**MIR204 POTENTIALLY PROMOTES NON-ALCOHOLIC FATTY LIVER DISEASE BY INHIBITION OF CPT1A IN MOUSE HEPATOCYES**

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**Objective:** Non-alcoholic fatty liver disease (NAFLD) is associated with hepatic metabolism dysfunction. However, the mechanistic role of miR204 in the development of NAFLD is unknown. We investigated the functional significance of miR204 in the evolution of NAFLD.

**Design and method:** NAFLD was induced in isocitrate dehydrogenase (IDH2) knockout (KO) mice by feeding them with a high-fat diet (HFD). Blood parameters and hepatic fat accumulation were evaluated in IDH2 KO mice and wild-type (WT) mice. A miR204 inhibitor was subcutaneously injected into mice using an osmotic pump. The expression of miR204 was analyzed by quantitative PCR (qPCR).

**Results:** IDH2 KO mice fed a normal diet (ND) or HFD showed significantly increased body weight, epididymal fat-pad weight, cholesterol, triglyceride, and macrophage marker (CD68), and inflammatory cytokine (tumor necrosis factor-a (TNF-a), interleukin (IL)-6 and IL-1b) expression compared to WT mice fed a ND or HFD. Moreover, the expression of miR204 was significantly increased in mice with IDH2 deficiency. miR204 regulates carnitine palmitoyltransferase 1a (cpt1a) synthesis, which inhibits fatty acid b-oxidation. Inhibition of miR204 prevents the disassembly of two fatty acid-related genes—peroxisomal acyl-coenzyme A oxidase 1 (ACOX-1) and peroxisome proliferator-acivated receptor alpha (PPARα)—by activating CPT1a expression, which decreases inflammatory cytokines, epididymal fat pad weight, cholesterol, low-density lipoprotein (LDL), and triglycerides.

**Conclusions:** miR204 promotes the pathogenesis of HFD-induced NAFLD by regulating hepatic metabolism and inflammation.

**CHREBP/CHREBP beta expression mediates the paradoxical effect of fructose on body weight of fructose-fed rats by brown adipose tissue activation**

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**Objective:** Western diet fructose content is a neglected nutrition component, with metabolic dysfunction. However, the mechanistic role of fructose in the regulation of hepatic metabolism and inflammation. CHREBP (ChREBP beta) is recognized now as the regulator of fructose metabolism. Brown adipose tissue (BAT) plays a key role in the regulation of fructose metabolism. CHREBP expression is associated with activating BAT and improving metabolic status. On the other hand, increased CHREBP beta seems to have a deleterious metabolic effect on BAT.

**Design and method:** Sprague-Dawley male rats, 8 weeks old were fed High Fructose Diet (HFD) or match regular chow for 6 weeks (n = 8). Body weight (BW) and precise food intake were measured weekly. Brown (peri-aortic and interscapular, PA and IS respectively) and white (mesenteric) AT were collected for further molecular studies.

**Results:** HFD-fed rats gain significantly less weight than the control group (from 236±2 to 397±8 vs. 233±2 to 430±9 gr. p<0.05) despite eating an equal food amount (23±1 vs. 29±1.5 g/rat/week). The expression of uncoupling 1 (UCP1) mRNA, a BAT activation marker, was significantly higher in BAT than in WAT. Fructose consumption increased its BAT expression compared to regular chow. However, the expression of CHREBP and CHREBP beta in BAT was significantly lower in HFD-fed rats.

**Conclusions:** In the HFD rat model of MeS, fructose consumption leads to lesser weight gain for the same caloric intake. This BW difference is accompanied by the activation of BAT in the HFD group. This paradoxical effect may be regulated by decreased CHREBP/CHREBP beta expression in response to fructose.

**IMPACT OF PROLONGED NOCTURNAL HYPOXEMIA ON LONG-TERM CLINICAL OUTCOMES IN PATIENTS WITH PRE-CAPILLARY PULMONARY HYPERTENSION**

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**Objective:** Obstructive sleep apnea (OSA) and/or nocturnal hypoxemia is prevalent in patients with pulmonary hypertension (PH). However, the pathophysiologic determinants of adverse outcomes remain ambiguous. We aimed to investigate the prognostic significance of various sleep parameters for long-term prognosis in patients with pre-capillary PH.

**Design and method:** Consecutive patients diagnosed with precapillary pulmonary hypertension (PH) by right heart catheterization who underwent overnight cardiorespiratory polygraphy for the assessment of OSA were enrolled. Time-to-event analysis was performed investigating cardiorespiratory indices (apnea-hypopnea index [AHI] and percentage total recording time <90% [T90]) and clinical worsening using the log-rank test and multivariable Cox proportional hazard models adjusted for multiple confounders.

**Results:** Of 440 eligible Chinese patients with PH, 134 (30.5%) had OSA and 147 (33.4%) had nocturnal hypoxemia (T90 greater than 10%). Over a median follow-up of 12.1 months, 72 (16.4%) patients experienced clinical worsening. AHI did not predict a higher risk of incident PH (Hazard ratio [HR]: 0.98, 95% confidence interval [CI]: 0.93-1.01, P = 0.225), whereas T90 was associated with an increased risk of PH (HR: 1.01, 95% CI 1.00-1.01, P = 0.018). The likelihood of CHW increased by 8% per 10-unit increase in T90 (90: 1.08, 95% CI 1.02-1.014, P = 0.018). Patients with nocturnal hypoxemia carried an HR of 1.89 for CHW events (HR: 1.89, 95% CI 1.19-3.00, P = 0.007) and these associations persisted after covariates adjustments. Clinical worsening-free survival probability over two-year follow-up periods for patients with nocturnal hypoxemia were 87% and 76.9%, respectively (Log-rank P = 0.006), while the trend towards a non-statistical significance of patients with and without OSA. The association of nocturnal hypoxemia reflected by T90 and CHW remained robust across different subgroups and did not potentially interact with potential effect modifiers including age, gender, BMI, and pulmonary hemodynamic parameters (P for interaction >0.05).

**Conclusion:** In patients with precapillary PH, nocturnal hypoxemia defined by T90 was a robust risk predictor of long-term clinical worsening. Investigation of nocturnal hypoxic burden in PH may aid in the early risk-stratification in patients with precapillary PH.

**THE IMPACT OF OBESITY ON THE CONTROL OF TREATED HYPERTENSIVE PATIENTS**

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**Objective:** Obesity is as a risk factor for hypertension, but there are few studies evaluating its impact on the response to antihypertensive drug and on the control of hypertensive patients. The aim of our study was to determine the effect of obesity on the control of treated hypertension.

**Design and method:** We analyzed recordings of ambulatory blood pressure measurement (ABPM) in 84 treated hypertensive patients aged > 18 years, in the cardiology department of Mohamed Taher Maamouri University hospital in Nabeul. Patients were stratified into two groups: obese (Body Mass Index (BMI) >30 Kg/ m2) and non-obese. Hypertension control is defined by 24-hour ambulatory blood pressure (BP) <130/80 mmHg, daytime <135/85 mmHg and nighttime <120/70 mmHg.

The comparisons of percentages were carried out by the Chi-square test.

**Results:** Our Population was composed of 33 obese and 51 non-obese patients. The mean age of our population was 59.37±13.1 years. BMI in obese was significantly higher than in non-obese (34.47±5.4 versus 25.36±2.5; p<0.001). The prevalence of uncontrolled patients was significantly higher in obese patients detected in 24-hour ABPM (75.8% versus 51%; p = 0.039), in daytime ABPM (69.7% versus 41.2%; p = 0.014) and in night-time ABPM (90.9% versus 68.6%; p = 0.018) than in normal weight patients.