Dysfunctional mitochondrial function is believed to play a vital role in the progression of nonalcoholic steatohepatitis (NASH) to advanced fibrosis and cirrhosis. However, most evidence arises from animal models while there is limited data in humans. The characteristic histological finding of NASH is hepatocellular injury with ballooning and inflammation, often associated with fibrosis in advanced disease. The aim of this study was to assess the role of mitochondrial function (eg, oxidative phosphorylation [OXPHOS] in patients with vs. without NASH and fibrosis. To this end, we recruited 38 patients with NAFLD with risk factors (obesity and/or type 2 diabetes) for NASH (age: 52±12 years; 37% male; BMI: 39.6±8.5 kg/m^2; HbA1c: 6.8±1.4%) in whom we assessed mitochondrial respiration and also performed measurements of insulin resistance (IR). Tissue was obtained by either a Tru-cut percutaneous liver biopsy (n=26) or a wedge biopsy during bariatric surgery (n=12). After tissue was separated for histological diagnosis, small liver samples (2–4 mg) were processed to quantify OXPHOS by measuring the mitochondrial oxygen consumption rate in individual complexes of mitochondria, expressed as pmol×mg wet weight^{-1}×s^{-1}, using high-resolution respirometry, Oxygraph-2k. Based on liver histology, patients with NASH (n=18) compared to without NASH (n=20), had worse hyperinsulinemia and HOMA-IR (25.2±10.5 vs 14.9± 6.7 μU/ml and 8.9±4.3 vs. 4.9±2.9 mg/dl × μU/ml, respectively) and higher OXPHOS (all p<0.05), although well matched for age, BMI, HbA1c and % with diabetes. This was likely an adaptation to IR and higher FFA flux to the liver. We then examined patients based specifically on disease activity, using a combined score of hepatocyte ballooning and inflammation (necroinflammation score [NIS]) and divided as mild (n=16), moderate (n=14) or severe (n=8) NIS (also well matched for relevant clinical parameters). Patients in the moderate vs. mild NIS group disease activity had increased mitochondrial respiration as represented by OXPHOS (45.9±11.8 vs. 31.3±9.8), electron transport chain activity (ETC) (61.0±17.6 vs. 46.4±15.2) and state 3 respiration induced by ADP (20.7±4.9 vs. 16.4±4.6 pmol×mg wet weight^{-1}×s^{-1}; all p<0.05). There was a trend for these parameters to decline in patients with severe vs. moderate disease activity, that was further accentuated when patients with NASH also had clinically significant fibrosis compared to those with mild or no fibrosis (OXPHOS: 37.9±7.8 vs. 49.8±12.5, p=0.04; and ETC: 49.8±13.4 vs. 67.5±16.1, p=0.02). Conclusion: In patients with NASH, there is an early hepatic mitochondrial adaptation to account for the state of more severe insulin resistance in steatohepatitis compared to simple steatosis. This adaptation is impaired when disease activity worsens and is most evident once patients develop steatohepatitis with significant fibrosis.

Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

The Absence of Cortisol Awakening Response Is Associated With Personality Traits in Bariatric Women

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Background: There is a large body of evidence linking obesity to the HPA axis and cortisol secretion or metabolism. Early work hypothesized that obesity onset may be associated with over-activation of the HPA axis, causing an extenuation of the system. The cortisol awakening response (CAR) has been suggested to be a reliable marker of HPA axis activity and has already been examined in samples of individuals with obesity. Our objective was to compare individuals showing a morning cortisol peak (CAR responders) from those who did not (non-responders) and identify possible metabolic or psychological differences among these two groups. Our hypothesis was that the two groups differed in the level of anxiety and aspects of their personality rather than in their metabolic profile. **Methods:** CAR response was determined using a baseline to peak cut-off of 2.5 nM. Nine CAR non-responder women awaiting bariatric surgery (BMI: 50.8 ± 4.6 kg/m^2) were compared to 9 sex- and age-matched CAR responders (BMI: 48.1 ± 5.9 kg/m^2). Participants collected salivary cortisol upon awakening as well as 15, 30 minutes after and responded to psychological questionnaires that measured anxiety (State and trait anxiety inventory questionnaire) and personality traits (Temperament and character inventory). **Results:** Non-responders were all non-diabetic women aged 37 ± 8 years. There was no significant difference between CAR responders and non-responders in terms of BMI or waist circumference. No difference was found in metabolic variables such as glycaemia or the lipid profile. As expected, non-responders had a significantly lower CAR AUCi when compared to responders (p<0.001). However there was no difference in awakening cortisol concentration. Despite our hypothesis, no significant difference was found in general level of anxiety between the two groups. Finally, we analyzed aspects of human personality. We found that CAR responders scored significantly higher in character traits such as self-directedness (p=0.02), cooperativeness (p=0.03) and self-transcendence (p<0.01). **Conclusion**: The CAR differences in women with severe obesity are not associated with adiposity. Our data show that non-responders exhibit traits related to reduced self-determination and responsibility but also lower level of self-consciousness and helpfulness, which could be associated with a reduction in patient compliance and possibly less weight loss after surgery.

Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

The J-Shaped Relationship Between Body Mass Index and Mortality in Patients With Covid-19: A Systematic Review and Dose-Response Meta-Analysis

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Introduction: Several studies have linked obesity to more severe illness and higher mortality in COVID-19 patients. However, the relationship between being underweight and COVID-19 mortality remains inconclusive. Previous dose-response meta-analyses did not enroll or specifically analyze the underweight population. Herein, we conducted a systematic review and dose-response meta-analysis to investigate the relationship between body mass index (BMI) and mortality in both obese and underweight patients with COVID-19. **Methods:** We searched PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases from inception until August 12, 2020 using the keywords "COVID-19," "body mass index," "obesity," "overweight", and "underweight." Three reviewers independently assessed the relevant articles, including the title, abstract, and full text, to identify eligible studies. We performed a two-stage random-effects dose-response meta-analysis, including only studies with at least three quantitative classifications for BMI. The nonlinear trend was evaluated using a restricted cubic splines model with three-knots at the 10th, 50th, and 90th percentiles. A sensitivity analysis was conducted by pooling only those studies which specifically evaluated underweight patients (BMI<18.5 kg/m^2). **Results:** Thirteen studies comprising 25,828 patients were included in the analysis. In the linear model, the mortality of patients with COVID-19 increased by 1.5% for each 1-kg/m^2 increase in BMI (pooled relative risk [RR] =1.015, 95% confidence interval [CI] =1.004−1.027). However, a significant non-linear relationship between BMI and mortality was observed (Wald test: $P_{non\text{-}linearity}$<0.001). We demonstrated a J-shaped curve, indicating that both underweight and obese patients had a higher mortality than those with normal weight. Interestingly, overweight patients (BMI, 25−30 kg/m^2) seemed to have the lowest mortality risk. Using a BMI of 15 kg/m^2 as the reference, the RRs of mortality decreased with BMI, and this trend continued until BMI of approximately 28 kg/m^2 (RR=0.743, 95% CI=0.576−0.959). The relationship between BMI and mortality was then reversed, and an upward trend was observed when BMI exceeded 30 kg/m^2; the RRs (95% CI) at BMIs 30, 35, 40, and 45 kg/m^2 were 0.745 (0.570−0.974), 0.841 (0.643−1.100), 1.082 (0.850−1.377), and 1.457 (1.129−1.879), respectively. **Conclusion:** This study is the first dose-response meta-analysis that showed both underweight and obese COVID-19 patients are at higher risk of increased mortality. A J-curve relationship was demonstrated between BMI and COVID-19 mortality.

Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

The Long-Term Safety and Efficacy of Metreleptin in Various Forms of Partial Lipodystrophy

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Metreleptin is an approved treatment for patients with generalized lipodystrophy but still under investigation for patients with partial forms of the disease in the US. This open-label single-arm study in partial lipodystrophy (PL) allowed continued treatment of patients who volunteered and completed treatment under our previous 1-year protocol and who derived significant clinical benefit. The primary outcome was percent change in fasting triglyceride levels and the secondary outcome was percent change in hemoglobin A1c levels (time frame: 5 years on metreleptin or last observation carried forward in both instances). The hypothesis was that these metabolic parameters would stay stable over the observation period. The study enrolled 11 participants (11 females; 3 ≤ 18 years; 8 between 18–65 years). Four patients had familial partial lipodystrophy type 2 (FPLD2) caused by *LMNA* pathogenic variants (R482Q in two subjects, R482W in one subject, and R349W in one subject), two patients had *POLD1* associated PL (E1067K), four patients had FPLD1, and one patient had atypical PL. Variants of uncertain significance (VUS) in genes of interest were detected in two patients with FPLD1 and one patient with atypical PL. Four subjects completed 48 months (actual 60 months on metreleptin). Data from 3 subjects were excluded from final data analyses due to early loss to follow-up (n = 1), serious adverse event withdrawal (n = 1; development of persistent neutralizing antibody shortly after 18 months of drug exposure), and death (n = 1). The remaining 4 subjects withdrew from the study either through their own volition or due to the investigator decision (last observation carried forward in these 4 subjects). As expected, the median percent change from baseline triglyceride and hemoglobin A1c levels were not significant (55.76 percent (range: -66.79 to 203.80; $p > 0.05$), and 2.55 percent (range: -27.52 to 25.00; $p > 0.05$), respectively). Serious adverse events were reported in 8 of 11 patients and additional adverse events were observed in all patients. Apart from neutralizing antibody development in one subject causing substantial metabolic derangement, adverse events were considered not to be directly related to the study drug. Death was caused by a sudden cardiac event related to the specific molecular etiology (*LMNA* R349W) in one case. This interventional study provided valuable information on the efficacy and safety of long-term metreleptin in PL. Although nonsignificant fluctuations were observed in triglycerides, hemoglobin A1c levels were generally stable over time and the initial improvement seen in the first year were sustained. Adverse events were common but more likely due to the complex nature of the underlying disease. Although rare, neutralizing antibodies can develop in patients with PL treated with metreleptin.