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Cancer of the Liver and its Relationship with Diabetes mellitus

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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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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 al[42] 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 $tRNA^{Leu}$ 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).

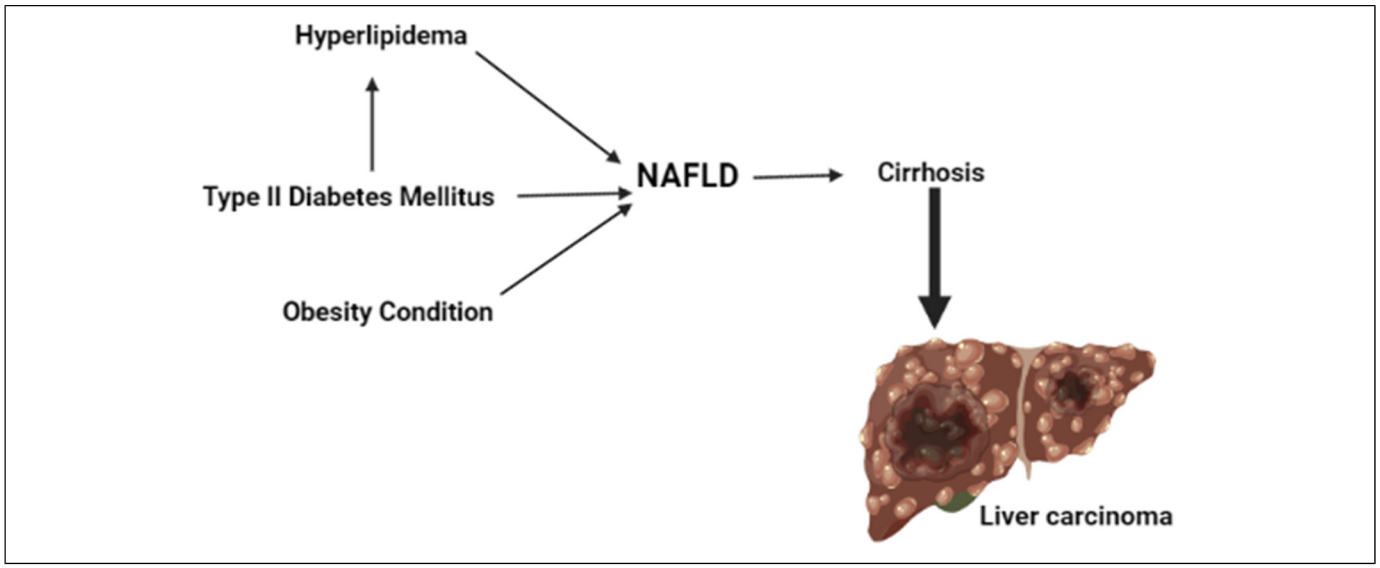

Figure 1. Non-alcoholic fatty liver disease (NAFLD), which can proceed to cirrhosis and hepatocellular cancer, can be caused by type 2 diabetes mellitus (HCC).

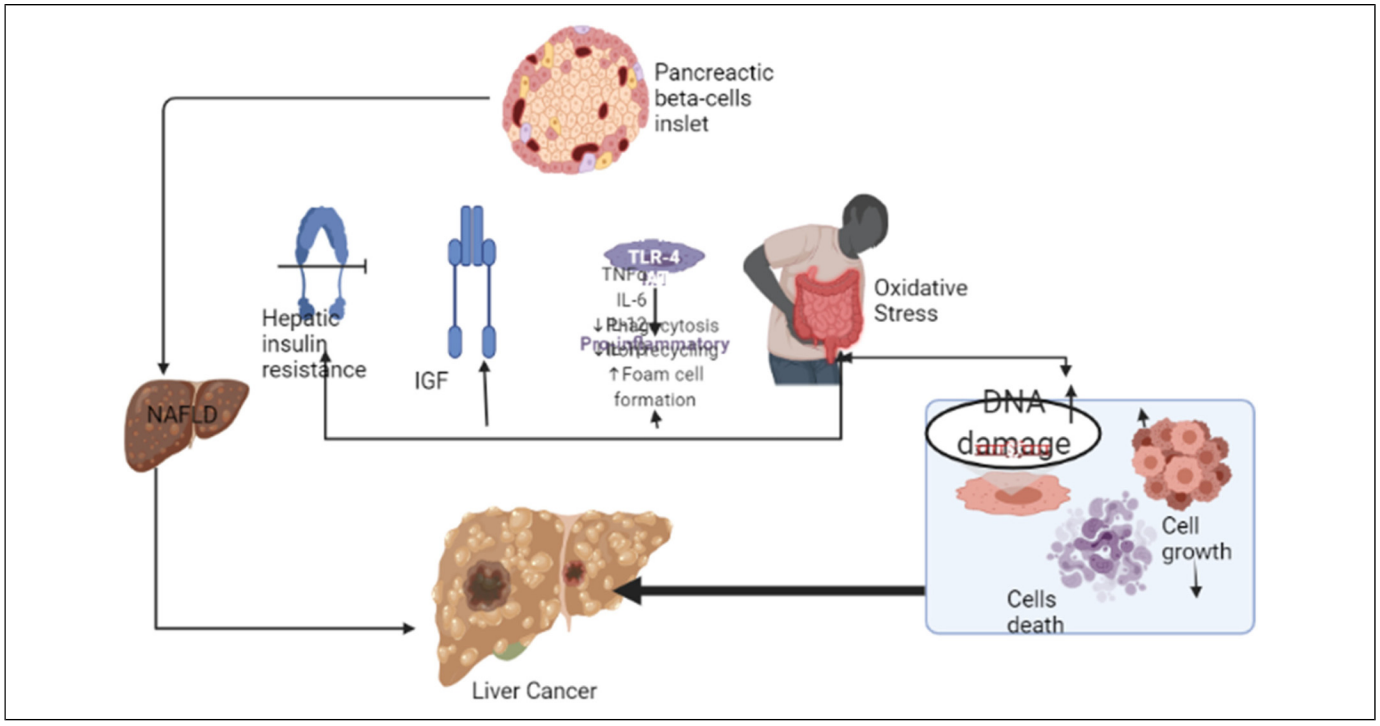

Figure 2. The details of pathophysiological links between T2DM, NAFLD, and liver cancer are unclear but the liver cancer mechanistic approach in relation to this context is increasingly improved recently with more research to find the pathophysiological link. Elevated levels of hepatic insulin resistance, oxidative stress, chronic low pro-inflammation level, and lipotoxicity are the strongest indicative stages that exist between T2DM and NAFLD.

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 between them. Elevated levels of hepatic insulin resistance, oxidative stress, chronic low pro-inflammation level, and lipotoxicity are the strongest indicators that exist between T2DM and NAFLD. This is because an increase in interleukin-1,

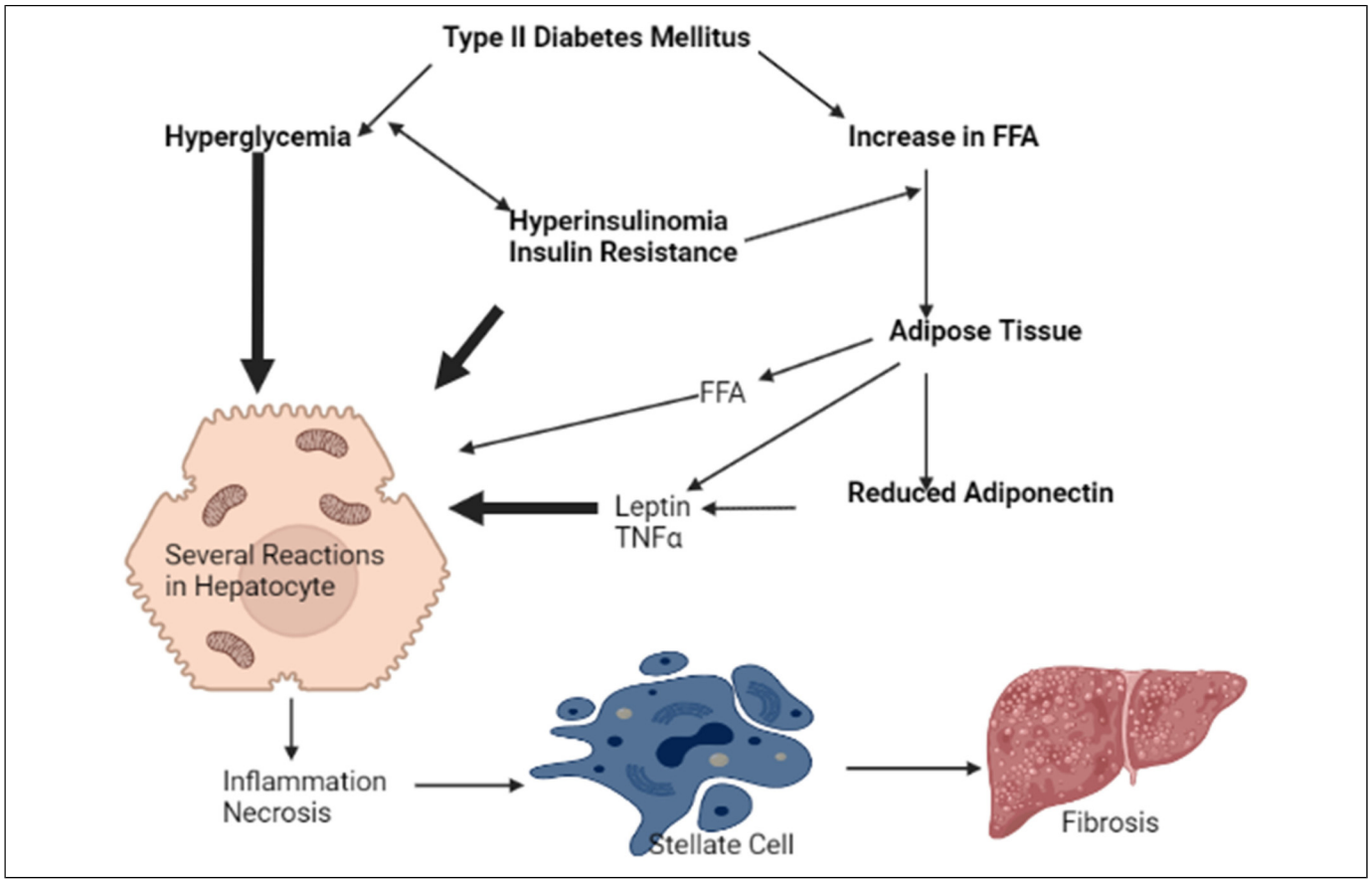

Figure 3. Result of diabetes type II in the damaged liver. Insulin resistance causes adipose tissue to emit free fatty acids (FFA). FFAs accumulate in liver cells, and de novo liponeogenesis (DNL) plays a role as well. Hepatic cells' decreased release of very low-density lipoprotein (VLDL) saturates hepatocytes, resulting in steatosis. Excess intracellular FFAs and the impact of adipokines (leptin and tumor necrosis factor-alpha (TNF-) exacerbate mitochondrial oxidative stress. Excessive oxidative stress results in the production of free radicals, which causes inflammation and cellular necrosis. The stellate cells are stimulated to make collagen by tissue inflammation.

interleukin-6, tumor necrosis factor-alpha, and tumor growth factor-beta occurred as a result of the development of insulin resistance and lipotoxicity.[21,63,64] 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.[60,65–69] 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.[67,69–72] (Figure 2).

Previous evidence revealed that T2DM was a bad prognostic factor for the long-term survival of cirrhotic patients.[73] This showed similar evidence in NAFLD because of their relationship in activating oxidative stress thereby release of reactive oxygen species (ROS).[70,74] Several studies revealed ROS is produced when hepatocytes are steatotic thereby promoting the development of liver cancer and other cancers.[64,65,75,76] 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.[76] Therefore, several reports have shown a closed relationship between T2DM and NAFLD due to their disrupted mitochondria as a result of ROS production.[64,76–78]

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.[79,80] 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 mitochondria oxidative stress on triglycerides, resulting in the formation of free radicals and peroxisomes.[81,82] 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 growth factor, and extracellular matrix, promoting fibrosis.[83–85] (Figure 3).

A recent report has also linked the gut microbiota with obesity, thereby alluding to the importance of gut microbiota, a key factor in energy production. Most metabolites generated from human mammalian blood come from gut microbiota with BA (bile acids) as the most important metabolite produced in the liver.[86,87] Therefore, an alteration of gut microbiota results in T2DM, NAFLD, and obesity pathogenesis with several pieces of evidence proving the possible implication of gut microbiota in hepatic carcinogenesis.[88–90]

In addition, cell cycle regulators in the gene encoding for albumin (TP53 and CDKN2A) and (CTNNB1 and AXIN1), genes of the β-catenin/WNT signaling pathway were revealed in wide studies of the pathophysiology of the cancer liver using the next generation sequencing and other omics techniques.[64,91,92] Other experimental reports revealed that patients suffering from NASH pose a risk of a high level of genomic instability, which results in the development of liver cancer.[93,94] Furthermore, there is increased evidence of the presence of the patatin-like phospholipase domain-containing protein-3 (*PNPLA3*) gene. This gene encodes for adiponutrin (protein) found in intra-hepatic lipid droplets, promoting lipogenesis and lipolysis. The gene has also been reported to be linked with an increased risk of NAFLD progression.[95–97] Therefore, there is a mechanism of *PNPLA3* I148M polymorphism of genotyping revealing the damaged hepatic failure and carcinogenesis.

Some Glucose-Lowering Medications and Their Relationship to Liver Cancer Risk

The liver as one of the most important organs that play a central role in the metabolism of drugs, xenobiotic, and nutrients are highly susceptible to drug-induced damage.[98] Apart from the study carried out by Evans et al in 2005 which suggested giving metformin, a glucose attenuating medication, for liver cancer in patients suffering from T2DM.[99] A group of scientists has demonstrated the evidence-based research on a population-based cohort of 10,309 T2DM patients followed up for nearly 5 years with the outcome revealing that cancer mortality significantly differed among the various treatments for diabetes at baseline: 3.5% for metformin users, 4.9% for sulphonylureas users and 5.8% for insulin users.[100,101]

Several other scientists have shown proven evidence in their research findings relating to those treated with metformin had a lower incidence of total cancer than those treated with sulphonylureas or insulin, independent of age, sex, BMI, hemoglobin A1c, smoking, and use of other medications including the hospital-based findings where sulfonylureas or insulin conferred the highest HCC risk, while the metformin or glitazones usage associated with a larger percent risk reduction in liver cancer in patients with T2DM.[102,103] Contrary to the above finding, Tsilidis *et al* revealed that users of sulphonylureas or metformin had similar incidence rates of total cancer over 5 years of follow-up in a retrospective cohort study of nearly 96,000 individuals with T2DM who make use of metformin or other oral glucose-lowering agents within 12 months of the diagnosis.[104]

Studies have also reported the beneficial effects of metformin as an anti-aging agent.[105] Metformin also acts as an endothelial protector[5] that inhibit tumor growth, and metastasis via an AMPK-dependent signaling network.[106] Interestingly, metformin has also been reported to synergize with and improved the activities and safety of clinical drugs for the treatment of lung cancer.[107] 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.[108,109]

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.

Declaration of Conflicting Interests

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