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# Lower alpha fetoprotein and higher risk of hepatocellular carcinoma, study from the type 2 diabetes mellitus patients

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ABSTRACT

*Aims:* To explore the association of type 2 diabetes mellitus (T2DM) with hepatocellular carcinoma (HCC) and alpha fetoprotein (AFP).

*Methods:* 750 patients with T2DM (T2DM group), 800 healthy people (control group) and 501 patients newly diagnosed with HCC were recruited from 2010 to 2016. The HCC patients were further divided into a HCC with T2DM (HCC+DM) group and a HCC without diabetes mellitus (HCC+NDM) group.

*Results:* The T2DM group had a 12.61% lower geometric mean AFP level than the healthy control group (2.08 vs. 2.38 μg/L, $P < 0.001$). Of 501 HCC patients, 230 (45.91%) had T2DM. When compared to the HCC+NDM group, the HCC+DM group had a higher negative rate of AFP (55.22% vs. 37.26%, $P < 0.001$), worse liver function ($P = 0.011$) and a 64.87% lower geometric mean AFP level (25.71 vs. 73.18 μg/L, $P < 0.001$). T2DM was significantly associated with the risk of high-grade (grade 3 and 4) HCC (OR = 2.02, 95% CI 1.18–3.44, $P = 0.010$).

*Conclusions:* T2DM was associated with lower AFP level, worse liver function and higher risk of high-grade HCC. We speculated that low AFP levels in diabetics might delay and interfere with HCC diagnosis, leading to higher degree of malignant HCC.



## 1. Introduction

The global incidence of hepatocellular carcinoma (HCC) has increased to more than 700,000 cases annually. HCC has emerged as the third leading cause of cancer-related mortality worldwide [1]. Type 2 diabetes mellitus (T2DM) is also a global health problem. In 2013, the International Diabetes Federation estimated that there were 380 million diabetics worldwide [2]. Seeing that the incidence of both HCC and T2DM are increasing rapidly, a subset of people must be affected with HCC and T2DM. Clinical data has shown an association between the presence of diabetes and higher incidence and poorer prognosis of HCC, which suggest that diabetes is an independent risk factor for the development of HCC [3]. Furthermore, a meta-analysis has concluded that diabetes is associated with a 2.5-fold greater risk of developing HCC [4]. The increased HCC risk observed in patients with T2DM remained statistically significant and was independent

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of alcohol consumption or hepatitis viral infections, indicating that the association is clinically reliable and robust [4,5]. Previous studies were most focused on the relationship between T2DM and the occurrence and prognosis of HCC, but detailed assessment of this association remains to be explored.

Alpha-fetoprotein (AFP) has been recommended as a serological marker in the screening and early diagnosis of HCC in clinical practice. An elevated AFP level is often found in liver carcinoma cells and is strongly correlated with the invasiveness of cancer cells [6]. At present, there is little research on diabetes and AFP, mainly focusing on the effect of maternal AFP level on screening Down syndrome and neural tube defects in gestational diabetes mellitus. It is agreed that whether in both type 1 and 2 diabetes, maternal serum AFP level is significantly lower than that of healthy pregnant women [7–9].

In the HCC population, it remains unknown whether diabetes has any impact on serum AFP level. Consequently, we analyzed the characteristics and association of serum AFP level in HCC patients complicated with T2DM.

## 2. Materials and methods

### 2.1. Subjects

A total of 750 patients with T2DM, 800 healthy people and 501 patients newly diagnosed HCC in Shanghai Tenth People's Hospital from January 2010 to December 2016 were enrolled in this study. The exclusion criteria of the T2DM group were as follows: (1) a combination of tumors; and (2) suffering from additional metabolic diseases. The exclusion criteria of the HCC patients were as follows: (1) the combination of additional malignant tumors; (2) suffering from additional metabolic diseases; (3) acute or chronic liver or renal dysfunction; (4) pregnancy or accompanied by reproductive tumors. This research had been approved by the Ethics Committee of Shanghai Tenth People's Hospital. Informed consent had been obtained from all patients.

### 2.2. Data collection

The following data were collected from clinical records: gender, age, height, weight, diabetes history, fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), AFP, C-reactive protein (CRP), prothrombin time (PT), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamine transferase (GGT), alkaline phosphatase (ALP), pathological grade of HCC. The body mass index (BMI) was computed as weight in kilograms divided by height in meters squared.

### 2.3. Diagnosis and definitions

Diabetes mellitus was defined based on the diagnostic criteria proposed by the American Diabetes Association (ADA) Guidelines in 2017 [10]. Diagnosis of primary HCC was based on the guideline from the European Association for the Study of the Liver [11]. The liver function was assessed according to the Child-Pugh classification criteria (Grade A, B and C). The cancer stage of HCC was obstained at the time of diagnosis based on the Barcelona Clinic Liver Cancer (BCLC) classification (Stage 0, 1, 2, 3 and 4). The pathological grade of hepatocellular carcinoma was divided according to Edmondson-Steiner pathology (Grade 1, 2, 3 and 4).

Our subjects included three types of patients: patients with T2DM (the T2DM group), healthy people (control group) and patients newly diagnosed with HCC. The HCC patients were further divided into an HCC with T2DM (HCC+DM) group and a HCC without diabetes mellitus (HCC+NDM) group. Patients were divided into different groups based on age: <50 years, 50–59 years, 60–69 years and ≥ 70 years. The diabetics were further divided into 3 groups based on HbA1c: <6.5%, 6.5–7.49% and ≥7.5%; and 3 groups based on duration of diabetes: 0–10 years, 11–20 years and >20 years. Subgroup analysis was conducted to analyze the association of diabetic severity with AFP.

### 2.4. Statistical analysis

All analyses were performed using SPSS v. 22.0 software. AFP values were natural-log-transformed to improve normality. Variables conforming to a normal distribution were expressed as mean ± standard deviation (SD), and comparison between two groups was performed using an independent-samples *t* test. Variables conforming to skewed distribution were expressed as median (upper and lower quartiles), and comparison between two groups was performed using the MannWhitney *u* test. Multivariate linear regression analysis was used to explore the relationship between T2DM and serum AFP level, and multivariate logistic regression was used to analyze the correlation between T2DM and pathological classification of HCC, adjusting factors like age, gender, BMI, albumin, AFP, with odds ratio (OR) as the risk indicator. Differences with $P < 0.05$ were deemed statistically significant.

## 3. Results

### 3.1. Comparison of T2DM group with healthy control group

*Basic characteristics* There was no significant statistical difference in gender and age between the T2DM group and the control group, while BMI was higher in the T2DM group (24.51 vs. 23.78 kg/m2, $P < 0.001$, Table 1).

*Lower levels of AFP were observed in the T2DM group.* The T2DM group had a 12.61% lower geometric mean AFP level than the healthy control group (2.08 vs. 2.38 μg/L, $P < 0.001$). Moreover, the AFP level was negatively correlated with age and diabetic duration ($r = -0.156$, $P < 0.001$; $r = -0.167$, $P < 0.001$). The AFP level displayed a decreasing trend with age (<50 years: 2.71 μg/L, 50–59 years: 2.25 μg/L, 60–69 years: 2.23 μg/L, ≥ 70 years: 1.75 μg/L, $P < 0.001$) and duration of diabetes (<10 years: 2.27 μg/L, 11–20 years: 1.93 μg/L, >20 years: 1.70 μg/L, $P < 0.001$, Table 2).