Cancer of the Liver and its Relationship with Diabetes mellitus

Sunday Amos Onikanni, PhD1,2, Bashir Lawal, PhD3,4, Oluwafemi Shittu Bakare, PhD5, Basiru Olaitan Ajiboye, PhD6, Oluwafemi Adeleke Ojo, PhD7, Abdullah Farasani, PhD8,9, Saeed M Kabrah, PhD10, Gaber El-Saber Batiha, PhD11, and Carlos Adam Conte-Junior, PhD12

Abstract
A high increase witnessed in type II diabetes mellitus (T2DM) globally has increasingly posed a serious threat to global increases in liver cancer with the association between diabetes mellitus type II and the survival rate in liver cancer patients showing unstable findings. An increase in the development and progression of chronic liver disease from diabetes mellitus patients may be connected to cancer of the liver with several links such as Hepatitis B and C virus and heavy consumption of alcohol. The link between T2DM patients and liver cancer is centered on non-alcoholic fatty liver disease (NAFLD) which could be a serious threat globally if not clinically addressed. Several reports identified metformin treatment as linked to a lower risk of liver cancer prognosis while insulin treatment or sulphonylureas posed a serious threat. Mechanistically, the biological linkage between diabetes type II mellitus and liver cancer are still complex to understand with only the existence of a relationship between NAFLD and high level of energy intake and diabetes mellitus induces hepatic damage, increased liver weight thereby causes multiple pro-inflammatory cytokines that lead to the development of liver cancer. Therefore, this review gives an account of the pathophysiological importance of liver cancer position with T2DM, with the role of NAFLD as an important factor that bridges them.

Keywords
liver cancer, diabetes mellitus, prognosis, cytokines, steatohepatitis, cirrhosis

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1 Department of Chemical Sciences, Biochemistry Unit, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria
2 College of Medicine, Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
3 PhD Program for Cancer Molecular Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University and Academia Sinica, Taipei
4 Graduate Institute for Cancer Biology & Drug Discovery, College of Medical Science and Technology, Taipei Medical University, Taipei
5 Department of Biochemistry, Adekunle Ajays University, Akungba Akoko, Ondo State, Nigeria
6 Biomedical Research Unit, Medical Research Center, College of Applied Medical Sciences, Jazan University, Jazan, Saudi Arabia
7 Phytomedicine, Molecular Toxicology Research Laboratory, Department of Biochemistry, Federal University Oye-Ekiti, Ekiti State, Nigeria
8 Phytomedicine, Molecular Toxicology, and Computational Biochemistry Research Laboratory (PMTCB-RL), Department of Biochemistry, Bowen University, Iwo, Osun State, Nigeria
9 Analytical and Molecular Laboratory Center (CLAn), Institute of Chemistry (IQ), Federal University of Rio de Janeiro (UFRJ), Cidade Universitária, Rio de Janeiro, RJ, 21941-909, Brazil

Corresponding Author:
Sunday Amos Onikanni, College of Medicine, Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan.
Email: onikannisa@abuad.edu.ng

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Introduction

Type II diabetes mellitus (T2DM) is a chronic metabolic disorder of global burden that is associated with impaired insulin secretion/function and glucose metabolism.1 Oxidative stress has been implicated in the etiology of T2DM with consequent secondary complications including neuronal impairment, kidney and liver damage, and liver cancer.2–4 Individuals with T2DM are at greater risk of developing cancer and dying from it.5

An increase in the death rate globally from chronic liver disease had been linked to T2DM patients and liver cancer.4 The serious threat posed by cancer and this metabolic disease to people’s health is alarming in both developed and developing nations. Although accumulating evidence has implicated genetic alterations in cancer development, progression, and worse clinical outcome,6–12 the question of whether T2DM influences cancer incidence or influences cancer’s natural history and vice versa remains an integral part for investigating the relationship between T2DM and liver cancer pathophysiology.13–17 Moreover, a higher level of energy intake against energy expenditure, which results in insulin sensitivity impairment, increase in liver weight, fat mass and non-alcoholic fatty liver disease (NAFLD) has been linked to evidence between T2DM and liver cancer.16–21

The attributed fact related to sporadic increase in T2DM patients and obesity with prevalence in NAFLD and increase in liver weight and other related symptoms posed a threat to the increase in liver cancer cases. The progressive hepatic damage from steatosis to steatohepatitis and cirrhosis surfaced in the larger percent of the patients, which have also been observed in T2DM conditions.22–25

Given the sharp increase in T2DM globally and its risk factors linked to NAFLD and liver cancer, scientists like diabetologists and oncologists considered managing diabetes patients who had been diagnosed with liver cancer because of the strong link between T2DM and liver cancer. The link between T2DM and HCC is mediated by a chronic inflammatory state.26–29 Indeed, the eradication of HCV infection with direct antiviral agents (DAAs), leading to a reduction of the chronic inflammatory state, determines the reduction both of the onset of type 2 diabetes,30 and the risk of HCC.31,32

In this review, we carefully examine the temporality of the relationship between T2DM and liver cancer with the aim to potentially evaluate the modification role of NAFLD and other potential risk factors in the context of the relationship between TDM2 and liver cancer.

Global Studies Show Linkage of T2DM to Liver Cancer Risk

Global data on T2DM has increased greatly in recent years with the progressive increase of T2DM worldwide.13,33,34 The estimated world prevalence of T2DM is approximated to be 51% higher by 2045 with 700 million people projected to be affected if not properly controlled.35 Similarly, around 10 million deaths were recorded in 2020 cancer cases with uncontrollable abnormal cell growth in the organ or tissue placing liver cancer as one of the leading causes of cancer death.17,36 An evidence-based study shows that T2DM is increasing by 2 to 5-fold in liver cancer patients after changing the biasing of other factors.37–40 A progressive increase of T2DM in diabetes conditions leads to an increase in liver cancer by 10-fold in the presence of viral hepatitis condition and alcohol intake.41 A Competing Risks Analysis study by Baena-Díez et al42 concluded that diabetes is associated with premature death from cardiovascular disease, cancer, and noncardiovascular, noncancer causes,42 and individuals with T2DM are at greater risk of developing cancer and of dying from it.5 An evidenced-based report of an Italian cohort over an 11-year period, in which death certificates were reviewed, showed that death from site-specific cancer of the liver showed a higher rate of patients dying with T2DM compared with other.16,43 Based on the same findings, which are similar to this evidence based on site-specific cancer in relation to T2DM, the American Diabetes Association and American Cancer Association agreed that the incidence rate of liver cancer is increasingly higher in patients suffering from T2DM.44–47 Thirty-four years ago, a link was reported among patients with T2DM and cancer of the liver where a case-control study involving 105 liver cancer patients and other related cancer cases were matched by age and sex.48 Between 1984 and 1989, La Vecchia et al revealed that out of 242 cases reported, patients with T2DM had an increase of 2.5-fold in liver cancer development and other independent metabolic factors and potential confounding variables.49 The result from epidemiologists revealed a high risk of liver cirrhosis connected with NAFLD patients leading to liver cancer.19,50 Therefore, more evidence is needed for the establishment of epidemiological relations and cause-effect association between T2DM and liver cancer disease.

Mitochondria compose a dynamic population of organelles, existing partly both as units and as an interconnected network viewed under the microscope as constantly moving.51 It takes the microtubule track through dynein motors for mitochondria to travel within the cell to regions of high-energy demand via the uptake of calcium by mitochondria regulating ATP production.52,53 Given the role of mitochondria in β-cells stimulus-secretion coupling, a few genetic studies in humans implicate mitochondrial dysfunction in the pathogenesis of diabetes mellitus.54–56 Nevertheless, research revealed that mutation in the mitochondrial tRNA synthase tRNAβ results in inherited diabetes while the variant in the mitochondrial transcription factor TFB1M has been implicated worldwide by GWAS (genome-wide association studies).56 The mitochondria and ER were larger in size, close to each other with mitochondria changing formation in diabetes conditions thereby reflecting the stress of ER and dysfunction of mitochondria.57

In recent years, it was reported that liver cancer not only developed in patients suffering from cirrhotic NAFLD but developed increasingly in non-cirrhotic patients with NASH.50,58–60 Other reports described the frequent consumption of alcohol and age-old condition as risk factors for the development of liver disease. In all the research studies carried out, the survival rate of patients with cirrhotic NAFLD and with liver cancer disease was significantly shorter compared with patients with liver cancer secondary to HCV cirrhosis due to their tenacity in older age and the possibility of larger tumor diameters with less surveillance to patients on liver cancer secondary to HCV cirrhosis.50,61,62 (Figure 1).
Pathophysiological Mechanism Between T2DM and NAFLD, a Potential Risk Factor for Liver Cancer

The details of pathophysiological links between T2DM, NAFLD, and liver cancer are unclear but the liver cancer mechanistic approach in relation to this context is increasingly being understood with more research in finding the pathophysiological link. Elevated levels of hepatic insulin resistance, oxidative stress, chronic low pro-inflammation level, and lipotoxicity are the strongest indicative stages that exist between T2DM and NAFLD. This is because an increase in interleukin-1,
interleukin-6, tumor necrosis factor-alpha, and tumor growth factor-beta occurred as a result of the development of insulin resistance and lipotoxicity. Moreover, there is an elevated level of vasoactive factors and pro-oxidant molecules in the blood bloodstream that results in hepatic cellular growth and multiplication with inhibition in cellular apoptosis, which eventually results in liver cancer. Observed concentration increases of insulin in the blood increases insulin-like growth factor-1 (IGF-1) thereby stimulating insulin receptor substrate-1 (IRS-1), an activator of some intracellular signaling pathways. (Figure 2).

Previous evidence revealed that T2DM was a bad prognostic factor for the long-term survival of cirrhotic patients. This showed similar evidence in NAFLD because of their relationship in activating oxidative stress thereby release of reactive oxygen species (ROS). Several studies revealed ROS is produced when hepatocytes are steatotic thereby promoting the development of liver cancer and other cancers. The increase caused by oxidative stress production results in DNA damage, cytotoxicity as well as activation and suppression of multiple genes that are potentially implicated in cellular proliferation and growth thereby producing hepatic carcinogenesis. Therefore, several reports have shown a closed relationship between T2DM and NAFLD due to their disrupted mitochondria as a result of ROS production.

The mechanistic process of NAFLD production from T2DM is complicated, and this has been explored in isolated biological systems. Fatty liver, obesity, and insulin resistance have all been shown to be co-factors in liver disease. Because of increased absorption of free fatty acids and de-novo liponeogenesis in hepatocytes, fatty liver results in an intracellular build-up of triglycerides. At the same time, the hepatic secretion of extremely low-density lipoproteins is reduced. The liver damage includes cellular necrosis and inflammation, which are caused by an increase in mitochondrial oxidative stress on triglycerides, resulting in the formation of free radicals and peroxisomes. Adipokines (cytokines generated by adipocytes), such as leptin and tumor necrosis factor (TNF), are produced in excess, and worsen mitochondria oxidative stress. The regulating adipokine adiponectin is reduced, thereby encouraging the action of inflammatory adipokines. These chemical mediators are produced as a result of inflammation, cell necrosis, and adipokines that stimulate liver stellate cells, causing them to produce more collagen, connective tissue.
tissue growth factor, and extracellular matrix, promoting fibrosis. Studies have also reported the beneficial effects of metformin as an anti-aging agent. Metformin also acts as an endothelial protector that inhibit tumor growth, and metastasis via an AMPK-dependent signaling network. Interestingly, metformin has also been reported to synergize with and improved the activities and safety of clinical drugs for the treatment of lung cancer. Altogether, it’s evident that metformin does not only alleviate hyperglycemia but also protects against the development of cancer and aging.

Thus, the idea that a medication designed for the use of diabetes treatment may either increase or decrease the risk of liver cancer, or even influence cancer prognosis is still unclear because most observational studies predict that metformin, one of the drugs for diabetes patients, might have chemopreventive potential against liver cancer and a biologically plausible mechanism also exists (metformin drug activates AMP-activated protein kinase (AMPK) and inhibits the PI3K/AKT/mTOR signaling pathway that is important in regulating the cell cycle). Furthermore, it is unclear whether an insulin-related increase in liver cancer risk is related to toxicity associated with the medication, or if it is simply reflective of increased HCC risk in patients with more severe T2DM.

**Conclusion**
The high increase witnessed in T2DM globally has increasingly posed a serious threat to the global increase in liver cancer with an association between T2DM and liver cancer. However, the involvement of several underlying pathophysiologies of this cancer is linked to several diseases like NAFLD, increased hepatic insulin resistance hyperinsulinemia, activated level of pro-inflammatory mediators, oxidative stress, JNK-1 activation, increased IGF-1 activity, altered gut microbiota, and immunomodulation. Therefore, in-depth knowledge of the underlying pathophysiology could provide treatment breakthroughs for patients being treated when confronted with both T2DM and liver cancer.

**Author Contributions**
OSA designed and conducted the study and B L., B.O.A, B.O., A.F., O.A.O., S.K., G.E., and A.J oversaw the study. All author read and approved the final version of the manuscript.

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