Prognostic Factors for Regression from Impaired Glucose Tolerance to Normal Glucose Regulation in Japanese Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Objective The aim of this retrospective cohort study was to assess the predictive factors for the regression from impaired glucose tolerance (IGT) to normal glucose regulation (NGR) in patients with nonalcoholic fatty liver disease (NAFLD).

Methods A total of 164 NAFLD patients who had IGT in the first 75-g oral glucose tolerance test (OGTT) and underwent a repeated OGTT five years later were enrolled. A multivariate logistic regression analysis was carried out to identify factors predicting the regression from IGT to NGR.

Results Out of the 164 patients, 29 regressed from IGT to NGR within five years after the first OGTT. The multivariate analysis by logistic regression showed that regression from IGT to NGR occurred when the patient was young (risk ratio for ten years: 0.38; 95% confidence interval [CI] 0.20-0.72; p=0.003), had a fasting plasma glucose (FPG) level of <100 mg/dL (risk ratio: 6.53; 95%CI 1.88-21.73; p=0.003), had a 2-hr post-load plasma glucose (PG) level of <160 mg/dL (risk ratio: 4.86; 95%CI 1.08-22.72; p=0.040), a body mass index (BMI) decrease of ≥1.5 (risk ratio: 5.20; 95%CI 1.41-19.24; p=0.014), physical activity of ≥2 Metabolic Equivalent of Task (MET) h/day (risk ratio: 5.57; 95%CI 1.68-18.44; p=0.005), and showed disappearance of the fatty liver by ultrasonography at five years (risk ratio: 9.92; 95%CI 2.87-34.34; p<0.001).

Conclusion Our results suggest that six factors: young age, FPG <100 mg/dL, 2-hr post-load PG of <160 mg/dL, BMI decrease of ≥1.5, physical activity of ≥2 MET h/day, and the disappearance of fatty liver predict the regression from IGT to NGR in NAFLD patients.

Key words: impaired glucose tolerance, regression, nonalcoholic fatty liver disease

from pre-diabetes to normal glucose regulation (NGR) in NAFLD patients. The strengths of the current study are the evaluation of insulin dynamics by repeated oral glucose tolerance test (OGTT) at interval of five years.

Materials and Methods

Patients

A total of 164 patients were selected according to the following inclusion and exclusion criteria. The inclusion criteria were: 1) a 2-hr postload plasma glucose (PG) of 140-199 mg/dL during a 75-g oral glucose tolerance test; 2) repeated OGTT performed at the interval of five years (from four to six years); 3) diagnosed with fatty liver by ultrasonography (17, 18); 4) daily alcohol intake of <20 g/day; 5) Japanese ethnicity; 6) body mass index ≥22 kg/m² at the first OGTT; 7) no underlying autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis and 8) negativity for hepatitis B surface antigen (HBsAg), hepatitis C virus antibodies, antinuclear antibodies, and antimitochondrial antibodies in serum, as determined by radioimmunoassay, enzyme-linked immunosorbent assay or indirect immunofluorescence assay. All participants had impaired glucose tolerance (IGT) at baseline. Subjects were excluded if they met the following criteria: 1) they had fasting plasma glucose (FPG) of ≥126 mg/dL; 2) they had illnesses that could seriously reduce their life expectancy; 3) they had a history of carcinogenesis or 4) they were taking medications that could seriously reduce their life expectancy; 3) they had a history of carcinogenesis or 4) they were taking medications known to alter glucose tolerance or had significant illness.

All of the studies were performed retrospectively by collecting and analyzing data from the patient records. This study was approved by the Institutional Review Board of our hospital.

Medical evaluation

The diagnosis of fatty liver was based on the presence of an ultrasonographic pattern consistent with bright liver (brightness and posterior attenuation) with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma, vessel blurring and narrowing of the lumen of the hepatic veins. US was performed with a high-resolution, real-time scanner (18).

All of the patients were interviewed by physicians or nursing staff members at Toranomon Hospital using a questionnaire that gathered information on their demographic characteristics, medical history and health-related habits, including questions on their smoking history, alcohol intake, and physical activity. The height and weight were recorded at baseline and the body mass index (BMI) was calculated. The hepatic fibrosis was evaluated by the aspartate aminotransferase to platelet ratio index (APRI) (19).

The physical activity other than daily work was evaluated. The patients were asked about the average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging and other miscellaneous exercise. The duration engaged in each activity in min/bout was multiplied by that activity’s typical energy expenditure, expressed as the Metabolic Equivalent of Task (MET) (20, 21). The overall activity was added to yield a MET h score per day.

Calculations of the insulin dynamic

A 75 g OGTT was performed after a 12-h fast. The plasma glucose and insulin levels were analyzed before and after the OGTT performed five years after the first OGTT: a NGR group, patients with a 2-hr post-load plasma glucose of <140 mg/dL; an IGT group, patients with a 2-hr post-load plasma glucose of 140-199 mg/dL and a DM group, patients with a 2-hr post-load plasma glucose of ≥200 mg/dL. The insulinogenic index (IGI) and homeostasis model assessment of insulin resistance (HOMA-IR) were calculated (23, 24).

Clinical and laboratory analysis

The laboratory analysis was performed using standard laboratory methods. The serum biochemical parameters included the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, FPG, insulin and the HbA1c. The serum insulin level was measured by a chemiluminescent enzyme-immunoassay (Fujirebio, Tokyo, Japan) and the HbA1c (%) value was estimated as the National Glycohaemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society) (%) + 0.4% (23).

Statistical analysis

The results are presented as the means ± standard deviation (SD) or as numbers with percentages. The statistical significance of differences in quantitative data was determined using the Mann-Whitney U-test and Kruskal Wallis test. The multivariate analysis was carried out using logistic regression models. The 24 variables were analyzed for potential covariates with the NGR. The Statistical Program for Social Sciences software package (SPSS 11.5 for Windows, SPSS, Chicago, IL) was used to perform the statistical analysis. A p value <0.05 was considered to be statistically significant.

Results

Patient characteristics

Table 1 shows the baseline characteristics of the enrolled
patients at the time of the first OGTT. The patients were divided into three groups based on the pattern of the OGTT at the repeated OGTT performed approximately five years later. Out of the 164 patients, 29 have regressed from IGT to NGR. There were significant differences in several baseline characteristics, such as the age, gender, HOMA-IR, FPG, 2-h PG and HbA1c, among patients divided by the different glucose pattern of the repeated OGTT.

Factors predicting a regression from impaired glucose tolerance to normal glucose regulation

The factors associated with the Regression from IGT to NGR in patients with NAFLD are shown in Table 2. The multivariate logistic regression analysis showed that the regression from IGT to NGR occurred more often when the patient was young (risk ratio by ten years: 0.38; 95% confidence interval [CI] 0.20-0.72; \( p=0.003 \)), had a FPG level of <100 mg/dL (risk ratio: 6.53; 95%CI 1.88-21.73; \( p=0.003 \)), had a 2-hr post-load plasma glucose (PG) level of <160 mg/dL (risk ratio: 4.86; 95%CI 1.08-22.72; \( p=0.040 \)), a BMI decrease of ≥1.5 after five years (risk ratio: 5.20; 95%CI 1.41-19.24; \( p=0.014 \)), physical activity of ≥2 MET h/day (risk ratio: 5.57; 95%CI 1.68-18.44; \( p=0.005 \)) and showed a disappearance of fatty liver by ultrasonography at five years (risk ratio: 9.92; 95%CI 2.87-34.34; \( p<0.001 \)).

Changes in insulin dynamics

Figure shows the changes of the IGI and HOMA-IR at five years. The HOMA-IR in the NGR group significantly decreased during the five-year period. There were no significant changes in the HOMA-IR in the IGT group and DM group. In addition, there were no significant differences in the changes of the IGI in the three groups.

Discussion

The factors predicting the regression from IGT to NGR in NAFLD patients have been described in the present study. The strengths of the current study are the evaluation of the glucose state by repeated OGTT at an interval of five years. The present study showed several findings with regard to the regression from IGT to NGR in NAFLD patients. First,
Table 2. Predictive Factors for Regression from IGT to Normal Glucose Regulation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Cox-regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age (years, per 10)*</td>
<td>0.55(0.37-0.82)</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>0.40(0.18-0.84)</td>
<td>0.017</td>
</tr>
<tr>
<td>BMI (&lt;25≥25) *</td>
<td>0.82(0.46-1.47)</td>
<td>0.495</td>
</tr>
<tr>
<td>FPG (mg/dL, &lt;100≥100)*</td>
<td>5.88(2.32-16.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2hr-PG(mg/dL, &lt;160≥160)*</td>
<td>6.67(2.08-20.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (NGSP%, &gt;6.1≥6.1)*</td>
<td>0.25(0.09-0.65)</td>
<td>0.005</td>
</tr>
<tr>
<td>AST(IU/L, &gt;34≤34) *</td>
<td>0.95(0.29-3.15)</td>
<td>0.930</td>
</tr>
<tr>
<td>ALT(IU/L, &gt;36≤36) *</td>
<td>0.91(0.37-3.98)</td>
<td>0.834</td>
</tr>
<tr>
<td>GGT (IU/L, &gt;109≤109)*</td>
<td>0.68(0.28-1.53)</td>
<td>0.240</td>
</tr>
<tr>
<td>Albumin (g/dL, &lt;3.9≥3.9)*</td>
<td>0.81(0.25-1.34)</td>
<td>0.094</td>
</tr>
<tr>
<td>Triglyceride (mg/dL, &gt;150≤150) *</td>
<td>0.80(0.36-1.78)</td>
<td>0.585</td>
</tr>
<tr>
<td>Cholesterol (mg/dL, &gt;220≤220)*</td>
<td>0.73(0.39-1.67)</td>
<td>0.460</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL, &gt;40≤40)*</td>
<td>0.92(0.39-2.17)</td>
<td>0.844</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL, &gt;140≤140)*</td>
<td>1.41(0.61-3.27)</td>
<td>0.420</td>
</tr>
<tr>
<td>IGI (0.75&lt;0.75)*, §</td>
<td>2.47(1.32-4.62)</td>
<td>0.004</td>
</tr>
<tr>
<td>HOMA-IR(0.25&lt;2.25)*, §</td>
<td>0.53(0.24-1.17)</td>
<td>0.117</td>
</tr>
<tr>
<td>APRI (≥0.38&lt;0.38)*, §</td>
<td>0.61(0.09-2.00)</td>
<td>0.411</td>
</tr>
<tr>
<td>Family history of T2DM (+/-)</td>
<td>0.30 (0.10-0.89)</td>
<td>0.030</td>
</tr>
<tr>
<td>Physical activity (MET h/day, ≥2&lt;2) †</td>
<td>6.48(2.67-15.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Decrease of BMI (≥1.5&lt;1.5) ‡</td>
<td>9.64(4.43-21.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Improvement of AST(IU/L, per one) ‡</td>
<td>1.01(0.96-1.05)</td>
<td>0.842</td>
</tr>
<tr>
<td>Improvement of ALT(IU/L, per one) ‡</td>
<td>1.02(0.99-1.06)</td>
<td>0.206</td>
</tr>
<tr>
<td>Improvement of GGT(IU/L, per one) ‡</td>
<td>1.03(1.01-1.05)</td>
<td>0.011</td>
</tr>
<tr>
<td>Disappearance of Fatty liver(+/-)‡</td>
<td>6.04 (2.53-13.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase, APRI: aspartate aminotransferase to platelet ratio index, AST: aspartate aminotransferase, BMI: Body mass index, CI: confidence interval, FPG: fasting plasma glucose, GGT: gamma-glutamyltransferase, HbA1C: hemoglobin A1C, HOMA-IR: homeostasis model for insulin resistance, HR: hazard ratio, IGI: insulinogenic index, IGT: impaired glucose tolerance, MET: Metabolic Equivalent of Task, NGSP: National Glycohemoglobin Standardization Program; *Evaluation value at the time of the first OGTT †Evaluation value during follow-up, † Evaluation activity of ≥120 minutes per week; ‡, physical activity of <120 minutes per week; §Median is as follows: IGT is 0.75, HOMA-IR is 2.25, APRI is 0.38.

Figure. The changes in the insulinogenic index (A) and homeostasis model for insulin resistance (B) at five years. The statistical significance of differences in quantitative data was determined using the Mann–Whitney U-test Panel.

the disappearance of fatty liver by US is the most effective predictor of the regression from IGT to NGR in NAFLD patients. Although NAFLD patients have a tendency to have insulin resistance and T2DM, their IGT is thought to be reversible. Thus, it is possible that the disappearance of the fatty liver could cause improvement of the IGT. Second, im-
The regression from IGT to NGR in the NAFLD patients. A BMI decrease of ≥1.5 predicts the regression of NGR, while physical activity of ≥2 MET h/day is useful for predicting in the regression of NGR. The 2 MET h/day corresponds to fast walking for 30 minutes. Third, in addition to the disappearance of fatty liver, improvement of the BMI and physical activity of ≥2 MET h/day, three other factors: younger age, a FPG of <100 mg/dL and a 2-hr PG of <160 mg/dL were also factors predicting the regression from IGT to NGR. The younger patients with a FPG of <100 mg/dL, and a 2-hr post-load PG of <160 mg/dL might indicate milder cases of IGT. Our results suggest that mild cases of IGT tend to recover from IGT to NGR. This result is agreement with the report by Hamman et al. (25). Thus, an early diagnosis and treatment for IGT is important for promoting the recovering from IGT to NGR in NAFLD patients.

The prevalence of T2DM is increasing dramatically in newly developed and developing countries, and many Asian nations, including Japan, have been seeing increases in the conditions during the past few decades (26, 27). Approximately 8~10 percent of adults in Japan have T2DM at present. The treatment for T2DM is not usually able to restore normoglycemia. However, our results suggest that NAFLD patients with IGT may be able to return to a normoglycemic state.

The present study was limited by its nature as a retrospective cohort trial. Thus, the energy intake was not fully evaluated. The second limitation was that most of the patients did not undergo a histological or morphological assessment by peritoneoscopy or liver biopsy. The third limitation of the study was that patients were treated with different types of drugs during the follow-up period. Finally, our cohort contained only Japanese subjects only.

In conclusion, our results suggest that six factors of a younger age, FPG of <100 mg/dL, 2-hr post-load PG of <160 mg/dL, BMI decrease of ≥1.5, physical activity of ≥2 MET h/day, and the disappearance of fatty liver predicted the regression from IGT to NGR in the NAFLD patients.

The authors state that they have no Conflict of Interest (COI).

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References


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