sex, age, BMI, and 24 h sodium urinary excretion in a multivariate analysis, the association of PAI-1 OR 1.090 [1.044–1.137], p< 0.0001) and adiponectin OR 0.634 [0.519 - 0.775], p < 0.0001) with MetS remained significant. Multivariate analyses support a model where PAI-1associate to waist_hip, SBP, DBP, and glucose (all p< 0.0001) and adiponectin associate to TG (p=0.03) and HDL-cholesterol (p=0.0001). **Conclusion:** PAI-1 and Adiponectin rendered the most robust associations with MetS components in a general population, indicating that unfavourable adipose tissue performance is a key contributor to these metabolic anomalies. Further prospective analyses should allow establishing whether these adipocytokines can anticipate the progress of MetS and cardiovascular risk. **Conflict of interest:** The authors declared no conflict of interest. **Funding:** This work was supported by Chilean grants CONICYT Fondo Nacional de Desarrollo Científico y Tecnológico, (FONDECYT) 1160695(CEF) and 1190419(RB); FONDECYT Post-doctorado 3200646(ATC); Millenium Institute of Immunology and Immunotherapy - ICM (P09/16-F)(AK-CEF).

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

Renal Outcomes One Year After Metabolic Bariatric Surgery: A Clinical Audit

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Introduction: Obesity increases the risk of incident chronic kidney disease (CKD), being one of the strongest risk factors for new-onset CKD even in the metabolically normal obese. Weight loss has been shown to reduce renal hyperfiltration and proteinuria. Metabolic Bariatric Surgery (MBS) remains an effective treatment for obesity and its metabolic related complications. However, literature on its impact on long term renal function remains limited.

Methods: This was an observational retrospective study in a tertiary centre in Singapore. MBS cases performed at the centre between 2008 and 2019 were included. The primary outcome measure was estimated Glomerular Filtration Rate (eGFR), calculated using the CKD Epidemiology Collaboration equation, and albuminuria (defined as urine Albumin-Creatinine Ratio (uACR) >3.5 mg/mmol) at baseline and at one-year post surgery.

Results: 557 patients were included. Baseline parameters are as follows: mean age 41.7 ±10.1 years; female 65.4%; ethnic composition: Chinese (35.2%), Malay (33.0%), Indian (26.9%); BMI 42.5 ±7.9 kg/m²; glycaemic status: Diabetes Mellitus (34.5%), Pre-diabetes (13.5%), Non-diabetic (52.1%); Hypertensive status: Hypertension (55.2%), Pre-Hypertension (1.9%), Normotensive (42.9%). Median eGFR was 110.9 (92.4 - 121.5) mL/min/1.73 m² and median uACR was 1.00 (0.40 - 3.55) mg/mmol. At one-year post surgery, patients achieved statistically significant reductions in mean BMI (-11.3 ±4.2 kg/m2), systolic BP (-3.24 ±19.3 mmHg), diastolic BP (-5.23 ±13.8 mmHg), fasting glucose (-1.95 ±2.89 mmol/L) and improvement in HDL (0.29 ±0.26 mmol/L). In addition, statistically significant reductions in the proportion of patients on antihypertensive (48.8% to 14.4%), anti-diabetic (34.1% to 12.7%) and lipid-lowering medications (37.8% to 20.4%) were seen. In particular, ACE-inhibitor and/or angiotensin receptor blocker (32.9% to 9.2%, p< 0.001) usage was reduced. At one-year post surgery, median eGFR increased by 1.66 mL/min/1.73 m² (p<0.001). Further stratification by glycemic status showed significant increases in GFR in patients without diabetes or pre-diabetes. There was a decrease in median uACR (0.30 mg/mmol, p=0.001) at one-year post surgery; this remained statistically significant in patients with diabetes and pre-diabetes. 12.9% of patients had improvements in CKD staging. The proportion of patients with albuminuria decreased from 24.8% at baseline to 1.89% one-year post surgery (p<0.001).

Conclusions: Metabolic bariatric surgery had a positive impact on renal function as shown by the improvement in eGFR in the non-diabetic group, and the reduction in albuminuria in the diabetes and pre-diabetes group at one-year post surgery. More adequately powered, longer-term data is required to investigate the durability of this impact.

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Safety and Tolerability of Concomitant Administration of Multiple-Dose AM833 With Semaglutide 2.4 MG for Weight Management

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Background: Combining weight management medications with different modes of action may provide more effective treatment options for people with obesity. Subcutaneous (sc) AM833, a long-acting amylin analog, and sc semaglutide 2.4 mg, a glucagon-like peptide-1 receptor agonist, are both under clinical development for weight management.

Methods: This was a randomized, double-blind, placebo-controlled, phase 1 trial to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of concomitant administration of six ascending doses of weekly AM833 (0.16, 0.3, 0.6, 1.2, 2.4, or 4.5 mg) + semaglutide vs placebo + semaglutide in subjects with overweight or obesity. The 20-week trial included a 16-week escalation period followed by a 4-week treatment period at target dose and a 5-week follow-up. Eligible subjects were male or female of non-childbearing potential, aged 18–55 years, with BMI 27–39.9 kg/m^2. The primary endpoint was number of adverse events (AE) from baseline to follow-up. Secondary endpoints included PK parameters (area under the curve [AUC] 0–168 h [$AUC_{0\text{-}168}$], maximum concentration [C_{max}], half-life [$t_{1/2}$] and time to C_{max} [t_{max}]). Changes in body weight (exploratory endpoint) were analyzed separately for AM833 0.16–2.4 mg + semaglutide (vs pooled placebo) and AM833 4.5 mg + semaglutide (vs matched placebo) due to a different semaglutide dose escalation regimen used in this treatment arm.
Results: Of 96 subjects randomized, 95 were exposed to treatment (59% male; mean age 40.6 years, body weight 95.7 kg, BMI 32.1 kg/m^2) and 80 (83%) completed the trial. The number of AEs ranged from 37–89 with AM833 (0.16–4.5 mg) + semaglutide and 132 with pooled placebo + semaglutide. Most AEs were mild or moderate and the proportion of subjects with ≥1 AE was similar across treatment arms. About one-third of all AEs were gastrointestinal (GI) disorders (n=207 of 566), primarily nausea, dyspepsia, and vomiting. A greater proportion of subjects reported GI AEs with AM833 1.2–4.5 mg + semaglutide vs placebo + semaglutide. The second most common AEs were injection site reactions (n=72), all mild and not dependent on AM833 dose. Exposure to AM833 was proportional to dose for both $AUC_{0\text{-}168}$ and C_{max}, and did not affect semaglutide exposure and elimination. AM833 0.16–4.5 mg $t_{1/2}$ ranged from 159–195 h and median t_{max} ranged from 24–72 h. At week 20, body weight changes from baseline with AM833 1.2 and 2.4 mg + semaglutide were greater vs pooled placebo + semaglutide (−15.7% and −17.1% vs −9.8%, respectively; p<0.001) and with AM833 4.5 mg + semaglutide vs matched placebo + semaglutide (−15.4% vs −8.0%; p<0.01). Conclusion: Treatment with AM833 at all tested doses + semaglutide was generally well tolerated with an acceptable safety profile. PK data support once-weekly dosing. The combination of AM833 1.2, 2.4, or 4.5 mg + semaglutide led to greater weight loss compared with placebo + semaglutide.

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Serum Levels of Lipocalin Are Lower in Adolescents With X-Linked Hypophosphatemia

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Individuals with X-linked hypophosphatemia (XLH) are at greater risk for being overweight or obese. It has generally been assumed that the primary reason for this is impaired mobility due to accelerated osteoarthritis, abnormal biomechanics of ambulation, pseudofractures and enthesopathy. These known complications limit the ability of patients with XLH to engage in regular aerobic exercise. Whether there are underlying metabolic abnormalities that also put patients with XLH at greater risk for excessive weight gain is largely unknown. A recent French study[1] confirmed that patients with XLH, especially adolescents, have a predilection to obesity. Evidence suggests that elevated circulating levels of fibroblast growth factor 23 (FGF23) are associated with an increase in fat mass and dyslipidemia in elderly normal individuals. Whether the elevated levels of FGF23 in XLH play a direct pathogenic role in the risk for excessive weight gain in XLH is unclear. Lipocalin (LCN2) has recently received considerable attention as a factor regulating energy consumption and specifically is postulated to be anorexigenic and improve insulin sensitivity. We therefore measured circulating levels of LCN2, leptin and insulin in 32 patients with XLH, ages 2–60 y.o., all of whom were being treated with burosumab and 40 Cntrl subjects, matched for age, sex, and BMI or weight/height z-score for children and adolescents. Serum was obtained from excess sample from clinical 25-hydroxy vitamin D testing in our laboratory. All patients were de-identified for the study. In 7 adults with XLH 20–60 y.o. (mean age 35) and 11 Cntrls (mean age 41), mean values for BMI, LCN2, leptin and insulin levels in the two group were as follows, (XLH vs. Cntrl); BMI: 36 vs. 34 kg/m^2, LCN2: 83 vs. 108 ng/mL, leptin: 26 vs. 39 ng/mL, insulin: 19 vs. 20 μIU/mL. The pediatric patients were separated into two groups: 2–10 and 11–18 y.o.. In the 2–10 y.o. group the mean values were (XLH vs. Cntrl); age: 5.5 y.o. vs. 5.8 y.o., weight/height Z-score: 0.8 vs. 1.1, LCN2: 47 vs. 60, leptin: 2.2. vs. 6.7, and insulin: 8.4 vs. 13. In the 11–18 group, mean values were (XLH vs. Cntrl); age: 14 y.o. vs. 14 y.o., weight/height Z-score: 1.0 vs. 1.2, LCN2: 65 vs. 105, leptin: 24 vs.19, and insulin: 17 vs. 48. In all age groups LCN2 was lower in the patients with XLH than Cntrls and this difference reached significance in the adolescents with XLH (p=0.04). No other parameters were significantly different among the groups. Since all patients with XLH were treated with burosumab it is unlikely that a direct effect of excess FGF23 production explains this finding. We conclude that reduced expression of lipocalin in adolescents with XLH may contribute to their risk for obesity.[1]Lecoq et.al. Obesity and Impaired Glucose Metabolism in Adult Patients with X-Linked Hypophosphatemia, J, Endo. Soc. 2020 *https://doi.org/10.1210/jendso/bvaa046.1355*

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Severe Disease Activity and Liver Fibrosis Are Associated With a Lack of Hepatic Mitochondrial Adaptation in Patients With NASH

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