



Preventive Role of Metformin Against Hepatocellular Carcinoma in Patients with Diabetes Mellitus - A Systematic Review

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Abstract. Diabetes mellitus (DM) and hepatocellular carcinoma (HCC) are very challenging health conditions. Although the relation between them is not completely understood, many factors contribute to this relation, including hyperinsulinemia, inflammatory reactions, and other co-modifiers as obesity. This study is designed to detect the role of metformin in preventing HCC in patients with DM compared to other anti-diabetic medications. We have screened the articles systemically in three databases such as PubMed, PubMed Central (PMC), and Medical Literature Analysis and Retrieval System Online (MEDLINE), using specific keywords and Medical Subject Heading (MeSH) terms for related published articles. Moreover, we have used Google Scholar, International Diabetes Federation (IDF), and American Diabetes Association (ADA). We have applied our inclusion/ exclusion criteria, and we have also applied the quality check assessment using Cochrane bias assessment, AMSTAR checklist, SANRA checklist, and New-Castle Ottawa tool. In the end, we reviewed ten studies that were strictly reviewed and analyzed. Based on our study, we reported that the major factor in the development of HCC in patients with DM is the duration, especially more than ten years. We concluded that the risk of development of HCC is directly proportional to the longer duration of DM. Our results show that metformin plays an important role in preventing HCC in patients with DM by decreasing insulin resistance. In contrast, the use of Insulin and drugs that promote insulin secretion is associated with increased incidence of HCC.

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1. Introduction & Background

Diabetes Mellitus is one of the fastest-growing health challenges in the 21st century, with the number of adults living with diabetes more than tripled over the past 20 years (Mantovani & Targher, 2017). Type 2 diabetes mellitus (T2DM) has been proven to be a great risk factor for hepatocellular carcinoma (HCC) development globally (Mantovani & Targher, 2017). Furthermore, T2DM can increase the recurrence and spread of HCC after curative and non-curative treatments, although the exact mechanisms remain unclear (Feng et al., 2011). A meta-analysis reported that the metformin treatment is associated with an increased overall survival rate of HCC patients with diabetes mellitus.

Hepatocellular carcinoma (HCC) is the most common type of primary hepatic cancer (Bertot & Adams, 2019). Many factors contribute to HCC, like hepatitis, alcohol, and non-alcoholic fatty liver disease (NAFLD). NAFLD is considered a major risk factor for HCC nowadays due to the increased prevalence of DM and obesity, which predisposes to NAFLD formation and,

consequently, hepatocellular carcinoma (Bertot & Adams, 2019). The prevalence of HCC is also rapidly increased. Hepatocellular carcinoma has been diagnosed annually in more than half a million people around the world. Hepatocellular carcinoma is the third leading cause of cancer-related death globally (Yang & Roberts, 2010). The prognosis of HCC is poor all over the world (Golabi et al., 2017). As a result, incidence and mortality rates are nearly the same.

Metformin is the first-line treatment of patients with T2DM, with a broad safety profile. Numerous epidemiological data have concluded that metformin use compared to dietary restrictions and other anti-diabetes medications is associated with the decrease of incidence of several cancers, including hepatocellular carcinoma in T2DM (Bo et al., 2012; Lee et al., 2012; Lee et al., 2011; Nkontchou et al., 2011). Despite these researches, there is still a huge knowledge gap that can clearly show if metformin use can prevent HCC. Our systemic review was done to review the published literature to determine the role of metformin in preventing HCC in diabetes mellitus.

We will be focusing on how metformin decreases the incidence of HCC in diabetic patients compared to other anti-hypoglycemic drugs.

2. Review

2.1. Protocol

We have conducted a systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (PRISMA) (Page et al., 2021).

2.2. Eligibility criteria

Diabetes Mellitus in adult human population, Articles published in English Language only in the last five years, papers relevant to the use of metformin in decreasing the incidence of hepatocellular carcinoma (HCC) in patients with diabetes mellitus (DM). We also included full-text papers and randomized clinical trials studies. We did not include the studies that discussed non-human species, studies other languages than English, articles older than five years old, Patients under 45 years old.

2.3. Data source and strategy

We conducted our research by using PubMed, PubMed Central (PMC), National Library of Medicine (MEDLINE), American Diabetes Association (ADA), and Google Scholar. Research in the database PubMed, PubMed Central (PMC), and MEDLINE were conducted on May 21, 2021. We used the specific medical subject heading (MESH) and keywords terms together to explore relevant articles on PubMed.

We have applied the search strategy using the keywords (Diabetes Mellitus, Metformin, Hepatocellular carcinoma) and on MESH through database PubMed, PubMed Central (PMC), and MEDLINE using the followings: Diabetes Mellitus OR glucose intolerance OR High blood glucose OR ("Diabetes Mellitus/complications"[Majr] OR "Diabetes Mellitus/drug therapy"[Majr] OR "Diabetes Mellitus/prevention and control"[Majr] OR "Diabetes Mellitus/therapy"[Majr]) AND Metformin OR Glucophage OR Dimethylguanylguanidine OR ("Metformin/chemistry"[Majr] OR "Metformin/metabolism"[Majr] OR "Metformin/pharmacokinetics"[Majr] OR "Metformin/therapeutic use"[Majr]) AND Hepatocellular cancer OR Adult Liver Cancer OR ("Liver Neoplasms/chemically induced"[Majr] OR "Liver Neoplasms/history"[Majr] OR "Liver Neoplasms/prevention and control"[Majr]) to find the relevant articles related to our research question.

2.4. Study selection and design

Once the relevant articles were identified, thorough screening was done by three authors. We did the screening by going through the titles first and then by the abstracts, and lastly by reading the full-text studies to shortlist the

relevant articles. We did a quality check of our shortlisted articles and selected only the articles that met the eligibility criteria and satisfied the quality check.

2.5. Risk bias assessment

The quality appraisal was done using the following tools; only those articles that satisfied above 70% of the quality checklist parameters were included in our review.

Table 1. Quality appraisal assessment tools

Quality Appraisal Assessment Tools	Articles Type
Cochrane Risk Bias Assessment Tool	Randomized Controlled Trials
Assessing the Methodological Quality of Systematic Reviews (AMSTAR) Checklist	Systematic reviews
Scale for the Assessment of Narrative Review Articles (SANRA) Checklist	Research paper w/out methods section
Newcastle Ottawa Scale	Observational studies

Table 1 shows the quality assessment tools for the reviewed articles.

3. Results

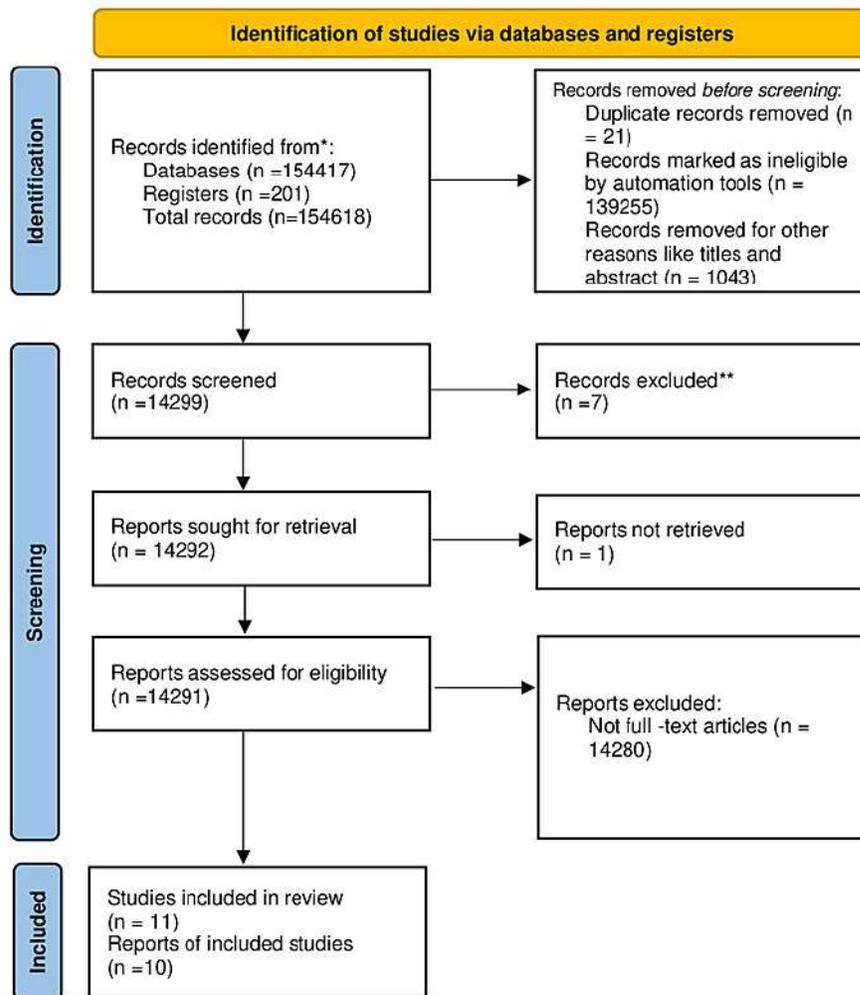
3.1. Search outcome

A total of 154618 papers were identified through databases search using PubMed (MeSH) and Google scholars using the keywords mentioned above. We removed duplicates and were left with 154597 papers. We applied titles and abstract screening and then by full text. In addition, eligibility criteria (inclusion and exclusion) were conducted, which provided the final number of articles in 11 articles. We have implemented the quality check, and the total number of articles was 10. The total 11 articles were: two systematic review articles, one epidemiological study, two retrospective cohort studies, and six meta-analysis studies. These articles included the effects of metformin lowering the incidence of HCC in patients with Diabetes Mellitus. In Figure 1, the PRISMA flow diagram shows the article screening process steps.

3.2. Findings of related studies

After we conducted our studies using the PRISMA. We have observed that patients with diabetes mellitus of longer duration are at a higher risk of developing hepatocellular carcinoma in comparison to a short duration of the disease (Rousseau et al., 2006). The first systematic review collected data from eight studies (four case-control studies, two retrospective cohort studies, and two

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

prospective cohort studies). All eight studies had proven the relation between the use of metformin and the lower incidence of HCC in patients with DM. All selected cohort studies have the Newcastle Ottawa Scale above the minimum recommended ones and were involved in the systemic analysis (Adami et al., 1991; Ruitter et al., 2012; Kasmari et al., 2017; Tseng, 2018). The second systemic review. The second meta-analysis study collected data from 19 studies involving 550,882 patients with diabetes mellitus; compared with metformin nonusers, metformin use reduced the ratio of liver cancer by 48% (Bosetti et al., 2015; Valent, 2015; Home et al., 2010; Ueyama et al., 2016).

We have made a brief study analysis of our selected articles for final review.

4. Discussion

4.1. Diabetes mellitus and hepatocellular carcinoma

Diabetes Mellitus has become one of the most worldwide challenging chronic diseases. It is a complex metabolic disorder in which the human body cannot secrete Insulin or normally respond to the secreted Insulin. Diabetes Mellitus is rapidly increasing nowadays worldwide and, according to the International Diabetes Federation, is predicted to reach more than 590 million by 2035 (American Diabetes Association, 2004).



Table 2: Summary of the related studies

Author name	Type of study	Year of publication	Purpose of the study	Study conclusion	Outcome
Cunha et al.	Systematic review	2020	Relation between metformin use and HCC	Strong association between metformin use and reduced HCC risk	The chi-square test of heterogeneity was significant (p -value = 0.0075). The Odds Ratio was 0.468 95% Confidence Interval: 0.275–0.799 (p -value = 0.0053).
Farmer et al.	Systematic review	2016	Diabetic therapies affect the risk of developing of HCC in DM	Most studies about association between metformin and cancer are liable to be biased	
Murff et al.	Retrospective cohort study	2018	Large sample size (more than 84K) to determine the preventive effect of metformin	A strong inverse between metformin and liver cancer	Metformin was inversely associated with liver cancer (adjusted hazard ratio [aHR] = 0.44, 95% CI 0.31, 0.64) compared to sulfonylurea.
Schulte et al.	Retrospective cohort study	2019	Assess whether treatment with metformin associated with prolonged survival in treatment of diabetic patients with HCC	Treatment with metformin improved survival in T2DM patients with HCC	patients on metformin had a significantly better hepatic function (Child-Pugh-Score A: 69.2% vs 47.4%, P
Shi et al.	Epidemiological study	2021	Progress of HCC in DM	Diabetes and obesity associated with increased risk of HCC but metformin is associated with decrease the incidence of HCC	T2DM has also been associated with a significant increased risk of non-cirrhotic HCC with a hazard ration (HR) of 3.05 and 95% confidence interval (CI) of 1.41–6.62.
Shi et al.	A meta-analysis study	2020	The genetic association between DM and HCC	Number of genes involved in association between DM and HCC. Metformin targets four of these genes	

Table 2 shows the final selected reviewed studies discussing, in brief, the year of publication, type of study, the purpose of the article, study conclusion and the outcome.

Table 2: Summary of the related studies

Author name	Type of study	Year of publication	Purpose of the study	Study conclusion	Outcome
Zhou et al.	A meta-analysis study	2020	Effect of metformin and other anti-diabetic medications in prolonging survival of HCC in DM	Metformin prolongs survival of HCC in T2DM patients.	The 1 yr., 3 yr., and 5 yr. RFS (recurrence free survival) in the patients receiving curative treatment for HCC in the metformin group were significantly longer than the non-metformin group (OR1 yr. = 2.52, 95%CI: 1.84–3.44; OR3 yr. = 2.87, 95%CI: 2.15–3.84; all $P < 0.00001$; and OR5 yr. = 2.26, 95%CI: 0.94–5.45, $P = 0.07$).
Li et al.	A meta-analysis study	2018	Mechanism of metformin for DM and cancer development	Metformin plays a role in decreasing tumorigenesis	
Ma et al.	A meta-analysis study	2017	Assess if metformin reduces the liver cancer in diabetic patients	A protection against liver cancer in patient using metformin	On the basis of 19 studies involving 550,882 patients with diabetes mellitus, compared with metformin nonusers, metformin use reduced the ratio of hepatic cancer by 48% (OR = 0.52; 95% CI, 0.40–0.68; $P < .001$), with substantial heterogeneity ($I^2 = 83.7\%$)
Zi et al.	A meta-analysis study	2018	Understanding the role of metformin in tumor formation	Diabetes Mellitus increases the cancer risk, but metformin use decreases the cancer incidence risk.	A meta- analysis revealed that cancer patients with a history of diabetes mellitus have an increased the mortality risk compared with those without diabetes mellitus “hazard ratio (HR), 1.4; 95% confidence interval (CI), 1.28-1.55”.
Fujita et al.	A meta-analysis study	2016	Evaluated the role of metformin in cancers	Metformin prevents the HCC and decrease the cancer mortality	Hepatocellular carcinoma incidence decreased (OR=0.79)

Table 2 shows the final selected reviewed studies discussing, in brief, the year of publication, type of study, the purpose of the article, study conclusion and the outcome.

The patients are suffering from Diabetes mellitus when their reserved insulin stores are depleted or their secreted Insulin not functioning well (insulin resistance). Diabetes mellitus affects the population in developed and developing countries, and it has many complications. One of the documented complications of diabetes mellitus (DM) is some cancers, including hepatocellular carcinoma. At the start of the 20th century, diabetes mellitus was first evaluated as a contributing factor for cancer death. An observational study discussing cancer death in the United States cities in 1910 concluded a relationship between

cancer and diabetes mellitus (Maynard, 1910). A huge cohort study in Uppsala, Sweden, documented a significant risk of hepatocellular carcinoma (HCC) and pancreatic cancer in diabetic patients with a relative ratio of approximately 1.5, which is more prevalent in males than females (Adami et al., 1991). Although the exact pathogenesis between diabetes mellitus (DM) and hepatocellular carcinoma is not completely understood, many factors are involved in this process, like Insulin resistance, insulin therapy, hyperglycemia, and chronic inflammation (American Diabetes Association, 2014).

Table 3: Quality appraisal of the included studies

Study	Tool used	Selection				Comparability	Outcome			Total
		1	2	3	4		1	2	3	
		1	2	3	4	2 (points)	1	2	3	9
Cunha et al. (2020)	Newcastle-Ottawa Scale	1	1	1		2	1	1		7
Farmer et al. (2017)	Newcastle-Ottawa Scale	1	1		1	1	1	1		6
Murff et al. (2018)	Newcastle-Ottawa Scale	1	1	1	1	2	1	1		8
Schulte et al. (2019)	Newcastle-Ottawa Scale	1	1	1		2	1	1		7
Shi et al. (2021)	Newcastle-Ottawa Scale	1		1	1	1	1	1		6
Shi et al. (2020)	Newcastle-Ottawa Scale	1	1	1	1	2	1	1		8
Zhou et al., (2020)	Newcastle-Ottawa Scale	1	1	1	1	2	1	1		8
Li et al., (2018)	Newcastle-Ottawa Scale	1	1	1	1	2	1	1		8
Ma et al., (2017)	Newcastle-Ottawa Scale	1	1	1	1	1	1	1		7
Zi et al., (2018)	Newcastle-Ottawa Scale	1	1	1	1	1	1	1		7
Fujita et al., (2016)	Newcastle-Ottawa Scale	1	1	1	1	1	1	1		7

Table 3 shows the summary of our quality assessment for the included studies.

Hepatocellular carcinoma (HCC) is one of the major causes of death related to cancer globally (Yang & Roberts, 2010). Hepatocellular carcinoma is also linked to obesity which is usually present in type 2 diabetes mellitus. Obesity promotes carcinogenesis through the secretion of proinflammatory cytokines from visceral adipose tissues (Fujita et al., 2016). It is worth mentioning that diabetes mellitus (DM) and obesity are synergistic effects in developing hepatocellular carcinoma (HCC) as each of both diseases can lead to liver damage, liver cirrhosis, and eventually hepatocellular carcinoma (Zaman et al., 1985). In patients with Diabetes mellitus who have chronic liver diseases (CLD), chronic poor control of their diabetes mellitus (DM), assessed by HbA1c testing, the results show a significant increase of the risk of hepatocellular carcinoma (HCC) by 26%-50% for each 1% increase in HbA1c level (Hassan et al., 2010).

The increase in insulin levels (either endogenous and exogenous) in diabetes mellitus (DM) caused by insulin resistance in multiple places like fat, muscle tissue, and liver are associated with an increased risk of hepatocellular carcinoma (HCC) inpatient with diabetes mellitus (DM) (American Diabetes Association, 2014). The high insulin levels in diabetes mellitus (DM) increase the insulin-like growth factor (IGF-1), which helps in liver

cell proliferation and inhibits the apoptosis that predisposes to HCC (Chou et al., 1987)

Another factor for developing hepatocellular carcinoma in patients with diabetes mellitus is that hyperinsulinemia stimulates insulin receptor substrate (IRS-1) to regulate numerous cytokine pathways (Mantovani & Targher, 2017). Insulin resistance is involved in the progression of hepatic steatosis and fibrosis by high free fatty acids levels, which in turn stimulates the formation of NAFLD and NASH. These factors, along with IGF-1, are associated with an increased risk of hepatocellular carcinoma (HCC) in patients with diabetes mellitus (DM).

We need to evaluate the exact duration for diabetes mellitus (DM) to lead to hepatocellular carcinoma. In Canada, a case-control study revealed that the hepatocellular carcinoma (HCC) risk was higher in patients with a longer history of diabetes mellitus (DM) (Rousseau et al., 2006). Also, a meta-analysis by Wang et al. showed that the hepatocellular carcinoma (HCC) risk increased with diabetes mellitus (DM) duration of more than ten years; however, this study had relatively low power due to the low number of involved studies (Wang et al., 2012). Hassan et al. published a study showing that, compared with patients with a diabetes mellitus (DM) duration of two to five years, the hepatocellular carcinoma risk was higher



in those with a duration of six to ten years of diabetes mellitus (adjusted OR, 1.8; 95% CI, 0.8-4.1) or >10 years (adjusted OR, 2.2; 95% CI, 1.2-4.8) (Hassan et al., 2010). A meta-analysis study conducted by Fuming Zi concluded that diabetes mellitus is associated with multiple cancers over a long period of the disease (Zi et al., 2018).

In conclusion, most of the published studies which show a positive relationship between diabetes mellitus (DM) duration and hepatocellular carcinoma (HCC) development suggest that duration of diabetes mellitus (DM) of more than ten years increases the risk of hepatocellular carcinoma (HCC). However, more extended clinical trials are needed to confirm these results as the follow-up studies for more than ten years are very challenging due to loss of follow-up, confounders, and multiple biases.

4.2. Metformin in patients with diabetes mellitus

Metformin is widely used in the treatment of patients with diabetes mellitus (DM); it helps in increasing insulin sensitivity and thus helps in the reduction of blood glucose. Metformin is also associated with a decrease in hepatic gluconeogenesis, and this is the main role in decreasing the blood glucose level in patients with diabetes mellitus (DM). Metformin also inhibits the muscle uptake of glucose, and this helps in increasing insulin sensitivity. Metformin targets the respiratory chain of mitochondria and promotes cellular energy stress. Metformin plays a pivotal role in weight loss through activation (phosphorylation) of adenosine monophosphate-activated protein kinase (AMPK) (DeFronzo, 1999; Schimmack et al., 2006). Metformin is also associated with reducing steatosis, reducing body weight, and improving liver enzymes. The use of metformin is also associated with a decrease in insulin resistance, thus decreasing the incidence of multiple cancers, including the HCC. Metformin has many side effects like diarrhea, nausea, abdominal pain, and lactic acidosis, especially in patients with renal impairment, but it is not common associated with hypoglycemic episodes (Hassan et al., 2010).

4.3. Role of Other Anti-Diabetic Medications

The other anti-diabetic medications like exogenous Insulin and medications acting by increasing the secretion of Insulin-like sulfonylureas both help increase insulin resistance. The insulin therapy in diabetes mellitus patients with chronic liver disease could be explained by the mitogenic effect of exogenic Insulin (insulin therapy) added to the already existing endogenous hyperinsulinemia.

Another anti-diabetic medication (Sulfonylureas) might involve increasing the secretion of endogenous Insulin and its precursors, which seems to be mitogenic in their effect (Giovannucci, 2003). In the end, any anti-diabetic medication that is involved in insulin resistance and hyperinsulinemia can play an important role in the

development of hepatocellular carcinoma in patients with diabetes mellitus.

4.4. Preventive role of metformin in decreasing the incidence of Hepatocellular carcinoma (HCC) in patients with diabetes mellitus (DM)

Metformin treatment has been independently associated with decreasing hepatocellular carcinoma (HCC) and liver-related mortality in patients with diabetes mellitus (DM) (Donadon et al., 2010). A case-control study reported an 85% reduction in the occurrence of hepatocellular carcinoma (HCC), especially in cirrhotic patients receiving metformin compared to other medications that increase insulin level (either exogenous Insulin or sulfonylureas that promote insulin secretion) (Nkontchou et al., 2011). Metformin has two roles in decreasing the incidence of hepatocellular carcinoma (HCC) in patients with diabetes mellitus. The direct role is in reducing the plasma insulin levels, increasing insulin sensitivity, and decreasing insulin resistance. The indirect role is related to the phosphorylation pathway mechanism by the metformin (activation of the AMP-K pathway). Activation of AMPK inhibits mTOR and also decreases the cellular proliferation and suppression of tumorigenesis (Kimura, 2003; Inoki et al., 2003). AMPK is a mediator factor for tumor suppressor liver kinase B1 (LKB1) (Hassan et al., 2010). AMPK and LKB1 interfere with insulin signals by degrading Insulin Receptor Substrate-1, resulting in suppression of Insulin and IGF-1 (the major contributor to the hyperinsulinemia, which is responsible for carcinogenesis in hepatocellular carcinoma) (Takano et al., 2001). These two mechanisms mediated by the metformin help reduce carcinogenesis, stimulation of the immune system decrease the risk of cancers, including hepatocellular carcinoma (HCC) in patients with diabetes mellitus [DeFronzo, 1999; Schimmack et al., 2006; Ong et al., 2006; Donnelly et al., 2006]. Additionally, a large cohort study by Lena Schulte in 2019 was conducted on 5093 with hepatocellular carcinoma (HCC); 1917 of them had diabetes mellitus, 338 out of 1917 were diabetic treated with metformin (Schulte et al., 2019). When they concluded the study, they found that patients with diabetes mellitus on metformin had a significantly better hepatic function and longer overall survival than diabetic patients on another anti-diabetic medication (Schimmack et al., 2006). Shujuan Ma figured a meta-analysis study in 2017 to assess if metformin can reduce the liver cancer incidence in diabetic patients, the study showed that there is a protective role of using metformin in the prevention of hepatocellular carcinoma (HCC) in patients with diabetes mellitus (Ma et al., 2017).

4.4. Limitations of the research

Diabetes Mellitus is a chronic debilitating lifelong disease that has many symptoms, signs, and complications. The treatment of patients with Diabetes mellitus has



several options like diet, Insulin, and metformin. According to the strict compliance to diet, medications, and follow-up, the complications will follow. If the patients don't strictly follow the medical advice, they will develop major complications up to cancers like hepatocellular carcinoma. Metformin is not used in all patients with diabetes mellitus due to its complications, especially in renal diseases. In the end, there is huge information about the pathogenesis of diabetes mellitus (DM) and hepatocellular carcinoma (HCC) and the role of metformin in decreasing the hepatocellular carcinoma (HCC) incidence in comparison to other anti-diabetic medication (especially those who secrete Insulin and exogenous Insulin). It is very difficult for us to involve all data in one single study. We used exclusion criteria like studies published only in English, recent studies of five years, and excluded the studies involving patients below 45 years; therefore, we may have any research publish before this date and in any other language.

5. Conclusions

We conducted this study to understand the role of metformin in preventing hepatocellular carcinoma (HCC) in patients with diabetes mellitus (DM). Hepatocellular carcinoma complication in a patient with diabetes mellitus is correlated to the longer duration of the disease. Obese patients with diabetes mellitus (DM) are at a higher risk of developing hepatocellular carcinoma. Metformin used as the first drug in the treatment of DM helps increase insulin sensitivity and decrease insulin resistance which is mainly responsible for hepatocellular carcinoma (HCC) development. The other anti-diabetic medications like exogenous Insulin and sulfonylureas that secrete endogenous insulin help increase insulin resistance which has a mitogenic effect that promotes the development of hepatocellular carcinoma (HCC). Metformin activates the AMPK/ LKB1 pathways that are responsible for the suppression of carcinogenesis. Therefore, it has a preventive role in decreasing the incidence of hepatocellular carcinoma (HCC) in patients with diabetes mellitus (DM). More researches are needed about the exact dose and duration of the use of metformin to get the preventive effect against hepatocellular carcinoma (HCC) in patients with diabetes mellitus (DM). We also recommend future researchers investigate if adding another medication to the metformin while treating patients with diabetes mellitus would affect the preventive role.

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