

Occult Hepatic Steatosis

How can we distinguish true treatment emerging liver signals from undetected, unrelated liver abnormalities?

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Background

Hepatic steatosis is fat accumulation in the liver, in the absence of significant alcohol consumption, hepatocyte injury, or inflammation [1]. It is a largely benign condition affecting up to 25% of the European population [2].

Epidemiological and clinical studies have established a correlation between fat deposition in the liver and elevated serum alanine transaminase (ALT) [3], therefore serum ALT has been proposed as a biomarker for hepatic steatosis, however in most cases hepatic steatosis correlates poorly with transaminase levels.

There is evidence that hepatic steatosis and steatohepatitis can affect drug metabolism [4].

When conducting clinical trials, the inclusion of volunteers with unknown liver abnormalities could impact data quality.

- Variability in pharmacokinetic data or derangement of liver markers may be misattributed to the drug being tested and therefore cast doubt over the viability of developing this treatment further. This in turn may lead to the discontinuation of development of a much needed new medicine.

It is desirable to find screening tests which more reliably identify hepatic steatosis.

Methods

We are conducting a prospective longitudinal study of individuals wishing to take part in future clinical trials. The final number of individuals was not restricted, and volunteers enrolled in this project were not obligated or guaranteed to take part in future studies.

- Subjects eligible if they were aged between 18 and 70, with no restrictions based on sex.

The cohort reported here consisted of 42 healthy Caucasian and Japanese volunteers throughout 2019. One was female and 41 were male.

Generic (i.e. not trial specific) screening was carried out:

- Routine measurements of liver markers (ALT, aspartate transferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], prothrombin time and albumin), body weight and BMI.
- Presence and severity of hepatic steatosis was determined using liver ultrasound and was reported by the sonographer.
- All assessments were carried out during a single, non-residential visit.
- Subjects fasted for 6 hours prior to assessment.
- The FIB4 score is a standard metric to estimate liver fibrosis, and is calculated using the formula: $\text{age (years)} \times \text{AST [U/L]} / (\text{platelets [10}^9\text{/L]} \times \text{ALT [U/L]}^{1/2})$ [5].

ANOVA and t-tests were carried out to determine correlations between serum biomarkers/BMI and disease state.

Acknowledgements

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References

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Results

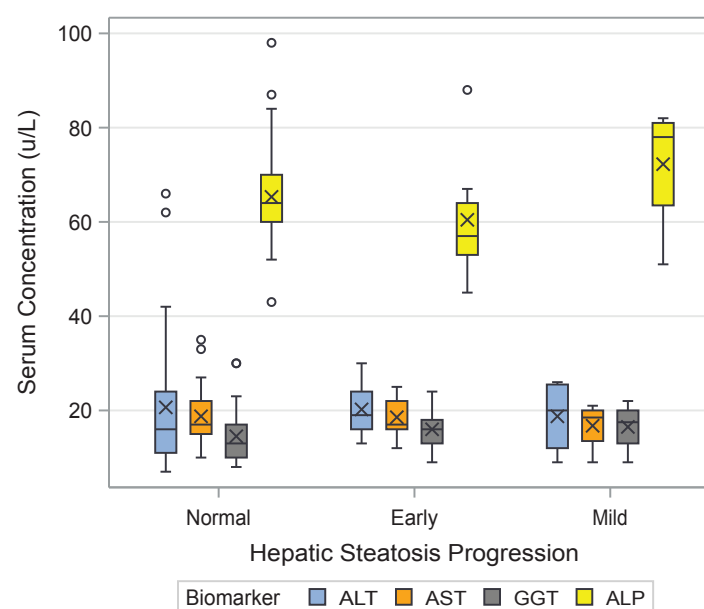


Figure 1: Box plot showing serum biomarker levels in individuals with different extents of hepatic steatosis progression. 'X' is the mean, the box indicates the 1st and 3rd quartiles, with the line in the centre indicating the median. Whiskers indicate minimum and maximum non-outlier values. Circles are outlier data

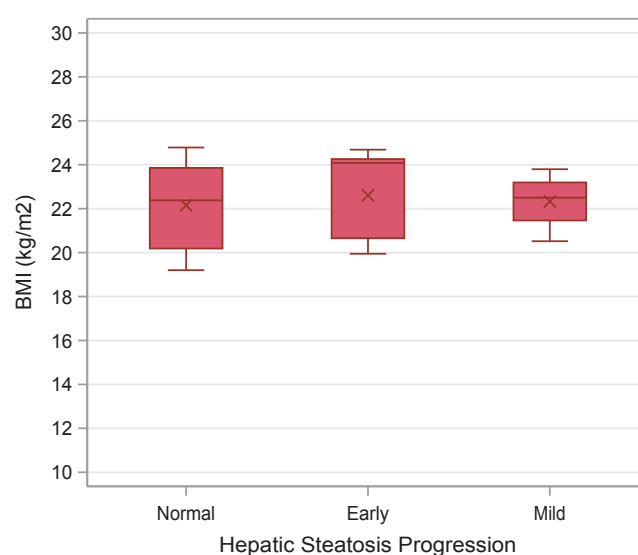


Figure 2: Box plot showing BMI in individuals with different extents of hepatic steatosis progression.

29 individuals (69%) had no hepatic steatosis, 9 (21%) had early hepatic steatosis, and 4 (10%) had mild hepatic steatosis. Of the 13 volunteers with some degree of hepatic steatosis, all had normal blood results and stable weight/BMI.

8 individuals had hepatomegaly, all of whom also had hepatic steatosis.

5 volunteers had liver abnormalities which were not hepatic steatosis. These abnormalities were gall bladder sludge (2 individuals), sphincter of Oddi dysfunction (1 individual), haemangiomas (1 individual), thickened gall bladder (1 individual) and gall bladder polyps (2 individuals).

One individual had liver markers well outside the normal range. This person did not present with hepatic steatosis. No tested serum biomarker correlated with hepatic steatosis progression, neither did BMI or FIB4 score.

Of those individuals who were told they had hepatic steatosis, 7 were improved at next visit, 6 months later (37%).

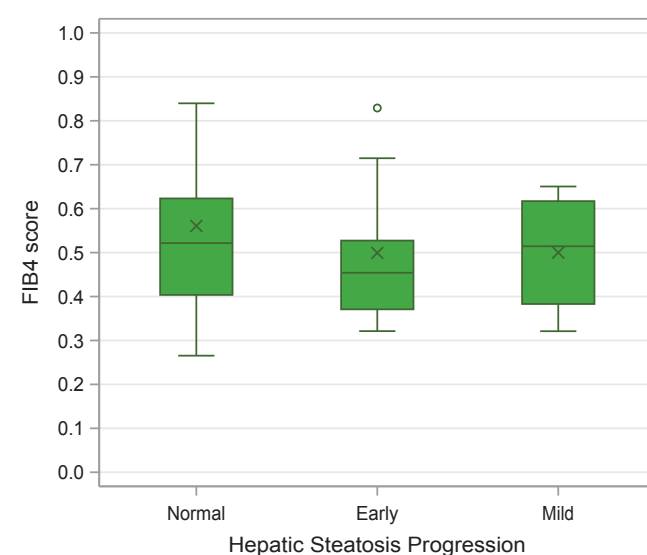


Figure 3: Box plot showing FIB4 score in individuals with different extents of hepatic steatosis progression.

Discussion

No clear correlation was found between weight or liver function tests and ultrasound evidence of hepatic steatosis.

The presence of hepatic steatosis in a significant proportion of healthy volunteers with normal BMI and LFT readings suggests that current measures to ensure no volunteer with hepatic steatosis enters a clinical trial may be inadequate.

To reduce the need for ultrasound scans on all prospective trial volunteers, the identification of predictive factors for hepatic steatosis is desirable. Further research will include studying more volunteers (>200) and examining a wider range of variables (lifestyle, demographics, past medical history and blood tests) to identify potential predictive factors. This may help to improve volunteer screening for clinical trials, which in turn would mitigate risk to volunteers and remove confounding variables that impact on data quality.