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Recent Perspectives for Combined Status of Type 2 Diabetes Mellitus (T2DM) and Non-Alcoholic Fatty Liver Disease (NAFLD)

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Abstract

The combination of Type 2 Diabetes Mellitus (T2DM) and Non-Alcoholic Fatty Liver Disease (NAFLD) has been a crucial problem. NAFLD means wide from Hepatic Steatosis (HS) to Nonalcoholic Steatohepatitis (NASH). NAFLD may be the predictor of causing Cardiovascular Disease (CVD). A dynamic association is found between NAFLD and Hepatic Insulin Resistance (IR). Treatments for T2DM and NAFLD include Glucagon-Like Peptide 1 Receptor Agonist (GLP-1 RA), Dipeptidyl-Peptidase 4 Inhibitors (DPP-4i) and Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i). An advanced NASH-specific agent is the Farnesoid X Receptor (FXR) agonist Obeticholic Acid (OCA). Further development of research and pharmaceutical industry will be expected.

Keywords: Type 2 diabetes mellitus, Non-alcoholic fatty liver disease, Dipeptidyl-peptidase 4 inhibitors, Agonist obeticholic acid.

Abbreviations: T2DM-Type 2 Diabetes Mellitus, NAFLD-Non-Alcoholic Fatty Liver Disease, NASH-Nonalcoholic Steatohepatitis, GLP-1 RA Glucagon-Like Peptide 1 Receptor Agonist, DPP-4i-Dipeptidyl-Peptidase 4 Inhibitors, SGLT2i-Sodium-Glucose Cotransporter 2 Inhibitors, FXR -Farnesoid X Receptor, OCA-Agonist Obeticholic Acid.

Type 2 diabetes mellitus (T2DM) has become a major health problem worldwide [1]. Furthermore, the increase in obesity has brought a crucial issue of fatty liver or Non-Alcoholic Fatty Liver Disease (NAFLD). NAFLD has been the most common chronic liver disease in the world [2]. In fact, T2DM has high incidence of the complication of NAFLD, and NAFLD increases the risk of type 2 diabetes. Furthermore, T2DM may increase the risk for the progression from fatty liver to Nonalcoholic Steatohepatitis (NASH). NASH may will increase the risk of Liver Cirrhosis (LC) and Hepatocellular Carcinoma (HCC). In recent years, with the development of research, it has been reported that NASH fibrosis has improved [3]. In addition, various agents are used for diabetes may cause liver dysfunction. This article introduces clinical topics about T2DM and liver disease.

The medical word NAFLD is an umbrella term. Then, it means multiple progressive liver disorders, from simple Hepatic Steatosis (HS) to NASH [4]. Approximately 35% of the cases with NASH shows progress to liver fibrosis and possibly to develop to HCC [5]. In European countries, NAFLD has been more prevalent with about 20-30 % of total population and been possibly influencing 45-75% of patients with T2DM [6]. In recent decade, the prevalence of NAFLD has been increasing, which are along with the progressing situation of T2DM and obesity [7]. As a matter of fact, both of T2DM and NAFLD have common risk factors epidemiologically [8]. T2DM has been a major chronic common disease for long, while NAFLD has been relatively rather new. Consequently, various treatments for both diseases will be necessary to evaluate from combined points of view [9].

NAFLD has been recently the most prevalent hepatic disease in the world and the most common etiology of hepatic disease for awaiting liver transplantation in adults of United States [10,11]. The presence of both T2DM and NAFLD will significantly show more incidence for developing NASH and LC, compared with the situation of NAFLD without continuing elevated glucose variability [8]. Some controversies are found that NAFLD may be the predictor of causing Cardiovascular Disease (CVD) with several discussions [12]. It is impressive situation that high mortality of NAFLD would be not from LC or HCC, but from exacerbated risk profiles of CVD associated with comorbidity of T2DM and other CVD risk factors [13]. Consequently, patients with both T2DM and NAFLD may have elevated CVD risk associated with increased mortality rates. As to NAFLD, there are recent advances of diagnosis and treatment of several phase III trials for NASH- specific therapies.

There has been a dynamic association between NAFLD and Hepatic Insulin Resistance (IR). Therefore, several attempts were found administrating ant diabetic agents to treat NAFLD [14]. Systematic review was conducted for glucagon-like peptide 1 receptor agonist (GLP-1 RA), Dipeptidyl-Peptidase 4 inhibitors (DPP-4i), and sodium-glucose cotransporter 2 inhibitors (SGLT2i) to treat T2DM, NAFLD relating with the improvement in Hepatosteatosis (HS) or Steatohepatitis (SH) [14]. These trials may support a future management paradigm for NAFLD in diabetics. However, further consideration will be needed. The relationship between commonly used for diabetes and hepatic function would be described as follows.

Regarding metformin, early studies showed improvement of surrogate outcomes, while no significant was found in the assessment of histological improvement [15]. In retrospective study of 191 cases of T2DM with biopsy-proven NASH and bridging fibrosis, metformin showed lower risk of overall mortality and liver transplant (HR:0.42) and HCC (sHR:0.25), respectively [16]. For current recommendations, pioglitazone or vitamin E are utilized as treatment options with biopsy-proven NASH [15]. However, vitamin E can be recommended for only non-DM cases, and thiazolidinedione's show the risk of congestive heart failure, weight gain, possibly bladder cancer and bone loss [15,17,18]. Among them, pioglitazone is the only diabetic medication in recent guidance from the American Association for the Study of Liver Diseases (AASLD) to treat cases with biopsy-proven NASH with or without T2DM [19].

GLP-1 RAs especially increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and decrease appetite [20]. GLP-1A was investigated for patients with NASH (the LEAN study), which was multicenter, double-blind, randomized, placebo-controlled phase two study [21]. Liraglutide group showed significant effect of NASH resolution compared with control group ($p=0.019$). Furthermore, semaglutide has been investigated in combination with other agents inhibiting hepatic de novo lipogenesis (DNL) and affecting acid-enterohepatic access. GLP-1A has been reported to show the risk of acute pancreatitis, but the conflicting evidence is recently found [22].

SGLT2i inhibits glucose reabsorption in the proximal tubule of the kidney, which brings significant decrease of glucose and calorie. Consequently, SGLT2i shows effective function of weight reduction, improved insulin sensitivity and the reduction in liver fat content [23]. Serum aminotransferases were reduced by the administration of several kinds of SGLT2i agents. There was a recent study for empagliflozin for two groups of patients with T2DM and NAFLD [24]. It is an E-LIFT Trial, which stands for Effect of Empagliflozin on Liver Fat in Patients with Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial. Liver fat was measured by the magnetic resonance imaging proton density fat fraction (MRI-PDFF). In comparison with control group, empagliflozin group showed significantly decreased liver fat by the measurement of MRI-PDFF. The data was from 16.2% to 11.3%, $p<0.0001$ in Empagliflozin group, and 16.4% to 15.5%, not significant, $p= 0.057$. Further studies on RCTs are necessary to determine the efficacy of SGLT2i on liver histology in NASH.

For NASH management in the future, combination therapy would be recommended in patients with coexisting T2DM and NASH. One attracting combined agents in order to improve NASH and to reduce CVD risk may be included as follows: i) low dose pioglitazone and GLP-1A, ii) low dose pioglitazone and SGLT-2i. As regards to such combined therapy, future detail investigations would be needed to explore clinical effect in diabetic medical practice [19].

In pharmaceutical industry worldwide, a new NASH-specific agent has been harnessing attention from federal and private funders. There were many trials on governmental registration. Among them, the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) is an advanced agent [25]. FXR has been a nuclear receptor, which shows high expression in small intestine and liver. They regulate lipid/glucose homeostasis, increase insulin sensitivity, and modify the situation of liver fibrosis.

In summary, recent topics concerning T2DM and NAFLD were described. Effective measures for many patients suffering these will be indispensable, and be expected in the near future.

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