MASLD is a night-time disease driven by nocturnal hepatic, adipose, and skeletal muscle insulin resistance

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Introduction: Rodent models show that hepatic lipid and glucose metabolism are under tight circadian control, yet there are no clinical studies exploring diurnal patterns in functional processes governing intrahepatic lipid accumulation

Methods: 12 patients with MASLD and 12 controls underwent detailed metabolic phenotyping including a 2-step hyperinsulinaemic euglycaemic clamp with stable isotope assessments of glucose utilization during the day (07:00–13:00) and at night (19:00–01:00) under standardised fasting conditions. Identical day and night investigations were performed in MASLD patients after a 12-week weight loss programme.

Results: In MASLD patients, glucose utilization (M/I value) was lower at night compared to day during both low- (1.12 ± 0.36 vs. 2.39 ± 0.54 mg/kg/min per mU/L; p=0.0161) and high-dose insulin infusions (1.40 ± 0.25 vs. 1.95 ± 0.32 mg/kg/min per mU/L; p=0.0189) indicative of night-time hepatic and skeletal muscle insulin resistance respectively. In contrast, control participants had no diurnal differences in glucose utilization. Endogenous glucose production (EGP) was also higher (p=0.0395) and glucose disposal (Gd) lower (p=0.0006) in MASLD patients at night compared to day. MASLD patients had elevated plasma non-esterified fatty acids (NEFA) at night compared to day during basal (p=0.001) and low-dose insulin phases of the clamp (p=0.006) reflecting nocturnal adipose tissue dysfunction. Although MASLD patients had hyperinsulinaemia relative to controls, they also had reduced plasma insulin concentrations at night compared to day despite identical rates of infused insulin. This was explained by striking diurnal differences in the metabolic clearance rate (MCR) of insulin with significantly higher values observed at night compared to day during both low (p=0.0005) and high dose insulin (p=0.0188). Plasma proteomics identified a number of metabolic and immune regulators which are differentially expressed at night compared to day (e.g. GDF15, CXCL5). Following 6% weight loss, MASLD patients exhibited global improvements in insulin sensitivity and adipose function however diurnal differences in M/I values (p=0.02), NEFA (p=0.0080), and MCR insulin (<0.0001) persisted. This suggests that night-time metabolic dysfunction may be a primary driver of hepatic steatosis. Across all

groups, there were no significant differences in calory intake, physical activity, and sleep quality in the week preceding day and night investigations indicating that observed metabolic differences were related to time-of-day rather than external lifestyle factors.

Conclusions: Night-time metabolic dysfunction may represent a unique risk factor for MASLD with greater IR across multiple tissue types observed at night compared to day. This IR is compounded by inappropriate upregulation of insulin clearance at night. These findings will help establish the optimal window for energy intake, exercise, and medication delivery in patients with MASLD.