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Reveiw Article

Glucagon Like Peptide-1: A Novel Therapeutic Strategy in Non-alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a main cause of liver disease and its global prevalence is estimated to be 24%. At present no approved medicines are available for NAFLD treatment. Glucagon-like peptide-1 (GLP-1) is a significant regulator of energy balance and shows potential efficacy in the management of NAFLD. GLP-1 and GLP-1 receptor agonist (GLP-1RAs) are attractive options for the treatment of type 2 diabetes (T2D), since they efficiently reduce weight, HbA1C and blood glucose without having a risk of hypoglycaemia. Because of normalization of insulin resistance (IR), oxidative stress, lipid accumulation, lipotoxicity, and liver cell apoptosis, this incretin hormone is proposed for the management of NAFLD and non-alcoholic steatohepatitis (NASH). Hence, the aim of this review was to discuss the useful effects of GLP-1, GLP-1RAs, and dipeptidyl peptidase-4 (DPP-4) on NAFLD. In this paper we provided a new finding which highlighted the role of GLP-1 and GLP-1RAs in the treatment of NAFLD.

Keywords: Glucagon like peptide-1, Non-alcoholic fatty liver disease, Diabetes mellitus, Dipeptidyl peptidase-4

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is known as a spectrum of clinico-pathological disorders of liver ranging from simple steatosis, to its more severe form, non-alcoholic steatohepatitis (NASH), with inflammation, hepatocyte injury, and often with fibrosis. NAFLD subjects generally are obese or have diabetes and are at an augmented risk of cirrhosis, liver failure, and hepatocellular carcinoma (1). A recent study has shown that the prevalence of NAFLD is about 24% in general population with maximum rates in the Middle East and South America. The prevalence of NAFLD in South America is 31%, in Middle East is 32%, in Asia is 27%, in the United States is 24%, and in Europe is 23% (2). In this respect, future experiments need to further attend this disorder and find potential treatment approaches and increase patient outcomes.

Abnormal glucose levels and insulin resistance (IR) have been documented as the main participating agents in NAFLD development, even in the subjects who are not overweight, hyperlipidemic or diabetic, and are the components recognized to rise risk of development of fatty liver disease (3). Type 2 diabetes (T2D) elevates the risk of developing NASH, liver fibrosis and cirrhosis (4). It has been reported that more than 70% of obese people and particularly the individuals with diabetes have NAFLD and as many as 50% of them may have NASH (5). Prevalence of NASH is also accompanied with cardiovascular disease (CVD) development (1,5).

Pathological Mechanisms of NAFLD and Progression to NASH

NAFLD is potentially related with metabolic syndrome, obesity, T2D, and CVD (5). However, the pathological mechanisms of NAFLD remain mainly unknown yet, but various metabolic changes like abnormal lipid metabolism, IR, increase of free radicals and inflammatory factors, and necro-apoptosis participate in NAFLD development. In the recent decade, "multi-hit" model has been defined as a main mechanism in the initiation and progression of NAFLD. In first hit, dysfunction of lipid metabolism can lead to IR and change signalling pathways, thus making the hepatocytes vulnerable to the subsequent multiple hits. In the "second hit", oxidation of mitochondrial fatty acids (FAs) and increase of reactive oxygen species (ROS), adipocytokines, pro-fibrogenic and pro-inflammatory markers are recognized as the possible causal factors involved in apoptosis and necrosis of hepatocytes.

In fact, "multiple hit" model revealed several insults which acted together to induce NAFLD, and offered an additional precise description of NAFLD pathogenesis (Figure 1) (6).

Treatment or Prevention of NAFLD

There is no well-known medicine for the treatment or prevention of NAFLD. For obese subjects, lifestyle changes (i.e., weight loss, regular physical activity, and dietary changes) and pharmaceutical therapies are commonly suggested as a first-line, but these interventions are difficult to be achieved or continued in clinical practice (3). On the other hand, pharmaceutical therapies such as insulin sensitizers, renin–angiotensin system blockers, lipid reducing drugs, vitamin E and natural antioxidants, have been used in clinical trials (7). For instance, herbal medicine and natural products can prevent or manage NAFLD or liver injury by various mechanisms, such as reducing liver lipid accumulation via reducing sterol regulatory element-binding protein 1c (SREBP-1c) expression, elevating β-fatty acid (FA) oxidation by increasing peroxisome proliferator activated receptor α (PPARα) expression, reducing IR, alleviating oxidative stress through increased antioxidant enzymes activity and suppressing inflammatory factors (8-15). Although natural products or various vitamins and some chemical drugs are used in liver damage, recent therapies for NAFLD show few positive outcomes and some adverse effects. Hence, an effective and novel medicine is needed.

Glucagon-Like Peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone, secreted after eating by enteroendocrine L-cells that affect food ingestion and increase glucose-induced insulin secretion from β-cells. This incretin is also synthesized and produced by nucleus tractus solitarius (NTS) of brainstem, and acts as a neuropeptide. NTS-synthesized GLP-1 have long projections to thalamus, cortical brain areas and hypothalamus (16). GLP-1 receptors (GLP-1R) are present broadly in the brain regions including the brainstem nucleus, hippocampus, cortex, thalamus, and hypothalamus. GLP-1 and other GLP-1 agonists can cross the blood brain barrier (BBB). Since GLP-1 and GLP-1R are present in both peripheral tissues and central nervous system (CNS), the influence of this incretin on energy balance is mediated by both peripheral nervous system (PNS) and CNS (17).

GLP-1 and Gut-Brain Axis

Generally, the brain receives information from peripheral organs via 2 different ways including neural and humoral pathways (16). The humoral signalling includes the BBB and the circumventricular system that has a leaky BBB. It has been documented that GLP-1 crosses the BBB and enters the brain (18). Nevertheless, endogenous gut-derived GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4). Hence, it is proposed that GLP-1 derived from the gut affects the brain chiefly by neural signalling, that includes the vagal afferent fibers at the hepatic portal area or intestine. Vagal afferents also directly sense the hormones like peptide YY3-36, leptin, nesfatin-1 and holecystokinin oxytocin, which manage metabolism and feeding. These hormones control feeding behaviour. It has been established that intraperitoneal injection of GLP-1RAs significantly inhibits food intake (18).

Physiological Importance of Endogenous GLP-1

Huge number of evidence shows potential therapeutic effects of GLP-1 in the body. It has been well-known that GLP-1 or its agonists stimulate insulin secretion, reduce IR, and improve insulin signalling in various tissues. It also decreases gastric emptying and appetite, thereby controlling food intake. Furthermore, this incretin reduces pancreas β-cell apoptosis and glucolipotoxicity,

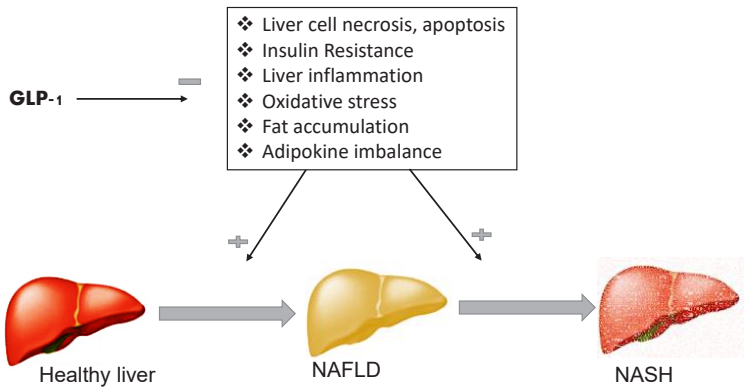

Figure 1. The Multiple-hit Mechanism of Non-alcoholic Fatty Liver Disease (NAFLD) (adapted from Buzzetti et al) (6).

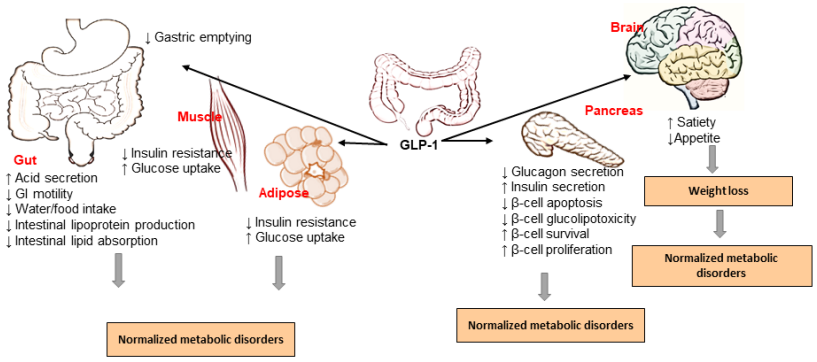

Figure 2. Metabolic Properties of Glucagon-Like Peptide-1 (GLP-1) (adapted from Kim and Schuppan) (19).

elevates pancreas β-cell proliferations, supress glucagon secretion, augments glucose uptake and metabolism in muscle, reduces liver gluconeogenesis, improves liver steatosis, and inhibits liver inflammation and free radical production. Other useful properties of GLP-1 are depicted in Figure 2.

GLP-1 Receptor Agonist and DPP-4 Inhibitors

A novel class of antidiabetic drugs that normalizes IR and hyperglycemia without unwanted side effects is GLP-1 receptor agonist (GLP-1RAs) or dipeptidyl peptidase-4 (DPP-4), an enzyme that quickly degrades GLP-1. Because of quick degradation by DPP-4 in the blood circulation, this incretin has a very short half-life (about 2 minutes). To overcome this problem, GLP-1RAs have presented resistance to DPP-4 (e.g., liraglutide and exendin-4), or DPP-4 inhibitors (e.g., linagliptin, alogliptin, sitagliptin, vildagliptin and saxagliptin) have been prescribed for human subjects and animal models (20).

Role of Glucagon-like Peptide-1 in the Treatment of NAFLD

GLP-1 secretes from intestine in response to food intake and motivates glucose-dependent insulin secretion, suppresses postprandial glucagon secretion, inhibits gastric emptying, increases survival of β-cell, and reduces its apoptosis (20).

Recent findings from animal and human studies support the beneficial effects of GLP-1RAs and DPP-4 inhibitors in the management of hyperglycemia and IR (21). Normalizing IR has been documented to associate with a decrease in total body fat, particularly in visceral adiposity, which in turn is involved in delivery of FAs to the hepatocyte (22). Subsequently, any intervention that causes the improvement of insulin sensitivity can help hepatic steatosis decline and consequently NASH development (3).

Recently, GLP-1RAs and DPP-4 inhibitors have represented a novel beneficial influence on NAFLD. Nevertheless, the mechanisms of these agents in the management of NAFLD have not been clarified exactly yet (23). Recent experiments have provided evidence that GLP-1RAs and DPP-4 inhibitors reverse NAFLD by an incretin effect and normalize inflammation and lipid metabolism in the hepatocytes (1,20,23,24).

Previous experiments established the presence of GLP-1R in human (24) and animal hepatocytes (25). The role of GLP-1 in the treatment of NAFLD is inadequately studied (24). A previous report showed the useful effects of GLP-1RAs and DPP-4 inhibitors on liver steatosis, NASH and liver fibrosis (1,20,23,24, 26). In the animal models, treatment with GLP-1RAs such as AC3174, exendin-4, GLP-1(28–36)amide, and liraglutide prevents or reverses hepatic steatosis. Liver biopsy samples from NAFLD subjects showed DPP-4 up-regulation and GLP-1R down-regulation (24). GLP-1 can alleviate NAFLD probably with different mechanisms, including inhibition of lipid accumulation, oxidative stress, increasing insulin sensitivity, weight loss, as well as suppression of liver cell apoptosis and necrosis. Inhibition of oxidative stress in the liver by GLP-1RA has been documented previously (20,23, 26-28). NAFLD and NASH treatment is directed at inflammation, oxidative stress and fibrosis (6). Medicines which reduce inflammation and oxidative stress (e.g., antioxidants) have a potential role in the treatment of liver steatosis (29).

In animal model of NASH, administration of exendin-4 significantly reduced liver inflammation and reduced the macrophages infiltration (30). In this non-obese NASH mice model, exendin-4 suppressed liver inflammation and steatosis by reducing hepatic oxidative stress and free fatty acid influx (23,26,31). Another study reported that GLP-1RAs decrease macrophages influx to the liver and normalize NASH inflammation (28). Previous evidence supports the claim that increasing the inflammatory factors and oxidative stress has a main role in NAFLD development, as the suppression of inflammatory pathways is associated with improved IR and NAFLD(32). GLP-1RAs show anti-inflammatory properties by reducing monocyte chemotactic protein 1 (MCP-1), interleukin 6 (IL-

6), and tumor necrosis factor-α (TNF-α) (33). Chen et al (34) reported that administration of exendin-4 suppressed TNF-α and IL-6 expression in the liver of animal models. This agent also inhibited 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced pro-inflammatory factors expression. Exendin-4 also alters pro-inflammatory cytokines expression trough the c-AMP signalling pathway (27). Treatment of T2D subjects and animal models with GLP-1 significantly reduced IL-6. GLP-1RAs also markedly reduced inflammatory adipokines (27).

Previous studies have shown that exendin-4 improves liver steatosis in animal models by normalizing insulin sensitivity and oxidative stress in the liver (31). Combination therapy of STZ-induced diabetic mice with 30 mg/kg/d omeprazole plus 8 μg/kg/d exendin-4 for 4 weeks, significantly reduced glucose levels compared with alone therapy, which was associated with elevated nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) expression and decreased peroxidation of liver lipid (31).

Treatment with exendin-4 can also normalize liver steatosis by reducing liver lipid accumulation and improving hepatic insulin signalling in human hepatocyte and *ob/ob* mice (4, 35) .T2D patients who received GLP-1RAs showed significant reduction in liver lipid (36). Exendin-4 can reduce apolipoprotein (apo) B, TGs and total cholesterol levels as well as elevating high-density lipoprotein (HDL) cholesterol. GLP-1 can also improve postprandial lipidemia (26). Furthermore, exendin-4 reduced gene expression and participated in VLDL production and lipogenesis in the liver, such as FA synthase and SREBP-1c, and activated PPAR-α (26,27,37), indicating that GLP-1RA alleviates liver lipid accumulation in animal models primarily by decreasing lipogenesis (25). Previous studies also established that GLP-1RA ameliorates hepatic and intestinal VLDL overproduction (38-41).

Accumulation of lipids in the liver has numerous outcomes: mitochondrial dysfunction and elevation of oxidative stress, upregulation of apoptosis and inflammatory factors (i.e., TNF-α and cyclooxygenase-2 (COX2)), stimulation of lipid peroxidation, and CYP 2E1 activation which generates ROS. The net influence, hence, is necroinflammation, apoptosis and fibrosis (29).

Administration of liraglutide to NASH subjects reduced lipotoxicity and significantly decreased circulating free fatty acids (FFAs) in both hyperinsulinaemic and fasting conditions whereas decreasing de-novo liver lipogenesis (42). Augmented liver lipogenesis provides a major source of the FAs that accumulate in the liver of NAFLD subjects(43). Therefore, influences of GLP-1RAs on liver lipid metabolism and de-novo liver lipogenesis are probably involved in the decrease of liver fat content observed in these patients(26). It has been documented that treatment with exenatide (exendin-4) decreased numerous lipogenic genes expression in the liver including tearoyl-CoA desaturase-1 (SCD-1), SREBP1, acetyl-CoA carboxylase (ACC) and Fatty acid synthase (FAS) (44). In animal NASH model, administration of exenatide also normalized expression of FFA oxidation genes such as PPARa, the Particle Physics and Astronomy Research Council (PPARC), protein kinase A (PKA), protein kinase B (PKB) and AMP-activated protein kinase (AMPK), that were reduced in NASH. In addition, liraglutide reduced liver glucose production and fasting hyperglycemia and restored hepatic IR, as already described by exenatide (44). Furthermore, GLP-1RAs can increase insulin sensitivity, improve insulin secretion, and reduce pancreas β-cell apoptosis (27). IR and dysfunction of β-cell have a main role in T2D pathogenesis and stimulate NAFLD by inhibiting the antilipolytic effect of insulin (45). These findings established that GLP-1RAs by normalizing dyslipidemia and IR play a main role in the management of NAFLD. It has been established that treatment of liver steatosis is inexorably correlated with obesity, dyslipidemia, and IR. As mentioned above, GLP-1RAs reduce liver steatosis by improving IR, dyslipidemia and weight loss (29,38).

As mentioned above, GLP-1RA and DPP-IV inhibitors cause significant weight and appetite loss (4). Weight loss can improve liver steatosis, necroinflammatory alterations, and fibrosis. Moreover, gradual weight loss has been documented to normalize IR and increase life quality. Regular exercise, diet and bariatric surgery can improve obesity (29). Previous studies established that bariatric surgery by increasing postprandial GLP-1 secretion leads to T2D remission and weight loss, indicating the role of GLP-1 in weight management (46).

Additional experiments have established GLP-1RAs can restore liver steatosis by increasing autophagy. These agents can also decrease endoplasmic reticulum (ER) stress-related apoptosis in human hepatocytes and animal models (23).

Adverse Effects of GLP-1RAs

Some experiments reported trivial adverse effects following GLP-1RAs use including vomiting, nausea, diarrhoea, abdominal pain, and reduced appetite. Generally, these adverse effects are resolved within a few weeks (35).

Conclusion

NAFLD is the most common form of liver disorder in the world. Currently there are not approved medicines for NAFLD treatment. However, there is increasing evidence

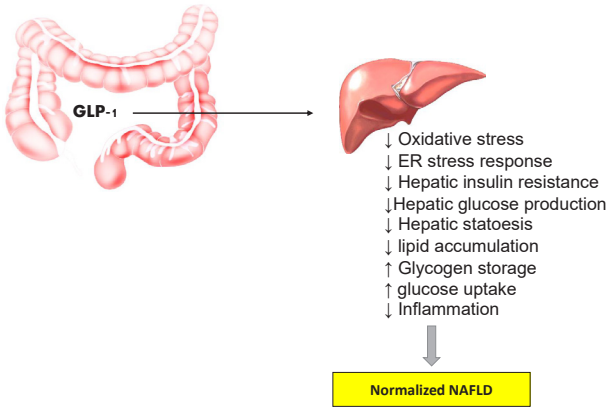

Figure 3. Glucagon-like Peptide-1 (GLP-1) Through Various Pathways Normalize Non-alcoholic Fatty Liver Disease (NAFLD) (adapted from Bernsmeier et al and Wang et al) (24,27).

showing that GLP-1RAs have potential therapeutic effects on NAFLD. GLP-1 and GLP-1R agonists through various pathways including normalization of dyslipidemia, inflammation, oxidative stress, liver apoptosis, hepatic IR and glucose production, and lipid accumulation can affect NAFLD in both animals and human subjects (Figure 3).

Conflict of Interest Disclosures

None.

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