What are the Important Lifestyle Interventions for Preventing the Progression of Impaired Glucose Tolerance (IGT) and Type 2 Diabetes in Non-alcoholic Fatty Liver Disease (NAFLD) Patients?

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With the increase in the rate of obesity, the number of non-alcoholic fatty liver disease (NAFLD) patients is expected to increase in years to come (1-3). Moreover, as a result of the aging population and improvements in the control of other major causes of chronic hepatitis B and hepatitis C, NAFLD has become an important issue of concern for many hepatologists (2). Epidemiological studies have demonstrated that NAFLD patients exhibit insulin resistance and impaired glucose tolerance (IGT) as complications. In particular, approximately 30% of patients with NAFLD have complications of type 2 diabetes mellitus (DM) (2, 4, 5). A large-scale prospective cohort study demonstrated that NAFLD is an independent risk factor for the future development of type 2 DM (6). It has also been demonstrated that the incidence of type 2 DM increases depending on the degree of NAFLD (6). A previous retrospective cohort study indicated that type 2 DM occurs in Japanese patients with NAFLD when the patient exhibits a pre-diabetic state with a mean serum γ-glutamyltransferase (GGT) level of more than 109 IU/L, a mean serum triglyceride (TG) level of more than 150 mg/L and a physical activity level of less than 60 minutes per day (7). Improving the pre-diabetic state and level of physical activity and normalizing the mean GGT and TG levels are important factors for preventing progression to Type 2 DM in NAFLD patients (7).

In this issue of the journal, Ogata et al. reported prognostic factors for regression from IGT to normal glucose regulation (NGR) in Japanese patients with NAFLD (8). A total of 164 patients with IGT and fatty liver confirmed on ultrasonography were selected in the current study. Of the 164 patients, 29 regressed from IGT to NGR. Ogata et al. also evaluated the level of physical activity using the metabolic equivalent of task (MET) expressed by the activity’s typical energy expenditure. A multivariate analysis with a logistic regression demonstrated that regression from IGT to NGR occurred in patients with a young age, fasting plasma glucose level of <100 mg/dL, 2-hour postprandial glucose level of <160 mg/dL, BMI decrease of 1.5± after five years, physical activity of ≥2 MET h/day and the disappearance of fatty liver on ultrasonography. The baseline fasting and 2-hour postprandial glucose levels, a younger age, weight loss and physical activity were extracted as key factors for regression from IGT to NGR.

The current study was a little weak, as it was designed as a retrospective cohort trial, and energy intake was unfortunately not fully investigated. Another limitation of this study is that most of patients were not investigated using histological assessments. Instead, hepatic fibrosis was indirectly evaluated based on the aspartate aminotransferase to platelet ratio index (9). NAFLD includes a wide spectrum of liver diseases, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), which causes cirrhosis and liver failure and sometimes even hepatocellular carcinoma (10-13). Therefore, liver biopsies are recommended as the gold standard method for diagnosing patients with NASH (14). The third limitation is that patients with NAFLD were treated with several types of drugs during the follow-up period. NAFLD patients frequently suffer from hyperlipidemia and/or hypertension (2). Lipid-lowering agents are reported to be safe and efficacious in NAFLD patients (15). Furthermore, several antihypertensive drugs are reported to be effective in NAFLD patients (16, 17). These medications may have influenced the regression from IGT to NGR in NAFLD patients in this study.

The diabetes prevention program research (PPR) group explored the contribution of changes in weight, diet and
physical activity to the risk of developing diabetes among patients treated with intensive lifestyle interventions (ILI), such as healthy eating with exercise (18). Increased physical activity was found to be important for sustaining weight loss, which was the dominant predictor of a reduced incidence of diabetes (18). The diabetes PPR group suggested that lower baseline fasting and 2-hour postprandial glucose levels, a younger age, greater insulin secretion, ILI and weight loss have significant and independent effects on the regression from IGT to NGR (19). The PPR group also indicated that the use of ILI predicts regression to NGR, independent of weight loss.

Although retrospective cohort studies have indicated that weight loss and physical activity are important lifestyle interventions for preventing the progression from NGR to IGT or type 2 DM in NAFLD patients, prospective studies are lacking in Japanese NAFLD patients. Further prospective cohort studies are needed to confirm the factors preventing progression from NGR to IGT in Japanese NAFLD patients.

At present, it is acceptable that the baseline fasting and 2-hour glucose levels and a younger age, weight loss and physical activity are key factors for regression from IGT to NGR. Weight loss and physical activity are important lifestyle interventions for preventing the progression from NGR to IGT or type 2 DM in NAFLD patients.

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**References**