The Development of Chronic Kidney Disease in Japanese Patients with Non-alcoholic Fatty Liver Disease

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Abstract

Objective Chronic kidney disease (CKD) is present in patients with nonalcoholic fatty liver disease (NAFLD). The aim of this retrospective study was to assess the cumulative development incidence and predictive factors for new onset of CKD in Japanese patients with NAFLD.

Methods A total of 5,561 NAFLD patients without CKD were enrolled. CKD was defined as either an estimated glomerular filtration rate of <60 mL/min/1.73 m² or dipstick proteinuria (>1). A blood sample and a urine sample were taken for routine analyses during follow-up. The mean observation period was 5.5 years. The primary goal is the new development of CKD. Independent factors associated with new development of CKD were analyzed by using the Kaplan-Meyer method and the Cox proportional hazards model.

Results Of 5,561 NAFLD patients, 263 patients developed CKD. The cumulative development rate of CKD was 3.1% at the 5th year and 12.2% at the 10th year. Multivariate Cox proportional hazards analysis showed that CKD development in patients with NAFLD occurred when patient had low level of GFR of 60-75 mL/min/1.73 m² [hazard ratio:2.75; 95% confidence interval (CI) =1.93-3.94; p<0.001], age of ≥50 years (hazard ratio: 2.67; 95% CI=2.06-3.46; p<0.001), diabetes (hazard ratio: 1.92; 95% CI=1.45-2.54; p<0.001), hypertension (hazard ratio: 1.69; 95% CI=1.25-2.29; p<0.001), and elevated serum gamma-glutamyltransferase of ≥109 IU/L (hazard ratio: 1.35; 95% CI=1.02-1.78; p=0.038).

Conclusion Our retrospective study indicates that the annual incidence of CKD in Japanese patients with NAFLD is about 1.2%. Five factors of low eGFR level, aging, type 2 diabetes, hypertension, and elevated gamma-glutamyltransferase, increases the risk of the development of CKD.

Key words: nonalcoholic fatty liver disease, chronic kidney disease, gamma-glutamyltransferase


Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the more common causes of chronic liver disease in Western world (1-4) and in many Asian nations (5, 6). NAFLD is considered to be the liver component of metabolic syndrome (7-9). It is associated with obesity, dyslipidemia, pituitary dysfunction, hypertension, sleep apnea, and type 2 diabetes mellitus (T2DM) (10-16). Moreover, NAFLD often causes cardiovascular disease and stroke (17, 18). Thus, NAFLD is emerging as a new significant health problem in many countries.

On the other hand, there has been a recent dramatic in-
crease in the prevalence of end-stage renal disease (ESRD) in USA and Asia (19-22). Chronic kidney disease (CKD) often progresses to ESRD with its attendant complications. CKD, a disease entity including mild to ESRD due to any etiology, was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and/or the presence of proteinuria (21). Recently, metabolic syndrome and NAFLD have been reported to enhance the new onset of CKD (23, 24). Although there is growing evidence to support the concept that metabolic syndrome is a risk factor for developing CKD, little research has been done to evaluate whether NAFLD is associated with the long-term development of CKD.

The present cohort study was initiated to investigate the cumulative incidence and risk factors of CKD after long-term follow-up in patients with NAFLD. The strengths of this current study are the large numbers of patients included and the long-term follow-up of patients.

**Methods**

**Patients**

The number of Japanese patients who were diagnosed with fatty liver by ultrasonography (25) between January 1997 and December 2007 in the Department of Hepatology and/or Health Management Center, Toranomon Hospital, Tokyo, Japan was 9,120. Of these, 5,561 Japanese patients satisfied with the following enrolled criteria; 1) no evidence of other chronic liver disease, and 3) refusal to be followed seriously reduce their life expectancy, 2) findings suggestive of chronic liver disease, and 3) refusal to be followed up after the diagnosis of fatty liver. Patients with the above criteria were enrolled regardless of whether the serum level of aminotransferase was normal or abnormal. Patients with any of the following criteria were excluded from the study: 1) illness that could seriously reduce their life expectancy, 2) findings suggestive of other chronic liver disease, and 3) refusal to be followed up after the diagnosis of NAFLD. A total of 3,559 out of 9,120 patients were excluded based on the following findings: 169 had a dipstick-positive proteinuria; 1,685 had alcohol intake of >20 g/day; 133 had positive serologic findings for either hepatitis B or C virus, a reported history of known liver disease, or decompensated liver cirrhosis; 36 had a history of malignancy; 26 had a history of cardiovascular disease; 11 refused the participation of prospective follow-up. Because some individuals were excluded for multiple reasons, the total number of eligible patients for the study was 5,561.

Patients were classified into three groups according to fasting plasma glucose (FPG): 1) those with FPG level of < 110 mg/dL (normal glucose group), 2) those with FPG level of 110-125 mg/dL (pre-diabetes group), and 3) those with FPG level of ≥126 mg/dL (diabetes group) (25). Patients were regarded as hypertension by the confirmation of blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic.

The primary goal was the new onset of CKD in patients with NAFLD. The end-point was defined as the first eGFR <60 mL/min/1.73 m² or dipstick proteinuria (≥ +1) for more than three months. Serum creatinine level was also measured using an enzymatic method, and the GFR was estimated from the Japanese Society of Nephrology CKD Practice Guide; eGFR (mL/min/1.73 m²) =194× (serum creatinine level [mg/dL]) -1.094× (age [y]) -0.287. The product of this equation was multiplied by a correction factor of 0.739 for women. CKD and its stages were defined from estimated eGFR of <60 mL/min/1.73 m² or dipstick proteinuria (≥ +1) as follows: stage I, eGFR≥90 and proteinuria (≥ +1); stage II, 90>eGFR≥60 and proteinuria (≥ +1); stage III, 60>eGFR≥30; stage IV, 30>eGFR≥15; and stage V, 15>eGFR. Patients with stage III-V were regarded as having CKD regardless of the absence of other markers of kidney damage (21, 22).

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

**Medical evaluation**

Fatty liver was diagnosed by the presence of an ultrasonographic pattern consistent with bright liver with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma (26). Ultrasonography test was performed with a high-resolution, real-time scanner (model SSD-2000; Aloka Co., Ltd, Tokyo Japan. Mode Logic-700 MR: GE-Yokokawa Medical Systems, Tokyo, Japan). Body weight was measured in light clothing and without shoes to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm. Height and weight were recorded at baseline and the body mass index (BMI) was calculated as weight (in kg) / height (in m²). All of the patients were interviewed in the Toranomon Hospital using a questionnaire that gathered information on demographic characteristics, medical history, and health-related habits including questions on alcohol intake at the time of diagnosis of fatty liver.

**Laboratory investigation**

At the first consultation anti-HCV and HBsAg were examined. Anti-HCV was detected using a third-generation enzyme-linked immunosorbent assay (Abbott Laboratories, North Chicago, IL). HBsAg was tested by radioimmunossay (Abbott Laboratories, Detroit, MI). Anti-HBs was not evaluated in the present study. Serum creatinine concentration was measured by a modified Jaffe method (creatinine
Table 1. Characteristics of Subjects Enrolled

<table>
<thead>
<tr>
<th>Total</th>
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<tbody>
<tr>
<td>Number of cases</td>
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<tr>
<td>Age (years)</td>
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<td>Sex (male/female)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<tr>
<td>Hypertension (+)</td>
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<td>Body Weight (kg)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Glucose status</td>
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<td>Hypertension (+)</td>
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</table>

Data are number of patients (percent) or mean ± standard deviation

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; WBC, white blood cell.

Results

Patients’ characteristics

Table 1 shows the characteristics in the 5,561 patients diagnosed as NAFLD in the present study. The mean age was 48 years. The mean BMI was 25.1. Patients with hypertension accounted for 13.0% and patients with T2DM accounted for 8.2%. The eGFR level was 74.6±11.9 mL/min/1.73 m². The mean follow-up period was 5.5 years.

Incidence of CKD in Patients with NAFLD

Of 5,561 NAFLD patients, 263 developed CKD. Figure 1 shows that the cumulative development rate of CKD was 3.1% at the 5th year and 12.2% at the 10th year in all patients with NAFLD. Cox proportional hazards analysis showed that CKD development in NAFLD patients occurred when patient had eGFR of 60-75 mL/min/1.73 m² [hazard ratio:2.75; 95% confidence interval (CI) =1.93-3.94; < 0.001], age ≥50 years (hazard ratio:2.67; 95% CI =2.06-3.46; p<0.001), T2DM (hazard ratio:1.92; 95% CI=1.45-2.54; p<0.001), hypertension (hazard ratio:1.69; 95% CI=1.25-2.29; p<0.001), and elevated serum GGT (hazard ratio:1.35; 95% CI=1.02-1.78; p=0.038) at the initiation of follow up (Table 2).

Figure 2 shows the cumulative development rate of CKD based on the difference of age and eGFR level at the starting time of follow-up. Figure 3 shows the cumulative development rate of CKD based on the difference of FPG, blood pressure, and serum GGT at the starting time of follow-up. On the difference of serum GGT level, the cumulative rate of CKD at 10th year in NAFLD was 11.3% in patients with routine analyses. Four hundred and ninety-two patients were lost to follow-up. Because the appearance of CKD was not identified in these 492 patients, they were considered as censored data in statistical analysis (27).

Statistical Analysis

The cumulative appearance rate of CKD was calculated from the starting time of follow-up to the development of CKD by using the Kaplan-Meier method. Differences in the development of CKD were tested using the log rank test. The Cox proportional hazard model analyzed independent factors associated with the development rate of CKD. The following variables were analyzed for potential covariates for incidence of CKD: age, BMI, T2DM, hypertension, and levels of eGFR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total protein, triglyceride (TG), total cholesterol level, high density lipoprotein (HDL) cholesterol uric acid, hemoglobin, white blood cell, platelet at the time of diagnosis of NAFLD. A p value of less than 0.05 was considered significant. Data analysis was performed using the computer program SPSS package (SPSS 11.5 for Windows, SPSS, Chicago, IL).
normal GGT level and 21.3% in those with elevated GGT level.

**Impact of GGT on the incidence of CKD**

In addition to elevated level of serum GGT, the four factors of ≥50 years, eGFR of 60-75 mL/min/1.73 m², T2DM, hypertension were high risk factors of developing CKD with statistical significance. Figure 4 shows the cumulative development of CKD based on the difference of serum GGT in NAFLD patients with each risk factor of age of ≥50 years, eGFR of 60-75 mL/min/1.73 m², T2DM, or hypertension. Elevated serum GGT enhances the new development of CKD with statistically significant differences in NAFLD patients with each risk factor of ≥50 years, eGFR of 60-75 mL/min/1.73 m², or hypertension. In NAFLD patients with T2DM, elevated serum GGT tended to facilitate the new development of CKD (p=0.068).
Elevated GGT heterogeneity makes it difficult to precisely interpret follow-up were not considered in the present study. Finally, and steatohepatitis. Next, prescribed agents during the trial. A blood sample and a urine sample were taken for routine analyses during follow-up. Next limitation of the study was that patients were treated with different types of exercise and diet for the NAFLD during follow-up. Moreover, although the NAFLD can be categorized into simple steatosis and steatohepatitis, the present study was undertaken without histological differentiation of simple steatosis and steatohepatitis. Next, prescribed agents during the follow-up were not considered in the present study. Finally, the interval of follow-up was different for each patient. This heterogeneity makes it difficult to precisely interpret the results of the study. On the other hand, the strengths of the present study are a long-term follow-up with a large numbers of patients included.

The present study shows several findings with regard to development of CKD in NAFLD patients. First, the CKD development rate in NAFLD patients with an elevated level of GGT was higher than that in those with a normal level of GGT. The fact that elevated GGT enhanced the onset of CKD is in accordance with the data reported by Chang et al (28), Ryu et al (29), and Fraser et al (30). Though the role of elevated GGT in the pathogenesis of CKD remains speculative, the following possible mechanism have been reported, 1) GGT is related to T2DM and/or insulin resistance by meta-analysis; insulin resistance may be associated with an increased risk for CKD (31-33). 2) GGT is linked with systemic low-grade inflammation; low grade inflammation may cause a change in kidney function (34). 3) GGT has been proposed as a sensitive marker of oxidative stress; oxidant stress plays an important role in renal damage (35).

Second, in addition to the elevation of GGT, the present study suggests that aging, eGFR of 60-75 mL/min/1.73 m², T2DM, and hypertension enhanced the development of CKD in NAFLD patients. The present findings of factors of metabolic syndrome such as T2DM and hypertension, which enhanced the new development of CKD is in accordance with the data reported by Chen et al (36), and Luk et al (37). Moreover, when GGT was elevated in NAFLD patients with each factor of ≥50 years, eGFR of 60-75 mL/min/1.73 m², or hypertension, the cumulative development rate of CKD increased with significant difference compared to those with a normal GGT level. In NAFLD patients with T2DM, an

Discussion

We have described the incidence of development of CKD in NAFLD patients. The present study indicates that the annual incidence of CKD for a prolonged follow-up among NAFLD patients is about 1.2% based on a follow-up of 10 years. The present study was limited by a retrospective cohort trial. A blood sample and a urine sample were taken for routine analyses during follow-up. Next limitation of the study was that patients were treated with different types of exercise and diet for the NAFLD during follow-up. Moreover, although the NAFLD can be categorized into simple steatosis and steatohepatitis, the present study was undertaken without histological differentiation of simple steatosis and steatohepatitis. Next, prescribed agents during the follow-up were not considered in the present study. Finally, the interval of follow-up was different for each patient. This heterogeneity makes it difficult to precisely interpret the results of the study. On the other hand, the strengths of the present study are a long-term follow-up with a large numbers of patients included.

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Figure 4. Cumulative development rate of CKD in NAFLD patients. Panel A: Cumulative development rate of CKD based on the difference of serum GGT level at the starting time of follow-up in NAFLD patients aged ≥50 years, Panel B: Cumulative development rate of CKD based on the difference of serum GGT level at the starting time of follow-up in NAFLD patients with eGFR of 60-75 mL/min/1.73 m² and absence of dipstick proteinuria (≥+1), Panel C: Cumulative development rate of CKD based on the difference of serum GGT level at the starting time of follow-up in NAFLD patients with T2DM, Panel D: Cumulative development rate of CKD based on the difference of GGT levels at the starting time of follow-up in NAFLD patients with hypertension
Table 2. Predictive Factors for CKD Development Based on the Clinical Data at the Starting Time of Follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Cox-regression</th>
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<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td>Age (years, ≥50/&lt;50)</td>
<td>2.92 (2.27-3.75)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>1.08 (0.73-1.60)</td>
<td>.706</td>
</tr>
<tr>
<td>BMI (≥25/&lt;25)</td>
<td>1.15 (0.90-1.46)</td>
<td>.270</td>
</tr>
<tr>
<td>Hypertension (+/-)</td>
<td>2.04 (1.55-2.69)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Smoking (+/-)</td>
<td>1.19 (0.63-2.24)</td>
<td>.588</td>
</tr>
<tr>
<td>AST (IU/L, ≥34/&lt;34)</td>
<td>1.25 (0.95-1.65)</td>
<td>.113</td>
</tr>
<tr>
<td>ALT (IU/L, ≥43/&lt;43)</td>
<td>1.06 (0.82-1.38)</td>
<td>.640</td>
</tr>
<tr>
<td>GGT (IU/L, ≥109/&lt;109)</td>
<td>1.43 (1.09-1.88)</td>
<td>.011</td>
</tr>
<tr>
<td>Diabetes (+/-)</td>
<td>2.42 (1.85-3.17)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>WBC (×10³/mm³, ≥5.0/&lt;5.0)</td>
<td>1.04 (0.80-1.35)</td>
<td>.770</td>
</tr>
<tr>
<td>Hemoglobin (g/dL, ≥15/&lt;15)</td>
<td>1.08 (0.84-1.39)</td>
<td>.552</td>
</tr>
<tr>
<td>Platelet (×10³/mm³, ≥25/&lt;25)</td>
<td>1.04 (0.80-1.34)</td>
<td>.770</td>
</tr>
<tr>
<td>Total protein (g/dL, ≥7.5/&lt;7.5)</td>
<td>0.84 (0.45-1.50)</td>
<td>.588</td>
</tr>
<tr>
<td>Triglyceride (mg/dL, ≥150/&lt;150)</td>
<td>1.58 (1.24-2.00)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL, ≥220/&lt;220)</td>
<td>1.17 (0.87-1.57)</td>
<td>.314</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL, ≥40/&lt;40)</td>
<td>0.94 (0.73-1.23)</td>
<td>.693</td>
</tr>
<tr>
<td>Uric acid (mg/dL, ≥7/&lt;7)</td>
<td>1.15 (0.86-1.53)</td>
<td>.330</td>
</tr>
<tr>
<td>eGFR (≥60 and &lt;75/&lt;75)</td>
<td>2.73 (1.92-3.88)</td>
<td>&lt; .001</td>
</tr>
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</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; HR, hazards ratio

elevated GGT indicated tendency to increase the cumulative development rate of CKD compared to those with normal GGT level.

Thus, the present results indicate that T2DM, hypertension, and elevated GGT enhance the new development of CKD in NAFLD patients. This means that in addition to the improvement of glucose level and hypertension, normalization of serum GGT could reduce the aggravation of kidney function.

NAFLD that is considered to be a risk factor for developing CKD is emerging into a new significant health problem in many countries. In addition, the life span in Japan has recently become long. In the near future, a large number of patients with NAFLD will be >60 years of age. CKD occurs more frequently in elderly patients than in young patients. Thus, it is reasonable to conclude that CKD will be increasing in NAFLD patients. CKD often progresses to ESRD with its accompanying complications. Medical physicians regarding the daily management of patients with NAFLD should check on the development of CKD in addition to the aggravation of liver function.

In conclusion, our retrospective study indicates that the annual incidence of CKD in Japanese patients with NAFLD is about 1.2%. The following five factors enhance the risk of development of CKD: low eGFR level, aging, type 2 diabetes, hypertension, and elevated GGT.

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

Acknowledgement

The present work was supported in part by the Japanese Ministry of Health, Labour and Welfare. Moreover, the authors greatly acknowledged the editorial assistance of Thomas Hughes.

References