per treatment group).

Results. HFD-induced impairment in body composition was more evident in female mice, with dapagliflozin treatment improving glucose tolerance only in male HFD mice. In female T2D mice, both dapagliflozin and liraglutide improved glucose homeostasis with no impact on body weight or composition. However, only SGLT2i treatment improved cardiac function (E/e' ratio, global longitudinal strain) and pathological remodelling (cardiomyocyte hypertrophy).

Discussion. In HFD mice, modest sex differences in disease phenotype and dapagliflozin-mediated improvements in glucose homeostasis were observed. Consistent with our previous report, greater improvements in cardiometabolic phenotype were observed with dapagliflozin treatment in female T2D mice. Our findings highlight the importance of continuing to interrogate sex-based differences in cardiometabolic disease and efficacy of contemporary therapeutics. This allows for the development of more targeted treatment approaches, which is especially important for women, as they are often underdiagnosed and undertreated for cardiometabolic diseases.