Review Article DOI: http://doi.org/10.4038/sjdem.v13i2.7465

Use of sulphonylurea in type 2 diabetes mellitus and incident risk of Hepatocellular Carcinoma : Are we safe to prescribe?

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Abstract

While Type 2 Diabetes Mellitus (T2DM) has become a global epidemic over the past few decades along with obesity and metabolic syndrome, there has been increasing evidence showing association between Diabetes and several cancers particularly hepatocellular carcinoma (HCC). HCC has become a prime cause of cancer related mortality across the globe, gaining attention on the potential aetiological factors for carcinogenesis. Insulin resistance and hyperinsulinemia associated with T2DM is postulated as the potential link between HCC and DM, and concerns were raised about the role of anti-diabetic medications particularly insulin and insulin secretagogues in the development of HCC. Despite the development of many anti-diabetic medications with multiple cardiovascular and renal benefits, Sulphonylurea (SU) plays a major role in achieving a good glycemic control among DM population in our part of the world (South-Asia) being widely used as a second line oral hypoglycemic after Metformin. Here, we give a brief review of literature on SU and incident risk of HCC among diabetic population in order to weigh the risk vs benefits for prescribing in patients.

Keywords: Sulphonylurea-Hepatocellular Carcinoma-Type 2 Diabetes Mellitus

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Introduction

Worldwide there is an exponential rise in the incidence as well as the mortality rate of HCC over the past few decades with increasing burden noted in the developing countries belonging to South-east Asia and sub-Saharan Africa. According to the current epidemiological data, it was declared as the seventh commonest cancer across the globe while securing its position as the second among the highest cancer related death rates. The incidence of HCC is highest in Asia and Africa, and China being accounted as the country with highest number of cases probably due to the double effect of an increased rate of HCC (18.3 per 100,000) as well as due to the fact that they own the world's biggest population (1.4 billion). Although changes have been noted in the incidence patterns in the regions across the globe, even with the expanding medical knowledge and recent advancement in modalities of treatment the prognosis remains poor, where the incidence rate and mortality rates are roughly being comparable. For example; in 2018, the estimated global incidence rate of HCC per 100,000 person-years was 9.3 while the corresponding mortality rate was 8.5. [1]

Prevailing data on incidence of HCC in Sri Lanka are scarce. However, as the neighboring country, Indian data shows, age adjusted incidence rate of HCC for men ranging from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 population per year. [2]

While excessive alcohol consumption, chronic hepatitis B and C infection are acknowledged as well-established risk factors for HCC, Diabetes mellitus (DM) and metabolic syndrome also have long been appreciated as a potential risk factor for HCC and many other cancers worldwide [3-5]. How DM increases the risk of HCC has become a matter of debate in the literature which is left with an answer that it is likely to be related to the interplay between

obesity, DM and carcinogenesis, with the underlying insulin resistance and hyperinsulinaemia playing critical roles. [6] In a meta-analysis conducted in 2014, it was estimated that metabolic syndrome is associated with an 81% enhanced risk of HCC. It is also found that longer the duration of diabetes: higher the risk of developing HCC, though the relationship between diabetes severity and HCC risk is unclear. [1]

With growing evidence around such a debatable topic, curiosity was raised on anti-diabetic medications, whether they can alter the risk of cancer particularly HCC. Indeed, several pre-clinical in vitro as well as in vivo experimental studies have shown such link. That is further consolidated by many recent research and epidemiological studies. Treatment with insulin and insulin secretagogues (such as sulfonylureas) will increase the risk of incidence and progression of HCC whereas metformin, thiazolidinediones (TZDs) have potential protective effect [7-11].

In contrast, the largest randomized controlled trials (RCTs) addressing the above question, namely, ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes), failed to demonstrate any protective effect of metformin on the generation of HCC when compared with TZDs, but further proved the potential advantage over Sulphonylurea (SU) (12). Thus, it remains an open topic for discussion whether the possible risk of HCC with SU outweighs the benefits of glycemic control it brings out among the Type 2 DM population. In this review we try to answer the question "Are we safe in using SUs; Incident Risk of Hepatocellular Carcinoma in Patients with Type 2 Diabetes treated with SUs?" summarizing the available literature and evidence.

Role of Sulphonylurea as an anti-diabetic agent

SUs as anti-diabetic agents used in the management of T2DM are efficacious, safe, less costly thus affordable, well tolerated, widely available, long being used and convenient choice after Metformin. Since the discovery in 1942, many SUs have been developed in the modern times with lesser side effects and better safety profiles such as Glimepiride, Glipizide, Gliclazide and Gliclazide modified release [MR] which are considered as second generation SUs. They act by enhancing the insulin secretion from β-cells of endocrine pancreas by blocking adenosine triphosphate-sensitive potassium channels (K_{ATP}), by binding to the Sulphonylurea Receptor (SUR) subunit present on the β-cell plasma membrane. They are capable of binding to a common SUR unit on β-cells leading to closure of the K_{ATP} channels thereby inhibiting the K^+ efflux. As a consequence, cell membrane gets depolarized facilitating influx of Ca^{+2} ions into the cytosol. This accumulation of Ca^{+2} ions in turn stimulate the exocytosis of secretory vesicles storing insulin. Because of the fact that this insulin secretion is non-glucose-mediated, conventional SUs have been linked with a higher risk of hypoglycaemia compared to many other anti-diabetic medications. [13] They are effective as monotherapy with glucose lowering capacity of 1-2% reduction of glycated haemoglobin (HbA1c) and has additive benefits with other antidiabetic medications. The most documented adverse effects of SUs are weight gain, symptomatic hyponatremia, alcohol induced flushing, cholestatic jaundice, skin rashes and blood dyscrasias other than hypoglycemia. [13-15]

Apart from the major anti-diabetic effects on the pancreas, SUs are known to play a minor role in insulin metabolism; reducing the hepatic uptake and metabolic clearance of insulin, which is accompanied by reduced 'Glucagon' secretion by pancreatic α-cells. Certain SUs are capable of potentiating the glucose uptake in skeletal muscles, thereby acting as insulin sensitizers due to enhanced expression of GLUT-4 transporters (Glucose Transporter type-4) and resulting in decrement of the insulin resistance in peripheral tissues. Noteworthy, SUs have few concerns with cardio-vascular safety as different SUs have differing pleiotropic effects; importantly certain SUs inhibit the K_{ATP} channels on sarcolemma and mitochondria located in cardiac myocytes, and K_{ATP} channels on vascular smooth muscle cell thus leading to impairment of ischaemic pre-conditioning (IPC), a cardio-protective phenomenon. Glimepiride on the otherhand, is devoid of such effect but it has anti-inflammatory, anti-oxidant and angiogenic activity in patients with T2DM. Gliclazide is capable of exerting haemo-vascular and anti-oxidant effects, decreasing micro-thrombosis by partial inhibition of platelet aggregation/adhesion, increasing vascular endothelium fibrinolytic activity, and reducing plasma lipid peroxide and increases erythrocyte superoxide dismutase. In contrast, Glibenclamide is linked with worsening of blood pressure, probably due to developing insulin resistance and activation of the sympathetic system. [15]

Sulphonylurea use in Chronic Liver Disease

There is paucity in evidence on SU use in liver disease.

First generation SUs carries a high risk of hypoglycemia and currently not in use worldwide. As most of the SUs are metabolized in liver, in liver disease, metabolism of drugs is affected thus prolonging their half-life & consequently increasing the potential for hypoglycaemia. Majority of SUs are albumin bound, therefore in hypoalbuminemia, the amount of free drug available in plasma is enhanced further enhancing the hypoglycemic risk. Patients suffering from advanced liver disease experience impaired defenses against hypoglycemia such as depletion of glycogen storage, and lack of gluconeogenesis, malnourishment, altered hepatic drug metabolism due to alcohol making SUs unsuitable for use.[16] Thus, insulin secretagogues like SUs are discouraged in liver failure. The use of SUs should be restricted to lower doses and the ones with shorter half lives in early chronic liver cell disease & better be avoided completely in advanced liver cell disease: Child-Pugh class C. [15]

Diabetes, Hyperinsulinemia and Development of Hepatocellular Carcinoma

It is in the second half of the nineteenth century, a hypothesis was developed linking T2DM and increase risk of cancer. Lawson et al. in 1986 showed this association of HCC risk in DM patients detected incidentally in a case-control study which was originally designed to unearth the possible relationship between primary liver cancer and prolonged exposure to anticonvulsants or contraceptives. [17]

Subsequently, many observational studies and systematic reviews were able to identify this relationship of HCC and DM. Not only the presence of DM, but also it uncovered the significance of duration of hyperglycemia as a risk modifier for HCC; longer the duration of DM since the diagnosis higher the risk of developing HCC. These observations were congruous across many different populations, diverse geographic areas, and a variety of control groups. The linkage between DM and perceived risk of HCC was statistically significant even after adjusting for excessive alcohol use and chronic viral hepatitis; the commonest risk factors known to be associated with HCC and chronic liver disease. [18]

The underlying pathophysiology behind T2DM and incident risk of HCC are multiplex and not entirely understood so far. T2DM along with metabolic syndrome, is strongly linked with the presence of abdominal obesity, marked peripheral and hepatic insulin resistance, chronic low-grade inflammation and enhanced oxidative stress that may in combination will lead to the generation and progression of HCC. These mechanisms will promote cellular growth and proliferation, assist angiogenesis, encourage DNA damage and result in inhibition of cellular apoptosis. The process is aided by the increased generation of insulin-like growth factor 1(IGF-1); the end product of persisting hyperinsulinemia and insulin resistance. Besides, persistent hyperinsulinemia leads to activation of insulin receptor substrate-1 (IRS-1), another obligatory factor regulating multiple cytokine pathways thus leading to the generation of HCC. In the literature, it is also found that insulin resistance may alter the gut microbiota (dysbiosis), which in turn embark on a cascade of events; generation of free fatty acids in excess thus promoting liver fat deposition (hepatic steatosis); a well-recognized association of HCC. [18-19]

Link between Sulphonylurea and Hepatocellular Carcinoma

The current evidence on SU and incident risk of HCC is perplexing.

In the current literature, most of the conventional antidiabetic agents and insulin were assessed with regard to the risk modification in HCC following the discovery of DM and HCC association. A systematic review & network meta-analysis by Zhou, Y.-Y. et al. observed an association of Metformin with significantly reduced risk of HCC (risk ratio [RR] 0.49, 95% CI 0.25–0.97), whereas insulin (RR=2.44, 95% CI 1.10- 5.56) was associated with an increased risk. They recognized Metformin as the best anti-diabetic medication for the prevention of HCC in order of preference compared to others. [20]

Another Systematic review and meta-analysis by Singh, Siddharth et al. found that metformin use can reduce the incidence of HCC by 50% (n=8 studies; OR 0.50,95%CI0.34-0.73), while SU use is associated with 62% increased risk of HCC (n=8 studies; OR 1.62,95%CI1.16-2.24) while 161% increase of incidence of HCC with insulin use (n=7; OR 2.61, 95% CI 1.46-4.65).

However, they failed to demonstrate any risk modification with TZDs (n=4; OR 0.54, 95% CI 0.28-1.02). They drew a conclusion that all the available anti-diabetic medications may alter the risk of HCC in patients with DM, though effect of each drug should be interpreted with caution according to the inherent properties of each drug class in cancer-prevention.[21]

Metformin is an insulin-sensitizing anti-diabetic medication which reduces the resistance at target tissues and currently being used worldwide as the most preferred 1st line agent for glycemic control in T2DM population. The main effect of Metformin is to reduce the hepatic gluconeogenesis and glycogenolysis while increasing the insulin stimulated skeletal muscle uptake of glucose through the activation of AMP-activated protein kinase (AMPK). Metformin suppresses the fatty acid oxidation and reduces the triglyceride levels finally leading to reduction of hyperinsulinemia, reduction of hepatic insulin resistance and steatosis improving liver enzymes. This will help the patient to have a neutral weight gain or possibly rewarded with a modest weight reduction compared to the significant gain of weight noted with insulin or insulin secretagogues, a highly undesirable side effect of these agents due to the raised levels of insulin. Cunha V, et al. performed a systematic review specifically targeting Metformin comparing with other antidiabetic medications, which further consolidated the above findings. [22]

A comprehensive systematic review and meta-analysis by Arvind, Ashwini et al. compared use of TZDs, SUs, alpha-glucosidase inhibitors and meglitinides as the 2nd line anti-diabetic agent in the management of T2DM and risk modification of HCC. They discovered the fact that TZDs are associated with reduced risk of HCC thus witnessing a protective effect as in the case with metformin, particularly among Asians. On the opposite, alpha-glucosidase inhibitors and SUs were linked with modest but significantly enhanced risk of HCC. [23]

TZDs are peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, acts by enhancing insulin sensitivity. They are capable of down triggering carcinogenic pathway by inhibiting cell proliferation and neo-angiogenesis, also promoting apoptosis, cell cycle arrest and cellular differentiation. [23] The beneficial effect of TZDs was further proved in a retrospective cohort study in diabetic patients with chronic hepatitis B infection in Hong Kong, which showed an arcuate relationship between HbA1c and liver related morbidity where higher the baseline HbA1c, higher the risk of developing liver-related morbidity. In this study, once again it was evident that insulin and SUs were linked with a higher risk of liver-related morbidity while use of Metformin, aspirin/clopidogrel, statins and ACEIs/ARBs were linked with a reduced perceived risk of liver related morbidity. [24]

In a nationwide, nested, case-control study done in South Korea (2003-2012) among patients with new onset diabetes (analysis was done with 241 HCC cases and 1205 controls), in contrast to those who were never exposed to SUs, the ones treated with SUs had a 1.7-fold escalated risk of incident HCC. Here, the individual SUs were analyzed in detail which showed that exclusive use of Glimepiride and Glibenclamide being associated with a significantly enhanced risk of HCC (AOR=1.89, 95% CI=1.02–3.47 and AOR=3.37, 95% CI=1.06–10.70, respectively) in comparison to those who never used. This effect was not noted among exclusive Gliclazide users. (OR=2.04, 95% CI=0.75–5.52). It was imputed to the fact that gliclazide, in addition to the glucose lowering effect, is capable of scavenging the free radicals thus acting as an anti-oxidant and protecting the cellular environment against the oxidative risk. [25]

Several studies focusing on the individual SUs are available in the literature highlighting the importance of independent effect of each on the development of HCC. A retrospective analysis between Gliclazide and Glimepiride done by Lee J-Y et al in 2016 found a protective effect of Gliclazide with a significantly decreased risk of HCC [odds ratio (OR): 0.29; 95% confidence interval (CI): 0.15–0.58; $P < 0.001$} compared with Glimepiride in patients with chronic liver cell disease. [26]

This was further recognized in a large Chinese cohort study by Yang et al. where ever-use of Gliclazide or Glibenclamide was discovered to have a dose dependent lower risk of cancer by 35%. (27) Another case-control study by Monami et al. proved that treatment with Gliclazide for more than three years was linked with a lowered risk of carcinoma (OR: 0.40; $P = 0.004$),while Glibenclamide was linked with an enhanced carcinoma risk (OR: 2.62; $P = 0.009$). [28]

Thus, evidence for SUs in enhancing the risk of HCC remains controversial. They increase the insulin secretion thereby either directly or indirectly increase IGF-1 activity leading to abnormal stimulation of multiple cellular signaling cascades, exaggerating cell growth, proliferation and metabolism. However, their beneficial effects in the management of DM esp. in our part of the world remains enormous due to the cost effectiveness, availability and patient preference. Hence, we need to take an individualized approach weighing the risk vs benefits: with careful selection of appropriate SUs considering the pharmacokinetic properties of each of them.

Table 1 : Summary of the findings from the literature on risk of HCC and anti-diabetic medications

Studies	Design	Conclusion
Zhou, Y.-Y. et al. [20]	Systematic review and network meta-analysis	Metformin and TZDs have beneficial effects on HCC incidence. Insulin and SUs may be associated with higher risk.
Singh, Siddharth et al. [21]	Systematic review and meta-analysis	In particularly western population, Metformin use may be associated with lower risk of HCC whereas SUs and insulin use may be associated with higher risk.
Cunha, Victor et al. [22]	Systematic review	Metformin was associated with reduced risk of HCC.
Arvind, Ashwini et al. [23]	Meta-analysis	TZD use was associated with reduced HCC incidence in Asians. Alpha-glucosidase inhibitor or SU use was associated with modestly increased HCC risk.
Yip, Terry Cheuk-Fung et al. [24]	Retrospective-cohort study	TZD use is associated with a lower risk of liver-related events in diabetic patients with Chronic hepatitis B.
Lee, Ji-Yeon et al. [25]	Case-control study	The association between the use of SUs and risk of HCC was different according to the type of SU. Glimepiride was associated with a significantly elevated risk while no such association with gliclazide.
Lee, J-Y et al. [26]	Comparative study	Gliclazide is associated with a lower incidence of HCC compared with glimepiride.
Yang, Xilin et al. [27]	Cohort study	Use of gliclazide and glibenclamide was associated with reduced cancer risk in a dose-dependent manner.
Monami, Matteo et al. [28]	Case-control study	Long-term use of SUs could have differential effects on the risk of cancer. Metformin and gliclazide were associated with a significant reduction in the risk whereas glibenclamide was associated with increased risk.

Conclusion

SUs are being widely used in this part of the world, mostly due to the low cost and availability seconding only to Metformin. The doubts on the effect of oncogenesis esp. regarding HCC are being raised compared to the anti-diabetic medications which reduce insulin resistance, although with a worldwide rise in incidence of HCC during the recent past. The current evidence is inconclusive to label SUs as 'carcinogenic'; hence further research is warranted to shed some light on this matter. The effectiveness of SUs should not be overlooked and be considered as a safe option esp. Gliclazide for optimal glycaemic control which will prevent the long-term morbidity and mortality related to T2DM.

References

1. McGlynn, K.A., Petrick, J.L. and El-Serag, H.B. (2021), Epidemiology of Hepatocellular Carcinoma. *Hepatology*, **73**: 4-13. https://doi.org/10.1002/hep.31288

2. Acharya SK. Epidemiology of hepatocellular carcinoma in India. *J Clin Exp Hepatol.* 2014 Aug;4(Suppl 3): S27-33. doi: 10.1016/j.jceh.2014.05.013. Epub 2014 Jun 20. PMID: 25755607; PMCID: PMC4284206.

3. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology.* 2004 Feb;**126**(2):460-8. doi: 10.1053/j.gastro.2003.10.065. PMID: 14762783.

4. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol.* 2006 Mar;**4**(3):369-80. doi:10.1016/j.cgh.2005.12.007. PMID: 16527702.

5. Donadon V, Balbi M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: potential role of insulin. *World J Gastroenterol.* 2008 Oct 7;**14**(37):5695-700. doi: 10.3748/wjg.14.5695. PMID: 18837086; PMCID: PMC2748204.

6. Donadon, V. et al. Antidiabetic therapy and increased risk of hepatocellular carcinoma in properties of each of them.

7. Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol.* 2012 Jan;**107**(1):46-52. doi: 10.1038/ajg.2011.384. Epub 2011 Nov 15. PMID: 22085817.

8. Bosetti C, Rosato V, Buniato D, Zambon A, La Vecchia C, Corrao G. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. *Oncologist.* 2013;**18**(2):148-56. doi: 10.1634/theoncologist.2012-0302. Epub 2013 Jan 23. PMID: 23345544; PMCID: PMC3579598.

9. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care.* 2006 Feb;**29**(2):254-8. doi: 10.2337/diacare.29.02.06.dc05-1558. PMID: 16443869.

10. Chen HP, Shieh JJ, Chang CC, Chen TT, Lin JT, Wu MS, Lin JH, Wu CY. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: *population-based and in vitro studies. Gut.* 2013 Apr;**62**(4): 606-15. doi: 10.1136/gutjnl-2011-301708. Epub 2012 Jul 7. PMID: 22773548.

11. Donadon V, Balbi M, Mas MD, Casarin P, Zanette G. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int.* 2010 May;**30**(5):750-8. doi: 10.1111/j.1478-3231.2010.02223. x. Epub 2010 Mar 12. PMID: 20331505.

12. Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, Viberti G; ADOPT Study Group; RECORD Steering Committee. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. *Diabetologia.* 2010 Sep;**53**(9):1838-45. doi: 10.1007/s00125-010-1804-y. Epub 2010 Jun 8. PMID: 20532476; PMCID: PMC2910882.

13. Kalra S, Aamir AH, Raza A, Das AK, Azad Khan AK, Shrestha D, Qureshi MF, Md Fariduddin, Pathan MF, Jawad F, Bhattarai J,

Tandon N, Somasundaram N, Katulanda P, Sahay R, Dhungel S, Bajaj S, Chowdhury S, Ghosh S, Madhu SV, Ahmed T, Bulughapitiya U. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. *Indian J Endocrinol Metab.* 2015 Sep-Oct;**19**(5):577-96. doi:10.4103/2230-8210.163171. PMID: 26425465; PMCID: PMC4566336.

14. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, Corlianò F, Fra GP, Bartoli E, Derosa G. Sulfonylureas and their use in clinical practice. *Arch Med Sci.* 2015 Aug 12;**11**(4):840-8. doi:10.5114/aoms.2015.53304. Epub 2015 Aug 11. PMID: 26322096; PMCID: PMC4548036

15. Kalra, S., Bahendeka, S., Sahay, R., Ghosh, S., Md, F., Orabi, A., Ramaiya, K., Al Shammari, S., Shrestha, D., Shaikh, K., Abhayaratna, S., Shrestha, P. K., Mahalingam, A., Askheta, M., A Rahim, A. A., Eliana, F., Shrestha, H. K., Chaudhary, S., Ngugi, N., Mbanya, J. C., … Das, A. K. (2018). Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus - International Task Force. *Indian journal of endocrinology and metabolism*, **22**(1), 132–157. https://doi.org/10.4103/ijem.IJEM_556_17

16. Khan R, Foster GR, Chowdhury TA. Managing diabetes in patients with chronic liver disease. *Postgrad Med.* 2012;**124**:130–7. [PubMed] [Google Scholar]

17. Lawson, D. H., Gray, J. M., McKillop, C., Clarke, J., Lee, F. D., & Patrick, R. S. (1986). Diabetes mellitus and primary hepatocellular carcinoma. *The Quarterly journal of medicine*, **61**(234), 945–955.

18. Mantovani A, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. Ann *Transl Med.* 2017;**5**(13):270. doi:10.21037/atm.2017.04.41

19. Chettouh, H., Lequoy, M., Fartoux, L., Vigouroux, C., & Desbois-Mouthon, C. (2015). Hyperinsulinaemia and insulin signalling in the pathogenesis and the clinical course of hepatocellular carcinoma. *Liver international: official journal of the International Association for the Study of the Liver*, **35**(10), 2203–2217. https://doi.org/10.1111/liv.12903

20. Zhou, Y. Y., Zhu, G. Q., Liu, T., Zheng, J. N., Cheng, Z., Zou, T. T., Braddock, M., Fu, S. W., & Zheng, M. H. (2016). Systematic Review with Network Meta-Analysis: Antidiabetic Medication and Risk of Hepatocellular Carcinoma. *Scientific reports*, 6, 33743. https://doi.org/10.1038/srep33743

21. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol.* 2013 Jun;**108**(6):881-91; quiz 892. doi: 10.1038/ajg.2013.5. Epub 2013 Feb 5. PMID: 23381014.

22. 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. https://doi.org/10.1016/j.aohep.2019.10.005

23. Arvind, A., Memel, Z. N., Philpotts, L. L., Zheng, H., Corey, K. E., & Simon, T. G. (2021). Thiazolidinediones , alpha-glucosidase inhibitors, meglitinides, sulfonylureas, and hepatocellular carcinoma risk: A meta-analysis. *Metabolism: clinical and experimental*, 120, 154780. https://doi.org/10.1016/j.metabol.2021.154780

24. Yip, T. C., Wong, V. W., Chan, H. L., Tse, Y. K., Hui, V. W., Liang, L. Y., Lee, H. W., Lui, G. C., Kong, A. P., & Wong, G. L. (2020). Thiazolidinediones reduce the risk of hepatocellular carcinoma and hepatic events in diabetic patients with chronic hepatitis B. *Journal of viral hepatitis*, **27**(9), 904--914. https://doi.org/10.1111/jvh.13307

25. Lee JY, Jang SY, Nam CM, Kang ES. Incident Hepatocellular Carcinoma Risk in Patients Treated with a Sulfonylurea: A Nationwide, Nested, Case-Control Study. *Sci Rep.* 2019 Jun 12;**9**(1):8532. doi: 10.1038/s41598-019-44447-1. PMID: 31189966; PMCID: PMC6561966.

26. Lee, J. Y., Kim, G., Lee, Y. H., Lee, B. W., Cha, B. S., Nam, C. M., & Kang, E. S. (2019). Comparison of hepatocellular carcinoma risk between patients treated with glimepiride and

gliclazide. *Diabetes & metabolism*, **45**(1), 83–85. https://doi.org/10.1016/j.diabet.2017.06.007

27. Yang, X., So, W. Y., Ma, R. C., Yu, L. W., Ko, G. T., Kong, A. P., Ng, V. W., Luk, A. O., Ozaki, R., Tong, P. C., Chow, C. C., & Chan, J. C. (2010). Use of sulphonylurea and cancer in type 2 diabetes-The Hong Kong Diabetes Registry. *Diabetes research and clinical practice*, **90**(3), 343–351. https://doi.org/10.1016/j.diabres.2010.08.022

28. Monami, M., Lamanna, C., Balzi, D., Marchionni, N., & Mannucci, E. (2009). Sulphonylureas and cancer: a case-control study. *Acta diabetologica*, **46**(4), 279–284. https://doi.org/10.1007/s00592-008-0083-2