Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Epidemiology

Hepatocellular Carcinoma and Diabetes

Dr. Sunanda Gupta[1*], Dr. Manya Prasad[2], Dr. Archana Ramalingam[3]

[1]Senior Resident, Department of Epidemiology, Institute of Liver and Biliary Sciences, New Delhi, India
[2,3]Assistant Professor, Department of Epidemiology, Institute of Liver and Biliary Sciences, New Delhi, India

DOI: 10.36347/sjams.2022.v10i06.010 | **Received:** 01.05.2022 | **Accepted:** 11.06.2022 | **Published:** 16.06.2022

***Corresponding author:** Dr. Sunanda Gupta
Senior Resident, Department of Epidemiology, Institute of Liver and Biliary Sciences, New Delhi India

Abstract **Review Article**

Liver cancer is the seventh most commonly occurring cancer and second commonest cancer in terms of mortality. Hepatocellular carcinoma (HCC) is the dominant type of liver cancer (Almost 75% of all liver cancers). In 2017, diabetes was the ninth cause of mortality and seventh leading cause of human suffering from disability-adjusted life years. In the five countries of the world, that report highest number of HCC cases (China, Japan, United States, India, Vietnam), the population attributable fraction of diabetes for hepatocellular carcinoma varies between 4.7% to 7.6% in men and 4.6%-7.1% in women. Though an association has been hypothesized between HCC and diabetes, the underlying mechanism is poorly understood with various theories of pathophysiology having been proposed. Moreover, there are other etiological factors that influence carcinogenesis in diabetes patients. Several risk score systems help in predicting liver cancer in diabetic population. Also, anti-diabetic agents are known to play a role in the development of liver cancer. This article aims to summarize the association of HCC and diabetes, pathophysiology of the association, influence of risk factors in development of HCC in diabetes patients, the risk scores used for prediction of liver cancer in diabetes patients, and role of anti-diabetic agents in HCC.

Key-words: Hepatocellular carcinoma, Diabetes, risk, non-communicable diseases.

INTRODUCTION

Magnitude of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the dominant type of liver cancer (almost 75% of all liver cancers) [1]. Liver cancer contributed to 4.7% of all new cancer cases, and 8.3% of cancer deaths, globally in the year 2020 [2]. Age-standardized incidence rate of liver cancer was 9.5 per 100,000, worldwide in 2020 [3]. This is the seventh most commonly occurring cancer and second commonest cancer in terms of mortality [3].

Magnitude of diabetes

Globally, 462 million individuals (6.28% of world's population) are diabetic. In 2017, it was the ninth most common cause of mortality and seventh leading cause of human suffering from disability-adjusted life years. This marks a sharp rise, since in 1900, type 2 diabetes was the eighteenth cause of worldwide mortality. Statistical modeling indicate prevalence of 7862 per 100,000 by the year 2040 [4]. The number of young people having diabetes is also on the rise [5, 6].

Concomitant prevalence of hepatocellular carcinoma and diabetes

Incidence of both HCC and diabetes are alarmingly on rise worldwide. The development of HCC is closely linked to presence of diabetes owing to several mechanisms and presence of other etiological factors like hepatitis infection. The concomitant prevalence of hepatocellular carcinoma and diabetes in total population is 0.016-0.14%.[7,8] In the five countries of the world that report highest number of HCC cases (China, Japan, United States, India, Vietnam), the population attributable fraction of diabetes for HCC varies between 4.7% to 7.6% in men and 4.6%-7.1% in women [9].

Objective of the review

This brief review aims to summarize the association of HCC and diabetes, influence of other factors in development of HCC in diabetes patients, the risk scores used for prediction of liver cancer in diabetes patients, pathophysiology of HCC in diabetes, and role of anti-diabetic agents in HCC.

Association between hepatocellular carcinoma and diabetes

Several studies have reported significant association of hepatocellular carcinoma with \diabetes, as described in table 1.

Table-1: Studies on association between hepatocellular carcinoma and diabetes

Observational studies			
Study	**Outcome**	**Effect measure**	**Effect size**
Meon, 2019[10]	HCC All types of hepato-biliary cancers	OR OR	1.85, 95%CI: 1.65–2.06 2.12; 95% CI:1.92–2.36
Nderitu, 2018[7]	Primary liver cancer	HR	4.21, 95% CI: 1.86-9.54
Yi S-W, 2018[11]	HCC	HR	1.80, 95%CI: 1.63-1.99
Simon, 2017[12]	HCC HCC stratified by diabetes duration	HR HR	4.59; 95% CI, 2.98-7.07 2.96 (95% CI, 1.57-5.60) for 0-<2 years 6.08 (95% CI, 2.96-12.50) for 2-<10 years 7.52 (95% CI, 3.88-14.58) for ≥10 years
Yang, 2016[13]	HCC	HR	1.9, 95% CI=0.9-3.7
Miele, 2015[14]	HCC	OR	2.25, 95% CI, 1.42–3.56
Toyoda, 2015[15]	HCC	RR	2.08; 95% CI1.01-4.01
Setiawan, 2014[16]	HCC	RR	Latinos = 3.36; 95% CI; 2.41-4.70, RR for Hawaiians= 2.50; 95% CI; 1.11-5.64, RR for Japanese 2.34; 95% CI; 1.60-3.42, RR for Whites; 2.15; 95% CI; 0.95-4.90, RR for Africans Americans; 2.02; 95% CI; 1.17-3.48
Turati, 2013[17]	HCC	OR	4.33, 95% CI; 1.89-9.86
Koh, 2013[8]	HCC	HR	2.14 , 95% CI: 1.69–2.71
Zheng, 2013[18]	HCC	OR	2.35, 95% CI; 1.36-4.05
Lai, 2012[19]	HCC	HR	1.73; 95% CI, 1.47-2.03
Meta-analysis			
Study	**Outcome**	**Pooled effect measure**	**Effect size**
Tanaka, 2014[20]	HCC	RR	2.18 (95% CI 1.78–2.69) Cohort studies: 2.10 (95% CI 1.60–2.76) Case-control studies: 2.32 (95% CI 1.73–3.12)
Wang, 2011[21]	HCC	RR	2.31, 95% CI: 1.87–2.84 Cohort studies: 2.23, 95% CI: 1.68–2.96 Case-control studies: 2.40, 95% CI: 1.85–3.11
Wang, 2011[22]	HCC	RR	2.01; 95% CI: 1.61-2.51
Noto H, 2010[23]	HCC	OR	3.64, 95% CI 2.61-5.07
Serang, 2006[24]	HCC	OR	Cohort studies: 2.5; 95% CI: 1.9–3.2 Case-control studies: 2.5; 95% CI: 1.8–3.5

*HR= Hazard ratio, OR: Odds ratio, RR: Relative risk.

Patho-physiology of HCC in diabetes

The process of carcinogenesis consists of: initiation, promotion and progression. The various mechanisms involved are as follows [25-30].

1. Abnormal metabolism: Elevated blood glucose, triglycerides, VLDL (very low density lipoproteins), low HDL (high density lipoproteins) promotes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), which subsequently lead to liver fibrosis and cirrhosis. Activation of lipid synthesis pathways also causes insulin resistance, hyperinsulinaemia. Type 2 diabetes mellitus (T2DM) is often associated with central obesity. This promotes carcinogenesis via secretion of proinflammatory cytokines by visceral adipose tissue [31]. Hyperglycemia causes glycosylation of haemoglobin, hence releasing iron. This further releases free radicals causing oxidative stress, resulting in carcinogenesis in liver. Hyperinsulinemia can also increase the secretion of matrix proteins and other precursors of hepatic

fibrosis by hepatic stellate cells and hence reduces mitochondrial β-oxidation of fatty acids. This is associated with hepatocellular injury, inflammation, and hepatic fibrosis [32].

2. Insulin/ Insulin-like growth factor signaling: Increased insulin and IGF levels in diabetic patients regulate cell proliferation, angiogenesis, immune modulation. This facilitates neoplastic cell proliferation and metastasis.
3. Platelet activation: Platelets are activated during postprandial phase of diabetic individuals (with low insulin level or insulin resistance). Platelets are involved in chronic inflammation and thrombotic processes. Platelet activation elevates cytokines (interleukin-1β (IL-1β), interleukin-8 (IL-8)) and platelet derived growth factors (transforming growth factor β (TGF-β) and vascular endothelial growth factor (VEGF)). These are stored in the cyclooxygenase 2 (COX-2) pathways in cancer cells. Activated platelets also release soluble CD40 ligand (CD40L), which is involved in pro-inflammatory processes. Also, platelet levels are an independent risk factor for advanced fibrosis in T2DM patients with NAFLD (odds ratio, 0.985; 95% CI, −0.972–0.999; P = 0.034) [33].
4. Chronic inflammation and epigenetic mechanism: Increased levels of tumor necrosis factor alpha, interleukin-6, interleukin 1ß associated with diabetes promotes cell proliferation, migration and metastasis. Several epigenetic events and methylated genes have been identified in patient tissues or serum with cancer diagnosis.
5. Epigenetic modifications like DNA methylation, histone modification, and RNA interference, can stimulate proinflammatory genes which encode nuclear factor kappa B (NF-κB) and proteins, which are involved in JAK/STAT signaling, subsequently leading to the hepatocellular transformation [34].
6. ROS (reactive oxygen species) /ER (endoplasmic reticulum) stress/autophagy: Insulin resistance is related with increased oxidative stress. The production of ROS leads to upregulation of pro-inflammatory cytokines like TNF-alpha. This induces DNA damage, stimulation of nuclear factor kappa light chain enhancer of activated B cells. Hence, both cancer causing genetic mutations and inflammatory dysregulated cell proliferation are facilitated.
7. Hub gene and microRNAs/Gut microbiota/ immunomodulation: This causes cell proliferation, angiogenesis, metastasis and stimulation of cell signaling.

Genetic association between HCC and diabetes mellitus

Two hundred fifty differentially expressed genes (DEG) were found to be associated with HCC and diabetes. Among those, there were one hundred and fifty five upregulation genes and one hundred and one down regulation genes. All the 10 hub genes (*CCNA2, CCNB1, MAD2L1, BU1B, RACGAP1, CHEK1, BUB1, ASPM, NCAPG* and *TTK*) have a strong association with lower survival in liver cancer patients and four genes (*CCNA2, CCNB1, CHEK1* and *BUB1*) have reduced expression in metformin-treated samples.[35] The nuclear receptor co-activator 5 (NCOA5) gene is a possible susceptibility gene for both type 2 diabetes (T2D) and HCC (HCC).[36] In the study by Wei *et al*., eight genes were found to be linked with development of HCC in diabetics. CDKNA1 gene was found to be diagnostic and potential marker in clinical management of HCC [37]. In another study by Liu *et al*., nine genes, namely, CDNF, CRELD2, DNAJB11, DTL, GINS2, MANF, PDIA4, PDIA6, and VCP, were recognized as hub genes those played important role in HCC development in diabetes patients[38].

Risk factors of hepatocellular carcinoma and diabetes

Risk factors of diabetes

Risk factors of diabetes include overweight and obesity, diet containing low quality fats and carbohydrates, sedentary lifestyle, smoking, low hip circumference, unhealthy dietary pattern having increased consumption of processed meat and sugar-sweetened beverages, decreased intake of whole grains, coffee and heme iron, low level of education and conscientiousness, increased duration of television watching, low alcohol drinking, air pollution, and some medical conditions like high systolic blood pressure, late menarche age, gestational diabetes, metabolic syndrome, preterm birth, family history of diabetes mellitus, urban dwelling, older age [39-42].

Risk factors of hepatocellular carcinoma

The different risk factors of hepatocellular carcinoma are hepatitis B (44% HCC are attributable to hepatitis B), hepatits C (21% HCC are attributable to hepatitis C), alcohol, obesity, diabetes, metabolic syndrome, ingestion of fungal metabolite aflatoxin B1, aristolochic acid, obesity, NAFLD, cirrhosis [9, 43, 44]

As we can observe, both the diseases have common risk factors like obesity, alcohol for development and worsening.

Risk factors which increase vulnerability for hepatocellular carcinoma in diabetic patients

Hepatitis C virus

There is a two-way association between diabetes and chronic hepatitis C infection. Chronic hepatitis C infection facilitates HCC development both directly and indirectly due to the virus's diabetogenic effects. Increased hepatic steatosis in hepatitis C patients is caused via increased production of lipogenic substrate, upregulation of lipogenesis, and disruptions

of fatty acid metabolism. This is worsened by insulin resistance in diabetes. Reduced insulin sensitivity also enhances release of free fatty acids from adipose leading to increased hepatic lipid deposition. Both increased hepatic lipid deposition and steatosis are independently associated with increased fibrosis in patients with genotype 1 HCV [45]. In the study by Yen *et al*., in 2018, the presence of diabetes mellitus was found to be an independent risk factor for HCC (hazard ratio = 2.78, 95% CI = 1.3-5.92) in chronic hepatitis C patients [46]. Huang *et al.,* in 2017, studied that diabetes significantly increased risk of HCC in hepatitis C infected patients; adjusted Hazards ratio being 2.61 (95% CI: 2.05–3.33) [47]. In the case-control study by Li *et al*., in 2017, it was found that the odds of HCC was two times among those with DM (adjusted odds ratio = 1.89, 95% CI: 1.17–2.75) in treatment naïve, chronic hepatitis C patients [48]. In a nation-wide cohort study by Huang *et al*., in 2015, the relative risk for cumulative incidence of HCC was reported to be 1.544, 95% CI = 1.000-2.387,with new onset diabetes, in patients of chronic hepatitis C infection [49]. The retrospective cohort study by Arase *et al*., in 2013 estimated that T2DM caused a 1.73-fold enhancement in HCC development in chronic hepatitis C patients [50]. In the systematic review, in 2016, by Dyal *et al.*, the authors evaluated the effect of DM on HCC in chronic hepatitis C patients. In 2015, Chen *et al.,* in their meta-analysis reported that summary relative risk for HCC in diabetes was 1.90 (95% CI 1.37-2.63) for patients with hepatitis C virus infection [51]. The risk was found to be significantly increased. The effect measures ranged between hazard ratio 4.63 (95% CI: 1.68–12.77) to 1.73 (95% CI: 1.30–2.30) [52]. Hence, studies reported high incidence of HCC in diabetics in chronic hepatitis C infected population. However, in the study by Yang *et al*., reported that in patients with Hepatitis C virus (HCV), there was no association between diabetes and HCC (hazard ratio; 0.8, 95% CI=0.4-1.8) [13].

Hepatitis B virus

Hepatitis B virus along with diabetes probably enhances risk of HCC via mechanisms of oxidative stress (chronic inflammation) and hepatic steatosis. In 2019, Shyu *et al*. reported that, the chronic hepatitis B patients with diabetes mellitus compared to the non-diabetic had significantly increased (3.3%) risk for HCC development and significantly increased (2.8%) risk of HCC-related mortality. The hazard ratio was calculated to be 1.35 (95% CI: 1.16-1.57) for incidence of HCC in diabetics of chronic hepatitis B population [53]. In 2018, Kim *et al*., in their study, observed that fasting serum glucose level of more than 140 mg/dL (HR = 1.46; 95% CI: 1.36-1.57; $p < 0.001$) and presence of T2DM (HR=1.23; 95% CI: 1.15-1.34; $p < 0.001$) were associated with an increased risk of HCC, in Korean men with chronic hepatitis B infection [54]. Another study in 2018, by Li *et al*., found that presence of diabetes increased the risk for HCC more than twicw (adjusted odds ratio: 2.402; 95% CI: 1.150-5.018) [55]. In 2018, another study by Yip *et al.* stated that diabetes was associated with significant increased risk of HCC (adjusted hazard ratio, 1.85; 95% CI, 1.04–3.28) in chronic hepatitis B patients after seroclearance of HbSAg [56]. After analyzing the Taiwanese National Health Insurance Research database, in 2015, it was reported that chronic hepatitis B patients with new onset diabetes had a significantly higher cumulative incidence of HCC (hazard ratio = 1.798, 95% CI = 1.194-2.707) [57]. In 2015, Chen *et al*., in their meta-analysis reported that summary relative risk for HCC in diabetes was 1.69 (95% CI 0.97-2.92) for patients with hepatitis B virus infection [51].

Contrary evidence was found in a study in the review. Li *et al*., in 2012, in a hospital based case-control study found that there was no association between diabetes and HCC in hepatitis B patients [58].

Non-alcoholic steatohepatitis (NASH)

The main pathogenic mechanism of hepatic steato-hepatitis is insulin resistance in liver, adipose tissue and skeletal muscle. These synergistically lead to systemic inflammation which subsequently causes the release of nephrotoxic factors. There is also, increased free fatty acids (FFAs) in ectopic tissues, due to an increased lipolysis in dysfunctional adipose tissue. This results in insulin resistance and hepatocyte necro-inflammation [59]. Yang *et al*., in 2020, reported an significantly increased association of increased risk of HCC and diabetes (hazard ratio = 4.2, 95% CI =1.2–14.2) in patients with NASH [60].

Alcohol

Diabetes mellitus is found to increase the risk of HCC in patients of alcoholic liver diseases. Alcohol-induced oxidative stress possibly increases the susceptibility of patients having diabetes mellitus to cirrhosis, DNA damage, and further to HCC development [61]. Over a 3 year median follow-up period, diabetics compared to nondiabetics had a higher probability to develop HCC (27% vs. 10%; p=0.045) [62]. In the study by Balbi *et al*., in 2010, presence of diabetes along with alcohol abuse showed an odds ratio of 49.0 (95% CI: 21.5−111.8) for incidence of HCC when compared to controls (alcohol abuse alone) [63].

Prediction of hepatocellular carcinoma in diabetic patients based on scoring system

A novel risk score was developed in 2020, with data of two parallel populations: National Health Insurance Service (NHIS)-National Sample Cohort (NSC) as derivation cohort, and Samsung Medical Center Health Promotion Center Cohort (SMCHPCC) as external validation cohort. With six variables age, sex, BMI, smoking, hypertension, diabetes, total cholesterol and ALT levels, a nineteen point scale was developed. The lowest score (0 point) showed a ten year HCC incidence rate of 0%, and the highest score (18

points) showed a ten year incidence rate of 6.16%. Hazard ratio for diabetics developing HCC was reported to be 1.97; 95% CI: 1.42-2.27 [64]. The study by Li *et al*., in 2017, developed a risk score system for prediction of HCC in type 2 diabetes patients. The Taiwan National Diabetes Care Management Program database was used. The retrospective cohort study included 31,723 Chinese individuals of age 30–84 years, who had type 2 diabetes. The mean follow-up period for the 748 incident HCC cases was 8.33 years. The final risk score system included age (-2 to 8 points), gender (0-2 points), smoking (0-2 points), variation in hemoglobinA1c (0-1 point), serum glutamic-pyruvic transaminase (0-6 points), liver cirrhosis (9 points), hepatitis B (4 points), hepatitis C (3 points), antidiabetes medications (0-3 points), and antihyperlipidemia medications and total/high-density lipoprotein cholesterol ratio (-4 to 2 points). The risk score was the sum of the individual scores (range -6 to 40). The area under the receiver operating characteristic curve (AUROC) for 3-, 5-, and 10-year HCC risks was 0.81, 0.80, and 0.77 respectively [65]. In the study conducted by Rau *et al*., in 2015, an artificial neural network and a logistic regression prediction model were constructed that included the variables: sex, age, alcoholic cirrhosis, nonalcoholic cirrhosis, alcoholic hepatitis, viral hepatitis, other types of chronic hepatitis, alcoholic fatty liver disease, other types of fatty liver disease, and hyperlipidemia. A web based application was based on these, that aimed at supporting doctors while treating diabetic patients for prediction of liver cancers [66]. In the single centre, retrospective cohort study by Si *et al*., in 2016, a scoring system was developed by utilizing potential predictors of increased risk of HCC from Cox proportional hazards model. The scores for each of the parameters (age > 65 years, low triglyceride levels and high gamma-glutamyl transferase levels) were the rounded quotient of corresponding estimated coefficient from logistic regression model. The weighted sum of this DM-HCC risk score ranged from 0 to 33. At the cutoff value of 16, the sensitivity, specificity and area under the ROC curve of DM-HCC risk score in the prediction of 10-yr HCC risk was 95.7%, 53.4% and 0.86, respectively, in derivation cohort, and 91.7%, 53.5% and 0.86, respectively, in validation cohort [67].

Role of anti-diabetic agents in HCC

In hepatocytes, metformin inhibits mitochondrial respiratory chain-1. This causes decreased ATP production and increased ADP and AMP level, subsequently leading to AMPK activation. Hence, this inhibits gluconeogenic gene transcription and lipogenesis and improves insulin sensitivity. Moreover, increased AMP leads to decrease in cAMP induced activation of protein kinase A (PKA) and reduces insulin resistance. Hence, metformin has protective effects on liver cancer [28]. Miyoshi *et al*., in his study concluded that metformin prevents both human HCC cell proliferation and tumor growth, probably by suppressing the cell cycle-related molecules via alteration of miRNAs [68]. The review article by Chen, discusses that metformin improves survival in early stage liver cancer, but fails to do so in advanced stages [69].

In a systematic review by Cunha *et al*., all studies reported reduced risk of HCC in patients with metformin use. A pooled odds ratio of 0.468; 95% CI 0.275–0.799 for the association between HCC and the use of metformin was calculated in the meta-analysis using data from the case control studies [70]. Another meta-analysis by Zhou *et al*., stated that treatment with metformin was associated with significantly longer overall survival ($OR_{1\ yr}$ = 2.62, 95%CI: 1.76–3.90; $OR_{3\ yr}$ = 3.14, 95%CI: 2.33–4.24; $OR_{5\ yr}$ = 3.31, 95%CI: 2.39–4.59, all $P < 0.00001$) and recurrence free survival ($OR_{1\ yr}$ = 2.52, 95%CI: 1.84–3.44; $OR_{3\ yr}$ = 2.87, 95%CI: 2.15–3.84; all $P < 0.00001$; and $OR_{5\ yr}$ = 2.26, 95%CI: 0.94–5.45, $P = 0.07$) rates vs. those with other anti-hyperglycemic agents after curative therapies for HCC [71]. A systematic review and meta-analysis conducted by Zhou *et al*., reported that metformin use was significantly associated with reduction in risk of HCC when compared to use of sulphonylurea (RR 0.45, 95% CI 0.27–0.74) and insulin (RR 0.28, 95% CI 0.17–0.47). Thiazoledinediones showed more beneficial effects against HCC incidence when compared with sulphonylurea (RR 0.47, 95% CI 0.22–0.97) and insulin (RR 0.30, 95% CI 0.14–0.61) [72]. In the meta-analysis conducted by Singh *et al*., reported that HCC incidence reduced with metformin use (OR 0.50, 95% CI 0.34-0.73), increased incidence with sulfonylurea (OR 1.62, 95% CI 1.16-2.24) or insulin use (OR 2.61, 95% CI 1.46-4.65), respectively.Thiazolidinediones did not change the risk of HCC (OR 0.54, 95% CI 0.28-1.02) [73].

In a population-based case control study by Lai *et al*., it was noted that increasing duration of thiazolidinedione use was associated with lesser incidence of HCC (odds ratio 0.94, 95% CI 0.92-0.97) [74]. A nested case control study based on the Italian healthcare utilization database showed that there was greater risk of HCC with use of insulin (odds ratio (OR) = 3.73, 95% confidence interval [CI] 2.52-5.51), sulfonylureas (OR = 1.39, 95%CI 0.98-1.99), and repaglinide (OR = 2.12, 95%CI 1.38-3.26), while a reduced risk was found for use of metformin (OR = 0.57, 95%CI 0.41-0.79). The risk of developing HCC increased with increasing duration of insulin use (OR = 2.52 for <1 year, 5.41 for 1-2 years, and 6.01 for ≥2 years; p for trend < 0.001) [75]. In a nested case-control study by Hagberg *et al*., use of any anti-diabetic medications in patients with type II diabetes was not found to be associated with liver cancers, only small protective effect for metformin was observed. The odds ratio reported for association were; compared to non-use (OR=0.74 (95% CI=0.45–1.20) for metformin-only, 1.10 (95% CI=0.66–1.84) for other oral hypoglycaemic

only, 0.89 (95% CI=0.58–1.37) for metformin+other oral hypoglycaemics, 1.11 (95% CI=0.60–2.05) for metformin and insulin, 0.81 (95% CI=0.23–2.85) for other oral hypoglycaemics and insulin, and 0.72 (95% CI=0.18–2.84) for insulin-only [76].

CONCLUSION

Diabetes is associated with increased incidence of hepatocellular carcinoma. The pathophysiology includes various complex mechanisms. Abnormal metabolism, increased insulin level, platelet activation, chronic inflammation, reactive oxygen species, hub gene expression are the different mechanism in the association. Hyperglycemia, hyperinsulinaemia, and insulin resistance facilitate the development and progression of carcinogenesis in diabetic patients. Other etiological factors that influence the development of hepatocellular carcinoma in diabetes patients are hepatitis B and C infection, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease and alcohol. Different anti-diabetic agents have varying effects on incidence of hepatocellular carcinoma. Metformin and thiazolidinedione have protective actions against development of carcinogenesis. Insulin and insulin secretagogues promote carcinogenesis by increasing g IGF-1 activities and subsequently stimulating hepatic cell proliferation.

Way forward

Research studies are needed for understanding the underlying mechanisms of association diabetes and hepatocellular carcinoma. Longitudinal studies with aim to explore the role of diabetes in the causality of hepatocellular carcinoma, and interaction with other etiological factors, should be conducted. Further researches and trials are also required for assessing the role of different anti-diabetic medications in initiation, development and progression of HCC.

REFERENCE

1. Petrick, J. L., Florio, A. A., Znaor, A., Ruggieri, D., Laversanne, M., Alvarez, C. S., ... & McGlynn, K. A. (2020). International trends in hepatocellular carcinoma incidence, 1978–2012. *International journal of cancer*, *147*(2), 317-330.
2. 11-Liver-fact-sheet.pdf [Internet]. [cited 2021 Mar 1]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf
3. Cancer today [Internet]. [cited 2021 Mar 1]. Available from: http://gco.iarc.fr/today/home
4. Khan, M. A. B., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., & Al Kaabi, J. (2020). Epidemiology of type 2 diabetes–global burden of disease and forecasted trends. *Journal of epidemiology and global health*, *10*(1), 107.
5. Alberti, G., Zimmet, P., Shaw, J., Bloomgarden, Z., Kaufman, F., Silink, M., & Consensus Workshop Group. (2004). Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. *Diabetes care*, *27*(7), 1798-1811.
6. Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes care*, *27*(5), 1047-1053.
7. Nderitu, P., Bosco, C., Garmo, H., Holmberg, L., Malmström, H., Hammar, N., ... & Van Hemelrijck, M. (2017). The association between individual metabolic syndrome components, primary liver cancer and cirrhosis: a study in the Swedish AMORIS cohort. *International Journal of Cancer*, *141*(6), 1148-1160.
8. Koh, W. P., Wang, R., Jin, A., Yu, M. C., & Yuan, J. M. (2013). Diabetes mellitus and risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *British journal of cancer*, *108*(5), 1182-1188.
9. Baecker, A., Liu, X., La Vecchia, C., & Zhang, Z. F. (2018). Worldwide incident hepatocellular carcinoma cases attributable to major risk factors. *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP)*, *27*(3), 205.
10. Menon, S., & Mathew, R. (2019). Association between metabolic syndrome and hepatobiliary cancers: A case-control study. *Indian Journal of Gastroenterology*, *38*(1), 61-68.
11. Yi, S. W., Choi, J. S., Yi, J. J., Lee, Y. H., & Han, K. J. (2018). Risk factors for hepatocellular carcinoma by age, sex, and liver disorder status: a prospective cohort study in Korea. *Cancer*, *124*(13), 2748-2757.
12. Simon, T. G., King, L. Y., Chong, D. Q., Nguyen, L. H., Ma, Y., VoPham, T., ... & Chan, A. T. (2018). Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: results from two prospective cohort studies. *Hepatology*, *67*(5), 1797-1806.
13. Simon, T. G., King, L. Y., Chong, D. Q., Nguyen, L. H., Ma, Y., VoPham, T., ... & Chan, A. T. (2018). Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: results from two prospective cohort studies. *Hepatology*, *67*(5), 1797-1806.
14. Yang, J. D., Mohamed, H. A., Cvinar, J. L., Gores, G. J., Roberts, L. R., & Kim, W. R. (2016). Diabetes mellitus heightens the risk of hepatocellular carcinoma except in patients with hepatitis C cirrhosis. *The American journal of gastroenterology*, *111*(11), 1573.
15. Diabetes and Insulin Therapy, but Not Metformin, Are Related to Hepatocellular Cancer Risk [Internet]. [cited 2021 Mar 5]. Available from: https://www.hindawi.com/journals/grp/2015/570356/
16. Toyoda, H., Kumada, T., Tada, T., Kiriyama, S., Tanikawa, M., Hisanaga, Y., ... & Ito, T. (2015). Risk factors of hepatocellular carcinoma

development in non-cirrhotic patients with sustained virologic response for chronic hepatitis C virus infection. *Journal of gastroenterology and hepatology*, *30*(7), 1183-1189.
17. Setiawan, V. W., Hernandez, B. Y., Lu, S. C., Stram, D. O., Wilkens, L. R., Marchand, L. L., & Henderson, B. E. (2014). Diabetes and racial/ethnic differences in hepatocellular carcinoma risk: the multiethnic cohort. *JNCI: Journal of the National Cancer Institute*, *106*(12).
18. Metabolic syndrome and hepatocellular carcinoma risk [Internet]. [cited 2021 Mar 6]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3553509/
19. Zheng, Z., Zhang, C., Yan, J., Ruan, Y., Zhao, X., San, X., ... & Fan, Z. (2013). Diabetes mellitus is associated with hepatocellular carcinoma: a retrospective case-control study in hepatitis endemic area. *PloS one*, *8*(12), e84776.
20. Lai, S. W., Chen, P. C., Liao, K. F., Muo, C. H., Lin, C. C., & Sung, F. C. (2012). Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Official journal of the American College of Gastroenterology| ACG*, *107*(1), 46-52.
21. Tanaka, K., Tsuji, I., Tamakoshi, A., Matsuo, K., Wakai, K., Nagata, C., ... & Tanaka, K. (2014). Diabetes mellitus and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Japanese journal of clinical oncology*, *44*(10), 986-999.
22. Wang, P., Kang, D., Cao, W., Wang, Y., & Liu, Z. (2012). Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes/metabolism research and reviews*, *28*(2), 109-122.
23. Wang, C., Wang, X., Gong, G., Ben, Q., Qiu, W., Chen, Y., ... & Wang, L. (2012). Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. *International journal of cancer*, *130*(7), 1639-1648.
24. Noto, H., Osame, K., Sasazuki, T., & Noda, M. (2010). Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. *Journal of Diabetes and its Complications*, *24*(5), 345-353.
25. El–Serag, H. B., Hampel, H., & Javadi, F. (2006). The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clinical Gastroenterology and Hepatology*, *4*(3), 369-380.
26. Shi, T., Kobara, H., Oura, K., & Masaki, T. (2021). Mechanisms underlying hepatocellular carcinoma progression in patients with type 2 diabetes. *Journal of Hepatocellular Carcinoma*, *8*, 45.
27. Li, X., Wang, X., & Gao, P. (2017). Diabetes mellitus and risk of hepatocellular carcinoma. *BioMed research international*, *2017*.
28. Wainwright, P., Scorletti, E., & Byrne, C. D. (2017). Type 2 diabetes and hepatocellular carcinoma: risk factors and pathogenesis. *Current diabetes reports*, *17*(4), 1-8.
29. Singh, M. K., Das, B. K., Choudhary, S., Gupta, D., & Patil, U. K. (2018). Diabetes and hepatocellular carcinoma: A pathophysiological link and pharmacological management. *Biomedicine & Pharmacotherapy*, *106*, 991-1002.
30. Reeves, H. L., Zaki, M. Y., & Day, C. P. (2016). Hepatocellular carcinoma in obesity, type 2 diabetes, and NAFLD. *Digestive diseases and sciences*, *61*(5), 1234-1245.
31. Noureddin, M., & Rinella, M. E. (2015). Nonalcoholic fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. *Clinics in liver disease*, *19*(2), 361-379.
32. Fujita, K., Iwama, H., Miyoshi, H., Tani, J., Oura, K., Tadokoro, T., ... & Masaki, T. (2016). Diabetes mellitus and metformin in hepatocellular carcinoma. *World journal of gastroenterology*, *22*(27), 6100.
33. Kar, M., & Chakraborti, A. S. (1999). Release of iron from haemoglobin-a possible source of free radicals in diabetes mellitus.
34. Tuong, T.T.K., Tran, D.K., Phu, P.Q.T., Hong, T.N.D., Dinh, T.C., Chu, D.T. (2020). Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes: Evaluation of Hepatic Fibrosis and Steatosis Using Fibroscan. Diagnostics (Basel), Mar 14;10(3).
35. Aggarwal, B. B., Kunnumakkara, A. B., Harikumar, K. B., Gupta, S. R., Tharakan, S. T., Koca, C., ... & Sung, B. (2009). Signal transducer and activator of transcription-3, inflammation, and cancer: how intimate is the relationship?. *Annals of the New York Academy of Sciences*, *1171*(1), 59-76.
36. Shi, Z., Xiao, Z., Hu, L., Gao, Y., Zhao, J., Liu, Y., ... & Huang, D. (2020). The genetic association between type 2 diabetic and hepatocellular carcinomas. *Annals of translational medicine*, *8*(6).
37. Liu, C. Y., & Feng, G. S. (2014). NCOA5, a molecular link between type 2 diabetes and liver cancer. *Hepatobiliary Surgery and Nutrition*, *3*(3), 106.
38. Wei, H., Wang, J., Li, W., Ma, R., Xu, Z., Luo, Z., ... & Tang, Q. (2019). The underlying pathophysiology association between the Type 2-diabetic and hepatocellular carcinoma. *Journal of Cellular Physiology*, *234*(7), 10835-10841.
39. Liu, G. M., Zeng, H. D., Zhang, C. Y., & Xu, J. W. (2019). Key genes associated with diabetes mellitus and hepatocellular carcinoma. *Pathology-Research and Practice*, *215*(11), 152510.

40. Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature reviews endocrinology*, *14*(2), 88-98.
41. Bellou, V., Belbasis, L., Tzoulaki, I., & Evangelou, E. (2018). Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. *PloS one*, *13*(3), e0194127.
42. Uloko, A. E., Musa, B. M., Ramalan, M. A., Gezawa, I. D., Puepet, F. H., Uloko, A. T., ... & Sada, K. B. (2018). Prevalence and risk factors for diabetes mellitus in Nigeria: a systematic review and meta-analysis. *Diabetes Therapy*, *9*(3), 1307-1316.
43. Asamoah-Boaheng, M., Sarfo-Kantanka, O., Tuffour, A. B., Eghan, B., & Mbanya, J. C. (2019). Prevalence and risk factors for diabetes mellitus among adults in Ghana: a systematic review and meta-analysis. *International health*, *11*(2), 83-92.
44. Asamoah-Boaheng, M., Sarfo-Kantanka, O., Tuffour, A. B., Eghan, B., & Mbanya, J. C. (2019). Prevalence and risk factors for diabetes mellitus among adults in Ghana: a systematic review and meta-analysis. *International health*, *11*(2), 83-92.
45. Fujiwara, N., Friedman, S. L., Goossens, N., & Hoshida, Y. (2018). Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *Journal of hepatology*, *68*(3), 526-549.
46. Hammerstad, S. S., Grock, S. F., Lee, H. J., Hasham, A., Sundaram, N., & Tomer, Y. (2015). Diabetes and hepatitis C: a two-way association. *Frontiers in endocrinology*, *6*, 134.
47. Yen, Y. H., Lin, M. T., Kuo, F. Y., Chang, K. C., Tsai, M. C., Tseng, P. L., ... & Chen, C. H. (2018). The association between steatosis and diabetes with hepatocellular carcinoma in non-genotype 3 chronic hepatitis C patients. *Liver International*, *38*(6), 1064-1073.
48. Huang, T. S., Lin, C. L., Lu, M. J., Yeh, C. T., Liang, K. H., Sun, C. C., ... & Chien, R. N. (2017). Diabetes, hepatocellular carcinoma, and mortality in hepatitis C-infected patients: a population-based cohort study. *Journal of gastroenterology and hepatology*, *32*(7), 1355-1362.
49. Li, X., Xu, H., Gao, Y., Pan, M., Wang, L., & Gao, P. (2017). Diabetes mellitus increases the risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis C patients in China. *Medicine*, *96*(13).
50. Huang, Y. W., Wang, T. C., Yang, S. S., Lin, S. Y., Fu, S. C., Hu, J. T., ... & Chen, D. S. (2015). Increased risk of hepatocellular carcinoma in chronic hepatitis C patients with new onset diabetes: a nation-wide cohort study. *Alimentary pharmacology & therapeutics*, *42*(7), 902-911.
51. Arase, Y., Kobayashi, M., Suzuki, F., Suzuki, Y., Kawamura, Y., Akuta, N., ... & Kobayashi, T. (2013). Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. *Hepatology*, *57*(3), 964-973.
52. Chen, J., Han, Y., Xu, C., Xiao, T., & Wang, B. (2015). Effect of type 2 diabetes mellitus on the risk for hepatocellular carcinoma in chronic liver diseases. *European Journal of Cancer Prevention*, *24*(2), 89-99.
53. Dyal, H. K., Aguilar, M., Bartos, G., Holt, E. W., Bhuket, T., Liu, B., ... & Wong, R. J. (2016). Diabetes mellitus increases risk of hepatocellular carcinoma in chronic hepatitis C virus patients: a systematic review. *Digestive diseases and sciences*, *61*(2), 636-645.
54. Shyu, Y. C., Huang, T. S., Chien, C. H., Yeh, C. T., Lin, C. L., & Chien, R. N. (2019). Diabetes poses a higher risk of hepatocellular carcinoma and mortality in patients with chronic hepatitis B: a population-based cohort study. *Journal of Viral Hepatitis*, *26*(6), 718-726.
55. Kim, K., Choi, S., & Park, S. M. (2018). Association of fasting serum glucose level and type 2 diabetes with hepatocellular carcinoma in men with chronic hepatitis B infection: a large cohort study. *European Journal of Cancer*, *102*, 103-113.
56. Li, X., Xu, H., & Gao, P. (2018). Diabetes mellitus is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis B virus infection in China. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *24*, 6729.
57. Yip, T. C. F., Wong, V. W. S., Chan, H. L. Y., Tse, Y. K., Kong, A. P. S., Lam, K. L. Y., ... & Wong, G. L. H. (2018). Effects of diabetes and glycemic control on risk of hepatocellular carcinoma after seroclearance of hepatitis B surface antigen. *Clinical Gastroenterology and Hepatology*, *16*(5), 765-773.
58. Fu, S. C., Huang, Y. W., Wang, T. C., Hu, J. T., Chen, D. S., & Yang, S. S. (2015). Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with new onset diabetes: a nationwide cohort study. *Alimentary pharmacology & therapeutics*, *41*(11), 1200-1209.
59. Li, Q., Li, W. W., Yang, X., Fan, W. B., Yu, J. H., Xie, S. S., ... & Kato, N. (2012). Type 2 diabetes and hepatocellular carcinoma: a case–control study in patients with chronic hepatitis B. *International journal of cancer*, *131*(5), 1197-1202.
60. Dharmalingam, M., & Yamasandhi, P. G. (2018). Nonalcoholic fatty liver disease and type 2 diabetes mellitus. *Indian journal of endocrinology and metabolism*, *22*(3), 421.
61. Yang, J. D., Ahmed, F., Mara, K. C., Addissie, B. D., Allen, A. M., Gores, G. J., & Roberts, L. R. (2020). Diabetes is associated with increased risk of hepatocellular carcinoma in patients with cirrhosis from nonalcoholic fatty liver disease. *Hepatology*, *71*(3), 907-916.
62. Hassan, M. M., Hwang, L. Y., Hatten, C. J., Swaim, M., Li, D., Abbruzzese, J. L., ... & Patt, Y. Z. (2002). Risk factors for hepatocellular carcinoma: synergism of alcohol with viral

hepatitis and diabetes mellitus. *Hepatology*, *36*(5), 1206-1213.

63. Raff, E. J., Kakati, D., Bloomer, J. R., Shoreibah, M., Rasheed, K., & Singal, A. K. (2015). Diabetes mellitus predicts occurrence of cirrhosis and hepatocellular cancer in alcoholic liver and non-alcoholic fatty liver diseases. *Journal of clinical and translational hepatology*, *3*(1), 9.
64. Balbi, M., Donadon, V., Ghersetti, M., Grazioli, S., Della Valentina, G., Gardenal, R., ... & Cimarosti, P. (2010). Alcohol and HCV chronic infection are risk cofactors of type 2 diabetes mellitus for hepatocellular carcinoma in Italy. *International journal of environmental research and public health*, *7*(4), 1366-1378.
65. Sinn, D. H., Kang, D., Cho, S. J., Paik, S. W., Guallar, E., Cho, J., & Gwak, G. Y. (2020). Risk of hepatocellular carcinoma in individuals without traditional risk factors: development and validation of a novel risk score. *International journal of epidemiology*, *49*(5), 1562-1571.
66. Li, T. C., Li, C. I., Liu, C. S., Lin, W. Y., Lin, C. H., Yang, S. Y., & Lin, C. C. (2018, October). Risk score system for the prediction of hepatocellular carcinoma in patients with type 2 diabetes: Taiwan Diabetes Study. In *Seminars in oncology* (Vol. 45, No. 5-6, pp. 264-274). WB Saunders.
67. Rau, H. H., Hsu, C. Y., Lin, Y. A., Atique, S., Fuad, A., Wei, L. M., & Hsu, M. H. (2016). Development of a web-based liver cancer prediction model for type II diabetes patients by using an artificial neural network. *Computer methods and programs in biomedicine*, *125*, 58-65.
68. Si, W. K., Chung, J. W., Cho, J., Baeg, J. Y., Jang, E. S., Yoon, H., ... & Kim, J. W. (2016). Predictors of increased risk of hepatocellular carcinoma in patients with type 2 diabetes. *PloS one*, *11*(6), e0158066.
69. Miyoshi, H., Kato, K., Iwama, H., Maeda, E., Sakamoto, T., Fujita, K., ... & Masaki, T. (2014). Effect of the anti-diabetic drug metformin in hepatocellular carcinoma in vitro and in vivo. *International journal of oncology*, *45*(1), 322-332.
70. Chen, P. H., Lu, G. D., Zhu, G. Z., Li, L., Chen, Y., Dai, H. Q., ... & Zhou, J. (2020). Distinct effects of anti-diabetic medications on liver cancer risk and patient survival. *Journal of BU ON.: Official Journal of the Balkan Union of Oncology*, *25*(5), 2147-2153.
71. Cunha, V., Cotrim, H. P., Rocha, R., Carvalho, K., & Lins-Kusterer, L. (2020). Metformin in the prevention of hepatocellular carcinoma in diabetic patients: a systematic review. *Annals of hepatology*, *19*(3), 232-237.
72. Zhou, J., Ke, Y., Lei, X., Wu, T., Li, Y., Bao, T., ... & Wang, L. (2020). Meta-analysis: The efficacy of metformin and other anti-hyperglycemic agents in prolonging the survival of hepatocellular carcinoma patients with type 2 diabetes. *Annals of hepatology*, *19*(3), 320-328.
73. Zhou, Y. Y., Zhu, G. Q., Liu, T., Zheng, J. N., Cheng, Z., Zou, T. T., ... & Zheng, M. H. (2016). Systematic review with network meta-analysis: antidiabetic medication and risk of hepatocellular carcinoma. *Scientific reports*, *6*(1), 1-10.
74. Singh, S., Singh, P. P., Singh, A. G., Murad, M. H., & Sanchez, W. (2013). Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Official journal of the American College of Gastroenterology| ACG*, *108*(6), 881-891.
75. Lai, S. W., Lin, C. L., & Liao, K. F. (2020). Association of hepatocellular carcinoma with thiazolidinediones use: A population-based case-control study. *Medicine*, *99*(17).
76. Bosetti, C., Franchi, M., Nicotra, F., Asciutto, R., Merlino, L., La Vecchia, C., & Corrao, G. (2015). Insulin and other antidiabetic drugs and hepatocellular carcinoma risk: a nested case-control study based on Italian healthcare utilization databases. *Pharmacoepidemiology and drug safety*, *24*(7), 771-778.
77. Hagberg, K. W., McGlynn, K. A., Sahasrabuddhe, V. V., & Jick, S. (2014). Anti-diabetic medications and risk of primary liver cancer in persons with type II diabetes. *British journal of cancer*, *111*(9), 1710-1717.