Impact of body mass index on cytochrome P450 3A phenotype

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Background

There is a large interindividual variability in CYP3A phenotype (CYP3A4 and CYP3A5) and high body mass index (BMI) is associated with low CYP3A4 expression in both the liver and the small intestine.

Aim

The aim of this study was to study the impact of BMI on CYP3A phenotype, measured as cholesterol-adjusted plasma levels of 4β-hydroxycholesterol (4βOHC); an endogenous CYP3A biomarker, and C4 midazolam (MDZ); the golden standard CYP3A biomarker, in obese patients and in normal weighted controls.

Methods

- **Plasma samples** from **40 obese patients** initiating a 9-week low and very low calorie diet, and from **18 normal weighted controls**, were included in the study.
- **4βOHC and MDZ** were measured by ultra-performance liquid chromatography-tandem mass spectrometry in samples collected at baseline and after 1, 2, 4, 12 and 24 months.
- **Wilcoxon signed rank tests** were used to compare paired 4βOHC to cholesterol ratios (4βOHC/C), C4 MDZ and BMI between the different time points.
- **Spearman's rank correlation tests** between 4βOHC/C, C4 MDZ and BMI were performed in both groups at baseline.

Results

- Median 4βOHC/C at baseline was significantly lower compared to the medians at the five follow-up time points (P<0.01, **Fig 1a**), and median C4 MDZ was significantly higher at baseline compared to the medians at the follow-up time points (P<0.03, **Fig 1b**).
- Median BMI was significantly higher at baseline compared to the medians at the follow-up time points (P<0.0001, **Fig 1a and 1b**), except of after 24 months (P>0.1, **Fig 1a**).
- In the group of obese patients, there was no correlation between 4βOHC/C and BMI (P>0.2, **Fig 2a**), but there was a significant negative correlation between C4 MDZ and BMI (P<0.01, **Fig 2c**).
- A significant correlation between 4βOHC/C and BMI was observed in the group of normal weighted controls (P<0.02, **Fig 2b**), while there was no correlation between C4 MDZ and BMI in this group (P>0.8, **Fig 2d**).

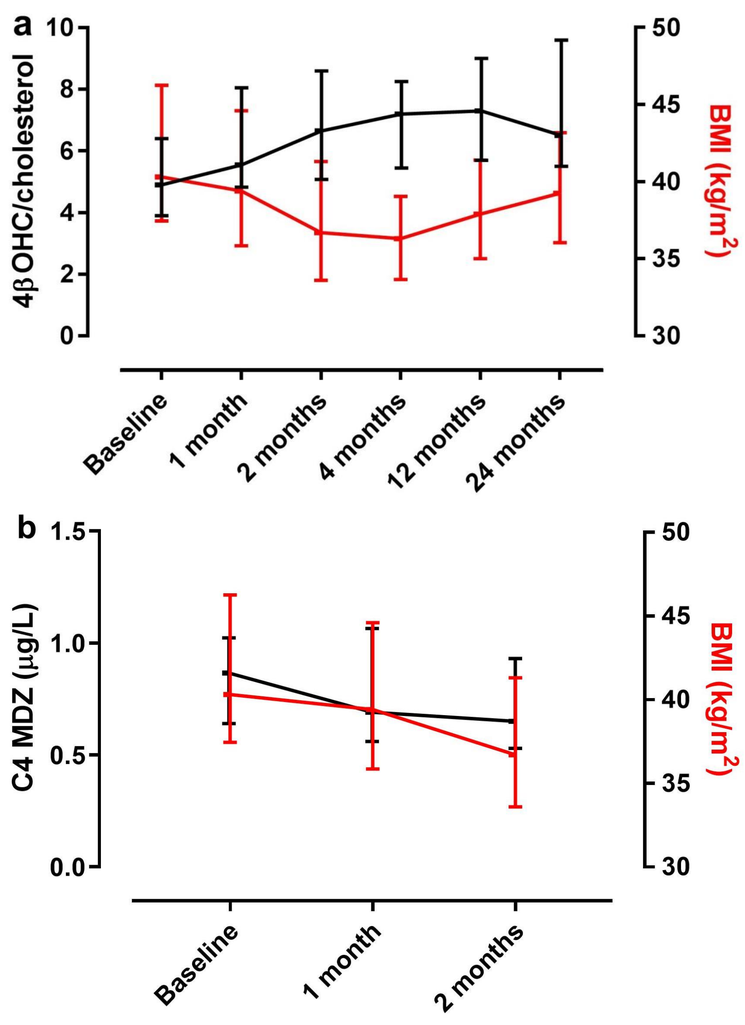

Figure 1. 4β-hydroxycholesterol (4βOHC) to cholesterol ratios (**a**), C4 midazolam (MDZ) (**b**) and BMI (**a and b**, right y axis) over time, in 40 obese patients initiating a low and very low calorie diet. Data presented as median IQR.

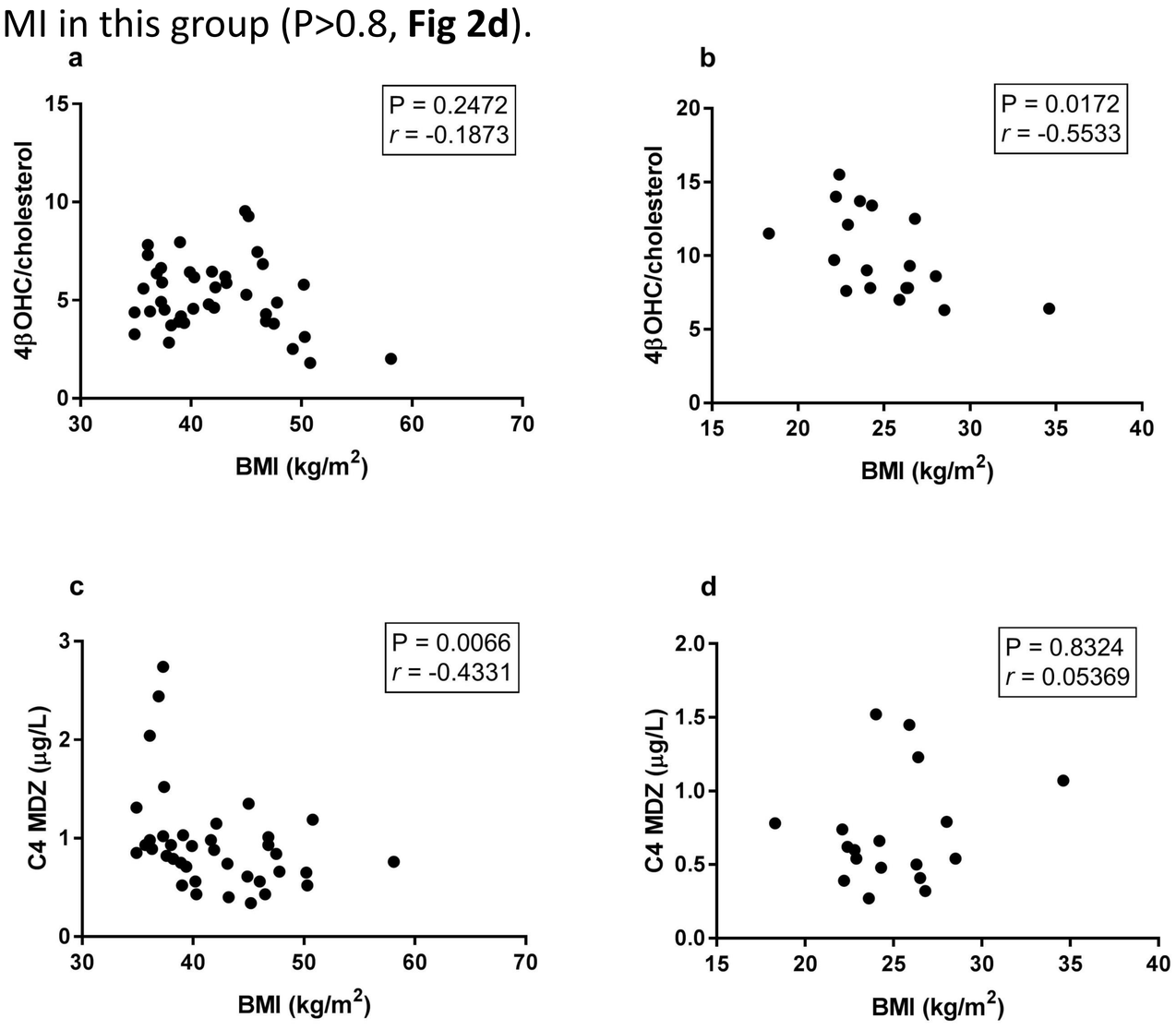

Figure 2. Correlations between 4β-hydroxycholesterol (4βOHC) to cholesterol ratios, C4 midazolam (MDZ) and body mass index (BMI), in 40 **obese patients** (**a and c, left panel**), and 18 **normal weighted controls** (**b and d, right panel**) at baseline. Estimated *r* and P values from Spearman's rank correlation tests are added on each illustration.

Conclusion

CYP3A activity increased in obese patients after initiation of a low and very low calorie diet. The changes were inversely related to the corresponding changes in BMI, however, plasma C4 MDZ, and not 4βOHC/C, was significantly correlated to BMI in the group of obese patients, whereas in the group of normal weighted controls, 4βOHC/C was significantly correlated to BMI and not C4 MDZ. A likely explanation of the latter finding is differences in sensitivity between the biomarkers to reflect CYP3A phenotype during the inflammatory state associated with obesity.