Obesity is the most common risk factor for chronic liver disease: Results from risk stratification pathway using transient elastography

Short running title: Obesity: the most common risk factor for CLD

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NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; AASLD, American Association for the Study of Liver; NHS, National Health Service; AUDIT, Alcohol use disorders identification test; TE, transient elastography; kPa, kilopascals; UK, United Kingdom; ALT, alanine aminotransferase

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R Harris, TR Card, T Delahooke, GP Aithal, IN Guha were involved in the study design and concept, implementation of the study in primary care, interpretation of results and editing of the manuscript. R Harris analysed the data set and wrote the initial manuscript draft. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. IN Guha is the guarantor. All authors approved the final version of this manuscript.

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Abstract

Introduction

Obesity has been associated with liver fibrosis yet guidelines do not emphasise it as an independent risk factor in which to have a high index of suspicion of advanced disease. We aimed to elucidate the effect of a raised body mass index on the risk of liver disease using data from a community risk stratification pathway.

Methods

We prospectively recruited patients from a primary care practice with hazardous alcohol use and/or type 2 diabetes and/or obesity. Subjects were invited for a transient elastography reading. A threshold of ≥8.0kPa defined an elevated reading consistent with clinically significant liver disease.

Results

Five hundred and seventy six patients participated in the pathway of which, 533 patients had a reliable reading and 66 (12.4%) had an elevated reading. Thirty one percent of patients with an elevated reading had obesity as their only risk factor. The proportion of patients with an elevated reading was similar among those with obesity (8.9%) to patients with more recognised solitary risk factors (Type 2 diabetes 10.8%; Hazardous alcohol use 4.8%). Obesity in combination with other risk factors further increased the proportion of patients with an elevated reading. In multivariate logistic regression, increasing BMI and type 2 diabetes were significantly associated with an elevated reading.

Conclusion

Obesity as a single or additive risk factor for chronic liver disease is significant. Future case finding strategies using a risk factor approach should incorporate obesity within proposed algorithms.

Introduction

Obesity is a major global health challenge and has been described as a pandemic of the 21st century. In 2013, 2.1 billion individuals worldwide were reported to be overweight or obese (1). This metabolic risk factor has had a dramatic impact on the increasing incidence and prevalence of multiple morbidities including chronic liver disease with non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, now estimated to affect 25% of the global population (2). Not only are these patients at risk of liver related outcomes but they are also at increased risk of cardiovascular disease and death (3-7).

Obesity or a raised body mass index (BMI (kg/m^2)) have been independently associated with liver fibrosis or a surrogate measure of clinically significant liver disease (e.g. elevated liver stiffness using transient elastography) (8-10). The risk of advanced liver fibrosis correlates with additional components of the metabolic syndrome including an elevated waist circumference as a surrogate measure of abdominal obesity (11). This correlation is observed even in the absence of type 2 diabetes as a feature of the metabolic syndrome (12). Similarly, in patients with hazardous alcohol use and a raised BMI a synergistic effect on liver disease mortality has also been observed (13, 14).

In view of the increasing morbidity and mortality associated with liver disease (15) and the unrelenting rise in underlying risk factors, case finding strategies to actively identify patients have been proposed. However unlike type 2 diabetes, current guidelines by the European Association for the study of Liver (EASL) (16) do not recommend identifying cases of advanced liver disease in those who have obesity as an independent risk factor.

Our own group has recently published a systematic review which demonstrated that non-invasive tests are now capable of stratifying liver disease risk in a community based setting. Studies which stratified patients according to an underlying risk factor reported detecting higher rates of significant fibrosis and cirrhosis; in a multivariate analysis a raised BMI independently predicted significant fibrosis (17). We have independently reported that implementation of a pathway focussed on the risk factors and using transient elastography leads to a 140% increase in the diagnosed cases of cirrhosis within the studied community population (18). A formal economic evaluation demonstrated that this approach is cost effective (19). Extension of this work to a larger population demonstrated that the presence of cirrhosis was significantly increased in obese patients with the predefined risk factors of type 2 diabetes or hazardous alcohol use (20). However, obesity as a solitary risk factor was not studied thus the proportion of disease within this at risk group remains unclear. This study addresses this gap in knowledge.

The aim of this study was to characterise the risk of clinically significant liver disease assessed by transient elastography within subpopulations of a community who were stratified based on their risk factors of obesity and/or type 2 diabetes and/ or hazardous alcohol use. The significance of a obesity as a risk factor on its own or in combination with other risk factors for chronic liver disease would be analysed.

Methods

Study setting

This was a prospective study with recruitment from a primary care (family medicine) practice in inner city Leicester, England. The study ran from January 2015 until March 2016. Local regulatory approval was obtained on 10th April 2013 from the Leicester Research Ethics Committee (13/EM/0123) and written informed consent was gained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. The study has been registered on a trials registry website (NCT02037867).

Clinical, anthropometric and biochemical data was obtained from the electronic primary care records (SystmOne, TPP, UK) within which data is stored as searchable numerical values or prospectively coded 'Read codes'. These Read codes, are a coded thesaurus of clinical terms that provide a standardised format for general practitioners to record patient findings and procedures, they have been used in the National Health Service (NHS) since 1985 and are part of standard clinical care

Patient selection

Recruitment occurred via an invitation to attend a community based risk stratification pathway for chronic liver disease (outlined below). Patients were initially identified from the electronic primary care records used as part of their routine clinical care. Adults (≥ 18 years) with one or more lifestyle related risk factors for chronic liver disease at the start of the study were invited. These included:

1. Hazardous alcohol use – defined as >14 units/week for women and >21 units/week for men, or an AUDIT questionnaire score ≥ 8, or presence of a Read code for alcohol misuse.

2. Type 2 diabetes - presence of a Read code related to the diagnosis

3. Obesity– presence of a numerical value for BMI recorded within the past 5 years indicative of obesity. A BMI cut off of ≥30.0 kg/m^2 was used for all patients of non Asian ethnicity whilst a lower cut off (≥27.5 kg/m^2) was agreed for patients of Asian ethnicity. This is in accordance with the World Health Organisation (21) who recommend different cut off points for the Asian population due to their higher risk of type 2 diabetes and cardiovascular disease at a lower BMI compared to European populations. A lower cut off ensured that patients of Asian ethnicity whose BMI was lower than the international cut off for obesity

(30.0 kg/m^2) but who were still at high risk of chronic liver disease would be invited to attend the risk stratification pathway.

Patients with any of the following were ineligible and not invited to attend the risk stratification pathway: 1. Contraindication to undertaking a transient elastography reading (e.g. pregnancy, implantable cardiac device) 2. Known diagnosis of chronic liver disease 3. Known malignancy or other terminal illness 4. Inability to consent to investigation or housebound and therefore unable to attend the practice.

Transient elastography

Transient elastography (TE) is a non-invasive diagnostic test which calculates the degree of liver stiffness by propagation of an elastic shear wave. Correlation between stages of liver fibrosis has been extensively evaluated and validated in all major aetiologies of chronic liver disease(22). Three experienced operators performed all the TE examinations as per the manufacturer's recommendations. All operators had completed more than 100 examinations prior to the start of the study using the portable FibroScan FS402 device (Echosens™, Paris). The technique for obtaining a TE reading has been previously described (23). Briefly, the patient is placed in the dorsal decubitus position and the tip of the transducer is placed within an intercostal space overlying the right lobe of the liver. All subjects were first examined with the M probe. Where this gave an unreliable reading, we went on, subject to patient agreement, to rescan with the XL probe. It was agreed a priori that if patients had readings with both probes the M probe reading would be utilised if reliable or if unreliable and no further reliable reading could be obtained with the XL probe. Ten valid measurements were collected with either the M or XL probe with the median value reported as the liver stiffness measurement. As an indicator of variability the ratio of the interquartile range of the liver stiffness to the median value (IQR/M) was also recorded. Examinations with fewer than 10 measurements and an IQR/M >30% were considered potentially unreliable according to the manufacturer's recommendations at the start of the study.

Risk stratification pathway

Once a patient was identified to have a lifestyle related risk factor for chronic liver disease they were invited to attend the risk stratification pathway based within their own primary care practice. Following the scan all patients were given lifestyle advice irrespective of their result. A threshold of ≥8.0kPa was agreed a priori to define elevated liver stiffness consistent with clinically significant liver disease irrespective of which probe was used to obtain a reading. This threshold has been used within other community based screening programmes (9) and has been demonstrated to have a high negative predictive value for advanced fibrosis (24). All patients with an elevated reading were

invited back to see a hepatologist (employed by the university hospital) in the primary care practice where further investigations were organised if deemed appropriate. Following the transient elastography reading and any further investigations a clinical diagnosis was made.

Statistical methods

Statistical analysis was completed using Stata version 14.2 (StataCorp LP). Characteristics of the study cohort are presented as numbers (percentage) for categorical data, and medians (IQR) for non-normally distributed continuous data. Variables were compared between all the adult patients in the primary care practice and the study cohort and between the study patients who had been stratified by their transient elastography reading. We used chi squared tests for categorical data and the Wilcoxon signed rank test for non-normally distributed continuous data. We constructed univariate and multivariate logistic regression models of the associations of an elevated transient elastography reading (≥8.0 kPa), considering associations with and between BMI, age, gender, type 2 diabetes, hazardous alcohol use, being a previous smoker, hypertension, hyperlipidaemia and ischaemic heart disease. Sub group analyses were completed on those patients who had only a obesity as a solitary risk factor for chronic liver disease, and on those with and without an elevated ALT.

In order to further evaluate obesityon its own or in combination with other risk factors we report the percentage of patients with an elevated TE reading (≥8.0 kPa) across BMI categories within three different subgroups of the study cohort (obesity only, type 2 diabetes and obesity, hazardous alcohol use and obesity). Finally we report the odds ratios for an elevated TE reading (≥8.0 kPa) across a range of BMI categories in the subset of patients studied who had type 2 diabetes or hazardous alcohol use as a risk factor.

Results

Baseline characteristics of the cohort

The primary care practice had a total adult population of 4150 of which 1023 patients were identified to have at least one of the defined risk factors for chronic liver disease and eligible to be invited to attend the community risk stratification pathway (Table 1). Of these, 576 patients attended the pathway of which 369 had obesity , 171 were diagnosed with type 2 diabetes and 165 had been identified to have hazardous alcohol use. The characteristics of the study patients are outlined in table 1. The median age of the cohort was 58 (IQR 48-68.5) and 52.8% were male. The majority of the patients were white (65.8%) although this was lower than the general population (87.2% in the UK) due to the high percentage of patients with Asian ethnicity (23.0%) in the community in which the risk stratification pathway was implemented. Seventy nine percent of the cohort had a single risk factor, whilst 19.3%% had a combination of two and 1.6% had all three risk factors. The median BMI was 30.6 (IQR 26.8-33.6). Ninety two percent of patients had a reliable TE reading with either the M or the XL probe with the proportion of reliable and unreliable readings outlined in Table 2.

Risk stratification of all patients

Of the 576 patients who attended the pathway, 533 patients had a reliable TE reading and 66 (12.4%) had a transient elastography reading of ≥8.0 kPa consistent with clinically significant liver disease. The characteristics of these patients are outlined in Table 3 stratified by their TE reading. Fifty six(84.8%%) of the patients with a raised TE reading accepted an invitation to be reviewed by a hepatologist in the community. Following this, 12 (18.2%) patients were diagnosed with cirrhosis based on a combination of TE, clinical acumen, radiology and endoscopy criteria. Patients with an elevated reading were significantly older, and more likely to have a raised BMI or have been diagnosed with other features of the metabolic syndrome (hypertension and hyperlipidaemia). In the subset of patients (n=504) in which the ALT was available there was also a significant difference in the average (median) between the two groups as well as the proportion with a raised ALT (≥45 U/L). However, only 27.3% of patients with an elevated TE reading had an ALT level above the upper limit of normal.

Of the patients who had obesity as a single risk factor for chronic liver disease, 8.9% had a TE reading ≥8.0 kPa. This proportion was similar to the patients who only had type 2 diabetes as a risk factor (10.8%). In those patients with hazardous alcohol use as a single risk factor the proportion with a TE reading ≥8.0 kPa was lower (4.8%) although the difference was not statistically significant in

comparison to the other risk factors (Table 3). Of all the patients with a single risk factor and an elevated TE reading (≥8.0 kPa), 60.0% had obesity as their only risk factor.

The proportion of patients with a TE reading ≥8.0 kPa increased with additional risk factors. Sixteen percent of patients with hazardous alcohol use and obesity had a TE reading ≥8.0 kPa. The proportion was greater in patients who had type 2 diabetes and obesity (36.7%) and highest in those with all three risk factors (44.4%) (Table 4). Thirty one percent of all of the patients with an elevated TE reading (≥8.0 kPa) had obesity as their only risk factor.

A univariate logistic regression analysis identified an increasing BMI and age, and diagnoses of type 2 diabetes, hypertension and hyperlipidaemia as significant variables associated with a TE reading ≥8.0 kPa. Using the dichotomised variable of obesity as a risk factor in the univariate analysis, instead of BMI as a continuous variable, we have shown that obesity is associated with a 3.13 fold increase in the odds of a raised TE reading respectively. This is comparable to the odds ratio for the risk of chronic liver disease between those with and without type 2 diabetes (odds ratio = 2.99). In the multivariate analysis only increasing BMI and having a diagnosis of type 2 diabetes remained significant variables and were therefore included within the final model. For every 1kg/m^2 increase in BMI the odds of having an elevated TE reading (≥8.0 kPa) increased by 17% (Table 5). BMI was an independent predictor of TE ≥8.0 kPa both in those without a raised ALT where the multivariate odds ratio for this outcome per unit rise in BMI was 1.16 (1.09-1.23) and in those with a raised ALT where it was 1.31 (1.10-1.55) (Supplementary data Table 1a and 1b).

Obesity as a single risk factor

Of the 533 people who attended the pathway and had a reliable TE reading, 235 had obesity as their only risk factor. (The characteristics of these patients are outlined in Supplementary data Table 2 stratified by their TE reading.) Patients with an elevated reading were significantly more likely to have a diagnosis of hypertension. The percentage of patients with a TE reading ≥8.0 kPa increased with increasing BMI (Figure 1). This trend was also observed in those patients with two risk factors (Supplementary data Figure 1). In those patients (n=216) in which the ALT was available there was a significant difference in the average (median) between the two groups as well as the proportion with a raised ALT (≥45 U/L) but still only 38.1% of those with a TE reading ≥8.0 kPa also had an ALT level above the upper limit of normal.

A univariate logistic regression analysis identified an increasing BMI and a diagnosis of hypertension as significant variables associated with a TE ≥8.0 kPa. In the multivariate analysis these variables remained significant (Supplementary data Table 3). Of the 21 patients with a TE ≥8.0 kPa, 57.1% had

a diagnosis of hypertension and 38.1% had a diagnosis of hyperlipidaemia. In 42.9% of patients obesity was their only diagnosed metabolic risk factor (Supplementary data Table 4).

Obesity as an additional risk factor

Combining all patients who had type 2 diabetes (n=143) or hazardous alcohol use (n=134) as a risk factor demonstrates the increasing odds ratios of having a TE reading ≥8.0 kPa across BMI categories (Figure 2). In a patient with type 2 diabetes and a BMI between 30-34.9 kg/m^2 the odds of a having a TE reading ≥8.0 kPa increased nearly fivefold (OR = 5.24, 95% CI 1.21-22.69, p value = 0.027) in comparison to a similar patient with a BMI <25 kg/m^2. An even greater difference in odds ratios was seen across BMI categories in those patients with hazardous alcohol use as a risk factor. In comparison to a patient with a BMI <25 kg/m^2 the odds ratio of having a TE reading ≥8.0 kPa was 8.40 (95% CI 0.80-88.41; p value = 0.076) in a patient with a BMI between 30-34.9 kg/m^2.

Discussion

Principal findings

In this study, obesity has been highlighted as a significant independent risk factor for detecting an elevated TE reading which is consistent with significant liver disease. Almost nine percent (8.9%) of patients with obesity as their only risk factor had an elevated TE reading (≥8.0 kPa) which is comparable to the subjects who had type 2 diabetes as a solitary risk factor (10.8%) and higher than those with only hazardous alcohol use (4.8%) as a risk factor. Furthermore, 31% of all of the patients with an elevated TE reading (≥8.0 kPa) had obesity as their only risk factor.

The synergism of a raised BMI in combination with other risk factors was also clearly demonstrated with an increased proportion of patients identified to have an elevated TE reading (Hazardous alcohol use + obesity= 16.1%; Type 2 diabetes + obesity = 36.7%). For a TE reading ≥8.0 kPa, a rise in odds ratios was observed across increasing BMI categories in patients who had two risk factors.

A multivariate logistic regression analysis of the studied cohort demonstrated that after adjusting for having a diagnosis of type 2 diabetes, a 1kg/m^2 increase in BMI resulted in the odds of a TE reading ≥8.0 kPa increasing by 17%.

Strengths and weaknesses

This is the first study assessing obesity as a single and additional risk factor within a community based risk stratification pathway. To limit selection bias we were able to identify and invite all eligible patients from a single primary care practice coded to have the relevant lifestyle related risk factors for chronic liver disease. Use of the electronic database also allowed us to obtain detailed data regarding patient alcohol intake and their BMI; 87.7% of patients within the practice had a BMI recorded within the past 5 years. This allowed us to stratify a large well characterised community cohort using transient elastography. However, implementation of a stratification pathway based on risk factors potentially biases the outcomes that have been observed. We are unable to determine the risk of chronic liver disease within the general population or indeed within patients without any risk factors at all as they were excluded from screening.

Of the patients invited to attend the pathway a response rate of 56.3% was achieved which is comparable to other community based case finding strategies for chronic liver disease (17) and better than those reported for national bowel cancer screening programmes (25). However, there may still be a responder bias and although patient uptake between the three different risk factors was equivalent, the patients who attended may not be representative of the whole spectrum of those within the at risk groups. This may have been the case in particular for those identified to

have hazardous alcohol use as a risk factor in which the proportion of those with an elevated TE reading was less than expected, although this was not statistically significant to the proportions observed with the other solitary risk factors. Also, identification of patients from the routine electronic primary care records is only as useful as the accuracy of the data recorded within it. If a patient has not been asked about their alcohol use or had an AUDIT questionnaire completed there will be no documentation within the electronic records from which all patients within the study were identified.

Use of transient elastography as a surrogate marker for clinically significant liver disease could also be viewed as a limitation. Although TE has been widely tested and validated across all aetiologies and against the gold standard of a liver biopsy (22) false positives may still occur due to steatohepatitis, cholestasis, congestive cardiac failure and particularly in those patients who continue to drink alcohol (26-28). Subsequently this may lead to an overestimation of those who have clinically significant liver disease. However a liver stiffness cut off of 8.0 kPa was used to increase the sensitivity of identifying all patients with advanced fibrosis (F3 disease) and cirrhosis (F4 disease). There has also been some debate as to whether a raised BMI in itself could be a confounding factor and falsely raise the liver stiffness measurement. Whilst studies of healthy volunteers have previously demonstrated a higher liver stiffness measurement in subjects who were obese compared to those with a normal BMI (29, 30), it must be noted that only the M probe was available in these studies. Subjects with a raised BMI are likely to have an increased skin to capsule distance which could result in an overestimation of their liver stiffness measurement with this probe. In studies of cohorts with chronic liver disease, liver fibrosis has been demonstrated to be the only consistent independent variable predicting the liver stiffness measurement (24, 31, 32).

Due to the ethical constraints of performing a liver biopsy in an asymptomatic community population we were not able to compare TE readings against histological findings, although a liver biopsy in itself has its own limitations (33). However if a liver biopsy was offered, it is unlikely that the whole cohort would have accepted this invasive test as demonstrated by previous studies in the community (17). Consequently the results would not have been representative of the population who have been risk stratified. The only true way to determine whether these patients have been stratified correctly is to follow up this cohort for long term clinical outcomes. This would aid justification of future randomised control trials to determine whether implementation of a case finding strategy as a whole (by actively identifying patients at risk and encouraging behavioural change at an earlier time point within their natural history) has a long term effect on health outcomes or mortality.

Relevance to clinical practice

The rise of obesity as a metabolic risk factor is already having a demonstrable effect on the prevalence of chronic liver disease within our community population – 12.4% of subjects had evidence of clinically significant liver disease (defined by a TE reading ≥8.0 kPa) with nearly a third of these having obesity as their only risk factor. This study provides a forecast of the impact liver disease associated with obesity will have on our hospital wards over the next 20-30 years.

Though we recognise that replication of our results in another cohort would provide stronger evidence that isolated obesity is a significant independent risk factor and that all other confounders have been excluded, we believe that some important implications should be pointed out even now. Whilst we agree with the clinical practice guidelines of the European Association of the study of liver disease (EASL) (16) which emphasise the importance for case finding of advanced liver disease in patients who are high risk (age>50 years, type 2 diabetes, metabolic syndrome), we would argue that the same importance should be afforded to patients who are obese. Omitting obesity as an independent risk factor from any proposed case finding strategy risks missing a large proportion of patients who already have established liver disease. This is of particular significance given the increasing prevalence of obesity within the general population. Between 1980 and 2013 the worldwide prevalence of adults who were overweight (BMI ≥25kg/m^2) rose by 27.5% and in Western Europe the prevalence of obesity is reported to be one fifth of the population (20.5% in men, 21.0% in women)(1).

Whilst the case for screening is far from proven case finding strategies to actively identify these patients will enable clinical trials to be conducted and allow therapeutic strategies for early liver disease to be tested, whether this be a trial of pharmacotherapy (e.g. pioglitazone which has recently been recommended for patients with biopsy proven NASH (16, 34)) or the effects of encouraging behavioural change.

Further work is also required to enrich the population which is stratified and increase the diagnostic yield of any case finding approach. The synergistic effect of having two risk factors clearly increases the likelihood of having an elevated TE reading. However, for those with solitary risk factors, an algorithm which includes patient related factors e.g. age and gender may be more effective for patient selection rather than being identified by a risk factor alone.

Stratifying patients at risk of liver disease will also create an opportunity for primary care physicians to identify those who would benefit from weight management and those who should be assessed for other associated health complications e.g. hypertension, hypercholesterolaemia and type 2 diabetes. Of the patients in this study who had an elevated TE reading (≥8kPa) and obesity as their

only risk factor, 42.9% had no other recorded metabolic risk factor yet had evidence of organ damage. Improvement in these other health outcomes could ensure a risk stratification pathway for chronic liver disease is cost effective despite the large number of individuals who would require assessment.

Conclusion

Obesity as a single or additional risk factor for chronic liver disease is significant and will continue to affect the Hepatology landscape over the next 20-30 years. Indeed it is already having an impact on the liver disease detectable within a community population. Population based interventions are urgently required to address this crisis but in the interim implementation of case finding strategies using a risk factor approach which includes obesity is feasible and offers an opportunity to conduct clinical trials of screening for liver disease. The study has been registered on a trials registry website (NCT02037867).

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Figure headings

Figure 1: Percentage of patients with a TE≥8kPa across different BMI categories according to obesity as a single risk factor

Figure 2: A comparison of odds ratio for TE≥8.0 kPa across a range of BMI categories in Type 2 diabetics (n=151) or Hazardous alcohol users (n=144)

Supplementary Figure 1: Percentage of patients with a TE≥8kPa across different BMI categories in patients with two risk factors (Type 2 diabetes and obesity, Hazardous alcohol use and obesity)