RESEARCH ARTICLE

Elevated Serum Insulin is an Independent Risk Factor for Hepatocellular Carcinoma: A Case Control Study from Nepal

Satrudhan Pd Gupta[1]*, Ankush Mittal[1], Brijesh Sathian[2], Dipendra Kumar Jha[1]

Abstract

Aim: To investigate associations of fasting insulin and glucose levels in serum with hepatocellular carcinoma risk. Materials and Methods: This hospital based study was carried out using data retrieved from the register maintained in the Department of Biochemistry of the Nepalese Army Institute of Health Sciences, between 1st December, 2011 and 31st June, 2013. The variables collected were age, fasting plasma glucose, fasting plasma insulin and ALT. Quantitative determination of human insulin concentrations was accomplished by chemiluminescence enzyme immunoassay. Results: Of the total 220 subjects enrolled in our present study, 20 cases were of HCC and 200 were healthy controls. The maximum number of cases of hepatocellular carcinoma in category cutpoints of fasting insulin levels fell in the range of >6.10 μU/ml. The highest insulin levels (>6.10 μU/ml) were seen to be associated with an 2.36 fold risk of HCC when compared with fasting insulin levels of (<2.75 μU/ml). Furthermore, the insulin levels (2.75-4.10 μU/ml) of category cutpoints also conferred a 1.57 fold risk for HCC when compared with lowest fasting insulin levels of (<2.75 μU/ml). Conclusions: The effect of an insulin level in increasing HCC risk appeared consistent, influencing incidence, risk of recurrence, overall survival, and treatment-related complications in HCC patients.

Keywords: Insulin - glucose - serum levels - HCC risk - Nepal

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer worldwide and the third most general cause of cancer transience (Chong et al., 2013). The despondent clinical consequences of HCC leads to a critical need for in-depth understanding of the relevant factors affecting HCC incidence and prediction (Ren et al., 2012). HCC has more than a few appealing epidemiologic features including dynamic temporal trends, marked variations among geographic regions, racial and ethnic groups, and between men and women; and the presence of numerous well-documented environmental potentially avoidable risk factors. Liver cancer is linked with a higher prevalence and casualty rate along with diabetic patients (Jha et al., 2012). Insulin secreted by pancreas absorbs through the portal circulation to the liver and renders the liver to excess of insulin (Mastracci et al., 2012). Hyperglycemia, hyperinsulinemia, dyslipidemia, obesity , non-alcoholic fatty liver disease, cirrhosis and abnormal fat retention are diabetes related factors that increase the risk of liver cancer (Hsiao et al., 2013). Hyperglycemia and hyperinsulinemia, which are the major abnormalities that characterize diabetes, can promote cancer via both independent and synergic mechanisms. Insulin is both a metabolic hormone and a growth factor that promotes cell proliferation. Hyperglycemia provides energy for malignant cell proliferation and, via the peculiar energy utilization of cancer cells, favors cancer growth and neoangiogenesis. Therefore, the main objective of our study was to investigate the association of fasting insulin and glucose levels with hepatocellular carcinoma risk.

Materials and Methods

It was a hospital based study carried out using data retrieved from the register maintained in the Department of Biochemistry of Nepalese Army Institute of Health Sciences, Nepal between 1st December, 2011 and 31st June, 2013. The variables collected were age, fasting plasma glucose, fasting plasma insulin and ALT. The transaminases (ALT) were estimated by liquid UV test (Henley et al., 1955). The assessment of fasting blood glucose was done by glucose oxidase and peroxidase method (Trinder et al., 1969). All these laboratory parameters were analyzed using Human reagent kits and with the help of semi autoanalyser (Humalyser 3500, Germany). The quantitative determination of human insulin concentrations in human serum was estimated by Chemiluminescence enzyme immunoassay (Kahn et al., 1979). Preceding the study, approval for the study was obtained from the institutional research ethical committee.

*[1]Department of Biochemistry, Nepalese Army Institute of Health Sciences, Kathmandu [2]Department of Community Medicine, Manipal College of Medical Sciences, Pokhara, Nepal *For correspondence: satrudhangupta4@gmail.com*

Analysis was done using descriptive statistics and testing of hypothesis.. The One way ANOVA was used to examine the statistical significant difference between groups. The Cox proportional hazards model was used to estimate the hazard ratios (HRs) for incident HCC. The data was analyzed using Excel 2003, R 2.8.0, Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version A p-value of <0.05 (two-tailed) was used to establish statistical significance.

Results

Of the total 220 subjects enrolled in our present study, 20 cases were of HCC and 200 were healthy controls.

Table 1 depicts that the maximum number of cases (11) of hepatocellular carcinoma were above 60 years of age. The fasting plasma glucose ≥126 mg/dL, was observed in 5 cases of hepatocellular carcinoma. Furthermore, the mean value of fasting plasma glucose was 95.5 mg/dl in cases of hepatocellular carcinoma. The mean value of fasting plasma insulin, was 5.78 μU/ml in cases of hepatocellular carcinoma (p value 0.0001*).

Table 2 illustrates that fasting insulin levels μU/ml were categorized into category cutpoints and quartile cutpoints. The maximum number of cases of hepatocellular carcinoma in category cutpoints of fasting insulin levels falls in range of >6.10 μU/ml. The highest insulin levels (>6.10 μU/ml) were seen to be associated with an 2.36 fold risk of HCC when compared with fasting insulin levels of (<2.75 μU/ml) of category cutpoints. Furthermore, the insulin levels (2.75–4.10 μU/ml) of category cutpoints also conferred a 1.57 fold risk for HCC when compared with lowest fasting insulin levels of (<2.75 μU/ml) of category cutpoints.

Table 1. Baseline Characteristics of HCC Cases and Non-Cases

Characteristic	HCC cases (20)	Controls (200)	p Value
Age, years, No. (%)			0.0001*
30–39	2(10.0%)	40 (20%)	
40–49	4 (20%)	90(45.0%)	
50–59	3 (15.0%)	50 (25.0%)	
≥60	11 (55.0%)	20 (10.0%)	
Smoking status, No. (%)			0.4121
Never	12 (60.0%)	130 (65.0%)	
Former	3 (15.0%)	30 (15.0%)	
Current	5 (25.0%)	40 (20.0%)	0.0001*
ALT≥>40 (U/l)No. (%)	6 (30.0%)	10(5.0%)	0.0001*
Fasting plasma glucose≥126 (mg/dl) No. (%)			
	5 (4.0%)	20 (10.0%)	0.4362
Fasting plasma glucose (mg/dl) (mean)			
	95.5	85.7	0.832
Fasting plasma insulin (μU/ml) (mean)			
	5.78	4.23	0.0001*

Table 2. HRs for Incident HCC by Metabolic Factors

Metabolic factors	HCC cases(20)	Controls (200)	Hazard Ratio	95% CI	p Value
Fasting insulin levels (μU/ml) Category cutpoints					0.0140*
<2.75	6(30%)	63(31.5%)	1	(0.66-1.73)	
2.75–4.10	2(10%)	37(18.5%)	1.57	(0.96–2.58)	
4.11–6.10	4(20%)	39(19.5)	1.28	(0.76–2.15)	
>6.10	8(40%)	61(30.5%)	2.36	(1.43–3.90)	
Fasting insulin levels (μU/ml) Quartile cutpoints					0.0403*
<2.27	5(25%)	48(24%)	1	(0.66-1.73)	
2.27–3.60	3(15%)	57(28.5%)	1.43	(0.89–2.30)	
3.61–5.36	4(20%)	47(23.5%)	0.95	(0.58–1.56)	
>5.36	8(40%)	48(24%)	1.78	(1.15–2.75)	
Fasting glucose levels (mg/dl)					0.0151*
<110	16(80%)	174(87%)	1	(0.76-1.53)	
110–125	3(15%)	19(9.5%)	1.4	(0.80–2.45)	
≥126	1(5%)	7(3.5%)	2.37	(1.12–5.04)	

Discussion

Higher threat of numerous malignancies along with individuals with elevated insulin levels, a end result of insulin resistance has been extensively assumed and explained by various mechanisms.The augment tumor cell production and metastasis can take place due to the unrelenting exposure to hyperglycemia and hyperinsulinemia (Richardson et al., 2005). IR, which show the way to the accretion of fat within hepatocytes, is allied to both excess BMI and NAFLD. Hepatic fat accrual generate oxidative stress, ensuing in inflammation and fibrosis. Our present study had reported that the maximum number of cases of hepatocellular carcinoma were above 60 years of age. The mean value of fasting plasma insulin, was 5.78 μU/ml in cases of hepatocellular carcinoma (p Value: 0.0001*). The highest insulin levels (>6.10 μU/ml) were seen to be associated with an 2.36 fold risk of HCC when compared with fasting insulin levels of (<2.75 μU/ml.) of category cutpoints. Our results concurred with the findings of Chao et al (Chao et al., 2011). Furthermore, the insulin levels (2.75–4.10 μU/ml) of category cutpoints also conferred a 1.57 fold risk for HCC when compared with lowest fasting insulin levels of <2.75 μU/ml) of category cutpoints. The chances of metastasis was increased as acute exposure to hyperglycemia and IGF increase endothelial cell permeability due to increased generation of reactive oxidative species and structural alteration in the basement membrane (Morss et al., 2007). IR encourage fibrosis succession, progress of hepatic steatosis, hyperleptinemia, increased TNF production and abridged expression of peroxisome proliferator activated receptors (Hsu et al., 2008). The increased levels of insulin and glucose possibly will endorse fibrogenesis by stimulating the liberation of connective tissue growth factor from hepatic stellate cells (Paradis et al., 2001). Conclusion: The effect of an insulin level in increasing HCC risk was consistent and influences incidence, risk of recurrence, overall survival, and treatment-related complications in HCC patients.

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