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Insulin Resistance, Resistin Hormone and Hepatocellular Carcinoma Interplay: A Review Article

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ABSTRACT

Background: The incidence rate of hepatocellular carcinoma (HCC) has risen in the last ten years, increasing the disease's burden in Egypt. Insulin resistance is a pathophysiological condition characterised by decreased insulin action in peripheral target tissues such as skeletal muscle, liver, and adipose tissue. Insulin resistance is thought to play a key role in the development of fibrosis as well as an increase in the risk of HCC. **Objective:** To assess the possible relation between serum levels of resistin and HCC in patients suffering of liver cirrhosis.

Methods: PubMed, Egyptian Knowledge Bank, Google Scholar, were used to search for information on Hepatocellular carcinoma, Insulin resistance and Resistin. The authors also analysed references from relevant literature, but only the most recent or thorough study from May 2005 to October 2021 was included. Documents in languages other than English were excluded because there were insufficient translation-related sources. Dissertations, oral presentations, unpublished manuscripts, conference abstracts, and other works not related to major scientific research were removed.

Conclusion: In conclusion, serum resistin level may serve as a new diagnostic marker for HCC patients, however, its accuracy in detection of early focal lesions and prognosis of these patients should be assessed in further larger studies.

Keywords: Hepatocellular carcinoma, Insulin resistance, Resistin.

INTRODUCTION

Primary liver cancer accounts for around 7% of all cancer diagnoses globally. It is the fifth most frequent cause of cancer in men and the seventh most frequent in women [(1)]. Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the third highest cause of cancer-related deaths worldwide [(2)].

The prevalence of HCC is increasing globally. Its prevalence gradually rises with age, peaking at approximately age 70. Regional variations in hepatitis virus exposure and other environmental illnesses are reflected in the distribution of HCC [(3)].

HCC development has been linked to several risk factors (Table 1). HCC is mostly brought on by chronic liver disease, alcoholism, chronic viral hepatitis, and liver cirrhosis. Even those with no known risk factors are susceptible to this [(4)]. Obesity and diabetes have been linked to the emergence of HCC and chronic liver disease, respectively [(5)].

Table (1): Etiology and hepatocellular carcinoma risk factors [(4-5)].

Chronic hepatitis B & C infection with/without advanced fibrosis or cirrhosis Alcoholic liver disease Hereditary hemochromatosis Porphyrias Wilson's disease Alpha1-antitrypsin deficiency Autoimmune hepatitis with cirrhosis Fatty liver disease not caused by alcohol - Primary biliary cirrhosis - Non-alcoholic steatohepatitis with cirrhosis	Hereditary tyrosinemia "Type 1" glycogen storage disease "Type 1 & 2" Hereditary ataxia-telangiectasia Hypercitrullinemia Aflatoxin exposure Other carcinogens Thorotrast Polyvinyl choloride - Carbon chloride

Insulin Resistance and Its Relationship with Liver Cirrhosis and Malignancy:

Peripheral tissues such the liver, adipose tissue, and skeletal muscle have decreased insulin activity is a pathological illness known as insulin resistance. The main effects include insulin's diminished capacity to increase peripheral glucose clearance and inhibit hepatic glucose synthesis. As a result of insulin resistance, blood glucose levels are probably going to increase. But since glucose is the primary secretory trigger for insulin, if cell activity is sufficient, bringing blood glucose levels back to normal. The resulting "compensatory hyperinsulinemia" is a distinguishing feature of insulin resistance [(6)].

There are several variables associated with insulin resistance, including ageing, obesity, central body fat distribution, metabolic syndrome, Type 2 diabetes, liver disease, subclinical inflammation, acromegaly, a high-glycemic-index diet, and a high-saturated-fat diet, which is also linked to a increased chance of cancer. The supporting records for this relationship have been carefully examined [(7)].

Chronic hyperinsulinemia may exacerbate cancer in people who already have it since insulin has the potential to induce it by improperly activating several cellular signalling cascades, cell metabolism alteration or direct stimulation of growth factor-dependent cell division [(6)].

By increasing hepatic IGF-I production and reducing the insulin-like growth factor 1 and 2 binding proteins expression, insulin increases IGF-I bioactivity (IGFBP-2). Many of insulin's mitogenic and antiapoptotic effects are thought to be arbitrated through the IGF-I system since elevated circulation levels IGF-I have been linked to an increased risk of developing several malignancies, including breast and prostate

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cancer. It has been demonstrated that insulin directly promotes the growth of tumours [8].

Free fatty acids, TNF-α, plasminogen activator inhibitor-1, leptin, adiponectin, free fatty acids, IL-6, and MCP-1 are just a few of the substances that are overproduced in fatness, the primary factor behind insulin resistance. These substances can promote the growth of cancer and/or malignant transformation. In this situation, oxidative stress and persistent hyperglycemia may increase the risk of cancer [6].

Cryptogenic cirrhosis, which is connected to non-alcoholic fatty liver disease (NAFLD), may have caused HCC in these patients. NAFLD is inclined to insulin resistance (IR), often known as frank diabetes, and visceral obesity [9].

Regardless of diabetes, insulin resistance is crucial for the fibrosis process and increases the risk of HCC [10]. Increased circulating free fatty acid (FFA) uptake, reduced hepatic synthesis of extremely low-density lipoproteins, and improved hepatocyte lipogenesis occur in tandem with increased peripheral lipolysis-derived free fatty acid (FFA) absorption in response to IR. Increased hepatic triglyceride accumulation, macrovesicular steatosis, and various degrees of necroinflammation and fibrosis are all characteristics of the resulting liver phenotype [11].

It has been demonstrated that molecularly, oxidative stress is elevated by fat accumulation inside hepatocytes. By phosphorylating insulin receptor substrates (IRS), fatty acids and reactive oxygen species (ROS) can directly interfere with insulin signalling pathways. This decreases the activation of downstream effector molecules in response to insulin. Hepatocytes' intracellular stress kinases are activated by fatty acids and ROS during this process. One of these, c-Jun N-terminal kinase (JNK), which raises IRS serine phosphorylation and causes insulin resistance, is the most renowned. Second, Kupffer cells, specialised macrophages present in the liver, are stimulated by ROS to produce pro-inflammatory cytokines [12].

The most fully studied of these cytokines, tumour necrosis factor (TNF), is well recognised because of its capacity to boost insulin resistance via activating JNK as well as for encouraging damage to liver cells and apoptosis. Deleting TNF, the TNF receptor, or JNK has been exposed to stop the development of insulin resistance brought on by steatohepatitis or obesity [13].

According to a study, the NS3 and NS5A proteins have a significant role in the development of HCC [14]. By enhancing insulin signal cascades, hyperinsulinemia may play a significant role in the onset or progression of HCC. By doing so, connective tissue growth factor, a fibrogenic growth factor that encourages fibrogenesis, would be produced by hepatic stellate cells [15].

Further, the relationship between insulin resistance and the development of HCC may change as a result of the production of other adipokines, including adiponectin, interleukin-6 (IL-6), and tumour necrosis factor (TNF). Insulin resistance has been associated to pro-inflammatory cytokine concentrations of TNF and IL-6 [16].

Adiponectin's anti-inflammatory and insulin-sensitizing effects have been linked to the development of HCC [17]. Adiponectin levels may increase in cirrhosis and severe fibrosis stages, claims one idea [18]. Adiponectin's significance in chronic hepatitis C is still unknown, and its association with the development of HCC is still up for debate.

The corpus of knowledge regarding the part played by chronic inflammation in the emergence of hepatocarcinogenesis has expanded thanks to research on mice with decreased nuclear factor kappa B (NF-B) activation. The IKK complex regulatory subunit NEMO, which controls NF-B activation and suppresses NF-B transcription, has been specifically deleted from hepatocytes. These rats displayed steatohepatitis, HCC, and enhanced cell death in addition to chronic liver inflammation [19]. These findings support the idea that persistent inflammation encourages the development of insulin resistance, liver damage, and cancer even in the absence of liver cirrhosis. Recent clinical studies that corroborate this idea revealed that patients with liver disease had higher levels of pro-inflammatory cytokines that promote IR and that those with chronic HCV infection have improved liver function, which delays the onset of diabetes [20].

Since they activate signalling pathways that encourage cellular proliferation and survival, insulin and insulin-like growth factor (IGF) are widely disputed for their role in the genesis of cancer [21]. IGF-II receptor deletion, which has been demonstrated to obstruct growth, is usually present in HCC. On the other hand, excessive amounts of IGF-I or II ligands and overexpressed IGF-I receptors promote the growth and proliferation of tumour cells. There are two insulin-induced signalling pathways that support carcinogenesis: the PI3K-Akt route and the Ras-Raf-MEK-Erk pathway [12].

Resistin:

Resistin is a 12.5 kDa adipocyte-specific hormone with a mature amino acid range of 108. It was first identified as a thiazolidinedione-downregulated gene in mouse adipocytes in 2001 due to its ability to withstand insulin action and jeopardise glucose homeostasis. Obesity, insulin resistance, and diabetes might be closely related [22].

In rats, the primary source of resistin is adipocytes. However, in humans, macrophages constitute the main source of expression. Additionally, it is believed that the primary sites for resistin production are intestinal epithelium and visceral adipose tissue. Additionally, considerable levels of resistin were found in the spleen, mononuclear leukocytes, and bone marrow cells [23].

Despite the fact that it was first demonstrated to have an impact on how insulin resistance and diabetes mellitus (DM) develop in humans. Its precise contribution to the emergence of type 2 DM, insulin sensitivity, and obesity are still being debated [(24)].

Inflammatory bowel illness, non-alcoholic fatty liver disease, rheumatoid arthritis, cancer, and chronic kidney disease have all been linked to resistin [(25)].

Role of Resistin in Cancer:

Pre-clinical and clinical investigations have shown that people with different malignancies have higher blood levels of resistin. It's noteworthy to note that higher resistin levels have also been found in cancers unrelated to obesity, such as lung, renal, and others, in addition to malignancies affected by fat, such as breast, colon, and others. In several cancer model studies, resistin has been connected to an augmented risk of metastasis, angiogenesis, and progression. Its role has also been linked to the development of cancer stemness and chemo-resistance, although important molecular characteristics still require more research[(26)].

The connection between resistin and cancer is made through the TLR4, PI-3K, and NF signalling pathways. In a variety of cancers, proliferation has been connected to the activation of several signalling pathways. While PI-3 K, NF, EGFR, and TLR4 receptors are mostly engaged in the growth of lung cancer, AKT plays a part in the advancement of prostate cancer [(27)]. Few studies have shown that pAKT and Cav-1 regulate resistin-induced proliferation in melanoma, whereas breast cancer incidence has been associated with IL-6- reliant on STAT 3 activation [(28)]. MiR let-7a, miR-200c, and miR-186 have been identified as the three major routes for progression brought on by resistin in ovarian cancer. Resistin and visfatin, on the other hand, encourage cell proliferation in stomach cancer cells by boosting the manufacture of the telomerase gene [(29)].

Resistin promotes angiogenesis by controlling a number of processes. Evidence suggests that it lowers miR-16-5p expression while increasing VEGFA expression in chondrosarcoma cells (through the PI3K and Akt signalling pathway). However, the PI3K/Akt-Sp1 path arbitrates the resistance-induced synthesis of VEGF in ovarian cancer cells (HO-8910). Resistin enhances angiogenesis and SDF-1 expression in human gastric cancer cells, according to the currently known studies. However, the VEGF-mediated angiogenesis in osteocarcinoma cells is primarily induced through the ERK, JNK, and p38 pathways. These signalling molecules limit the endothelial cell migration and tube creation progenitor cells by inhibiting VEGF-A [(26)].

Numerous studies have shown that greater serum resistin levels are related to liver cirrhosis. Serum resistin levels steadily increase as liver function decreases according to Child-Pugh class [(22-26)].

HCC patients exhibited considerably higher resistin mean values than cirrhotic patients and control participants, according to **Elsayed *et al.*** [(30)] research (p 0.01). Furthermore, **Mohamed *et al.*** [(31)] found that cirrhotic HCC patients had serum resistin levels mean values that were 17.6 and 9.8 ng/ml, respectively, higher than cirrhotic patients without HCC (p-value: 0.001). **Elbedewy *et al.*** [(32)] made similar discoveries about serum resistin in HCC patients as opposed to those without. Resistance to inflammation and hepatic fibrosis are positively correlated, demonstrating the role of resistin in the aetiology of liver fibrosis. In a number of liver diseases, human resistin expression is increased [(33)].

Resistin is said to increase angiogenesis by regulating a number of pathways. According to evidence, it boosts VEGF-A and miR-16-5p levels in chondrosarcoma cells via the PI3K and Akt signalling pathway, increasing angiogenesis [(34)].

In ovarian cancer cells, the PI3K/Akt-Sp1 pathway stimulates VEGF synthesis (HO-8910). According to recent study [(26)], Resistin increases angiogenesis and SDF-1 expression in human gastric cancer cells. However, in osteocarcinoma cells, VEGF-mediated angiogenesis is largely stimulated via the ERK, JNK, and p38 pathways. These signalling molecules impede EPC migration and tube formation by limiting VEGF-A production [(26)].

According to **Mohamed *et al.*** [(31)]**,** patients with multiple, smaller (below 3 cm), bigger (> 3 cm), and portal vein invasion also had significantly greater serum resistin levels than patients with a single, larger (below 3 cm), and no portal invasion. Despite the fact that there was no statistically significant difference in their child's scores based on whether or not they had abdominal ascites.

In conclusion, serum resistin level may serve as a new diagnostic marker for HCC patients, however, its accuracy in detection of early focal lesions and prognosis of these patients should be assessed in further larger studies.

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