Exploring phenotypes and mechanisms of fasting and postprandial hyperinsulinemia in young adults with normal glucose tolerance

Hyperinsulinemia often occurs concurrently with obesity and insulin resistance. However, the precise role of hyperinsulinemia in the trajectory of metabolic disease is unclear. Hyperinsulinemia can manifest in both the fasted and postprandial state, yet little is known about these different phenotypes. We explored mechanisms of fasting and postprandial hyperinsulinemia in young individuals without obesity and with normal glucose tolerance.

We screened 147 volunteers (78 females; 69 males, age: 25±5y, BMI: 23.8±2.4kg/m2) via a 2h OGTT. Predetermined cut-offs relating to the 90th percentile of fasting and postprandial insulin were used to classify individuals as having i) normal fasting and postprandial insulin (NI, n=81), ii) normal fasting insulin with isolated postprandial hyperinsulinemia (IPH, n=26) or iii) fasting and postprandial hyperinsulinemia (HI, n=32). Mechanisms of hyperinsulinemia were examined in a subset of individuals (n=40) via a graded glucose infusion (GGI) combined with stable isotope tracer methodology to assess glucose flux. Glucose was infused for 1h at rates of 1, 4 and 8 mg/kg/min to achieve physiological increments in glucose and insulin.

BMI was similar between groups, but body fat percentage was significantly higher in IPH and HI vs. NI (P<0.01). Blood glucose was similarly elevated in all groups during the GGI (P>0.05). Insulin concentrations and insulin secretion rates (ISR) rose significantly and incrementally from baseline during the GGI (P<0.01) with insulin and ISR highest in HI (P<0.05). ISR plotted against plasma glucose demonstrated increased beta-cell sensitivity and responsivity to glucose in HI vs. NI (P<0.05). Glucose flux was similar in all groups at all stages of the GGI.

HI and IPH are not caused by disturbances in glycemia, but rather by increased beta-cell sensitivity and responsivity to glucose. IPH appears as an intermediatory phenotype with future work required to understand the metabolic and cardiovascular health trajectory of those with IPH.