

Potential Effect of DPP-4 Inhibitors Towards Hepatic Diseases and Associated Glucose Intolerance

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Abstract: Dipeptidyl-peptidase-4 (DPP-4) is an enzyme having various properties and physiological roles in lipid accumulation, resistance to anticancer agents, and immune stimulation. DPP-4 includes membrane-bound peptidases and is a kind of enzyme that cleaves alanine or proline-containing peptides such as incretins, chemokines, and appetite-suppressing hormones (neuropeptide) at their N-terminal dipeptides. DPP-4 plays a role in the final breakdown of peptides produced by other endo and exo-peptidases from nutritious proteins and their absorption in these tissues. DPP-4 enzyme activity has different modes of action on glucose metabolism, hunger regulation, gastrointestinal motility, immune system function, inflammation, and pain regulation. According to the literature survey, as DPP-4 levels increase in individuals with liver conditions, up-regulation of hepatic DPP-4 expression is likely to be the cause of glucose intolerance or insulin resistance. This review majorly focuses on the cleavage of alanine or proline-containing peptides such as incretins by the DPP-4 and its resulting conditions like glucose intolerance and cause of DPP-4 level elevation due to some liver conditions. Thus, we have discussed the various effects of DPP-4 on the liver diseases like hepatitis C, non-alcoholic fatty liver, hepatic regeneration and stem cell, hepatocellular carcinoma, and the impact of elevated DPP-4 levels in association with liver diseases as a cause of glucose intolerance and their treatment drug of choices. In addition, the effect of DPP-4 inhibitors on obesity and their negative aspects are also discussed in brief.

Keywords: DPP-4, insulin, incretins, glucose intolerance, liver diseases, sitagliptin, DPP-4 inhibitors

Introduction to DPP-4 Enzyme

In 1966, Hopsu-Havu and Glenner found dipeptidyl peptidase-4 (DPP-4) in rat liver during the processing of the cells and commercially enzymatic preparations as an activity that liberates naphthylamine from Gly-Pro-2-naphthylamide, and it was originally called glycylproline naphthylamidase.¹ Meanwhile, the protein characteristics and distribution were intensively investigated, and it was rediscovered numerous times as a binding protein and a cellular marker.² DPP-4 is the enzyme for the immune response which is known as antigen CD26 co-stimulator of T- cell, having a multiuse protein that serves as a binding protein and a ligand for a range of extracellular molecules in addition to its catalytic activity.³ It is a membrane protein that is expressed on cells all over the body, but it is also detached from the membrane and comes into circulation in the plasma as a soluble protein.^{4,5} Lymphocytes, fibroblasts, endothelial cells, and apical portions of acinar and epithelial cells express DPP-4, which is also found in plasma as in soluble circulating form.^{6,7}

All membrane-bound molecules like proline or alanine-specific exopeptidases have been proposed to have a biological function in the degradation of bioactive peptides,⁸ but the DPP-4 role has been explored and reported most. In comparison to other peptidase enzymes, like aminopeptidase and carboxypeptidase, which have a limited distribution, DPP-4 is found in almost all vertebrate tissues, but its activity varies greatly.⁹

The enzyme is found largely in the cortical region and in the brush-border and microvillus portions of the kidney and hepatocytes at the cytoplasmic membrane surrounding bile canaliculi and on epithelial of the bile duct in the liver. It can also be detected on pancreatic duct epithelial cells.¹⁰ DPP-4 is thus present in body compartments/fluids engaged in nutrition and excretion (bile, pancreatic fluid, intestinal lumen, urine). As a result, DPP-4 plays a digestive role in the final breakdown of peptides produced by other endo and exo-peptidases from nutritious proteins and their absorption in these tissues.¹¹ In both rats and humans, DPP-4 is a ubiquitous enzyme, including the exocrine pancreas, biliary tract, spleen, small intestine, and brain.^{12,13} DPP-4 possesses differentially expressed biological functions, as evidenced by its extensive organ distribution. The liver is among the organs with the highest levels of DPP-4 expression.¹⁴ DPP-4 marking is high in hepatic acinar zones 2 and 3, but never in zone 1, in a normal healthy liver.¹⁵ DPP-4 may be implicated in the control of hepatic metabolism, based on the uneven lobular distribution.¹⁶

DPP-4, on the other hand, is in direct touch with hormones flowing in the blood, as it is present on blood vessels' endothelial cells¹⁷ and as a mobile enzyme in plasma. DPP-4 is expressed on excited T-helper lymphocytes¹⁸ as well as fractions of macrophages¹⁹ among immune system cells.²⁰ DPP-4 is highly expressed in the endocrine organs, but occasionally in parenchymal cells, such as thyroid follicular epithelial cells and luteal cells.²¹ DPP-4 is expressed in specialized fibroblasts in a variety of tissues, including the skin, mammary gland, and synovia.²² The concentration and activity of DPP-4 in different organs/tissues/cells are shown in Figure 1.

Molecular Biology of DPP-4

DPP-4 includes membrane-bound peptidases like fibroblast activation protein (FAP)/seprase, resident cytoplasmic enzymes, and nonenzymatic members, which are found in neuronal membranes, as well as prolyl endopeptidase. Despite other major changes in sequence, the position and identity of the residues are crucial for catalytic activity within the C-terminal region of these related enzymes and are highly conserved in prokaryotes and eukaryotes.²³ DPP-4 interacts with other membrane proteins and sends signals across cell membranes. The molecular structure of DPP-4 is shown in Figure 2.

Notably, the majority of the protein is extracellular, including the catalytic domain at the C-terminus, a cysteine-rich region, and a large glycosylated region connected to the transmembrane portion by a flexible stalk. Only six amino acids at the N-terminus are expected to reach into the cytoplasm. DPP-4 can form tetramers between two soluble proteins or

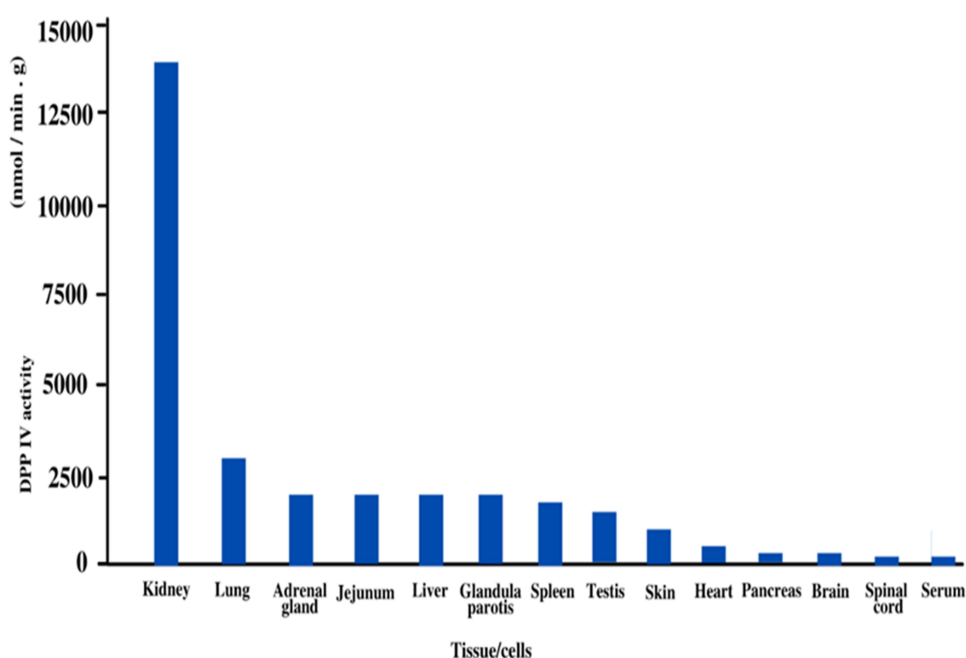


Figure 1 Graphical representation of the concentration and activity of DPP-4 in different organs/tissues/cells.

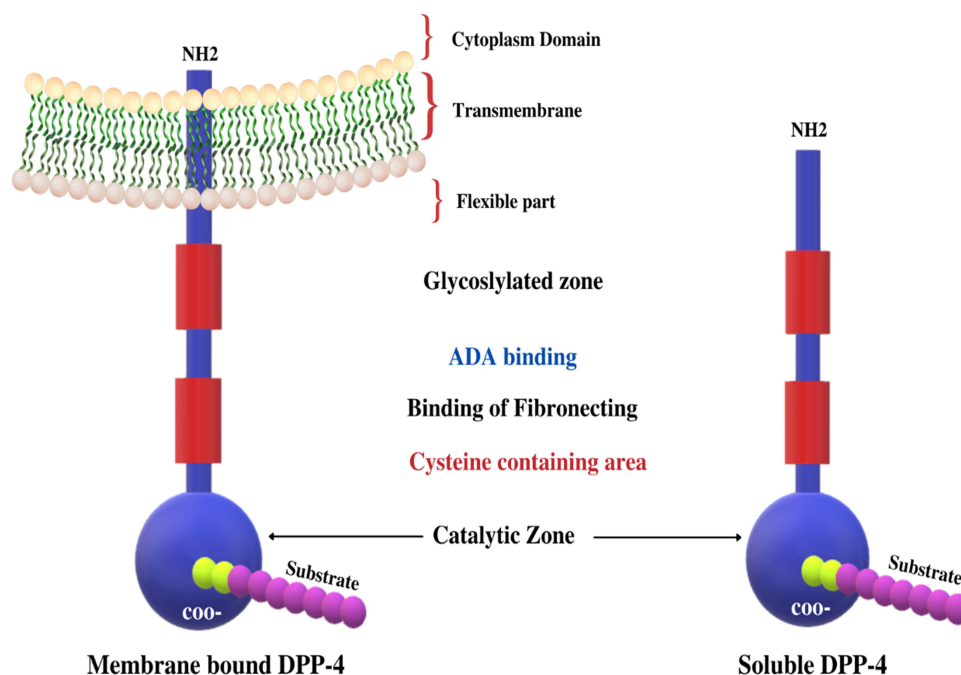


Figure 2 Molecular structure of DPP-4.

two membrane-bound proteins, which could alter the efficiency of substrate entrance and cleavage by the catalytic active site or facilitate cell–cell communication, as reported in a study of the protein crystal structure.²³

The intracellular signalling of membrane-bound DPP-4 is initiated by the interactions with T-cell antigen CD-45, Adenosine deaminase (ADA), caveolin-1, and the caspase recruitment domain-containing protein 11.^{24,25} DPP-4 binds to the extracellular matrix proteins, collagen, and fibronectin, as well as ADA, binding to these proteins and ADA, is mediated by amino acid residues that are not part of the substrate-binding site^{26,27} (Figure 2). DPP-4 which is catalytically active is released from the plasma membrane, resulting in DPP-4 (727 aa), a soluble circulating form that lacks the intracellular tail and transmembrane portions (cytoplasmic domain, flexible stalk)^{28,29} and accounts for a significant amount of DPP-4 activity in human blood.³⁰ Moreover, both membrane-bound and circulating soluble DPP-4 share some domains such as ADA binding domain, glycosylated region, cytosine-rich domain, catalytic domain, fibronectin domain, and the disulfide bonds.²⁵ Here are some examples of target peptides of DPP-4 as shown in Table 1.

DPP-4 Physiological Properties

DPP-4 is a kind of enzyme that cleaves alanine or proline-containing peptides such as incretin, chemokines, and appetite-suppressing hormones (neuropeptide) at their N-terminal dipeptides. GLP-1, peptide YY, GLP-2, chemokine ligand 12/stromal-derived factor-1 (CXCL12/SDF-1), and substance P are examples of potential targets. Consequently, DPP-4 peptidase activity has different modes of action on glucose metabolism, hunger regulation, gastrointestinal motility, immune system function, inflammation, and pain regulation. Figure 3 shows that DPP-4 has different modes of action on chemokine production and metabolism through its peptidase activity. DPP-4 is also implicated in immunological stimulation, anti-cancer drug resistance, and ECM (Extracellular Matrix) binding and breakdown. DPP-4 also has an impact on lipid build-up.

Role of Incretins and DPP-4 in Glucose Regulation

The functions and abundance of DPP-4 in the body have already been discussed in the above section. But the major focus is on the cleavage of alanine or proline-containing peptides such as incretins by the DPP-4 and its resulting consequences.

Table 1 Various Target Peptide of DPP-4

Peptide	Function	Reference
GIP Glucagon PACAP-38 GLP-1	Glucose metabolism	[31–34]
Peptide YY	Appetite regulation	[35]
IGF-1 GHRH GLP-2 VIP NPY GRP	Growth Gut Motility	[36,37] [35,38–40]
CCL11/eotaxin CXCL9/Mlg CCL22/MDC CCL5/RANTES CXCL10/IP10 CXCL12/SDF-1 CXCL11/I-TAC	Chemokine	[41–47]
Prolactin hCG α LH α	Reproduction	[36,37,48]
Enkephalin Endomorphins Substance P	Pain regulation	[49–51]
Thyrotrophin α	Homeostasis	[52]
Vasostatin-I	Endothelial cell growth inhibition	[53]

Incretins are hormones with an important role in the homeostasis of glucose, type 2 diabetes pathophysiology, and other metabolic disorders.⁵⁴ These incretin hormones help in lowering the blood glucose level by stimulating the release of insulin and insulin opens the GLUT4 channel so that glucose can enter the cell and is utilized by the cells for energy production.⁵⁵ There is an interesting fact that oral administration of glucose stimulates more insulin release than the intravenous administration of glucose while the concentration of glucose reaches circulation remains the same.⁵⁶ This situation is known as the incretin effect and it is credited to specialized cells enteroendocrine present in the gut and coupled with glucose absorption. When glucose is administered orally, it reaches the enteroendocrine cells during absorption, and incretin hormones like glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide (GLP-1) are released from enteroendocrine cells, which stimulate pancreatic β -cells to release insulin.⁵⁷ On the other hand, in the intravenous administration of glucose, the enteroendocrine cells are bypassed and thus less availability of incretins leads to less stimulation of pancreatic β -cells as compared to oral administration of glucose at the same concentration.^{56,58} When blood glucose concentrations rise beyond a threshold of roughly 66 mg dL⁻¹, gut hormones including incretins generated in response to dietary absorption of glucose which provides the endocrine signal to the pancreatic β -cells, boosting insulin production and modifying glucagon secretion.⁵⁹ Incretin hormones stimulate insulin secretion physiologically, whereas physiological degrees of hyperglycemia constitute to provide a stimulus accordingly for the release of insulin.^{56,60,61} An “isoglycemic” intravenous glucose administration induces an identical increase in arterial blood glucose level just as an oral glucose load leads to a rise in insulin secretion that is around one-third of the

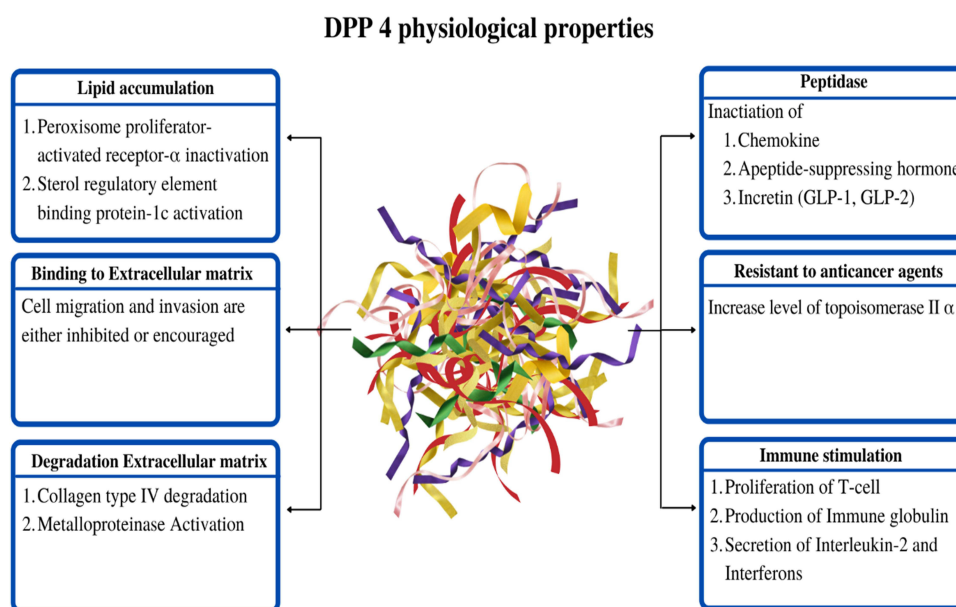


Figure 3 Physiological properties of DPP-4 in various regions.

stimulation responses induced by oral glucose, which is the combined action of hyperglycemia and incretin hormones.⁶² The contribution of incretin hormones in the secretion of insulin responses following oral glucose administration is estimated to be in the range of 25% and 75%, depending on the dosage of glucose used. Undoubtedly, this measurable contribution supports incretin hormones' physiological role in the maintenance of normal glucose homeostasis.⁵⁶ The endocrine pancreas receives three signals from the gut, which is possible due to three substrates viz. incretin hormones, glucose, and neural signals by the autonomic nervous system.^{62,63}

After the utilization of glucose by the cells throughout the body, insulin release is reduced accordingly and extra available incretins are degraded by the enzyme DPP-4 as a part of homeostasis. However, excess availability of enzyme DPP-4 leads to a condition by unnecessarily inhibiting the activity of incretins, which leads to a reduction in the secretion of insulin, and reduced insulin is not able to open the sufficient amount of glucose channels GLUT4 leads to cause glucose intolerance or hyperglycemia. As the intestinal hormone, glucagon-like peptide-1 (GLP-1) was discovered to be a DPP-4 substrate, the relationship between DPP-4 and glucose homeostasis was discovered.^{64,65} GLP-1 role in managing glycemia was discovered in 1986⁶⁶ when this unknown peptide was discovered to have dramatic effects on the endocrine pancreas. Denmark and the United States researchers described potent insulinotropic⁶⁷ and glucagonostatic effects.⁶⁸ Whenever the level of glucose increases then incretins stimulate the release of insulin which lowers the blood glucose, but when the DPP-4 level increases due to any cause, it metabolizes the GLP-1 and reduces the availability of the incretin hormones. The level of glucose continuously increases but incretin hormones are unable to stimulate insulin release which can result in hyperglycemia or glucose intolerance due to the high availability of DPP-4³² (Figure 4). It is observed that the level of DPP-4 is increased in various liver conditions. The pathological role of DPP-4 in liver diseases and associated glucose intolerance with their therapeutic management are discussed below in detail.

DPP-4 in Liver Conditions and the Potential Effect of DPP-4 Inhibitors in Reducing the Risk of Liver Conditions

As per research, as the DPP-4 level increases in individuals with liver conditions^{69–71} and up-regulation of hepatic DPP-4 expression is likely to be the cause of glucose intolerance or insulin resistance.^{72,73} The effects of DPP-4 on each liver disease with pathology are described below.

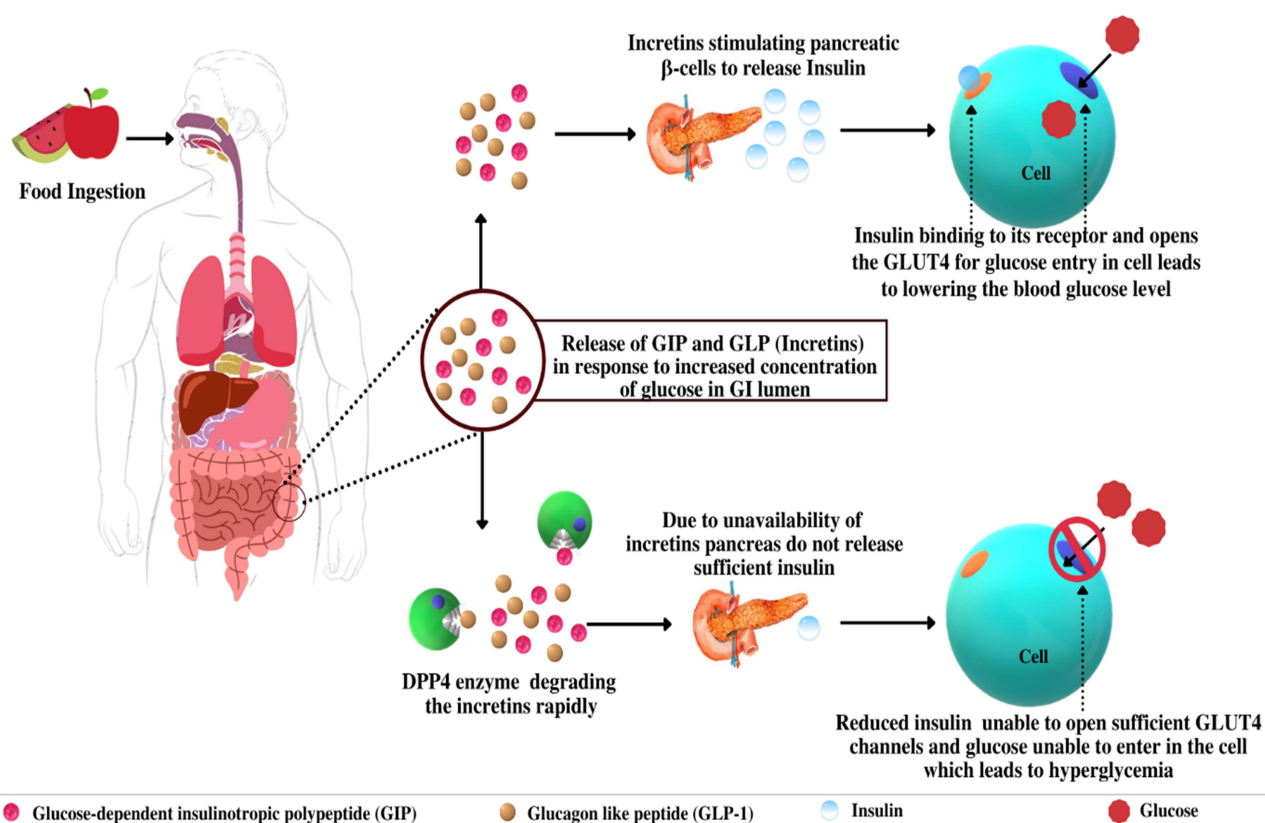


Figure 4 Role of Incretins and DPP-4 in glucose regulation.

DPP-4 Inhibitors in Hepatitis C Virus (HCV)

HCV is a serious public health concern around the world. Consequently, HCV has a high proclivity for causing severe infection, and chronic hepatitis C affects 58 million people worldwide, with about 1.5 million new infections occurring per year as per reports by WHO. This can progress to severe hepatic fibrosis, cirrhosis, and hepatic cancer in the long run. As a result, in developed countries, HCV is a very common reason for liver transplantation.⁷⁴ Interferon has always been the cornerstone of HCV treatment for almost two decades. In 1998, ribavirin was added to the medication, and subsequently, in 2001–2002, the interferon (INF) molecule was linked to polyethylene glycol (PEG) to enhance treatment responses.^{75,76} IP-10 (interferon-inducible protein of 10 kDa), commonly known as chemokine ligand 10 (CXCL10), is a CXC chemokine that binds to chemokine receptor 3 (CXCR3) and plays a vital role in selecting candidates for T lymphocytes and natural killer cells. IP-10 and other chemokines are secreted by hepatocytes infected with the hepatitis C virus to boost the adaptive and innate immune response.²⁰ Surprisingly, elevated blood levels of IP-10, a powerful chemoattractant, have been linked to PEG-IFN and ribavirin therapy failure. IP-10 is usually changed by DPP-4, which produces the antagonist version of IP-10 by cleaving two amino acids from the amino terminal portion of IP-10. Antagonist version of IP-10 has the ability to bind to the IP-10 receptor but does not cause signalling. CD8⁺ T-cells, which express DPP-4, have also been seen in the portal and periportal areas of patients with HCV infection. In hepatocytes, DPP-4 expression is enhanced in patients with HCV infection.^{69,77} In patients with HCV infection, a high baseline blood soluble DPP-4 concentration is linked to poor treatment results. The IP-10 and DPP-4 proteins' expression and binding capabilities are affected by genetic differences in the IP-10 and DPP-4 genes.^{78,79}

According to lymphocyte subset analysis, HCV attacks CD8⁺ T-cells; hence, HCV-infected T-cells could be blamed for the elevated blood DPP-4 activation in HCV patients. DPP-4 alters the immune response by cleaving two amino acids from the amino-terminal portion of IP-10 which suppress the immune responses toward the HCV which may lead to more severe hepatic infection.^{80,81} Furthermore, Hepatitis-C is related to hyperglycemia and insulin sensitivity, which is linked to the progression of the disease and prognosis because of elevation in DPP-4 level.^{82–89} HCV is engaged in the

development of insulin resistance by the disruption of signaling pathway substrate,⁹⁰ in addition to hepatic inflammation and steatosis. Furthermore, Hepatitis-C has been linked to higher DPP-4 expression in the intestinal lumen, hepatic portion, and blood.^{77,91} Transfection of hepatocyte cell lines with cDNA expressing a portion of the Hepatitis viral non-structural genomic region 4B/5A increases DPP-4 expression.⁹² HCV infection may directly upregulate DPP-4 activity, resulting in glucose metabolism impairment.^{16,77} Inhibition of DPP-4 is significant in HCV infection as well as in glucose intolerance as successfully shown in Figure 5.

Hence, interferon therapy for HCV eradication lowers serum DPP-4 levels and helps in treating the HCV,^{90,93–96} and Sitagliptin treatment dramatically improves HCV-related glucose intolerance.^{97,98}

DPP-4 Inhibitors in Non-Alcoholic Fatty Liver Disease (NAFLD)/ Nonalcoholic Steatohepatitis (NASH)

NAFLD is the most prevalent cause of chronic liver disease.^{99–102} It is a hepatic expression of metabolic syndrome. Whereas many factors contribute to the formation of NAFLD, elevated blood glucose has been observed, stimulated by DPP-4 expression in hepatoma cells (HepG2), and the amount of liver DPP-4 mRNA activity in the liver is much higher in NAFLD patients than in healthy subjects.¹⁰³ Cui et al 2016 conducted a randomized controlled trial for NAFLD by DPP-4 inhibitor (sitagliptin) versus placebo. Researchers randomized, double-blind, placebo-controlled clinical study to compare the effectiveness of sitagliptin (100 mg/day orally) versus an identical placebo for 24 weeks to improve hepatic steatosis as measured by MRI-PDFF (Magnetic Resonance Imaging Proton Density Fat Fraction), which is a proven, precise, and quantifiable biomarker for hepatic steatosis. Fifty patients of NAFLD were randomised to receive sitagliptin and placebo from January 2014 to March 2015. The research included 84 patients in total. The primary outcomes of their study towards the liver fat which is measured by MRI-PDFF, when compared to the placebo group, was not substantially lowered in the sitagliptin group. Sitagliptin was not really substantially superior than placebo for lowering liver fat as evaluated by MRI-PDFF in this randomised, double-blind, placebo-controlled clinical study. Sitagliptin did not outperform placebo in terms of improving supplementary targets such as LDL, AST, ALT, and HOMA IR. Sitagliptin did not markedly reduce fibrosis as determined by MRE, despite the fact that participants in the placebo group had more fibrosis. In the conclusion, it is reported that sitagliptin was shown to be safe but ineffective in lowering liver fat in persons with

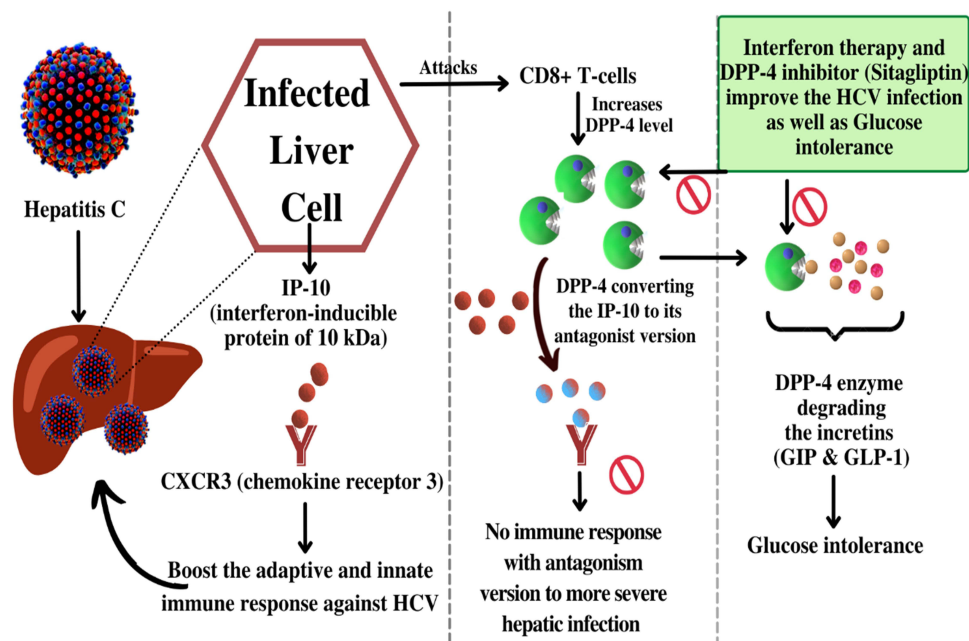


Figure 5 Schematic representation of HCV infected hepatocytes releases IP-10 responsible for an immune response towards HCV infection but DPP-4 level elevated due to CD8+ cells attacked by HCV. Increased DPP-4 converted the IP-10 into an inactive form which suppresses the immune response and on the other hand DPP-4 results in glucose intolerance by degrading incretins. Interferon and DPP-4 inhibitors are found to be significant in both HCV resulting conditions.

NAFLD who were pre-diabetic or diabetic, and this trial was observed for 24 weeks only.¹⁰⁴ On the other hand, Alam et al¹⁰⁵ conducted a randomized controlled trial for the impact of sitagliptin on nonalcoholic steatohepatitis patient's hepatic histological activity and fibrosis which was observed for 12 months in a randomized control study. That randomized controlled research found that using sitagliptin (100 mg daily) for one year, a DPP-4 inhibitor reduces steatosis and swelling in NASH patients. The NAS (score for NASH) in coupled biopsy samples was considerably reduced as a result of these two adjustments. This intervention did not affect fibrosis. The control group's NAS was likewise reduced by steatosis reduction, although hepatocyte ballooning remained the same. The sitagliptin group was shown to have a much larger reduction in steatosis and NAS than the control group. Regardless of diabetes condition, sitagliptin (100 mg once daily) for a year reduces NAS through alleviating steatosis and hepatocyte enlargement. Sitagliptin has a more powerful effect than weight loss. Sitagliptin has identical safety profile to the control. To validate and solidify these findings, future major, double-blind, randomised control clinical studies are recommended. In a study of fructose-fed rats with metabolic syndrome, sitagliptin shown to be reduced liver steatosis, β -cell apoptosis, and insulin sensitivity.¹⁰⁶ Another animal research in Japan found that sitagliptin helps to reduce hepatic steatosis in mice fed a high-fructose diet and prevents the growth of NAFLD by suppressing inflammatory cytokines and the expression levels of genes involved in lipid production in the liver.¹⁰⁷ The study's most important conclusion was that sitagliptin reduced the severity of hepatocyte ballooning hepatic histopathology. Ballooning degradation, which was identified as a characteristic of steatohepatitis, is connected to cytoskeletal damage in NASH and is associated with cell swelling.^{108,109} As a result, it is tempting to say that DPP-4 inhibitors may improve histology activity by lowering steatosis and swelling. Another uncontrolled experimental trial from Turkey found a similar histologically verified advantage.¹¹⁰

Apart from DPP-4 inhibitors, Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a kind of glucose-lowering medication that has been authorized to treat Type 2 diabetes.¹¹¹ Large randomized controlled trials on GLP-1 RAs have also consistently shown that these medicines reduce the risk of adverse cardiovascular events, all-cause morbidity, and nephropathy worsening in T2DM patients^{112,113} GLP-1 RAs reduce body weight and insulin sensitivity while improving glycemic management.¹¹¹ A number of RCTs have recently investigated the putative positive hepatic effects of liraglutide and other long-acting injectable GLP-1 RAs among individuals with NAFLD, regardless of diabetes status. GLP-1 RAs were studied for their effectiveness and safety in treating NAFLD or NASH in people either with or without pre-existing T2DM. Mantovani et al¹¹⁴ compared and conducted the largest and most up-to-date systematic review and meta-analysis of RCTs that used different GLP-1 RAs (including two new long-acting injectable GLP-1 RAs, such as dulaglutide and semaglutide) for the treatment of NAFLD or NASH, regardless of T2DM status. Treatment given with GLP-1RAs was observed to be related to a substantial improvement in the absolute percentage of liver fat content, as measured by magnetic resonance-based methods, as well as blood liver enzymes (particularly serum ALT and GGT levels), as compared to control or standard therapy. The current meta analysis does not include a detailed examination of the hypothesized molecular pathways via which GLP-1 RAs may help people with NAFLD. However, it is plausible to infer that liraglutide's and other GLP-1 RAs' good effects on individual NASH histologic scores are multidimensional and a result of their combined effects on hyperglycemia or insulin resistance, weight loss, and a direct positive impact on the liver (beyond the reduction in body weight and hyperglycemia). In reality, GLP-1 RAs are effective in the treatment of T2DM and can also help people lose weight (on mean 4–5 kg).¹¹⁵ GLP-1 RAs are also able to alleviate hepatic steatosis through lowering de novo lipogenesis, boosting fatty acid oxidation, and improving several aspects of the insulin signaling pathways, according to experimental findings based on both human hepatocytes and animal models.^{116–120} Furthermore, preclinical NASH investigations have revealed that GLP-1 RAs may lower hepatic inflammation via independent pathways, at least in part, of body weight loss.¹²¹ Obesity could be a reason for NAFLD and for that cause GLP-1 RAs could be a choice, as recent clinical studies have been shown to successfully promote weight loss in diabetic individuals. The existing evidence suggests that weight loss caused by GLP-1R agonism in humans is mostly due to reduced food consumption. GLP-1 (glucagon-like peptide-1) is known as an endogenous peptide produced in the gastrointestinal tract by enteroendocrine specifically by L cells. GLP-1RAs can help with glucoregulation by promoting satiety, delaying stomach emptying, and lowering calorie intake. The only GLP-1RA licensed for the treatment of obesity is liraglutide. Semaglutide's first Phase III clinical trial has finished, and the results indicated a considerable weight loss benefit. GLP-1RAs have been shown in clinical studies to be effective and safe, and they are regarded as potential anti-

obesity medications.¹²² On the other side, according to Velija-Asimi et al 2013, it is found that DPP-4 inhibitors in combination with metformin were related to improved glycaemic control and a decrease in body weight in obese adults with type 2 diabetes.¹²³

The increase of intrahepatic triglycerides (TGs) is the major symptom of NAFLD, which affects 75–90% of people with type 2 diabetes.^{124,125} NAFLD can proceed to NASH, which is marked by extensive histologic transformation, such as hepatocellular ballooning, lobular inflammation, fibrosis, and an increased risk of hepatocellular carcinoma. Various pharmacotherapies are being explored since insulin resistance, oxidative stress, lipotoxicity, immunology, mitochondrial damage, the cytokine system, and apoptosis are all implicated in the pathophysiology of NASH. Although no medicine is available for the evidence-based therapy of NASH, antidiabetic therapies may be beneficial in individuals who also have diabetes mellitus. Several investigations have found a relationship between DPP-4 and hepatic insulin sensitivity. Upregulation of DPP-4 in hepatocytes is linked to hepatic insulin resistance and liver steatosis as observed in rats,⁷³ whereas knocking down DPP-4 optimizes insulin sensitivity and lowers lipid buildup in cultured hepatocytes.¹²⁶ DPP-4 has also been linked to the occurrence of insulin sensitivity and glucose intolerance in the liver and adipose tissue, according to other research. Obesity and accompanying visceral adipose tissue inflammation cause insulin sensitivity in mice, a process that appears to be driven by increased hepatic DPP-4 production and release, since abolishing hepatocyte DPP-4 expression reduces inflammation and improves insulin sensitivity. DPP-4 is thought to be a new adipokine that affects insulin sensitivity in both autocrine and paracrine ways. DPP-4 release is closely correlated with adipocyte size, suggesting that adipocytes may be a major source of DPP-4.¹²⁷ The more fat in the liver, the higher the activation of hepatokine DPP-4, which might lead to NAFLD and subsequently, NASH in a paracrine and autocrine manner. Thus, omarigliptin may inhibit the activity of DPP-4, which is abundantly released from the liver in NAFLD/NASH, preventing the stimulation of adipose inflammation and insulin resistance in the liver.¹²⁸ According to Wang et al 2021, study findings show that the major cause of hepatic inflammation like NFκB pathway activation, oxidative stress, and cell apoptosis inhibition reduces hepatic inflammation. In the study, sitagliptin was found to be restricting the DPP-4 activity in hepatocytes reducing NFκB pathway activation and oxidative stress, as well as cell apoptosis, in diabetic conditions, and sitagliptin's ROS cleaning function promotes NFκB pathway deactivation; additionally, sitagliptin can reduce Streptozotocin chronic hepatotoxicity and oxidative stress. Under diabetes circumstances, sitagliptin inhibits DPP4 activity in hepatocytes, resulting in reduced NFκB pathway activation, oxidative stress, and cell death.¹²² The inactivation of the NFκB pathway is promoted by sitagliptin's ROS cleansing action and DPP-4 inhibitors are also known for the reduction in body weight in obese adults with type 2 diabetes.¹²² But there is vildagliptin, which is also a strong and selective DPP-4 inhibitor that is weight neutral in type 2 diabetic patients in several solotherapy and combined studies. Because of its glucose-dependent mode of action, vildagliptin has a reduced risk of hypoglycemia, which eliminates the “defensive eating” that can emerge with insulin injections or independent glucose-insulin secretagogues. More data show that vildagliptin may affect postprandial lipid and lipoprotein metabolism by decreasing the absorption of triglyceride from the gut and boosting sympathetically triggered lipid mobilization and catabolism in the postabsorptive phase. Additional research into these pathways might offer a molecular foundation for understanding the weight-loss benefits of vildagliptin medication.¹²⁹ Vildagliptin is an important DPP-4 inhibitor that may be used for lowering the risk or decreasing hepatic inflammation without body weight reduction.

In reality, hepatic DPP-4 expression and serum DPP-4 activity are linked to hepatic steatosis and fatty liver grading.^{130,131} Furthermore, as compared to wild-type rats, DPP-4 deficient animals have lower levels of liver pro-inflammatory and pro-fibrotic cytokines, as well as less hepatic steatosis. These beneficial alterations in lipid metabolism are not caused by changes in glucose metabolism.¹³² In individuals with NAFLD, DPP-4 activity in serum and liver specimens correlates with indicators of hepatic injury like blood gamma-glutamyl transferase (GGT) and alanine aminotransferase amounts, but not with fasting blood glucose levels or glycosylated hemoglobin (HbA1c) values, similar to the findings in animal studies. As a result, hepatic DPP-4 expression in NAFLD could be linked to hepatic lipogenesis and liver damage.^{133,134} In humans and rodents, a DPP-4 inhibitor has been shown to ameliorate hepatic steatosis.¹³⁵ The activity of DPP-4 inhibitors is successfully shown in Figure 6.

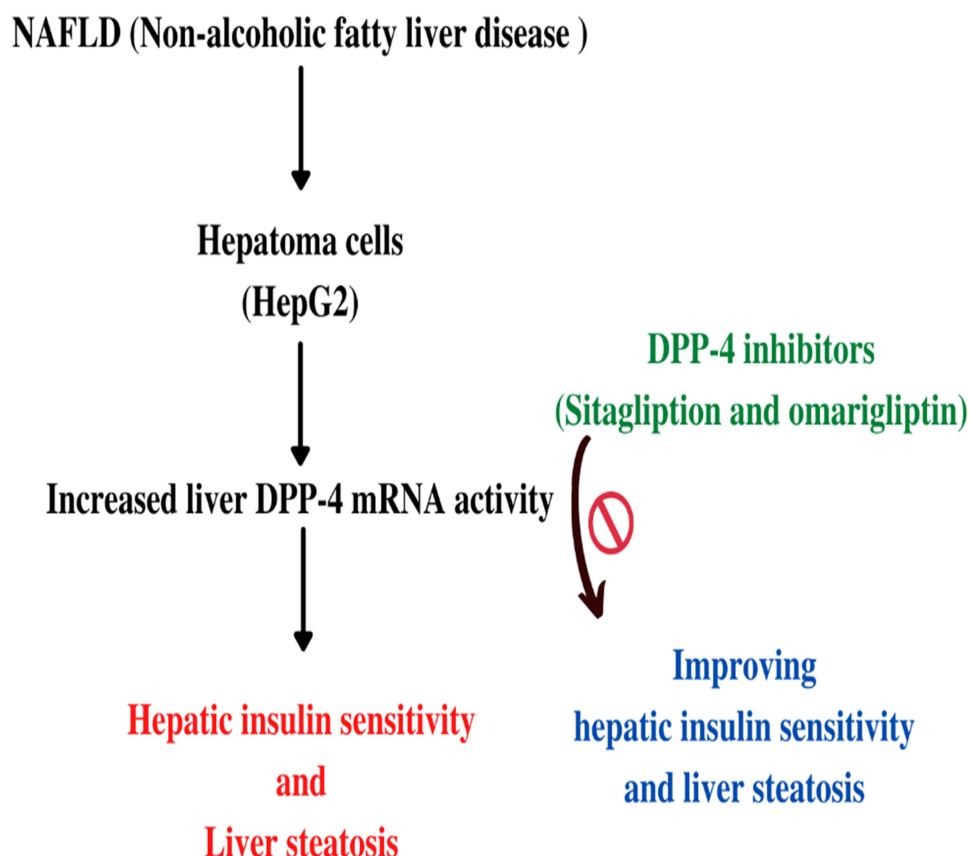


Figure 6 Non-alcoholic fatty liver disease results in an increased level of DPP-4 expression leads to hepatic insulin sensitivity and liver steatosis but sitagliptin and omarigliptin improve the conditions.

A case of refractory fatty liver that was successfully treated with sitagliptin, a DPP-4 inhibitor.¹³⁶ In addition, omarigliptin and sitagliptin have been shown to reduce liver enzymes and hepatocyte ballooning in patients with NASH.^{110,128} These data suggest that DPP-4 inhibitors may help patients with NAFLD with hepatic damage and glucose intolerance.

DPP-4 Inhibitors in Hepatic Regeneration and Stem Cell

The cirrhotic liver has been shown to have increased hepatic DPP-4 expression.^{128,137} Although the consequence of increased DPP-4 expression is unknown, recently showed that human liver stem cells express DPP-4 but not CD34 or CD45, which are markers of hematopoietic stem and endothelial progenitor cells.¹³⁸ If we understand the concept of Cell-released chemokines, cytokines, and other growth-modulating substances that elicit their effects through particular receptor-mediated intracellular signaling modulate hematopoietic progenitor cell (HPC) and hematopoietic stem cell (HSC) functions in a paracrine manner.¹³⁹ Other progenitor and stem cell types are regulated by these proteins, and also impact the more mature cell's function. On HPCs expressing CD26, inhibiting DPP4 enzymatic activity with short peptides such diprotin A (ILE-PRO-ILE) or VAL-PYR improves chemotaxis to the chemokine stromal cell-derived factor-1 (SDF-1/CXCL12)¹⁴⁰ as well as homing and engraftment of HSCs.^{141–143} CXCL12 with a DPP4 truncation lacked chemotactic efficacy but prevented chemotaxis triggered by full-length SDF-1.¹⁴⁰ A pilot clinical trial evaluated the effects of sitagliptin (inhibitor of DPP4 used to treat type 2 diabetes)¹⁴⁴ administration to patients with high-risk hematologic malignancies receiving single-unit cord blood transplants. With the findings that DPP4 has a detrimental effect on CSFs6, which nourish immature cell types in the bone marrow, attempts are being made to change the dosing schedule of sitagliptin to improve the time to engraftment of cord blood.¹⁴⁵ Chemokines are important for degranulation, angiogenesis, and leukocyte trafficking in the immune system,¹⁴⁶ and DPP4 may have

a major impact on the activity of chemokine. DPP4 induces negative feedback by lowering CCL22/MDC activity, similar to its actions on CXCL.^{140,147,148} CCL22 purportedly possesses anti-HIV-1 action and attracts activated lymphocytes, dendritic cells, natural killer cells, and monocytes. In CCR4-transfected cells, DPP4-truncated CCL22 fails to desensitize calcium mobilization by full-length CCL22 or thymus and activation-regulated chemokine.¹⁴⁹ HUT-78 T-cell chemotactic activity is reduced by truncated CCL22, which is 100 times less effective than full-length CCL22. As a result, DPP4's N-terminal truncation of CCL22 has various effects on its multiple immunologic roles. Eosinophils are drawn to allergic inflammation and parasite infections by the CCL11 (eotaxin) and, CC chemokine. When DPP4 truncates it, its chemotactic potency for signaling capability and blood eosinophils through CCR3 are lowered 30-fold.⁴⁴ These examples show the importance of DPP4 in infectious processes and inflammatory, as well as in steady-state hematopoiesis. It has been documented that the DPP4-truncated versions of the chemokines studied (CCL2, CCL3, CXCL8/IL-8, and CXCL9) lost their suppressive effect and blocked myelosuppression in vitro and in vivo when compared to their full-length counterparts. The shortened molecule functions as a dominant-negative or competitive inhibitor form of the full-length molecule in both circumstances. This could lead to feedback regulation of their full-length molecules' actions. It's also possible that DPP4 truncation enhances a molecule's stimulatory or inhibitory activity beyond that of the full-length version.¹⁴⁵ It's critical to double-check protein sequences in databases containing potential DPP4 truncation domains on a regular basis to make sure they have not been altered. TGF-, for example, once had a DPP4 truncation site; however, the sequence has since been changed and no longer possesses a DPP4 site. Finally, biochemical and biological (in vitro and in vivo) studies are needed to confirm whether the putative DPP4 truncation sites are true truncation sites for each protein, especially when different alanine, proline, serine, or other potential DPP4 truncation sites are present at the N-terminus of every molecule. If that is the case, it is crucial to figure out whether the abbreviated form's activity differs from that of its full-length counterpart, and if so, how. Overall understanding of the in vitro and in vivo control of various stem, progenitor, and more mature hematopoietic and other kinds of cells might result from such studies. This data might have therapeutic implications.¹⁴⁵

Through activation of insulin resistance (IR), obesity-related inflammation raises the risk of type 2 diabetes mellitus (T2DM), obstructive sleep apnea syndrome (OSAS), and polycystic ovary syndrome (PCOS).¹⁵⁰ In obesity-related NAFLD, IR is nearly universally found, leading to the development of the metabolic syndrome and hepatocarcinoma.¹⁵¹ Stem cell growth factor-beta (SCGF- β) has been shown to have activity on macrophage/granulocyte progenitor cells.^{152,153} C-reactive protein (CRP) levels were found to be elevated only in one-third of obese patients in the investigation, indicating a link with SCGF. The study characterizes itself by the prediction of homeostatic metabolic assessment (HOMA) values by SCGF levels, possibly mediated by indicators of inflammation, offering some insight on processes inducing/worsening IR in male patients with obesity-related NAFLD. M-CSF, TNF-, IL-12p40, and IL-6, among other pro-inflammatory cytokines, were not linked with HOMA values, with the exception of IL-6, which predicted a reduced chronic inflammation state. The small rise in CRP levels supports this notion. According to the study of Tarantino et al 2020, suggest that barely raised CRP levels might make IL-10 more accessible in an attempt to partially decrease inflammation, the major cause of IR, in line with data that CRP affects the anti-inflammatory or pro-inflammatory balance, exacerbating inflammation. In this regard, we would like to call attention to our results, which include the presence of IR in almost half of the obese individuals, increased levels of IL-10, and IL-12p40's defensive response. SCGF- serum concentrations might also be due to hematopoietic stem or progenitor cells' limited autocrine/paracrine activity. It is thought that by switching M1 to M2, inflammation could be reversed and IR reduced. Even though our median HOMA values overlapped according to gender, individuals with a more prominent HOMA had a greater frequency of moderate-to-severe steatosis than those with a HOMA below the median. The finding that SCGF levels solely predicted the severity of hepatic steatosis in men might indicate that these patients' obesity influences their inflammatory state and/or immune system. As a result, only males' CRP and IL-6 levels predicted SCGF-concentrations. These findings support the observation that SCGF levels solely predict IR, as measured by HOMA, in males. CRP's mediating involvement is conceivable when we consider its functional role in inflammation. In summary, this study is characterized by the estimation of HOMA values by SCGF levels, which is likely mediated by inflammation, providing insights on processes worsening IR in male patients having

obesity-related NAFLD.¹⁵⁴ As a result, DPP-4 is a particular marker of adult hepatic stem and progenitor cells, suggesting that it may play a role in liver regeneration in chronically inflamed patients. CXCL12/SDF-1 is a chemokine that promotes the homing of hematopoietic stem cells (HSCs) and is critical for hepatic regeneration.^{155,156} CXCL12/SDF-1 is a DPP-4 target peptide, and inhibiting cell-surface DPP-4 activity promotes CXCL12/SDF-1 directed chemotaxis, homing, and engraftment in HSC/hematopoietic progenitor cell populations. As a result, inhibiting DPP-4 might be a good way to improve the efficacy and success of HSC/hematopoietic progenitor cell transplantation.¹⁵⁷ DPP-4 suppression also increases the number of progenitor cells, and DPP-4 inhibition can stabilize endogenous CXCL12/SDF-1, which could be a promising technique for increasing the sequestration of regenerative stem cells.¹⁵⁸

DPP-4 Inhibitors in Hepatocellular Carcinoma

Breast cancer,^{159,160} malignant mesothelioma,¹⁶¹ lung cancer,¹⁶² and squamous cell laryngeal carcinoma¹⁶³ are all known to have increased DPP-4 expression. Increased DPP-4 expression is also found in liver tissues and serum from rats¹⁶⁴ and humans with hepatocellular carcinoma (HCC).¹⁶⁵

Higurashi et al (2016) conducted a multicentre double-blind, placebo-controlled, randomized Phase 3 trial for the chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes and it is observed that non-diabetic patients were given a small dose of metformin for a year with no side effects. After polypectomy, a small dose of metformin decreased the prevalence and quantity of metachronous adenomas or polyps. Metformin shows the potential to prevent colorectal cancer through chemoprevention. However, further large-scale, long-term studies are required to draw definitive results.¹⁶⁶

Kawakita et al (2021) observed the potential influence of DPP-4 inhibitors and DPP-4 on cancer with diabetes and states that there is currently no obvious link between DPP-4 inhibitors and cancer incidence or prognosis in diabetic individuals, according to available clinical evidence. However, the safety profile of a DPP-4 inhibitor (which is the same as different anti-diabetic medications) on cancer development or recurrence has yet to be shown. The results suggested for further mechanistic studies into the relationship between DPP-4 inhibitors and cancer biology, particularly in diabetic situations, are an important study subject in both diabetes and oncology.¹⁶⁷ Zhao et al 2017 worked on a meta-analysis of randomized clinical trials on DPP-4 inhibitors and cancer risk in patients with type 2 diabetes and there were 72 studies in all, with 35,768 and 33,319 patients recruited in the DPP-4 inhibitors and comparator medicine trials, respectively. In comparison to the usage of other active medicines or placebo, no significant connections between DPP-4 inhibitor use and cancer development were found. The findings were similar in pre-defined subgroups stratified by DPP-4 inhibitor type, cancer kind, comparative medication, trial duration, or baseline characteristics. The findings of this meta-analysis reveal that people with type 2 diabetes who take DPP-4 inhibitors have no increased risk of cancer than people who take a placebo or other medicines. Wilson et al 2021 provide clear evidence data that the currently authorized medication sitagliptin (DPP-4 inhibitors) can boost antitumor immunity in a syngeneic ovarian cancer mouse model, lowering metastatic burden and lengthening longevity. Our findings suggest a method for improving immune responses in ovarian cancer patients, as well as a justification for using DPP4 inhibitors as a fast translatable 2nd line therapy for this illness.¹⁶⁸

According to Hsu et al 2021, DPP-4 inhibitors can lower the incidence of hepatocellular carcinoma in individuals with chronic hepatitis C infection with type 2 diabetes. In this study, individuals with type 2 diabetes and persistent HCV infection who used DPP-4 inhibitors had a decreased risk of HCC. DPP-4 inhibitors were associated with a greater incidence of HCC-free patients. This suggests that DPP-4 inhibitors may help people with type 2 diabetes and persistent HCV infection avoid developing HCC. DPP-4 inhibitors may be used as a second-line treatment after metformin for individuals with type 2 diabetes with persistent HCV infection.⁶⁹

DPP-4 inhibition suppresses tyrosine kinase in human hepatoma cells, resulting in anti-apoptotic effects.¹⁶⁵ Recently, a case has been discussed in which a patient with HCV-related chronic hepatitis experienced remarkable HCC reduction following four weeks of treatment with a DPP-4 inhibitor (Figure 7). Although it is unclear whether the DPP-4 inhibitor is directly involved in the regression of HCC, a significant invasion of CD8+ T-cells around the HCC tissue was observed, suggesting that the DPP-4 inhibitor may have improved the immune response, which has

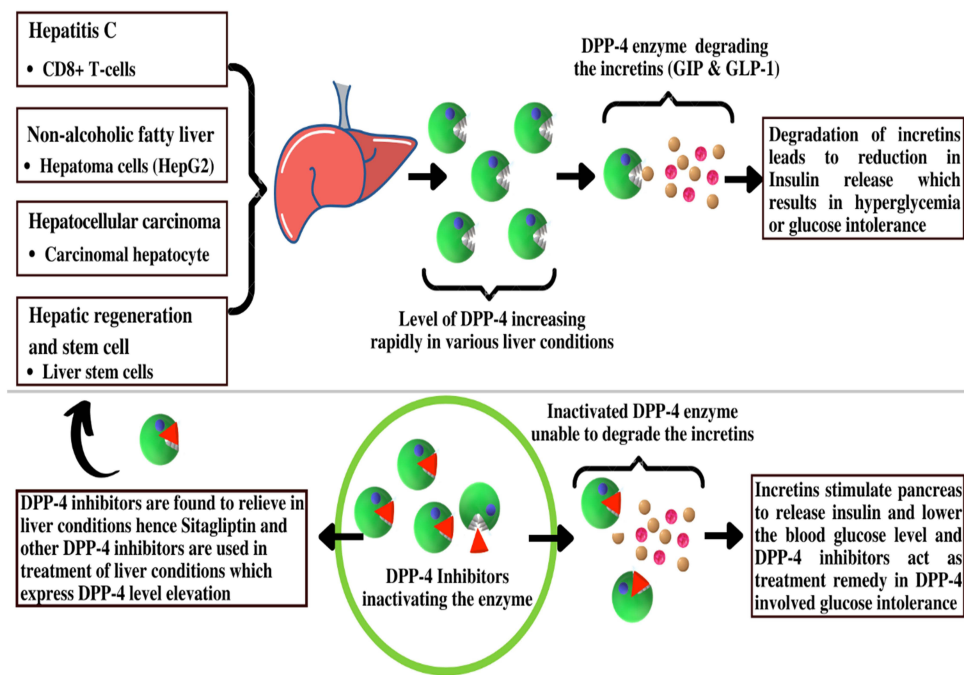


Figure 7 Liver diseases cause an increase in DPP-4, which causes glucose intolerance and DPP-4 inhibitors lead to relief in glucose intolerance as well as in liver conditions.

been compromised by chronic HCV infection.¹⁶⁹ Whereas treatment with exogenous insulin or sulfonylureas raises the risk of HCC,⁸⁵ treatment with a DPP-4 inhibitor had no tumor-promoting effects in mice.¹⁷⁰ As a result, a DPP-4 inhibitor may have a safe effect on HCV-related HCC through modulating immunity.

This review discussed the various liver conditions and glucose intolerance management with DPP-4 inhibitors. The summarizing table with the mechanism of action and treatment of liver conditions associated with DPP-4 is given in Table 2.

DPP-4 elevation could be considered a biomarker for diabetes and is a very interesting molecule in understanding the relationship between diabetes and liver or other organs, and inhibition of DPP-4 could help to reduce the risk of its associated diseases but, on the other hand, DPP-4 inhibitors have some negative aspects. DPP-4 inhibitors have been linked to an increase in gastrointestinal side effects in 24-week research, 1091 T2DM patients were randomly assigned to different combinations of sitagliptin and metformin.¹⁷³ There have been a number of instances of allergic responses occurring spontaneously in people using sitagliptin and angioedema has also been documented with DPP-4 inhibitors, usually commonly within the first three months of therapy, with some responses occurring even before the first dosage.^{174–176} As per the study design of saxagliptin (2.5mg/day v/s 5mg/day v/s 10mg/day) with placebo on metformin for 24 weeks revealed that skin disorders, nasopharyngitis, headache, sinusitis, urinary tract infection, and arthralgia are the adverse effects produced by saxagliptin which are in high proportion than the placebo.¹⁷⁶ Alogliptin versus placebo (Population 5380 and duration is 18 months) study showed the adverse effects of alogliptin at more proportion than placebo such as acute and chronic pancreatitis, angioedema, malignancy, renal dialysis, and hypoglycemia but without a comparison of proportions of alogliptin and placebo showed non-fatal myocardial infarction or non-fatal stroke.¹⁷⁷ Similarly, other DPP-4 inhibitors also showed some side effects such as musculoskeletal disorders, infections (immune-related disorders such as irritable bowel syndrome, arthritis, and multiple sclerosis because of their potential influence on immunological function), nervous system (Headache and dizziness), Fertility (A 39-year-old physician started on sitagliptin, he had issues with spermatogenesis, according to a case study), and Blood effects (increase in white blood cell count).¹⁷⁸

Table 2 Various Mechanisms of Action and Management of Some DPP-4-Associated Liver Diseases

Disease	Area of Concern	Mechanism of Action	Management/Reduce the Risk of Concern Disease	Reference
Hepatitis C	CD8+ T-cells	HCV attacks CD8+ T-cells, hence HCV-infected T-cells could be blamed for the elevated blood DPP-4 activation and DPP-4 inactivate of the incretins which lead to hyperglycemia.	Interferon therapy for HCV and Sitagliptin	[80,81]
Non-alcoholic fatty liver	Hepatoma cells (HepG2)	Elevated blood glucose is stimulated by DPP-4 expression in hepatoma cells (HepG2), and the amount of liver DPP-4 mRNA activity in the livers. Hepatic DPP-4 expression and serum DPP-4 activity are linked to hepatic steatosis and fatty liver grading. DPP-4 amount elevation causes glucose intolerance	Sitagliptin	[103,130]
Hepatocellular carcinoma	Carcinomal hepatocyte	Increased DPP-4 expression is also found in liver tissues and serum from rats and humans with hepatocellular carcinoma (HCC). DPP-4 inhibition suppresses tyrosine kinase in human hepatoma cells, resulting in anti-apoptotic effects. Recently, a patient with HCV-related chronic hepatitis experienced remarkable HCC reduction following four weeks of treatment with a DPP-4 inhibitor.	DPP-4 inhibitors like Sitagliptin, saxagliptin, linagliptin, and alogliptin.	[165,171,172]
Hepatic regeneration and stem cell	Liver stem cells	CXCL12/SDF-1 is a chemokine that promotes the homing of hematopoietic stem cells (HSCs) and is critical for hepatic regeneration. CXCL12/SDF-1 is a DPP-4 target peptide, and inhibiting cell-surface DPP-4 activity promotes CXCL12/SDF-1. As a result, inhibiting DPP-4 might be a good way to improve the efficacy and success of HSC/hematopoietic progenitor cell transplantation. DPP-4 suppression also increases the number of progenitor cells, and DPP-4 inhibition can stabilize endogenous CXCL12/SDF-1 which also helps in the reduction of hyperglycemia.	DPP-4 inhibitors	[155,157]

Conclusion

In glucose regulation, the role of incretins (GIP & GLP-1) is very important. They are released from the GIT lumen in response to the increased level of glucose during absorption and then stimulate pancreatic beta-cells to release insulin which lowers the blood glucose level by enhancing the entry of glucose in the cell through the GLUT4 channel and the cell utilizes the glucose to form energy. But there is an enzyme that inhibits this process by degrading the incretins and creating low availability of incretins which leads to reduced signaling towards pancreatic β -cells to release insulin resulting in an increased level of blood glucose as glucose remains in the blood, unable to enter in the cell through GLUT4. Apart from that, it is commonly observed that in various liver disorders such as hepatitis C, Non-alcoholic fatty liver, hepatocellular carcinoma, hepatic regeneration, and stem cell the serum level of DPP-4 is increased and leads to glucose intolerance. It is observed and reported that DPP-4 inhibitors are commonly used as a reliever in glucose intolerance and diabetes and have potential activities to improve liver conditions also. Hence, DPP-4 inhibitors like Sitagliptin could be a choice of drug in DPP-4-associated glucose intolerance because of various liver conditions and also in the therapy of liver conditions.

Abbreviations

GIP, Glucose-dependent insulintropic peptide; GLP, Glucagon-like peptide; VIP, Vasoactive intestinal peptide; PACAP-38, Pituitary adenylate cyclase-activating polypeptide-38; GRP, Gastrin-releasing peptide; NPY, Neuropeptide Y; RANTES, Regulated upon activation; CCL, Chemokine (C-C motif) ligand; CXCL, Chemokine (C-X-C motif) ligand;

SDF-1, Stromal-derived factor-1; MDC, Macrophage-derived chemokine; MIG, Monokine induced by gamma interferon; IP-10, Protein 10 from interferon (γ)-induced cell line; GHRH, Growth hormone-releasing hormone; I-TAC, Interferon-inducible T-cell α chemoattractant; LH α , Leutinizing hormone α chain; IGF-1, Insulin-like growth factor-1; CGRP, Calcitonin-related peptide; hCG α , Human chorionic gonadotropin α subunit.

Disclosure

The authors declare no conflicts of interest in relation to this work.

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