The liver plays an important role in the carbohydrate metabolism. Approximately 70% of patients with cirrhosis (CH) are glucose intolerant and 20-30% eventually develop frank diabetes mellitus.[1,2] Studies have shown that hepatitis C virus (HCV)-related liver disease is significantly associated with the occurrence of type 2 diabetes mellitus (DM-2).[3-11] Age, body mass index (BMI), and alcohol consumption have also been shown to be associated with the occurrence of DM-2.[3,5,6] The liver plays an important role in the carbohydrate metabolism. Approximately 70% of patients with cirrhosis (CH) are glucose intolerant and 20-30% eventually develop frank diabetes mellitus.[1,2] Studies have shown that hepatitis C virus (HCV)-related liver disease is significantly associated with the occurrence of type 2 diabetes mellitus (DM-2).[3-11] Age, body mass index (BMI), and alcohol consumption have also been shown to be associated with the occurrence of DM-2.[3,5,6] The liver plays an important role in the carbohydrate metabolism. Approximately 70% of patients with cirrhosis (CH) are glucose intolerant and 20-30% eventually develop frank diabetes mellitus.[1,2] Studies have shown that hepatitis C virus (HCV)-related liver disease is significantly associated with the occurrence of type 2 diabetes mellitus (DM-2).[3-11] Age, body mass index (BMI), and alcohol consumption have also been shown to be associated with the occurrence of DM-2.[3,5,6] The liver plays an important role in the carbohydrate metabolism. Approximately 70% of patients with cirrhosis (CH) are glucose intolerant and 20-30% eventually develop frank diabetes mellitus.[1,2] Studies have shown that hepatitis C virus (HCV)-related liver disease is significantly associated with the occurrence of type 2 diabetes mellitus (DM-2).[3-11] Age, body mass index (BMI), and alcohol consumption have also been shown to be associated with the occurrence of DM-2.[3,5,6] The liver plays an important role in the carbohydrate metabolism. Approximately 70% of patients with cirrhosis (CH) are glucose intolerant and 20-30% eventually develop frank diabetes mellitus.[1,2] Studies have shown that hepatitis C virus (HCV)-related liver disease is significantly associated with the occurrence of type 2 diabetes mellitus (DM-2).[3-11] Age, body mass index (BMI), and alcohol consumption have also been shown to be associated with the occurrence of DM-2.[3,5,6]
**HBV-related liver disease:** Patients with liver disease (CH or HCC) with HBsAg positivity but negative for anti-HCV antibodies.

**HCV-related liver disease:** Patients with liver disease (CH or HCC) with anti-HCV positivity but negative for HBsAg.

**DM-2:** Two or more readings of random blood sugar levels (BSL) of >200 mg% or fasting BSL of >126 mg% or patient being already on medications (oral hypoglycemics and or insulin).

### Serological tests
Third generation enzyme-linked immunosorbent assay (ELISA) tests were performed on the sera of the patient using commercial kits from Abbott Diagnostics, Chicago, IL, USA for HBsAg and Murex III; and Murex Diagnostics, Dartford, UK for anti-HCV.

### Statistical methods
The statistical package for social sciences (SPSS) was used to analyze the data. Chi square or Fisher’s test was used to compare proportions. Multivariate logistic regression analysis was used to determine factors that could affect the occurrence of DM-2.

### RESULTS
Comparing patient demographics, HCC patients were significantly older and had more HBV-related liver diseases compared to patients with CH (61.0 ± 10.8 years vs. 54.7 ± 16.8 years, P = 0.0003; 56 vs. 43%, P = 0.007, respectively) [Table 1]. Seventy-six percent of HCC patients had associated CH based on the criteria as defined earlier.

The prevalence of DM-2 in the whole group (CH + HCC) and in patients with CH was higher as compared with the control group (15.2 vs. 9.2%; P = 0.025; odd ratio [OR] 1.6 [95% confidence interval (CI) = 1.1-2.54] and 19.2 vs. 9.2%; P = 0.002; OR 2.03 [95% CI = 1.19-3.44], respectively). In contrast, the prevalence of DM-2 was similar in patients with HCC and the control group (10.9 vs. 9.2%; P = 0.52; OR = 1.15 [CI = 0.61-2.16]). On univariate analysis, diabetics in comparison to non-diabetics were older (60 ± 12 vs. 53 ± 18 years; P = 0.02) and more likely to have hypertension (21 vs. 4%; P = 0.0002). Further, on multiple regression analysis, age and hypertension independently predicted the occurrence of DM-2 in patients with liver disease (P = 0.014 and 0.001, respectively). Other factors such as the presence or absence of HCC, viral status (HBV vs. HCV), Child’s status of liver disease, and sex did not predict the presence of DM-2.

Viral markers (HBsAg and anti-HCV antibodies) were available for 180 patients, of which 89 had HBV-related liver disease and in 19 patients, liver disease was related to HCV infection. Although the prevalence of DM-2 was higher in patients with HCV-related liver disease (26.3%) in comparison to HBV-related liver disease (15.7%), the difference was not found to be significant (P = 0.31) [Table 2]. Similar trends for higher prevalence of DM-2 in patients with HCV-related liver disease in comparison to HBV-related liver disease were noted for patients with CH (30.7 vs. 20.5%) and patients with HCC (16.6 vs. 12.7%); however, the differences were not significant [Table 2].

### DISCUSSION
The prevalence of DM-2 in the general population in Saudi Arabia varies from 2.5 to 23.7% amongst seven different studies reported between 1982 and 2004.[17] Prevalence rate in our control group was 9.2%, which is lower than the recently reported prevalence in the same age group.[17] The prevalence has been shown to be higher in the urban population as compared to the rural population.[17] Gizan, a southwestern province is a relatively rural population and this could possibly account for the lower prevalence in our control group. Moreover, our control group consisted of patients admitted to the hospital for various reasons, but without any past or present liver disease whereas most of the reports are epidemiologic field based studies. Small number of subjects (n = 400) in our control group in contrast to 3158-23493 in other studies could also be responsible for this difference.[17]
The prevalence of DM-2 in cirrhotics alone as well as the whole group of patients with liver disease (cirrhotics and HCC) was significantly higher in comparison to the control group. These data are similar to the studies reported earlier. Age is a known risk factor for DM-2, as observed in our study, with diabetics being a decade older compared to nondiabetics. Twenty-one percent of diabetics had hypertension in our study population. Hypertension is known to be more prevalent in patients with DM-2 in the KSA and 46% of diabetics were found to be hypertensive in a hospital-based study from the KSA. Insulin resistance and metabolic syndrome (hypertension, obesity, and hypertriglyceridemia, and DM-2) is one of the principal mechanisms in the pathogenesis of DM-2. In the present report, data on height/weight/body mass index, family history, and lipid profile were not available to substantiate whether DM-2 in our patients was a component of metabolic syndrome.

DM-2 has been consistently linked with HCV infection. HCV core protein downregulates insulin receptor substrates, thereby causing a state of insulin resistance leading to DM-2. After adjusting for factors such as race, alcohol consumption, and socioeconomic status, DM-2 was shown to be 3.77 times more common in patients with HCV infection than those without HCV infection in persons above 40. The prevalence of DM-2 in patients with HCV-related liver disease has been reported to be 14-40% in various studies. In the present report, 26% patients with HCV-related liver disease had DM-2. This is comparable to 22% prevalence of DM-2 in patients with HCV infection reported earlier from the KSA.

Although a trend for higher prevalence of DM-2 was observed in patients with HCV-related liver disease in comparison to HBV-related liver disease, the difference was not statistically significant. This could have been due to a small sample size of 19 patients with HCV-related liver disease in the present series.

Lecube et al. have shown DM-2 to be three times more common in patients with HCV-related chronic hepatitis compared to non-HCV related hepatitis. However, when patients with CH were compared, there was no significant difference irrespective of the presence or absence of HCV infection. Our study population consisted of patients with advanced liver disease (CH and HCC) and did not include patients with chronic hepatitis. The lack of significant association of the prevalence of DM-2 with HCV infection in the present study could also have been partly due to this factor.

On the other hand, the prevalence of DM-2 in patients with HCC was comparable to the control group. This is despite the fact that patients with HCC were elderly compared to cirrhotics. The overexpression of fructokinase gene with consequent higher utilization of glucose has been described in all malignancies including HCC. Moreover, patients with HCC are known to secrete insulin-like substances as a part of paraneoplastic manifestations. It is possible that these mechanisms may counteract the hyperglycemia of CH and explain our observations. Well-designed prospective studies in patients with CH and diabetes mellitus with long-term follow-up for the development of HCC can answer and provide us with a better understanding of the association between HCC and DM-2. Moreover, 76% of HCC patients had underlying CH. Patients with HCC in comparison to cirrhotics had more HBV-related liver diseases (41 vs. 31%; \( P = 0.007 \)) and less HCV-related liver diseases (4 vs. 9%; \( P = 0.16 \)). This could have partly explained this observation. It may also be argued that the biological behavior of the virus is different in HCC patients and in cirrhotics. Molecular biological studies to analyze this host-virus interaction can answer this question.

In summary, DM-2 occurs more frequently in patients with chronic liver disease, particularly amongst cirrhotics without HCC in KSA. Age and hypertension are independent predictors for the occurrence of DM-2 in patients with liver disease. The prevalence of DM-2 is higher in patients with HCV-related liver disease, although the difference did not reach statistical significance. Further studies with a large sample size of HCV-related liver diseases are suggested. Additional research is also required to better understand and explore the relationship of HCC and DM-2.

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