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Review

Mechanistic Insights into the Diabetes–Cirrhosis–Hepatocellular Carcinoma Axis: Molecular Mechanisms and Therapeutic Perspectives

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Abstract

Hepatocellular carcinoma (HCC) cellular metabolism is also directed toward glycolysis in order to improve the synthesis of metabolic chemicals utilized by cancer cells to produce proteins, lipids, and nucleotides and maintain a high rate of cell proliferation. Several hepatic conditions are strongly associated with diabetes mellitus (DM), including non-alcoholic fatty liver disease (NAFLD), steatohepatitis, and liver cirrhosis. Recent findings also support that DM can predispose individuals to various forms of malignant neoplasm including renal, endometrial, breast, gallbladder, colorectal, pancreatic, and liver cancer likewise the HCC. This process promotes uncontrolled cellular proliferation and increases reactive oxygen species (ROS) production, contributing to cellular damage, which may cause cell death. Numerous risk factors of both DM and cancer share so much, yet the relationship between the two is imprecisely stated. Some epidemiologic studies have established a correlation between pathogenic and prognostic attributes of DM and increased incidence of HCC and, therefore, depict DM as a single risk factor in the development of HCC. The etiological and pathophysiological relationship between DM and HCC has been given in this review, which links hyperglycemia, hyperinsulinemia, insulin resistance, and the activation of insulin-like growth factor (IGF) signaling pathway and pharmacological treatment of the HCC in DM. The HCC treatment targets in these pathways, hyperinsulinemia, insulin resistance and IGF signaling pathways activation and pharmacological control of HCC related to DM were potential targets.

Highlights

- Diabetes mellitus (DM) significantly increases the risk of hepatocellular carcinoma (HCC) through metabolic and inflammatory pathways.
- Insulin resistance, hyperinsulinemia, and insulin-like growth factor (IGF) signaling are central drivers of hepatocarcinogenesis.
- Oxidative stress and chronic inflammation contribute to genomic instability and tumor progression.
- Metabolic reprogramming, including enhanced glycolysis, supports HCC growth and survival.
- The diabetes–cirrhosis–HCC axis represents a multi-step, interconnected disease process. Mechanism-based therapeutic strategies may improve treatment outcomes in diabetes-associated HCC.

1. Introduction

The sixth most common and the fourth most common cause of cancer-related mortality is hepatocellular carcinoma (HCC) [1,2]. In most instances, HCC occurs in a multi-step progression, on a backdrop of liver damage [3-5]. There is a change in the metabolism of cancers whereby there is elevation of the uptake of glucose and lactate production under the presence of oxygen [6,7]. Another key role in liver carcinogenesis is played by oxidative stress [8,9]. It is brought about by the unbalanced oxidative species production and antioxidant molecules generation in cells. The reactive oxygen species (ROS) are the most profuse [10,11]. High levels of ROS generation are a major factor in cellular damage in diabetes. High ROS concentrations may cause oxidative injuries to the DNA resulting in the presence of the oxidative tools of 8-hydroxy-2 deoxyguanosine and a rise in the rate of genetic alterations. ROS also cause damage to RNA molecules and distortion of lipid structures in cell membranes, which elevates membrane permeability and eventually leads to cell death. Moreover, oxidative stress may change the conformation of proteins, affecting their biological activities, or causing their complete loss of activity [12]. ROS stimulate cell proliferation, apoptotic avoidance, angiogenesis, tissue invasion and metastasis [13]. It has been shown that diabetes mellitus (DM) increases the risk of developing multiple cancers such as renal, breast, colorectal, gallbladder, endometrial, pancreatic, and hepatic

malignancies [14]. The most prevalent primary liver malignancy with higher and faster mortality rate in the entire world is the HCC. HCC is a common illness that arises among those with underlying chronic liver conditions. HCC occurs in about 70.90 percent of cases in the setting of cirrhosis and also about 50.85 percent of the new infections are caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) and chronic alcohol use [8]. Cirrhosis and advanced liver fibrosis is a major risk factor in the development of HCC as is chronic HBV infection is [9]. Aflatoxin are exposed to primary biliary cirrhosis, obesity, and non-alcoholic fatty liver disease (NAFLD) [10,13]. Others less frequent but significant major etiological factors include hemochromatosis and glycogen deposition disorders, 1 -antitrypsin insufficiency, hereditary tyrosinemia type 1, and wilson disease [14,15]. DM is one of the elements of metabolic syndrome that has been widely studied in terms of its pathogenic and prognostic significance in HCC. Several epidemiological researches have revealed a strong relationship that exists between diabetes and the elevated prevalence of HCC, indicating that DM could be a risk factor in the occurrence of HCC by itself. The mechanisms that cause their connection to DM and HCC can be related to metabolic dysfunctions, including insulin resistance, hyperglycemia, and insulin-like growth factor (IGF), and hyperinsulinemia, cell signaling pathways activation. These metabolic alterations may also influence the therapeutic response to pharmacological treatments in patients with HCC [16]. Collectively, these processes support a stepwise disease model in which metabolic dysfunction in diabetes initiates hepatic injury, promotes fibrosis and cirrhosis, and ultimately drives HCC through sustained oncogenic signaling and microenvironmental alterations.

2. Epidemiological and Clinical Associations Linking DM to HCC

2.1 HCV Infection

HCV infection is a cause of metabolic dysregulation that directly affects pancreatic β-cells, thereby disabling insulin secretion. HCV infection also induces T-lymphocyte-mediated immunity responses, resulting in a more powerful production of pro-inflammatory cytokines (tumor necrosis factor-alpha, TNF-α and interleukin-6, IL-6). Such inflammatory mediators enhance insulin resistance and interfere with the normal insulin signaling pathways [16,17]. Moreover, HCV infection enhances hepatic steatosis and progressive fibrosis and accelerates oxidative stress leading to inflammation of cells and further intensifying insulin resistance [18]. Genetic vulnerability in the host can also result in the generation of insulin resistance that will ultimately result in type 2 diabetes mellitus (T2DM). The level of adipokine is unbalanced and liver fibrosis exists because of HCV, therefore, puts the individual at risk of getting HCC [19]. Figure 1 illustrates the pathogenesis of HCV-induced T2DM and clinical outcomes related to it:

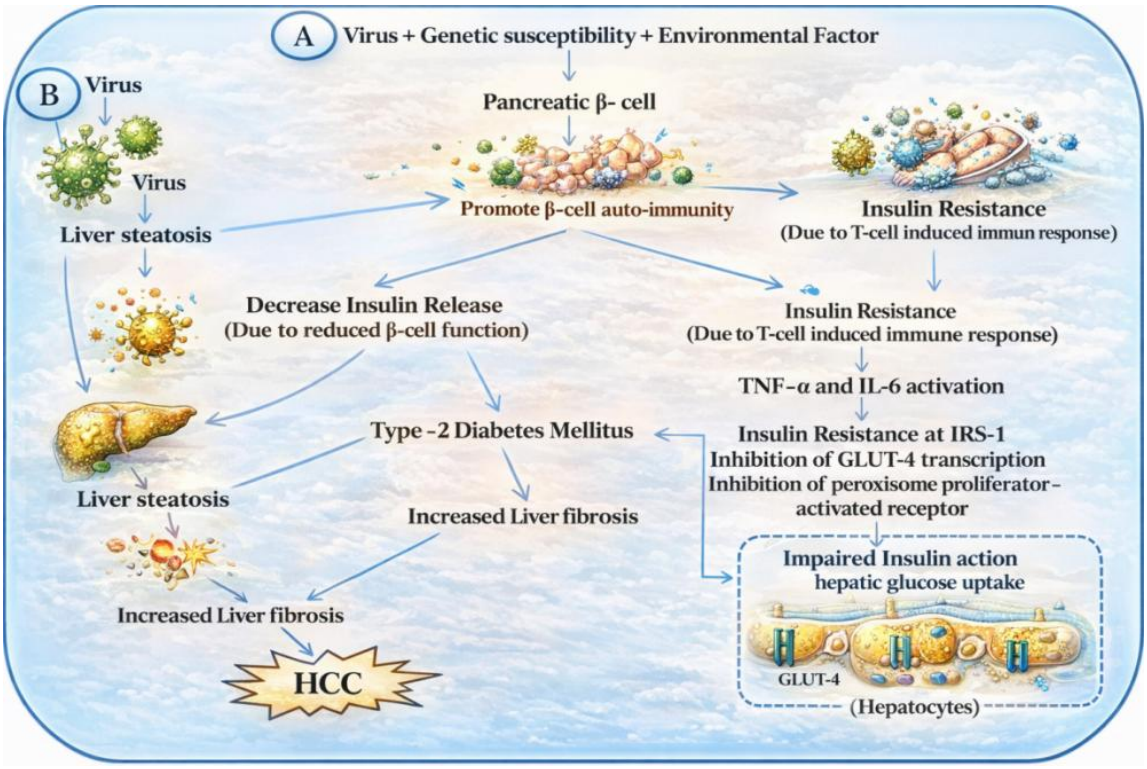

Figure 1. Schematic overview showing how viral infection together with genetic and environmental susceptibility promotes pancreatic β-cell dysfunction, immune activation, and insulin resistance. These interconnected pathways contribute to liver steatosis, progression to T2DM, and ultimately enhanced liver fibrosis leading to HCC. (Source: Self-made by BioRender.com)

2.2 NAFLD, Steatohepatitis, and Liver Cirrhosis

T2DM, insulin resistance, NAFLD, metabolic syndrome and obesity constitute metabolic disorders that are closely related [20]. NAFLD is also marked by a build-up of lipids in the hepatocytes, mitochondrial dysfunction, immune imbalances, gut microbiota changes, genetic susceptibility, dietary and contemporary sedentary life. Insulin resistance is a key factor of NAFLD onset and progression [21]. Close correlation between NAFLD and T2DM has been indicated and the prevalence of non-alcoholic steatohepatitis (NASH) is very high [22]. NASH is the more severe type of NAFLD, which is marked by inflammatory infiltration, fibrosis, and hepatocellular damage. NASH constitutes a major risk factor for the development of liver cirrhosis and HCC. Adipose tissue and skeletal muscle resistance to insulin is a factor in the development of NAFLD. In the condition of hyperinsulinemia, the augmented de novo lipogenesis encourages the surplus lipid deposition in the liver [23]. Insulin resistance, obesity, chronic inflammation, and oxidative stress, are associated with the pathogenesis of NAFLD and T2DM, thereby can add to the progression of HCC through growth enhancement (Figure 2) Theoretical pathogenesis of T2DM and associated clinical phenotypes in HCV: (A) Virus, multiple environmental, genetic and viral diseases may cause direct cytotoxic activity on pancreatic β-cells and result in excessive secretion of pro-inflammatory cytokines like TNF-α. These proinflammatory factors decrease insulin release and, at the same time, enhance insulin resistance. As a result, it impairs insulin absorption by tissues, thereby fostering persistent hyperglycemia and the subsequent development of T2DM. (B) HCV induces hepatic fibrosis, and augmented oxidative stress results in the additional growth of hepatic fibrosis. The growth of liver fibrosis and the protracted virological reactions and T2DM evolve to hepatocarcinogenesis [24].

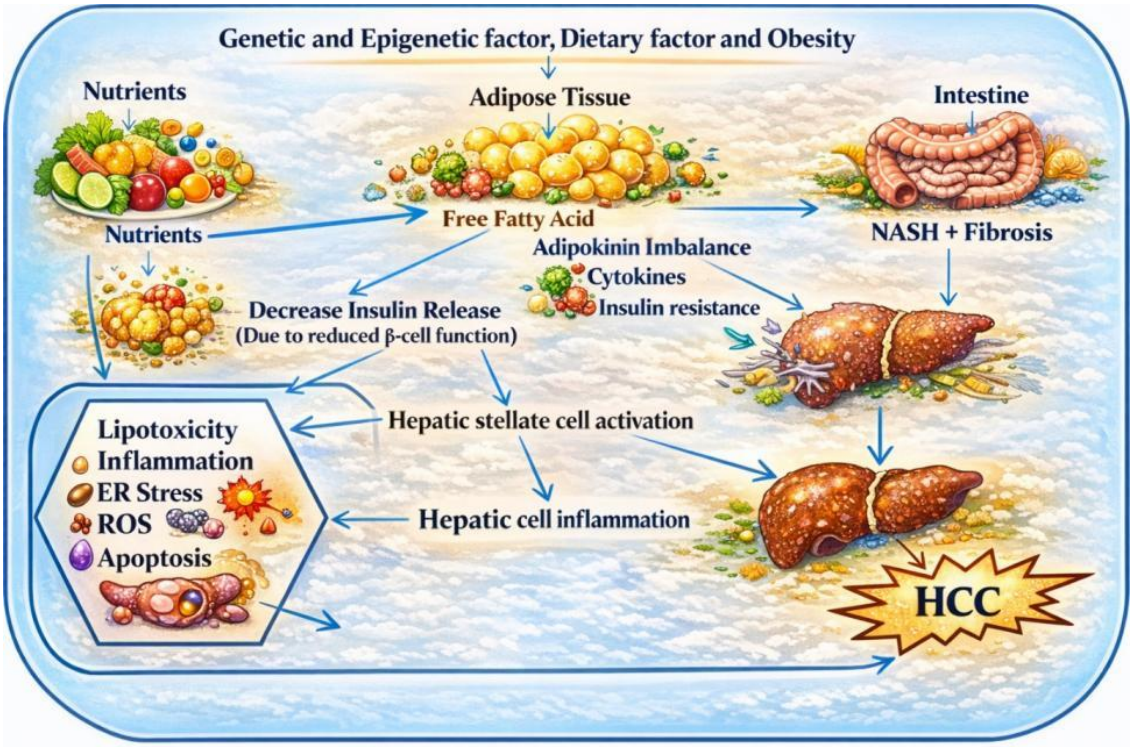

Figure 2. Pathogenesis of NASH and associated clinical phenotypes: Lipotoxicity, endoplasmic reticulum (ER) stress, ROS production, apoptosis, and inflammation in the hepatocytes are caused by genetic and epigenetic changes, obesity and dietary factors, such as nutritional imbalances, adipose tissue activation, and gut microbiota changes. This results in damage of hepatocytes that causes hepatic stellate cell activation, resulting in NASH-associated fibrosis exhibit an elevated susceptibility to hepatocarcinoma. Excess insulin-like growth factor I (IGFI) synthesis occurs in both resistance to insulin and hyperinsulinemia, which can stimulate proliferation while inhibiting hepatoblast apoptosis. (Source: Self-made by BioRender.com)

2.3 Autoimmune Diseases

Type 1 diabetes melitus is an organ-localized autoimmune disease, which is caused by disruptive damaging effects of autoreactive insulin-producing cells through proinflammatory CD^{4+} and CD^{8+} T cells [25,26]. Autoimmune hepatitis (AIH) is a systemic inflammatory disorder of the liver that is linked with environmental factors, immune imbalance, and genetic causes. All these factors contribute to the development of progressive hepatic necroinflammation and fibrosis [27]. AIH presents autoantibodies of insulin and an islet cell antibody. Nonetheless, AIH is also occurring in AIH type 1 pancreatic cells: dysfunctional and structural insufficiency leading to hyperglycemia. Glutamic acid decarboxylase 65 (GAD65) is a major autoantigen associated with autoimmune diabetes, particularly type 1 diabetes mellitus (T1DM) [28]. TNF-α and IL-1 cytokines may be involved in the development of insulin deficiency in T2DM and, therefore, insulin resistance through the suppression of insulin receptors (IRs) and the stimulation of IL-1. Therefore, there is a possibility that

inflammation could be one of the components of autoimmune response to pancreatic cells: dysfunctional and structural insufficiency leading to hyperglycemia. However, GAD65 autoantibodies are not typically considered characteristic biomarkers of classical T2DM [29,30]. Autoimmune diseases like AIH are relatively less prone to HCC development as associated to other persistent hepatic disorders.

2.4 Hepatogenous Diabetes (HD)

It is a type of diabetes that develops as a secondary event to chronic liver disease. It can be divided into two, generally, genetically T2DM and HD. Metabolic syndrome is often attributed to hereditary T2DM, which may cause NAFLD, liver cirrhosis, and HCC. Conversely, hepatogenous diabetes (HD) occurs in chronic liver disease and may arise in a person with no history of diabetes or other classical risk factors of metabolism like obesity and hyperlipidemia. HD possibly un-tolerant to glucose or DM despite having normal levels of fasting glucose. HCV and alcohol are the causes of HD in patients who have liver diseases [31]. In HD, there are different structural changes in the liver which reduce the use of insulin, thus raising the systemic insulin. Several structural and physiological changes in liver disease cause metabolic dysregulation. They are (a) decreased hepatic mass, thereby lowering the insulin uptake by Kupffer and vascular endothelial cells [32,33], and (b) development of portosystemic collateral circuits, which divert blood around the liver, thus lowering hepatic first-pass insulin clearance and raising insulin levels in the circulation [34]. The resultant chronic hyperinsulinemia can then cause insulin resistance by down-regulating IRs and decreasing their receptor affinity, availability and signaling efficacy. Multiple metabolic and inflammatory mediators, including hormones, growth factors, and cytokines, may contribute to insulin resistance and metabolic dysregulation in chronic liver disease [35]. The insulin resistance in muscle, liver, adipose tissue, and pancreatic β-cells also leads to impaired glucose tolerance and the subsequent development of DM in liver disease patients [36]. The HD, insulin resistance, viral infections including those of hepatitis B (HBV) or hepatitis C (HCV) and progressive hepatic fibrosis and necroinflammation may hence lead to HCC [37].

2.5 Obesity

Obesity can be described as a disease associated with adipose tissue in connection with metabolic syndrome. When a person consumes high lipid food, adipocytes absorb lots of lipid thereby causing more insulin to be released in the bloodstream. The adipocytes promote insulin sensitivity and fatty acid oxidation while suppressing lipogenesis through the secretion of adiponectin. Obesity causes the adipocytes to become swollen, dedifferentiated and decreases the production of adiponectin. Where there is low secretion of adiponectin, macrophage infiltration takes place, and this adds in inflammatory reaction in adipocytes [38]. The breakdown of lipid in the fatty tissue emits free fatty acids (FAs) of accumulated triglycerides. Higher levels of triglycerides are directly linked with insulin resistance and can also be responsible of hepatic steatosis. Due to the amplified hepatic lipogenesis, adipocyte differentiation and fatty acid oxidation, ROS production and inflammatory reaction, collectively, encourage liver injury and could be involved in hepatocarcinogenesis. Moreover, chronic inflammation may affect the immune surveillance, thus, allowing the survival and progression of malignant cells. Obesity is related to NAFLD, a hepatic metabolic syndrome. In the recent past, obesity and associated metabolic shortages have been cited as significant causes of the HCC development [39]. Obesity-related metabolic imbalances such as insulin resistance, insulin-like growth factor I receptor (IGF-IR)/insulin-like growth factor I (IGFI) signaling axis disregulation, and adipokines secretion disturbances have a strong pathophysiology link to the occurrence of hepatic carcinogenesis. The genration of pro-inflammatory cytokines is also promoted by insulin resistance. The mal-regulation of these cytokines leads to hepatic steatosis and hepatic inflammatory reactions in the liver, which facilitates the development of the disease and the development of HCC. While these conditions establish the clinical and epidemiological link between diabetes and HCC, they are underpinned by shared pathogenic mechanisms that drive disease progression at the molecular level [40].

3. Molecular and Signaling Mechanisms

3.1 Hyperglycemia

Building upon the shared pathogenic drivers described above, several molecular and signaling pathways mediate the progression from metabolic dysfunction to HCC. It triggers the change in the cell vascular network and causes endothelial cell damage, therefore, cells obtain new underpinning with compromised normal functions. Endothelial lining cell dysfunction is typified by a number of pathological changes, which comprise less nitric oxide (NO) bioavailability, deformation of vascular hemodynamics, impaired fibrinolytic activity as well as augmented creation and consumption of growth factors. Moreover, the injury of endothelium is connected with increased expression of adhesive molecules and inflammatory genes, higher generation of ROS, improved levels of oxidative stress, and cellular permeability. Unremitting hyperglycemia also enhances the speed of endothelial dysfunction by fostering the development of advanced glycation end products (AGEs), diacylglycerol, reactive Amadori compounds, 3-deoxyglucosone, methylglyoxal, ROS and nitrosylated compounds [41]. ROS initiates plasma membrane peroxidation thereby triggering 4-hydroxynonenal, consequently resulting in the formation AGEs, PKC, enhanced proinflammatory cytokines and PI-3-kinase signaling pathways disruption. The presence of metabolic pathways with an enormous contribution to cell-damaging effects due to hyperglycemia that trigger ROS production and activate cytokines, is an imperative role in the inflammatory response and a change in the homeostasis of liver and induces the emergence and progression of HCC [42].

3.2 Insulin Resistance and Hyperinsulinemia

Excessive intake of nutrients accompanied by adipose tissue insulin resistance is the cause of obesity that leads to the deposition of toxic metabolites in the microenvironment of the cells. Insulin resistance is clinically expressed as various metabolic disorders, such as DM, obesity, impaired glucose tolerance, and metabolic disorder, which are closely linked with endocrine, and immune regulatory mechanism [43]. Multiple mechanisms contribute to the onset of insulin resistance with such factors as peptide hormones, inflammatory mediators, and intracellular stress signaling pathway activation [44]. Cytokines or adipokines (secreted by adipocytes) are of central importance in in initiation and progression of insulin resistance. These molecules contribute to the dysregulation of breakdown in cases where adipocytes surpass their lipid storage capacity leading to the abnormal redistribution of lipids to peripheral tissues and organs [45]. Leptin is one of these adipokines that have been closely linked with hyperphagia, hyperlipidemia and insulin resistance [46]. Other bioactive peptides that are secreted by adipose tissue include adiponectin, IL-6, retinol-binding protein-4, resisting, and TNF-α [47]. The reduction of triglyceride synthesis, β -oxidation, and insulin activity in liver and skeletal muscle are both typical of leptin and adiponectin, thus suggesting insulin resistance in the adipocyte [48]. Insulin resistance and sensitivity are determined by the leptin to adiponectin ratio [49].

Collectively, the changes in the level of hormones and cytokines secretion by the hepatic, adipose tissue, and invading immunological cells in reaction to the permanent lipid storage and the metabolic stress become the main contributors to the insulin resistance development. Defects in β-cell signaling can impair glucose-stimulated insulin secretion and contribute to metabolic dysregulation [50]. There is a close interconnection between hyperinsulinemia, insulin resistance and the malevolent glucose-stimulated insulin secretion. Any of these metabolic imbalances could trigger the onset of the other two disorders quite rapidly. Hyperinsulinemia has several repercussions on notable metabolic pathways, such as elevated ROS and AGEs synthesis, greater IGF-I levels, heightened hyperglycemia, and augmented fatty acid and triglyceride synthesis. These metabolic alterations also activate the release of a lot of hormones and cytokines. ROS have interactions with different cellular macromolecules, such as DNA, lipids, and proteins. Oxidative damage is especially sensitive to polyunsaturated FAs, which trigger lipid peroxidation, which interferes with cellular membrane integrity and fluidity. This is one of the key mechanisms that should be held accountable for causing endothelial cell membrane injury [51]. Moreover, the growth-stimulating factors, including insulin, interleukin-I and vascular endothelial growth factors (VEGF), can be used to activate the growth of several cell types, including hepatocytes [52]. Hyperinsulinemia has been associated with enhanced cellular proliferation and activation of mitogenic signaling pathways in several cancer types [53]. The role of insulin resistance and IGF signaling in tumor progression is depicted in Figure 3.

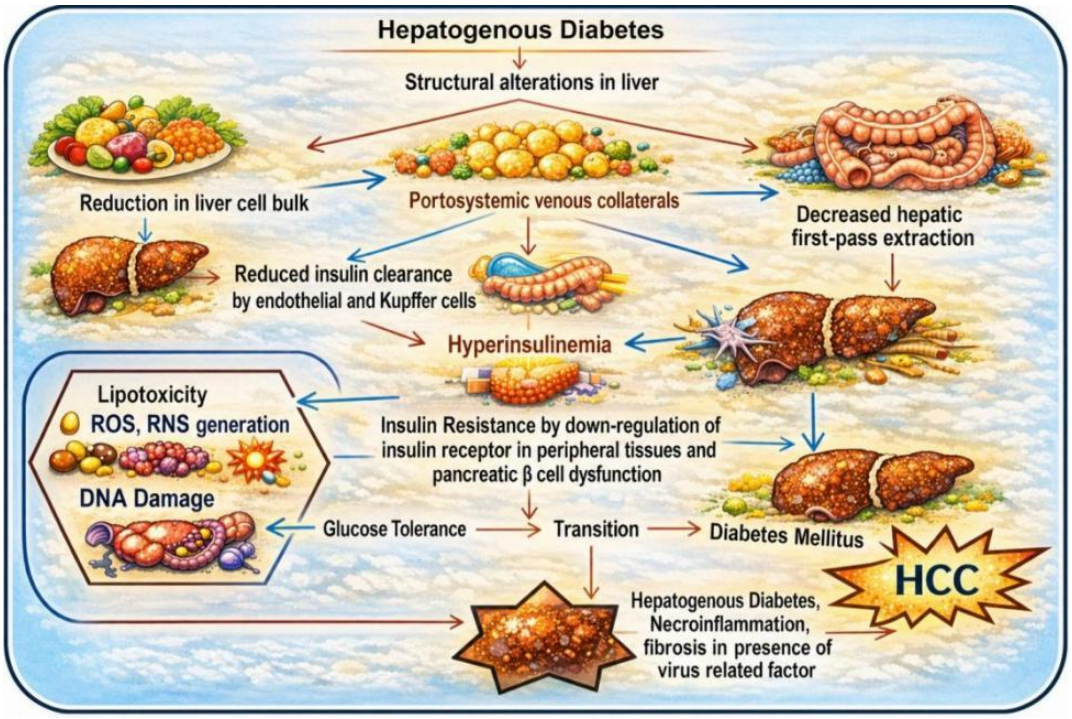

Figure 3. Hepatogenous diabetes (HD) can play an important role in the pathogenesis of hepatocarcinoma. Alterations in the liver structure such as a decrease in the hepatocyte mass and the development of portosystemic venous collaterals, cause deficits in the hepatic insulin clearance and resultant hyperinsulinemia. This metabolic condition facilitates insulin resistance, lipotoxicity, and augmented ROS production as well as modified RNA production which finally leads to insulin resistance in the form of impaired glucose tolerance. Oxidative stress and metabolic imbalance caused by diabetes trigger the occurrence of DNA damage and hepatic fibrosis, which combined in turn can lead to the development HCC. (Source: Self-made by BioRender.com)

3.3 HCC, Insulins and Glucose Metabolism

There is metabolic reprogramming of HCC cells with an enhanced glucose uptake using glucose transporter-1 (GLUT1) channels [54,55]. High expression of GLUT1 has been highly correlated with the aggressiveness, invasiveness and proliferation of tumors in HCC. Higher levels of uptake of the glucose analog ^18F-flurodeoxyglucose PET-CT widely used for tumor detection imaging are commonly associated with high GLUT1 levels in cancer tissues of HCC [19,55]. After accessing the cell, the glucose is changed into glucose 6-phosphate (G6P) through the hexokinase (HK) family of enzymes. These metabolic alterations include the overexpression of hexokinase-2 (HK2), a key glycolytic enzyme that promotes aerobic glycolysis and supports HCC progression [49]. The last process in glycolysis involves the production of pyruvate by the enzyme family pyruvate kinase (PK). There are four isoforms of this enzyme family, which are encoded by two paralogous genes, PKL and PKM [31]. PKL is a coded expression of the PKL isoform that is mainly found in the liver and kidney, and PKR is found in erythrocytes. PKM gene is subjected to alternative splicing to form two isoforms PKM1 and PKM2. PKM1 is mainly expressed in tissues like the fibroblast, brain, bladder, and adult muscle whereas PKM2 is normally expressed during embryonic development and is significantly enhanced in the presence of several cancers [24,29]. PKM2 mRNA and protein are greatly up-regulated in HCC tissues compared to the normal liver tissue and have been linked with violent tumor behavior and poor prognosis [56]. Pyruvate may then be transformed into lactate by the action of lactate dehydrogenase (LDH) in the presence of NADH and H^+ to produce NAD^+ as a by-product [57]. There are five types of LDH isoenzymes in the human tissues. These are tetrameric enzymes that are an amalgamation of two subunits namely M and H. The M subunit is mainly present in skeletal muscle and the H subunit in cardiac muscle. Isoenzymes that have higher concentrations of B chains (LDHB) are more likely to enhance the pyruvate to acetyl- CoA conversion, compared to those with more A subunits (LDHA), which are more likely to convert pyruvate to lactate. Of these, the most widespread of the isoenzymes to be overexpressed in malignant cells is LDHA [19]. The lactate that is generated via this route is then removed out of the cell via monocarboxylate transporters (MCTs) [21]. The glycolytic pathway cannot stay on without the production of lactate [17]. LDH is one of the major factors of proliferation and invasion by HCC tumor. HCC patients the serum samples of the patients were analyzed to suggest serum LDH to be used as a prognostic factor [58]. It has been demonstrated through experimental studies that MCT4 and CD147 are very high in HCC tissues. CD147 is a transmembrane glycoprotein the effect of which is to stimulate the production of matrix metalloproteinases (MMPs) and interacts with MCT4 to transport lactate of cancer cells [36,39]. In the glycolysis bypass, G6P is diverted to the PPP to be macromolecularly biosynthesized, the glucose-6-phosphate dehydrogenase (G6PD) oxidizes it to 6-phosphogluconolactone and was also found to be up-regulated in HCC [7,12,42]. The subsequent reaction in the G6PD-catalyzed reaction is the formation of NADPH which further reacts with the GSSG form to GSH [22,53].

On the other hand in contrast to gluconeogenesis, glycolysis pathway is suppressed in HCC [22,24]. One of the key rates of gluconeogenesis is fructose-1,6-bisphosphatase (FBP), which catalyzes the fructose-1, 6-bisphosphate into fructose-6-phosphate, which serves as a major precursor of glucose-6-phosphate (G6P). There are two large isoforms of this enzyme: FBP1 which is mainly found in the liver and kidney, and FBP2 which was firstly identified in muscle tissue, but was subsequently found in various other cell types [59]. Cases of HCC would show a markedly reduced expression of FBP1 as a result of loss of copy number or methylation of the promoter of FBP1 implying that the corresponding FBP1 protein plays a vital role in tumorigenesis of HCC [60].

One of them is Nur77, a nuclear receptor coded by NR4A1 gene and regulates gluconeogenesis in the liver through the promotion of FBP1 and FBP2 transcription [61]. Besides that, Nur77 also serves as a tumor suppressor by binding with phosphoenolpyruvate carboxykinase (PEPCK1) thus inhibiting its degenration leading to gluconeogenesis of oxaloacetate to phosphoenolpyruvate [62]. PEPCK has two major isoforms including PEPCK-C (PEPCK1), a cytoplasmic isoform that is highly expressed in the liver, kidney and adipose tissue, and PEPCK-M, which is found in the mitochondria [63]. Nur77 was observed to be reduced between Stage I and III in HCC samples [43]. The same pattern was identified in the levels of PEPCK1 expression [64]. The AMP-activated protein kinase (AMPK) is another glycolysis-gluconeogenesis regulator. AMPK is an intracellular energy sensor that has significant functions in metabolism and cell growth regulation [40]. Under physiological states, it controls the concentration of ATP, bringing it back to the state when required [65]. The stimulation of the AMPK suppresses the expression of proteins, DNA, RNA and lipids that are essential to the proliferation and growth of cells [38]. AMPK can influence HCC tumorigenesis and development [66]. The stimulation of AMPK was reported to cause cell-cycle arrest and the survival of cancer cells and at the same time lead to the loss of their capacity to metastasize [67]. On the other hand, inhibition or silencing of AMPK prevents the occurrence of apoptosis and cell-cycle inhibition, which would otherwise be triggered by circumstances of glucose deprivation [68]. Several pharmacological agents that can activate AMPK have thus been explored as possible treatment interventions of HCC. One of them is the anti-diabetic medication metformin which has been widely investigated since it can induce AMPK signaling pathways [37]. Metformin action in the process of its activation causes the effect on the AMP / ATP level as well as on the mitochondrial respiration complex I, as well as activates the liver kinase B1 (LKB1) [69]. Metabolic reprogramming and glycolytic alterations in HCC cells are illustrated in Figure 4.

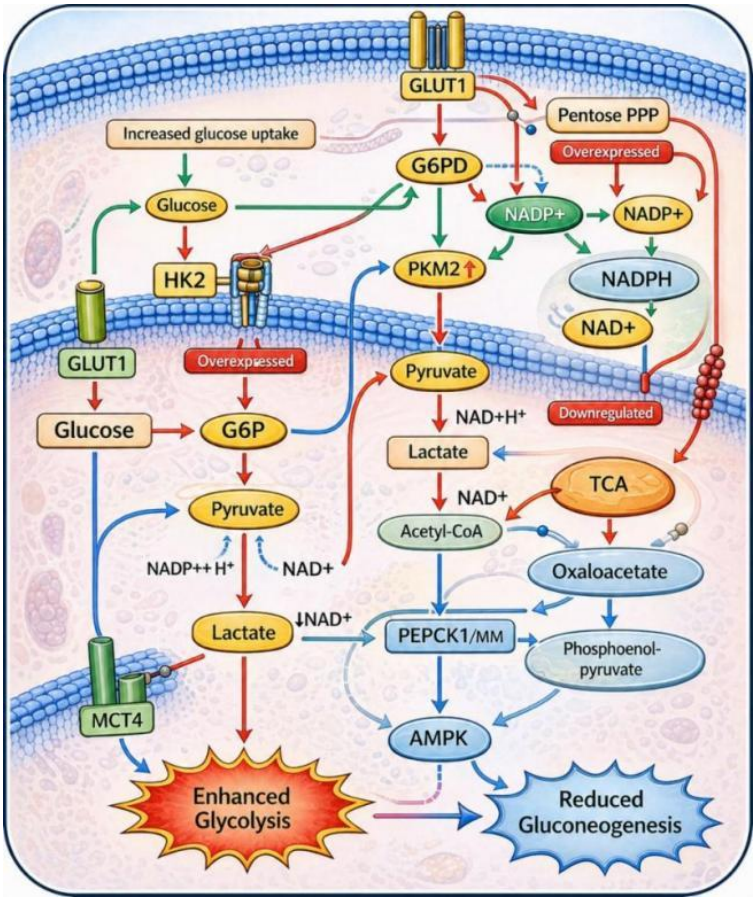

Figure 4. Schematic representation of metabolic reprogramming in HCC showing GLUT1-mediated glucose uptake, activation of glycolysis and the pentose phosphate pathway, and suppression of gluconeogenesis. (Source: Self-made by Canva)

3.4 Activation of IGF Signaling Pathway

The IGF signaling system is a ligand-receptor-binding protein complex that regulates cellular metabolic activity, cell growth, differentiation, and programmed cell death of most cell types. This system involves 3 ligands, 3 receptors and six receptors of high affinity in the IGF-binding proteins that regulate both the availability and the biological activity of the IGF. IGF-I and insulin-like growth factor II (IGF-II) both mediate the action of growth hormone. Such ligands react with insulin-like growth factor binding proteins (IGFBPs) that control their stability, availability, and binding capacity. Insulin is mainly acting via IRs, meanwhile IGF-I and IGF-II are acting primarily via the IGF-I receptor (IGF-IR). Activation of IGF-IR has been widely reported to promote cell proliferation, survival, and anti-apoptotic signaling, primarily through downstream PI3K/AKT and MAPK pathways. The IGF signaling axis has been found to mediate the development and progression of many forms of cancer by dysregulation. Everybody in this pathway experiences a number of modifications that give them deregulation and mitogenic property [70]. The significant physiological changes that are related to hepatocarcinogenesis are:

3.4.1 Insulin-Like Growth Factor I (IGF-I)

It is the most essential ligands of the IGF signaling system, is mainly produced at the liver and thus becomes significant in cellular growth and metabolism. IGF-I has been identified as a mitogenic factor that plays a role in the pathogenesis of various malignancies. Nevertheless, when applied to HCC, the expression of IGF can demonstrate antitumorigenic effect. Since liver cirrhosis is one of the leading precursors of HCC, decreased hepatic secretion of IGF-I which is usually apparent in cirrhotic states may be one of the contributors towards hepatocarcinogenesis and therefore may be one of the contributors to the progression towards HCC [50,51]. IGF-I level is low in chronic hepatitis and it is related to HCC. Indeed, a drastic reduction in the level of IGF-I and the degree of deterioration of hepatic functions triggers the development of HCC. The low concentration of IGF-I is linked to more tumor invasiveness and lower prognosis [71].

3.4.2 Insulin-Like Growth Factor II (IGF-II)

The decrease in the amount of IGF-I can result in compensatory stimulation of the signaling pathway by other ligands, i.e., insulin or IGF-II. Such ligands are capable of excessive showing the IGF-I receptor (IGF-IR) which is one of the regarded prominent processes in hepatocarcinogenesis. IGF-II overexpression or increased activity has been linked to the promotion of cellular proliferation in liver tumor and also in hepatic neoplastic lesions before cancer. This finding indicates that IGF-II plays an important role in cell multiplication in regenerative hepatic nodules and HCC cells of malignant HCC. In addition, IGF-II is a potent autocrine and paracrine signaling pathway growth factor with the

ability to cause mitosis and promote the increase of HCC cells [28,57].

3.4.3 Insulin-Like Growth Factor Binding Proteins (IGFBPs)

It mediate the biological activity of the IGF ligands by attaching and binding to IGF-I and IGF-II and alter the interaction between them and IGF receptors. In these regulatory processes, IGFBPs mediate a variety of cellular activities such as growth, proliferation, differentiation, and survival through IGF-IR signaling pathway. In some settings, IGFBPs may restrict the bioavailability of IGF ligands, and, as such, may have an inhibitory activity on tumor progression. A number of the IGFBP family have been shown to have antiproliferative effects on various forms of malignancies such as prostate, ovarian, breast, non-small cell lung, bladder cancers, and HCC [72]. IGFBP-3 bears the IGF-dependent antiprolliferative actions that include the suppression of EGR1 transcription as well as the inhibition of the growth factor autocrine and paracrine loops, which include the inhibition of PDGF synthesis. IGFBP-3 is the potent antagonist of IGF signaling pathway that inhibits the IGF-I mediated IGF-IR cascade. This is inhibited by inactivation of downstream signal transducing via protein kinase B (AKT) and extracellular signal-regulated kinase (ERK). IGFBP-3 also inhibits the release of pro-angiogenic and proliferative cytokines including fibroblast growth factor-2 (FGF-2) and platelet-derived growth factor (PDGF) that are secreted by HCC cells and lead to tumor growth. Therefore, IGFBP-3 decreases the supply of these cytokines by blocking their binding to cell-surface receptors, and therefore prevents tumor cell proliferation and growth [73]. IGFBP-1, 3, and 4 are downregulated and this enhances the IGF-mitogenic effect of HCC in humans [69,70]. IGFBP 7 is found to be one of the most under-expressed tumor suppressor genes in HCC. The diminution of IGFBP-7 expression has been linked to lower survival and higher recurrence rates in patients of HCC [58,59]. High concentrations of IGFBP-7 may induce the formation of ROS, DNA damage, and activation of the p38 mitogen-activated protein kinase (MAPK) signaling pathway, which eventually results in the induction of apoptosis. IGFBP-7 works through the inhibition of insulin/IGF and MEK/ERK. Nonetheless, IGFBP-7 has antitumor activity as it suppresses the activity of IGF, and IGFBP-2 and 5, have been associated with IGF stimulation in HCC. In line with this, there has been adoption of prominent levels IGFBP-2 in HCC [64].

3.4.4 Extracellular Proteases and IGFBPs

The extracellular matrix (ECM) proteins are used to delimit and strengthen hepatocytes: integrins, tenascin, and collagen type I, III and IV. Some of the cellular processes that are regulated by ECM proteins are, proliferation, migration, survival, adhesion, differentiation, and apoptosis. through extracellular compartment to nucleus signal transmission [74]. The possibility of the ECM to experience structural alterations via accumulation of collagen type I, IV and laminin may induce neoplastic progression, which results in survival and invasive behavior of tumor cells [75]. The increase in the number of laminin receptors and isoforms might be associated with the occurrence and progression of HCC [76,77]

3.4.5 Insulin-Like Growth Factor I Receptor (IGF-IR)

In hepatocarcinogenesis, abnormal regulation of the IGF signaling pathway, such as changes in IGF-IR and IGF-I and IGF-II ligands, is also critical [78]. IGF-IR is a major regulatory substance in different cellular functions like mitogenesis, apoptosis, proliferation and angiogenesis. Signaling cascades dysregulation, including those associated with phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK) pathways, is involved in the abnormal activities of IGF-IR and the progression of tumors [79].

Normal, fully differentiated hepatocytes express IGF-IR at low or no levels. In HCC, however, excessive pathway use of IGF-IR is caused by elevated levels of receptor expression and higher levels of IGF ligands [80]. IGF-IR signaling may be activated to induce VEGF and angiogenesis, as well as tumor progression. On the other hand, the IGF-IR signaling inhibits VEGF synthesis and angiogenesis [81]. Moreover, IGF-IR stimulation increases insulin receptor substrate-1 (IRS-1), which contributes to hepatocellular injury and may promote the development of HCC. The majority of the hepatocytes have been overactivated with IRS-1 and IRS-2 and natural overactivation of IRS-1 facilitates the cell growth and alteration. The HCC is, however, also of the IRS-2 upregulation in addition to the IRS-1 alone that is characterized in hepatocarcinogenesis [82]. Downstream signaling pathways, including PI3K/AKT and MAPK, are shown in Figure 5.

3.4.6 Insulin-Like Growth Factor II Receptor (IGF-IIR)

The overactivated IGF-IR is counteracted by the excessive IGF-II molecule, which activates IGF-IIR, that binds IGF-II but not IGF-I, thus decreasing the IGF-II concentrations, thus counteracting the IGF-II mitogenic effects [83]. Inhibition of the expression of IGF-IIR can elevate the levels of IGF-II. In this way, the decrease in the level of IGF-IIR results in the elevate in the level of IGF-II and a reduction in the level of TGF-B (growth suppressor), which leads to cell growth [84]. IGF-IIR is a anti-oncogenic protein and its downregulation is also common in various cancers such as HCC. IGF-IIR levels in HCC have been shown to be lower than normal induced by genomic imprinting defects, loss of heterozygosity (LOH), and gene alteration as well as the factors that lead to loss of control of the IGF signaling pathway [85]. Potential therapeutic targets and intervention strategies are summarized in Figure 6.

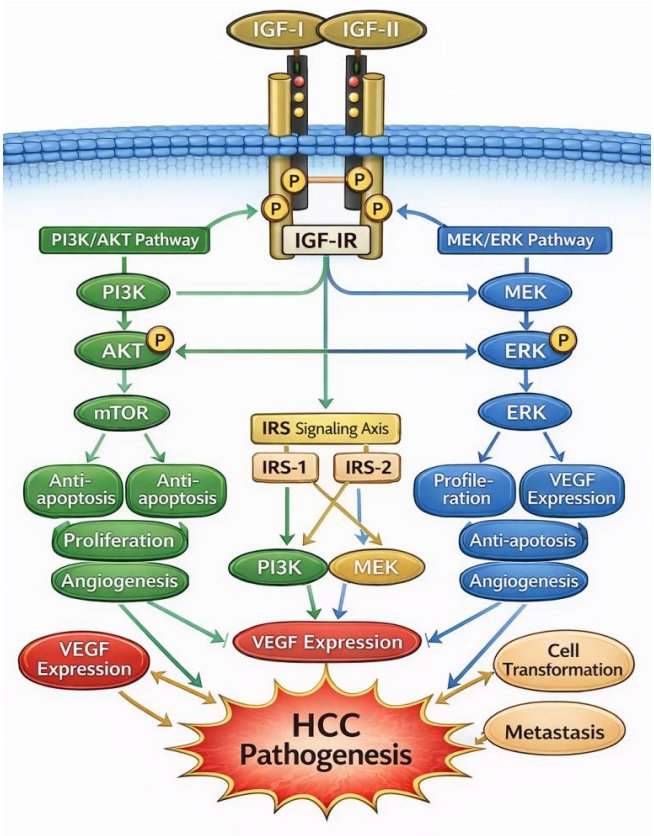

Figure 5. IGF signaling system is an interaction between the ligands, receptors and downstream signaling pathways. IGF-II in combination with IGF-I and insulin interacts with the IGF-I and IGF-II receptors to control metabolic and mitogenic signaling pathways, which are essential in cellular growth, proliferation, and development. (Source: Self-made by BioRender.com)

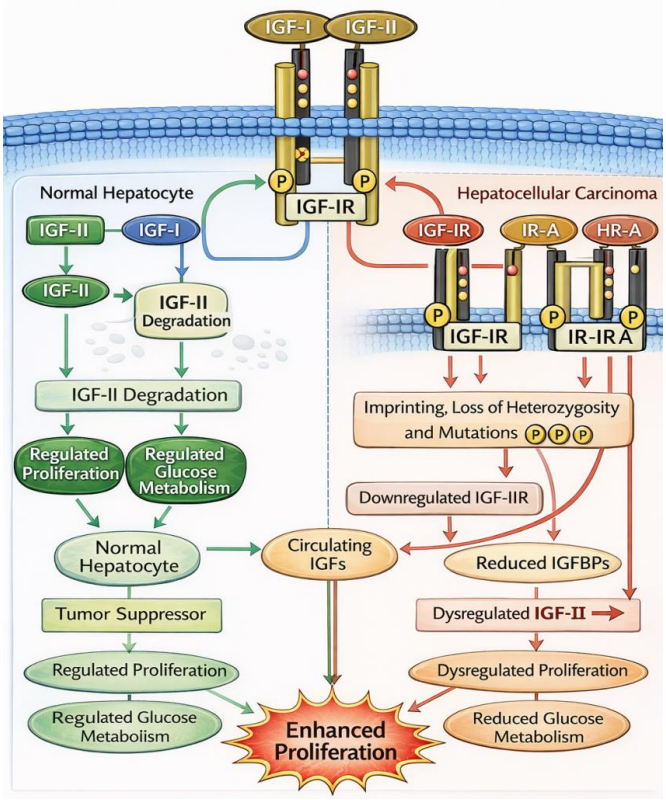

Figure 6. IGF signaling axis in HCC: In healthy hepatocytes, IGF-I reacts preferentially to IGF-IIR and IR-B, and insignificantly to IGF-IR. HCC, on the other hand is marked by augmented IGF signaling that transpires as a result of augmented expressions of receptors and ligands. HCC overexpression of IGF-II can be due to re-expression of the fetal promoter of the IGF-II gene, lowering of circulating levels of IGF-binding proteins (IGFBPs), or lower levels of degradation by IGF-IIR. (Source: Self-made by BioRender.com)

3.4.7 Insulin Receptor

The signal transduction moves through IR and IGF-IR to mediate the insulin/IGFs axis. Moreover, IGF-IR overexpression induce homodimeric IR-A receptors or heterodimeric IR-A and B complexes that result in reduced metabolic signaling and cell growth in HCC [86]. The IR exists in two isoforms, IR-A and IR-B, generated through alternative splicing. IR-A is more frequently associated with mitogenic signaling and has higher affinity for IGF-II, whereas IR-B is predominantly involved in metabolic regulation. Alterations in the IR-A/IR-B ratio have been observed in various cancers, including HCC, and may shift signaling toward proliferative pathways; however, the extent and functional consequences of this shift remain context-dependent. Although multiple molecular pathways have been implicated in the association between DM and liver damage, these mechanisms are highly interconnected rather than independent [87]. Hyperglycemia, insulin resistance, and hyperinsulinemia act as central drivers that converge on key oncogenic signaling pathways, including the IGF, PI3K/AKT, and MAPK cascades [88]. Among these, insulin resistance and compensatory hyperinsulinemia appear to play a more dominant role by simultaneously promoting mitogenic signaling and inhibiting apoptosis. In contrast, oxidative stress and ROS primarily contribute to genomic instability and DNA damage, thereby facilitating tumor initiation rather than progression alone. Similarly, metabolic reprogramming in HCC represents a downstream adaptation that supports rapid tumor growth but is largely driven by upstream metabolic dysregulation [89]. Importantly, the transition from diabetes to cirrhosis and ultimately HCC reflects a progressive, multi-hit process in which chronic inflammation, fibrosis, and metabolic stress act synergistically. Therefore, rather than functioning as isolated factors, these pathways collectively form a dynamic network that drives hepatocarcinogenesis. Understanding this integrated framework is essential for identifying effective therapeutic targets [42,79,90].

4. Pharmacotherapy of HCC in DM

DM is a metabolic disease, one of the prominent manifestations of which is hyperglycemia. It may be through hyperglycemia that mediates or indirectly causes the tumor cell growth. One of the symptoms of metastatic tumors is transient hyperglycemia. The duration of DM in the patient may be crucial information about the patient that would facilitate the management of hepatocarcinoma cell and diabetes. It has also been noted that good management of DM can prevent the risk of developing HCC but there is yet no standardized mode of treatment that can be used to treat HCC and diabetes at the same time [91]. Both conditions have to be treated in conjunction in clinical practice, which makes the process of making therapeutic decisions difficult. Knowledge on the pathophysiology of the related HCC diabetes is still deficient, but the metformin application in reducing the frequency of HCC is an excellent success so far. Research on glucose-lowering drugs that do not relate to metformin on the prognosis of HCC is in insufficient and troublesome to interpret [92,93]. More studies are needed to control diabetes-related HCC. There are various modalities of treatment that are required in the management of HCC, which include curative, liver transplant, radiofrequency ablation, transarterial chemoembolization, radioembolization and systemic pharmacological resection. The number of pharmacological agents used to treat HCC in diabetics are varied and include hypoglycemic agents, antineoplastic agents and many others pharmacological agents including statins and aspirin [94].

5. Therapeutic Perspectives and Clinical Implications in Diabetes-Associated HCC

5.1 Current Systemic Therapies for HCC

The therapeutic landscape of HCC has evolved significantly, with multiple systemic therapies now available for advanced disease. Multikinase inhibitors such as sorafenib and lenvatinib have been widely used as first-line treatments, targeting angiogenesis and tumor proliferation pathways. More recently, immune checkpoint inhibitors, including programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, have demonstrated improved survival outcomes, particularly in combination regimens such as atezolizumab plus bevacizumab. Second-line agents including regorafenib, cabozantinib, and ramucirumab further expand treatment options. However, therapeutic responses remain heterogeneous, highlighting the need for improved patient stratification [95].

5.2 Impact of Diabetes and Metabolic Status on Therapy

DM and associated metabolic dysfunction may influence both the efficacy and safety of HCC therapies. Insulin resistance, chronic inflammation, and altered cytokine profiles can modify tumor biology and the tumor microenvironment, potentially affecting response to targeted therapies and immunotherapy. Additionally, comorbid diabetes may increase the risk of treatment-related adverse effects and complicate clinical management. Therefore, metabolic status should be considered when selecting therapeutic strategies for HCC patients [96].

5.3 Role of Antidiabetic Drugs in HCC

Antidiabetic medications may exert differential effects on hepatocarcinogenesis. Metformin, in particular, has been extensively studied for its potential anticancer properties, primarily through activation of AMPK and inhibition of Mechanistic target of rapamycin (mTOR) signaling, leading to reduced cell proliferation and enhanced apoptosis [49]. In contrast, some insulin secretagogues and exogenous insulin therapies have been associated with increased cancer risk in certain contexts, although findings remain inconsistent. Thiazolidinediones such as pioglitazone have shown potential benefits in improving insulin sensitivity and reducing hepatic steatosis, but their role in HCC

prevention or treatment remains inconclusive. Overall, the impact of glucose-lowering therapies on HCC outcomes requires further investigation in well-designed clinical studies [97].

5.4 Mechanism-Guided Therapeutic Strategies

Advances in understanding the molecular interplay between diabetes, cirrhosis, and HCC provide opportunities for mechanism-based therapeutic strategies. Targeting key pathways such as IGF signaling, PI3K/AKT/mTOR, and metabolic reprogramming may offer novel treatment approaches. For example, inhibition of glycolytic enzymes or modulation of lipid metabolism could selectively impact tumor cells exhibiting metabolic dependencies [78]. Furthermore, biomarkers reflecting insulin resistance, inflammatory status, or metabolic reprogramming may aid in patient stratification and personalized therapy. Integrating metabolic and oncogenic signaling insights into clinical decision-making represents a promising direction for improving outcomes in diabetes-associated HCC. Collectively, these insights highlight the importance of integrating metabolic context into therapeutic decision-making and support the development of personalized treatment strategies for patients with diabetes-associated HCC [98].

6. Conclusion

DM is a condition that correlates with the elevated risk of various cancers, one of them being HCC. The pathophysiological mechanisms of the relationship between DM and HCC are complicated. Hyperglycemia, excess insulin circulation, impaired insulin sensitivity, and dysregulation of the IGF signaling pathway are considered to be among the key contributors to hepatocarcinogenesis. The IGFs and receptors have been observed in most cases to be downregulated and play a role in the evolution and progression of HCC. The HCC regulation in DM is complicated due to the complexity of various signaling pathways in the disease process as a whole, such as the AMPK, PPAR, JNK, PDGF, Ret and c-kit pathways. The therapeutic goal in HCC related to diabetes can hardly be met by working with one agent, which is why combination therapy with multiple molecular pathways is often necessary. Metformin has demonstrated positive results in HCC and diabetic patients because it can decrease the incidence, recurrence and mortality rates in patients associated with hepatocarcinogenesis. Glibenclamide and pioglitazone can be considered a comparatively safe long-term therapy of diabetic patients with fatty liver disease and HCC, with gliclazide being considered a lower risk compared to glimepiride. HMG-CoA reductase inhibitors showed hepatoprotective activity of HCC as well as can be applied in the palliative care. Sorafenib is the sole approved systemic medication against advanced HCC whether a patient has or does not have diabetes at present. Other agents include brivanib, linifanib, everolimus and regorafenib among many other agents had undergone various stages of clinical trials but none of them are of as much safety and effectiveness as sorafenib; therefore, a thorough study is required to discover an appropriate drug candidate and an appropriate combination of the agents in DM presence or absence to treat HCC.

Abbreviations

AGEs: Advanced glycation end products

AIH: Autoimmune hepatitis

AKT: Protein kinase B

AMPK: AMP-activated protein kinase

DM: Diabetes mellitus

FAs: Fatty acids

FBP: Fructose-1,6-bisphosphatase

G6P: Glucose-6-phosphate

G6PD: Glucose-6-phosphate dehydrogenase

GAD65: Glutamic acid decarboxylase 65

GLUT: Glucose transporter

HBV: Hepatitis B virus

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

HD: Hepatogenous diabetes

IGF: Insulin-like growth factor

IGFBPs:Insulin-like growth factor binding proteins

IGF-I: Insulin-like growth factor I

IGF-II: Insulin-like growth factor II

IGF-IR: Insulin-like growth factor I receptor

IGF-IIR: Insulin-like growth factor II receptor

IL-6: Interleukin-6

IR: Insulin receptor

IRS: Insulin receptor substrate

LDH: Lactate dehydrogenase

MAPK: Mitogen-activated protein kinase

MCTs: Monocarboxylate transporters

mTOR: Mechanistic target of rapamycin

NAFLD: Non-alcoholic fatty liver disease

NASH: Non-alcoholic steatohepatitis

PD-1: Programmed cell death protein 1

PD-L1: Programmed death-ligand 1

PI3K: Phosphoinositide 3-kinase

ROS: Reactive oxygen species

T2DM: Type 2 diabetes mellitus

T1DM:Type 1 diabetes mellitus

TNF-α: Tumor necrosis factor-alpha

VEGF: Vascular endothelial growth factor

Autor's Contribution

CA, FZ and SHK designed the project. CA, AB and NHZ contributed to the literature search and drafting of the manuscript. SHK, AB and NHZ assisted in organizing content and editing. CA supervised the work and provided critical revisions.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Data Availability

All data collected for this manuscript are included.

Ethics Statement

N/A

Generative AI Statement

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