The impact of diabetes and glucose-lowering therapies on hepatocellular carcinoma incidence and overall survival

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ABSTRACT

Purpose UK hepatocellular carcinoma (HCC) incidence has increased 60% over ten years. The obesity and type 2 diabetes epidemics are contributing factors. In this paper we examine the impact of diabetes and glucose lowering treatments on HCC incidence and overall survival (OS).

Methods Data from 1064 patients diagnosed with chronic liver disease (CLD) (n=340) or HCC (n=724) were collected between 2007-2012. Patients with HCC were followed up prospectively. Univariate and multivariate logistic regression determined HCC risk factors. Kaplein Meier curves were used to examine survival and cox proportional hazards analysis estimated hazard ratios (HR) for death according to use of glucose lowering therapies.

Findings Diabetes prevalence was 39.6% and 10.6% within the HCC and CLD cohorts respectively. The odds ratio (OR) for having HCC in patients with diabetes was 5.55 ($p<0.001$). Univariate analysis demonstrated an increased association of HCC with age, sex, cirrhosis, haemochromatosis, alcohol abuse, diabetes and Child's Pugh score. In multivariate analysis age, sex, cirrhosis, Child's Pugh score, diabetes status and insulin use retained significance. Diabetes status did not significantly impact OS in HCC, however in people with diabetes and HCC, metformin treatment was associated with improved OS (mean survival 31 vs. 24 months, $p=0.016$; HR for death 0.75, $p=0.032$).

Implications Diabetes is significantly associated with HCC in the UK. Metformin treatment is associated with improved OS following HCC diagnosis. Treatment of diabetes should be appropriately reviewed in high risk populations, with specific consideration as to the potential hepatoprotective effects of metformin in HCC.

KEYWORDS

Diabetes

Hepatocellular carcinoma

Metformin

Insulin

INTRODUCTION

Type 2 diabetes (T2D) is associated with an increased risk of death from liver disease and hepatocellular carcinoma (HCC),[1] in addition to extra-hepatic malignancies of the gastrointestinal tract, pancreas, breast, ovaries, endometrium, uterus, bladder and kidneys.[1,2] Common lifestyle risk factors including increasing age, obesity, physical inactivity and

smoking all likely contribute to the overall increased cancer risk in patients with T2D. Although the mechanistic process that links diabetes to cancer is not yet completely appreciated, such biological mechanisms as hyperglycaemia, hyperinsulinemia/insulin resistance, increased bioactivity of insulin-like growth factor 1, oxidative stress, dysregulation of sex hormones, and chronic inflammation may drive the association.[3]

Hepatocellular carcinoma (HCC) is one of the malignancies whose incidence and mortality is most rapidly increasing in the general population and patients with T2D. In the UK, the age-standardised incidence rates for liver cancer have increased by 60%, and mortality rates have increased by almost half over the last decade.[4] The magnitude of the risk varies between studies but is consistently higher (odds ratio (OR) 2-3) than age- and body mass index (BMI)-matched controls without T2D.[5,6] The risk of HCC appears to be related to T2D disease duration with the greatest risk being in those who have had diabetes for >10 years.[7] The development of HCC in patients with T2D may also be related to a background of non-alcoholic fatty liver disease (NAFLD), often complicated by overweight/obesity. NAFLD has been found to lead to an increased risk of HCC even in the absence of cirrhosis, and a greater proportion of these individuals have components of the metabolic syndrome.[8] There is also evidence that people with T2D are more likely to develop cirrhosis in the context of NAFLD,[8,9] putting them at higher risk of HCC. The risk of HCC in T2D is likely dependent on its interaction with obesity/BMI and may synergistically increase the risk of HCC in patients already at higher background risk of HCC such as those with pre-existing chronic liver disease (CLD).[10] In a study of over 135,000 patients with NAFLD from four European primary care databases, the strongest independent predictor of a diagnosis of HCC or cirrhosis was baseline diagnosis of diabetes.[11] In addition to its association with a higher incidence of cancer and HCC, T2D also adversely impacts upon the outcome associated with an increased cancer mortality.[12]

There is increasing evidence that certain glucose lowering therapies may modify cancer risk and outcomes. A recent meta-analysis suggests that treatment with metformin may be associated with a lower risk of HCC and may beneficially influence HCC prognosis, whereas treatment with insulin or sulphonylureas appears to be associated with a higher HCC risk.[13,14] There is similar evidence of a reduction in the incidence of liver cancer with thiazolidinediones, with more potent protective effects occurring with a higher cumulative dose and longer duration of treatment.[15,16] Metformin particularly appears to have anti-neoplastic and tumour-suppressing activity for a number of tumour types and thus appears to have a chemo-preventive and chemo-therapeutic effect.[17] Newer therapies, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide (GLP)-1 receptor agonists, have only been

licensed and used in the last few years so their longer-term effects of hepatocarcinogenesis in people are not yet known.

The aim of this study was to determine whether, and to what extent, diabetes represents a risk factor for HCC, to assess the impact of concomitant diabetes on overall survival from HCC and examine the influence of various glucose lowering therapies on HCC survival.

PARTICIPANTS AND METHODS

Ethical approval

Data was collected as part of a larger biomarker study. The study received approval by the South Birmingham Research Ethics Committee (Reference 06/Q2707/182).

Data collection

We conducted a single-institution study at University Hospital Birmingham, a regional referral centre within the UK. Data was collected from patients seen with either a diagnosis of CLD (defined as NAFLD, alcohol-related liver disease, chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV), genetic haemochromatosis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, or another cause of metabolic liver disease) or HCC between January 2007 to March 2012. Patients with a diagnosis of HCC were followed up prospectively to the end of the study.

Demographic, biochemical and clinical data

We collected data on demographics (age, sex, ethnicity), liver biochemistry (liver enzymes, markers of liver synthetic function and serum alpha-fetoprotein), risk factors for HCC and CLD including diabetes, severity of liver disease (Child's Pugh classification), HCC stage, treatment received and survival. A diagnosis of cirrhosis was made using histology, imaging or via the presence of features of decompensation or portal hypertension. HBV and HCV infection were defined by the presence of Hepatitis B surface antigen or anti-HCV respectively. Alcohol abuse was defined as drinking > 20g alcohol per day for women, or > 30g alcohol per day for men. HCC was diagnosed by imaging (computerised tomography or magnetic resonance imaging) or lesional liver biopsy with histopathological confirmation. All cases were reviewed in a specialist regional liver unit by experienced radiologists and histopathologists as part of a weekly multidisciplinary meeting.

Diabetes and glucose-lowering therapies

A diagnosis of diabetes was taken from the patient's medical records and where relevant, details of glucose-lowering therapy (oral agents and subcutaneous insulin) were recorded. Unfortunately we did not have access to data to allow differentiation between type 1 and type 2 diabetes. Treatment of diabetes was analysed by reviewing all drugs taken within the course of the patients' disease to determine whether treatment had been administered and at what time point. For a patient to be categorised as a user they were required to have been taking the drug for at least 6 months. Patients were categorised according to the different types of anti-diabetes treatment: i) metformin, ii) sulphonylureas, iii) insulin. The study was conducted before the use of more contemporary glucose lowering therapies such as SGLT2 inhibitors and GLP-1 receptor agonists.

Statistical Analysis

The Mann-Whitney U test and chi-square test were used to compare continuous and categorical data respectively. Univariate and multivariate analysis was performed using logistic regression to determine factors associated with HCC using the CLD group as controls. Kaplan Meier analysis was used to compare survival for patients with and without diabetes, in addition to different diabetic treatments. Cox proportional hazards analysis was used to estimate the hazard ratio (HR) for death for HCC patients with different glucose lowering treatments. Propensity score analysis was used to examine the impact of demographics, liver disease severity and performance status on this relationship.

RESULTS

Demographic details and co-morbidities

Overall population

The cohort consisted of 1064 individuals (724 with HCC and 340 CLD controls). The study flow chart is shown in Figure 1. The mean age of all patients within this study was 60.1 (+/-14) years. The patient population was of mixed ethnicity: 79% of patients were white, 12% Asian Indian, 3% Afro Caribbean, 3% Asian Oriental and 4% other ethnic origin.

Comparison of patients with HCC and CLD (controls) (table 1)

Patients with HCC were on average 11 years older than those with CLD (63.6 +/- 12.7 vs. 52.8 +/- 13.7 years). The majority of participants were male (81% in the HCC cohort and 63% in the CLD control group). There were a number of co-morbid diseases present within both groups due to the nature of the population selection. HBV infection was present in 14% and 20%, HCV infection in 24% and 33%, alcohol-related liver disease was diagnosed in 37% and 28% and NAFLD in 8 and 10% of the HCC group and CLD controls respectively. In total 71% and 47% of HCC patients and CLD controls had a diagnosis of cirrhosis. There was a significant difference in the disease prevalence of diabetes between the HCC cohort and the CLD controls (39 vs. 11%; $p<0.001$).

Comparison of patients with and without diabetes (table 2)

For the HCC and CLD groups combined, patients with diabetes were on average 9 years older (66.1 +/- 9.7 vs. 57 +/- 14.7 years) than those without diabetes with a similar sex distribution between the two groups (81% and 72% male, diabetes vs. no diabetes). Ethnicity distribution was also comparable. Co-morbidities differed in distribution within the two groups. HBV was seen in 9% and 19%, HCV in 19% and 30%, haemochromatosis in 7% and 2%, primary biliary cholangitis in 2% and 6%, and NAFLD in 18% and 5% of patients with or without diabetes (all $p<0.05$), i.e. metabolic disease was found more commonly in people with diabetes, and viral hepatitis was found more commonly in people without diabetes. The frequency of alcohol abuse was similar between groups (35% and 34%). The prevalence of cirrhosis was higher in people with diabetes (70% vs. 61%, $p<0.05$).

Glucose-lowering therapies in patients with diabetes

Some patients were treated with lifestyle intervention only (diet and exercise). Metformin was the most commonly prescribed drug in 53%, subcutaneous insulin in 39% and sulphonylureas in 36% of all patients. There were no significant differences in the diabetes therapies used between group, including the prescription of insulin (41% of HCC group vs. 25% of CLD; $p=0.069$) (table 3). The use of lifestyle intervention alone however was more common in HCC patients compared with CLD patients (30% vs. 14%; $p=0.046$).

Factors associated with incidence of HCC: case-control data

Demographic and clinical risk factors

HCC patients and CLD controls were subjected to univariate analysis on factors known to increase the risk of HCC. The presence of diabetes produced an OR of 5.55 (95% CI 3.81 – 8.08; p<0.001). Other factors with ORs reaching significance included age, sex, cirrhosis, haemochromatosis, alcohol abuse and Child's Pugh score (table 4). NAFLD was not significantly associated with HCC risk, OR 0.86 (95% CI 0.55-1.34). Multivariate logistic regression was performed to identify whether the role of diabetes in HCC retained independence when additional variables were added to the model. All factors that had shown significance within univariate analysis were added to the model. Factors maintaining significance were age, sex, cirrhosis, Child's Pugh score, diabetes and insulin (table 4).

Effects of glucose lowering therapies on the presence of HCC

Univariate analysis was also performed to examine the relationship between treatment of diabetes and HCC. In univariate analysis all treatments showed an increased OR for the presence of HCC. However, when adjusted for diabetes, only insulin and diet retained an increased OR to a significant level (p<0.05) (table 5). Multivariate analysis allowed adjustment for the effects of all diabetic treatments within the same model, along with the presence of diabetes itself. When the model contained either diet or insulin alongside diabetes, the independent effect of the two factors entered into the model was maintained. However, when both insulin and diet were added together to the model, the significance of diabetes was lost (table 5).

Survival analysis for patients with HCC: prospective data

The median follow up time for people with HCC was 25 months (range 0 – 139 months). Kaplan Meier curve analysis showed no difference in survival when comparing people with and without diabetes (p=0.56) (Figure 2). The percentage of patients with cirrhosis (71% in both groups) and features of hepatic decompensation at the time of HCC diagnosis was comparable between groups, as was the Barcelona Clinic Liver Cancer (BCLC) stage and broad treatment category (palliative or curative intent) (supplementary table 1).

The impact of glucose-lowering therapies on overall survival was also examined. Metformin was associated with a beneficial effect on survival, with a mean survival of 31 months versus 24 months for other glucose-lowering therapies (p=0.016) (Figure 3A). Metformin had a lower HR for death (HR 0.75, 95% CI 0.57 – 0.98, p=0.032) in contrast other glucose-lowering therapies (insulin HR 0.90, 95% CI 0.69 – 1.19, p=0.453; sulphonylureas HR 0.81, 95% CI 0.60 – 1.09, p=0.155). The survival benefit from metformin lost statistical significance

however following a propensity score analysis which adjusted for Child's Pugh score, performance status, age and gender (HR 0.77, 95% CI 0.59 - 1.00, p=0.055). Although, no other treatment option had a significant effect on survival (Figure 3B, 3C), metformin taken in combination with insulin, was associated with an increase in survival time compared with those patients taking insulin alone; mean survival was 31.2 months in the combined group versus 21.4 months in the insulin alone group (p=0.008) (Figure 3D).

DISCUSSION

Main findings

In this cohort of patients with HCC and a CLD control group, we demonstrate a significant association between diabetes and HCC. The absence of any pharmacological glucose lowering therapy (*i.e.* dietary management) was significantly associated with developing HCC, as was insulin use in a multivariate model, although we did not have the available data to analyse how this relates to glycaemic control, or diabetes duration. Metformin use was not found to be associated with HCC incidence. In those individuals who developed HCC, treatment with metformin was associated with a longer overall survival: a more than 30% prolongation in median survival time compared to other glucose-lowering therapies. The beneficial association of metformin use and survival lost statistical significance however following propensity score analysis.

Comparison to the existing literature

These findings support the substantial body of evidence, which has identified diabetes as a significant risk factor for liver cancer.[1,5–7,18,19] We did not however observe any difference in survival according to diabetes status among individuals with HCC in contrast with other major studies, and disease stage in terms of cirrhosis severity and BCLC cancer staging were comparable between groups at the time of diagnosis.[12]

This study adds to our understanding of the influence of glucose-lowering therapies on the development of cancer including HCC. Metformin was first demonstrated to be associated with reduced cancer risk in people with diabetes in 2005, with the adjusted OR reducing proportionately with increasing duration of exposure and cumulative dose dispensed.[20] Several meta-analyses have demonstrated an attenuated risk of developing liver cancer in metformin users of 50-60%, although significant heterogeneity was observed.[6,13,14,21] A nationwide study of nearly 100,000 HCC patients with matched controls demonstrated that each incremental year

increase in metformin use resulted in a 7% reduction in HCC risk.[22] The preventative role of metformin against incident HCC has been contested however, as is the case in this study.[7,23–25] A meta-analysis identified that the protective effects observed for metformin use were not supported by randomised control trial data.[23] Furthermore a retrospective cohort study of nearly 96,000 people with T2D failed to show that users of metformin benefited from protection against all cancers including HCC compared to those taking sulphonylureas.[24] We did however observe a significant association between metformin use and improved survival from HCC, and these findings are consistent with the existing literature.[26–28] In contrast, use of insulin and insulin secretagogues (e.g. sulphonylureas) has been associated with an increased risk of liver (and other including colorectal, lung, stomach and pancreatic) cancer, consistent with the findings presented here.[6,13,21,29] Whether these relationships are causal or influenced by the duration or severity of diabetes, or associated of obesity, remains unclear. The relationship of risk with glycaemic control in T2D is also not fully understood, although one study highlighted the additional risk observed in the group with poor metabolic control.[30]

Despite having been used for nearly a century,[31] metformin is still recommended in all guidelines as first-line therapy for T2D.[32] The mechanism of its glucose lowering action maybe mediated through its ability to activate the AMP-activated protein kinase in peripheral insulin-sensitive tissues, stimulating skeletal muscle glucose uptake and inhibiting hepatic gluconeogenesis. However, the upstream regulator of AMPK is liver kinase B1 (LKB1), a tumour suppressor gene, and it appears that metformin can suppress tumour formation and inhibit cell growth by inhibiting the mechanistic target of rapamycin (mTOR) pathway through an LKB1-AMPK dependent mechanism.[33] This negative correlation between AMPK activity and proliferation of HCC (assessed with Ki67 level, a proliferation marker and tumour size) has been shown in cell lines, rodent models and in clinical samples.[34] The molecular pathway appears to involve phosphorylation and inactivation of Sirtuin1, the p53 deacetylase, promoting p53 acetylation and apoptosis of HCC cells.[35]

Of note we found that the prevalence of patients with HCV infection was lower in patients with diabetes (19%), than those without (30%). This is not consistent with the literature, which has found that HCV can increase insulin resistance.[36]

Importance of the study

The prevalence of liver disease is increasing dramatically with fourfold increases in the UK standardised mortality rate since 1970.[37] While much of this overall mortality relates to excess alcohol, the exponential rise in the prevalence of overweight and obesity, and in parallel T2D,

cannot be overlooked. With 63% of UK adults now classified as overweight or obese, NAFLD (i.e. hepatic steatosis associated with obesity, T2D and other components of the metabolic syndrome) is becoming increasingly common. NAFLD represents a disease spectrum ranging from simple steatosis (fatty infiltration), non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. In the next decade, NAFLD is predicted to become the primary cause of liver transplantation.[38] It is reckoned that 40-70% of people with T2D have NAFLD, a risk factor for HCC, so considering the current obesity/T2D epidemic, the high prevalence of NAFLD may partly explain the doubling of rates of HCC in the last few decades and their projected rise by 38% by 2035.[39] The frequent co-existence of NAFLD and T2D likely also contributes to the higher incidence and risk of mortality from liver cancer and cirrhosis that is approximately two fold higher in patients with T2D.[40–43] Furthermore, additional risk factors may also be evident with a synergistic effect. The risk of developing CLD including cancer is supra-additive when obesity and excess alcohol intake co-exist,[44] while T2D magnifies the risk of cirrhosis, liver cancer and liver-related deaths for people with other aetiologias of liver disease, including viral hepatitis.[10,45] Increased recognition of the significant role of diabetes in the development of end stage liver disease and liver cancer is therefore a priority.

Clinical implications

Clearly the liver-related complications are significant in T2D but as the absolute risk of HCC remains small it currently is not a complication that is screened for. There is no universally accepted algorithm to screen for NAFLD-related liver fibrosis in individuals with obesity, metabolic syndrome and T2D with discordance between international guidelines (NICE, EASD/EASO/EASL and AASLD).[46–48] The American Diabetes Association recommend that patients with T2D/prediabetes with elevated liver enzymes or fatty liver on ultrasound should be evaluated for presence of NASH and liver fibrosis.[49] Further studies on the cost-effectiveness of case finding for liver fibrosis in this setting are required, and this may provide a positive step forward to improve HCC screening in this higher risk cohort. Given the balance of evidence generally in favour for a chemo-preventive role against HCC (and other malignancies) among patients with diabetes, and improved survival, metformin should be continued in patients even with cirrhosis (excluding those with decompensation) to provide this benefit.

Study strengths and limitations

To the best of our knowledge this is the first prospective UK study to look at diabetes as a risk factor for liver cancer survival, and the first prospective UK study to examine the role of diabetic therapies on cancer risk and survival in the setting for HCC specifically. A significant strength is that the data was collected prospectively with a 5 year follow up. We acknowledge some limitations to the study, partly a reflection of the time period in which the data was first collected. Most significantly we were unable to assess if the relationships observed between diabetes and HCC were independent of body mass index (BMI) and the presence of NAFLD. This was due to the fact that at the time of data collection, only a minority of participants had BMI data recorded, and a significant proportion were labelled as having an unknown cause of liver disease, many of which in hindsight probably had NAFLD. Unfortunately, we were unable to access this data retrospectively. Furthermore, data pertaining to glycaemic control, specific diabetes sub-type (most likely >90% had T2D) and disease duration was also not available in the majority of people with diabetes so we could not examine the impact of this on the observed effects of diabetes therapies on HCC incidence and survival. This may be particularly pertinent to the relationship between insulin and HCC incidence as this may be confounded by poorer glycaemic control or longer disease duration. Similarly, it may be true for those not on any glucose lowering treatment that this reflected chronic poor/sub-optimal glycaemic control. The study was undertaken before widespread prescription and availability of more contemporary glucose-lowering therapies such SGLT2 inhibitors and GLP-1 receptor agonists (that may also modulate liver steatosis +/- fibrosis) and so their impact on HCC could not be assessed.

CONCLUSIONS

We demonstrate a significant association between HCC and diabetes, but highlight the significant improvement in overall survival in those people with HCC treated with metformin. These data highlight an emerging, but thus far frequently overlooked, epidemiologically significant complication of the diabetes and obesity pandemics. The study findings raise important questions about the value of closer screening for CLD, cirrhosis and even HCC in people with diabetes and the potentially hepatoprotective effects of metformin.

Ethics approval and consent to participate: Data was collected as part of a larger biomarker study. The study received approval by the South Birmingham Research Ethics Committee (Reference 06/Q2707/182). The study was performed in accordance with the Declaration of Helsinki.

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Declaration of interests: None

Figure Legends

Figure 1. Kaplan Meier analysis demonstrating no survival difference for HCC patients with or without diabetes (p=0.561, log rank test).

Figure 2. Kaplan Meier analysis demonstrating survival for HCC patients prescribed (A) metformin (p=0.016) , (B) insulin (p=ns) and (C) sulphonylureas (p=ns) compared to other diabetic treatments, and (D) HCC patients prescribed insulin and metformin combined, compared with insulin alone (p=0.008).

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