colchicine use in our study, suggesting that colchicine's systemic, rather than local, anti-inflammatory effects may be more consequential in ameliorating AT metabolic pathways in MetS. Further studies are warranted to elucidate the biological mechanisms underlying colchicine's effects in AT, as these investigations could potentially shed light on treatments to improve metabolic outcomes in human obesity.

Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Efficacy and Safety of Once-Weekly Subcutaneous Semaglutide 2.4 MG in Adults With Overweight or Obesity (STEP 1)

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Background: Despite the increasing global adverse health impact of obesity, there are few pharmacological options for effective weight management. STEP 1 investigated the efficacy and safety of the glucagon-like peptide-1 analogue, subcutaneous (s.c.) semaglutide, for weight management in adults with overweight or obesity.

Methods: This randomized, double-blind, placebo-controlled, phase 3 trial was conducted at 129 sites across 16 countries (NCT03548935). Adults aged ≥18 years with either body mass index (BMI) ≥30 kg/m^2 or BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity, without type 2 diabetes, were randomized 2:1 to 68 weeks' treatment with once-weekly s.c. semaglutide 2.4 mg or placebo, both as adjunct to lifestyle intervention. The co-primary endpoints were percentage change in body weight and achievement of weight loss ≥5%. Cardiometabolic risk factors, patient-reported outcomes, and safety/tolerability were also assessed. Two estimands were defined: treatment policy (effect regardless of treatment adherence and use of rescue intervention) and trial product (effect assuming treatment adherence and without rescue intervention); results are presented for the treatment policy estimand, unless stated otherwise. P values for parameters marked with # were not controlled for multiplicity.

Results: 1961 randomized participants (mean age 46 years, body weight 105.3 kg, BMI 37.9 kg/m^2; 74.1% female) were included. Mean body weight change from baseline to week 68 was −14.9% in the semaglutide group vs −2.4% with placebo (estimated treatment difference [ETD]: −12.4%; 95% confidence interval (CI): −13.4, −11.5; p<0.0001). Similar results were obtained with the trial product estimand: mean body weight change# was -16.9% for semaglutide vs -2.4% for placebo (ETD: -14.4%; 95% CI: -15.3, -13.6; p<0.0001). Participants were more likely to achieve weight loss ≥5%, ≥10%, ≥15%, and ≥20%# with semaglutide vs placebo (86.4% vs 31.5%, 69.1% vs 12.0%, 50.5% vs 4.9%, and 32.0% vs 1.7%, respectively; p<0.0001 for all). Greater improvements were seen with semaglutide vs placebo in waist circumference, BMI#, systolic and diastolic# blood pressure, glycated hemoglobin#, fasting plasma glucose#, C-reactive protein#, fasting lipid profile#, and self-reported physical functioning (p<0.05 for all). No new safety signals with semaglutide were observed. The most frequent adverse events with semaglutide were gastrointestinal disorders (typically transient and mild-to-moderate).

Conclusion: In adults with overweight or obesity, once-weekly s.c. semaglutide 2.4 mg plus lifestyle intervention induced a mean weight loss of approximately 15% by week 68. Clinically beneficial weight loss of ≥10% was achieved by over two-thirds of participants and ≥20% by one-third of participants, along with associated improvements in cardiometabolic risk factors and physical functioning.

Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Efficacy and Safety of Semaglutide 2.4 MG Once-Weekly in Adults With Overweight or Obesity and Type 2 Diabetes (STEP 2)

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