

Results: Kruskal-Wallis/Dunn test showed a significant difference in BMI between the urban group and the rural ones (KW: $X^2 = 11.987$, $p < 0.001$). Lower average light exposure between 7 am and 5 pm was significantly correlated with higher BMI (Spearman, $r = -0.296$, $p < 0.001$). Also, higher average light exposure at night (from 1 am to 6 am) was significantly correlated with higher BMI (Spearman, $r = 0.256$, $p = 0.002$). **Conclusions:** Our results support the hypothesis that low amplitudes of light exposure may be a risk factor contributing to the high prevalence of obesity worldwide. Studies have previously shown associations between BMI and social jetlag, suggesting the correlations found in our study may be related to higher levels of circadian misalignment, more often present where zeitgeber strength is lower, as in urban environments. Future research is needed to address causal relationships between light exposure and excessive body mass in humans. Provided light exposure is a risk factor for obesity, these results point to potential new targets for intervention and prevention strategies.

Adipose Tissue, Appetite, and Obesity INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Baseline Metabolomic Profile as Potential Biomarker for Weight Change After Roux-en-Y Gastric Bypass Surgery

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Introduction: Weight loss surgery (WLS) has emerged as an effective treatment for severe obesity (BMI ≥ 40 kg/m² in adults) and Type 2 diabetes (T2D). There is a wide spectrum of long-term response, both in weight change and resolution of T2D after WLS. Younger age at surgery, white race and the extent of weight loss prior to surgery are the known traits associated with favorable outcomes. The aim of this study was to investigate untargeted metabolite profile prior to surgery as a potential biomarker for long-term weight change response to WLS.

Methods: Latent class growth mixture modeling (LCGMM) was used to classify the longitudinal weight change trajectories in a cohort of individuals who underwent Roux-en-Y gastric bypass (RYGB). Untargeted metabolite profile was done on a 4-module Liquid Chromatography/ Mass Spectroscopy (LC-MS) platform on the pre-surgery fasting plasma samples from subjects with weight regain or sustained weight loss. Metabolite wide association studies followed by pathway analysis was undertaken using Mummichog and GSEA algorithms. Partial least-square discriminant analysis (PLS-DA), a supervised classification framework used for datasets with thousands of correlated variables and a small number of samples that performs variable selection and classification as a one-step procedure, was used to identify the informative features that defined the two groups.

Results: LCGMM identified 3-classes of weight change in a cohort of 1589 subjects who had undergone RYGB – a) typical trajectory with significant weight loss by 12 months with plateau at ~80% weight loss ($n = 1357$, 85.4%), b) sustained weight loss without plateau (SWL, $n = 116$, 7.3%) c) weight regain (RGN, 116, 7.3%). Samples from 80 subjects each with RGN or SWL (age 42.5 ± 10 years, 55% F, Excess body weight 221 ± 40 lbs) were used for untargeted profiling of 37,570 metabolite features (564 known). After QC and adjusting for age, sex, race and fasting time, 1920 features (37 known) were associated with the weight category at nominal significance ($p < 0.05$). Amongst the known metabolites, the pathways represented in RGN were amino acid metabolism, branched chain and other essential amino acids that have been previously identified as markers of insulin resistance and T2D, while those with SWL were from sphingolipid metabolism. Dimethylguanidino valeric acid, a marker of liver fat and predictor of T2D was higher in individuals with SWL. Pathway analysis of the known and unknown metabolites together revealed pathways in urea cycle, pyrimidine, glutamate, essential amino acids, and butyrate metabolism. Features identified by PLS-DA overlapped with these pathways.

Conclusions: Untargeted baseline metabolites may serve as predictive biomarkers for weight change after RYGB. Future work will focus on developing a metabolite risk score and replication in other cohorts.

Adipose Tissue, Appetite, and Obesity INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

BIO89-100 Demonstrated Robust Reductions in Liver Fat and Liver Fat Volume (LFV) by MRI-PDFF, Favorable Tolerability and Potential for Weekly (QW) or Every 2 Weeks (Q2W) Dosing in a Phase 1b/2a Placebo-Controlled, Double-Blind, Multiple Ascending Dose Study in NASH

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Background: FGF21 is an endogenous hormone that regulates carbohydrate, lipid and energy metabolism. FGF21 analogs improve liver and metabolic abnormalities in non-alcoholic steatohepatitis (NASH). BIO89-100 is a long-acting glycoPEGylated FGF21, with promising tolerability and pharmacodynamic effects and potential for QW or Q2W dosing. **Methods:** This Phase 1b/2a trial enrolled 81 subjects with liver fat $\geq 10\%$ by MRI-PDFF and either biopsy-confirmed NASH (BC-NASH) or phenotypic NASH (PNASH: central obesity with either type 2 diabetes mellitus or with evidence of liver injury by ALT or FibroScan

vibration controlled transient elastography score above defined thresholds). Subjects were randomized to 12 weeks of treatment at one of 6 doses (3, 9, 18 or 27mg weekly [QW]; 18 or 36mg Q2W) or placebo. Key endpoints were safety, tolerability, pharmacokinetics, change in liver fat content as measured by MRI-PDFF and liver and metabolic markers. **Results:** Baseline characteristics were generally similar between pooled BIO89-100 v. pooled placebo groups, and between BC-NASH v. PNASH subjects. At week 13, all BIO89-100 dose groups showed significant relative reductions up to 70% (placebo adjusted $p < 0.001$) in MRI-PDFF. Up to 88% of BIO89-100 subjects achieved $\geq 30\%$ MRI-PDFF reduction v. baseline ($p < 0.001$). Decreased liver fat was accompanied by decreased LFBV of up to 305 mL or 65% from baseline ($p < 0.001$). Significant decreases in ALT vs. placebo were observed with BIO89-100, maximal with 27 mg QW (30 U/L decrease from baseline, $p < 0.001$) and prominent in the subgroup ($n = 17$) with baseline ALT > 45 U/L (35 U/L decrease from baseline, $p < 0.05$). Metabolic benefits of BIO89-100 included a favorable effect on lipids with significant improvements in triglycerides (TG; up to 28% reduction in overall population, up to 49% in the subgroup [$n = 15$] with baseline TG ≥ 200 mg/mL); non-HDL cholesterol and LDL-C (up to 15% and 16%) and increased adiponectin (up to 61%). There were no deaths or related serious adverse events; one BIO89-100 treated subject discontinued due to a related adverse event (localized skin rash). Mild increased appetite (15.9% in pooled BIO89-100) was the most common treatment-related AE. The frequency of gastrointestinal (GI) AEs compared favorably to placebo; diarrhea (BIO89-100 12.7%, placebo 22.2%) and nausea (BIO89-100 7.9%, placebo 16.7%) were the only GI AEs in $\geq 5\%$ BIO89-100-treated subjects. There were no hypersensitivity reactions or adverse effects on blood pressure or heart rate. **Conclusion:** In subjects with NASH, BIO89-100 led to significant and clinically meaningful reductions in liver fat and LFBV assessed by MRI-PDFF with concurrent metabolic benefits. These effects were observed with both QW and Q2W dosing, with a good safety and tolerability profile. A Phase 2b study in NASH is planned and there is an ongoing proof of concept study in patients with severe hypertriglyceridemia.

Adipose Tissue, Appetite, and Obesity INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Cancer Risk of Patients With Overweight and Obesity: A Predictive Model

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Obesity is the most common chronic disease in the U.S. Patients with obesity have many risk factors for cancer, often modifiable. It is important to identify patients with obesity at high risk of cancer to be able to appropriately direct treatment and resources. Given that the risk pool is large, it is imperative to identify a clinically meaningful metric for risk stratification to help guide interventions.

We conducted an observational study of electronic medical records data for 394,161 adults aged between 18 and 80, with BMI ≥ 25 kg/m² and without baseline history of cancer between 2000 and 2019. We first identified a literature-based pool of risk factors for cancer onset and conducted variable selection by applying least absolute shrinkage and selection operator (LASSO) penalized Cox regression with ten-fold cross-validation on an 80% training dataset. Effects of the selected variables on risk of cancer (excluding non-melanoma skin cancer) onset were assessed using Cox regression on the 80% training dataset. The resulting model accuracy was evaluated using Cox regression on a withheld 20% validation dataset.

Participants had a mean age of 46.7 (SD: 15.5) years and mean body mass index (BMI) of 30.5 (SD: 5.4) kg/m²; 51.9% were women. Over a mean of 7.5 years of follow-up, 34,679 (8.8%) of study patients developed cancer. The predictive model achieved a Harrell's C-statistic of 0.73. The greatest risk of cancer incidence was associated with HIV infection (HR 2.22; 95% CI 1.88–2.63; 0.27% of patients), older age (HR 2.05 per 1 SD = 15.5 years; 95% CI 2.01–2.09), hepatitis C infection (HR 1.48; 95% CI 1.34–1.63; 0.96% of patients), and family history of cancer (HR 1.44; 95% CI 1.41–1.48; 42.5% of patients). Additional patient characteristics found in $>5\%$ of patients that also carried risk included proteinuria (5.8% of patients; HR 1.23; 95% CI 1.18–1.29) and history of smoking (40.7% of patients; HR 1.20; 95% CI 1.17–1.23). Each standard deviation increase in BMI (5.4 kg/m²) was associated with a hazard ratio of 1.06 (95% CI 1.05–1.07) for incident cancer.

It is feasible to use predictive modeling to identify patients with overweight and obesity at high cancer risk. This approach could be utilized to guide population management and clinical treatment decisions.

Adipose Tissue, Appetite, and Obesity INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Changes in Visceral Fat and Its Correlation With Changes in Metabolic Variables After Bariatric Surgery

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Obesity is a health problem. There is a relationship between visceral adipose tissue (VAT) and various metabolic components. So far the most effective treatment for weight reduction and control of comorbidities is bariatric surgery. After bariatric surgery there is a reduction in VAT and a correlation with better control of metabolic variables would be expected.

Objective: To determine the decrease in VAT, calculated by bioimpedance at 3 and 6 months after bariatric surgery and its correlation with changes in metabolic parameters (fasting glucose, HOMA, HbA1c, lipid profile). **MATERIAL AND METHODS:** Patients belonging to the HECMNSXXI Obesity Clinic undergoing bariatric surgery during 2020 who agreed to participate in the study were included. VAT volume was determined before surgery and at 3 and 6 months after the