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A Longitudinal Increase in Serum Gamma-Glutamyl Transferase Levels, but Not in Alanine Aminotransferase Levels, Improves the Prediction of Risk of Impaired Fasting Glucose in Male

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: Impaired fasting glucose (IFG), being a pre-diabetic condition, can increase the risk of overt diabetes; thus early detection and prediction of IFG are important to reduce the incidence of overt diabetes. Some predictive factors, including serum alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), have been reported in several studies, but none of the studies have investigated the effect of longitudinal changes in individual serum ALT and GGT levels on the risk of IFG.
Methods: We aimed to investigate the association between changes in the serum ALT and GGT levels and the risk of IFG using a checkup database between 1999 and 2014.
Results: A total of 3,598 males and 3,275 females were enrolled in the study. We performed a follow-up test of serum ALT or GGT in each individual, and classified the cases in which the serum ALT or GGT level was increased or decreased during the follow-up test compared to the baseline. According to the multivariate Cox proportional hazards model, the hazard ratio was 1.76 (95% confidence interval, 1.45–2.12; $P < 0.001$) in male subjects with an increased serum GGT level compared to male subjects with a decrease in the serum GGT level at follow-up compared to the baseline. However, the relationship between the serum ALT level and incidence of new-onset IFG was not statistically significant in both sexes; and in females, the relationship between the serum GGT level and incidence of new-onset IFG was also not statistically significant.
Conclusion: We revealed that a longitudinal increase in serum GGT levels was related to an increased risk of IFG in males. Therefore, monitoring the changes in serum GGT levels is important for predicting new-onset IFG, and it can be used as an early indicator of onset of overt diabetes in males.

Keywords: Impaired Fasting Glucose; Gamma-Glutamyl Transferase; Alanine Aminotransferase

Author Contributions

Conceptualization: Im J, Kim KN. Data curation: Im J, Yang Y. Formal analysis: Jung S, Kim KN. Investigation: Im J, Jung S. Methodology: Yang Y, Kim KN. Resources: Yang Y. Software: Jung S. Visualization: Jung S, Yang Y. Writing - original draft: Im J, Kim KN. Writing - review & editing: Kim KN.

INTRODUCTION

Impaired fasting glucose (IFG) belongs to the category of abnormal glucose metabolism, and it is defined as a blood sugar level of 100 to 125 mg/dL without any caloric intake for at least eight hours.[1] IFG can increases the risk of developing type 2 diabetes mellitus; thus it is regarded as one of the high-risk categories for new-onset overt diabetes.[1,2] Given the marked increase in the prevalence of diagnosed diabetes[3,4] and several serious or life-threatening comorbidities of diabetes,[4] early diagnosis and prevention of diabetes are most important real-world issues. Therefore, early detection or prediction and proper intervention in the state of pre-diabetes, such as IFG, can be key factors to reduce the incidence of overt diabetes.

Numerous observational studies have demonstrated that liver enzymes, such as alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), were positively associated with the risk of IFG and diabetes mellitus.[5-12] Liver plays an important role in regulating glucose metabolism, and serum ALT levels increase when the hepatocytes are damaged. GGT is widely present on the surface of cell membranes, and it plays an important role in the synthesis of glutathione, a representative molecule with antioxidant activity in the body. Glutathione is a powerful antioxidant at the cellular level, and its level is increased when oxidative stress and inflammation occur in body tissues.[13,14] Oxidative stress and inflammation play an key role in the development of insulin resistance.[15] Our previous study has also reported that the risk of IFG was further increased when elevations in serum ALT and GGT levels occurred concurrently.[16] However, since most of the above-mentioned studies were cross-sectional studies, it was difficult to confirm the causality. Even if one study was a longitudinal study, only the occurrence of IFG during follow-up was investigated based on the baseline ALT and GGT values. In other words, these studies had a limitation as they did not track the increase or decrease in the ALT and GGT values while they were followed. In addition, the relationship between levels of all serum liver enzymes and occurrence of IFG is not consistent, and different results have been reported for different ALT and GGT levels according to the sex. Therefore, we aimed to investigate which liver enzyme level was associated with the occurrence of IFG if its level was actually increased during the longitudinal follow-up of serum liver ALT and GGT levels by sex.

METHODS

Study population

We retrospectively reviewed checkup databases at the Health Promotion Center, Ajou University Hospital, Suwon, Korea, between 1999 and 2014. We included subjects with more than two health checkup databases, and we regarded the first and last checkup dates as the baseline and endpoint of the study, respectively. We firstly excluded IFG patients who were defined as those with a fasting serum glucose level of 100–125 mg/dL at the baseline. Additionally, we excluded those who had been diagnosed with diabetes, cardiovascular disease, or cancer; had history of chronic liver disease, such as hepatitis B or C or liver cirrhosis; had been taking a drug metabolized through the liver; had enough alcohol consumption to damage the liver (> 30 g/day in males and > 20 g/day in females)[17,18]; had no medical record information, such as fasting blood glucose and serum ALT, AST, and GGT levels. We also excluded those who had normal GGT levels (> 198 U/L) more than three times to exclude the secondary effects caused by viral and toxic substances. Finally, a total of 6,873 subjects were enrolled in our longitudinal study.

Measurements

All enrolled subjects had laboratory findings, such as fasting blood glucose, liver enzyme level, uric acid, total cholesterol, triglycerides (TGs), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (LDL-C), which were collected on the morning of the hospital visit after more than 8 hours of fasting before the visit. We also collected medical records of blood pressure, body mass index (BMI), and past medical history.

Statistical analysis

A χ^2 test or *t*-test was performed to compare the baseline characteristics of subjects according to the cases in which serum ALT or GGT levels were decreased or increased compared to the baseline during follow-up. In the longitudinal evaluation, we utilized Cox proportional hazard regression analysis to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). For multivariate analysis, the Cox proportional hazard regression analysis was performed after adjusting for variables, such as age, BMI, log-transformed weekly alcohol consumption, hypertension, dyslipidemia, and current smoking. Logarithmization was applied to weekly alcohol consumption because it was skewed to the right. The result was considered statistically significant when a two-tailed *P* value was < 0.05. Statistical analyses were performed using SPSS v20.0 software (SPSS Inc., Chicago, IL, USA).

Ethics statement

Subjects undergoing health examinations filled out written informed consent forms permitting the use of their data for research purposes. The Institutional Review Board of Ajou University Hospital (Suwon, Republic of Korea) approved the study (Approval No.: AJIRB-MED-MDB-16-063).

RESULTS

A total of 3,598 males and 3,275 females were included at the time of the study entry date. **Table 1** shows the results of a comparative analysis of baseline demographics and clinical characteristics of subjects whose serum ALT levels were decreased or increased during the follow-up according to sex. Male subjects with decreased delta ALT levels had a statistically significantly higher age, BMI, total cholesterol, TG, LDL-C, and ALT levels than male subjects with increased delta ALT levels, but the values of these clinical indicators were within the normal range. There were no differences between the two groups in the prevalence of hypertension and dyslipidemia, the number of current smokers, and the amount of alcohol consumed per week. In females, there were no statistical differences in the other demographics and clinical characteristics except for ALT levels in female subjects with decreased delta ALT levels compared to female subjects with increased delta ALT levels. **Table 2** shows a comparative analysis of the baseline clinical characteristics of subjects whose serum GGT levels were decreased or increased during the follow-up compared to the baseline by sex. Total cholesterol, TG, and LDL-C were statistically significantly increased in male subjects with decreased delta GGT levels compared to male subjects with increased delta GGT levels, but there was no difference between the two groups in the prevalence of dyslipidemia. In females, there was a statistically significant difference between the two groups only in the baseline serum GGT level, but the average value was within the normal range in both groups.

Table 3 shows the Cox proportional hazard regression analysis for the occurrence of new-onset IFG when serum ALT levels were increased versus decreased at follow-up. In males,

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Table 1. Baseline characteristics of subjects as the serum ALT level was increased or decreased at the end of follow-up

Characteristics	Male (n = 3,598)		*P* value	Female (n = 3,275)		*P* value
	Decrease in the serum ALT level (n = 2,526)	Increase in the serum ALT level (n = 1,072)		Decrease in the serum ALT level (n = 2,070)	Increase in the serum ALT level (n = 1,205)	
Age, yr	55.42 ± 8.36	54.42 ± 8.43	0.001	53.60 ± 9.10	54.32 ± 7.97	0.019
Body mass index, kg/m^2	23.53 ± 2.79	22.79 ± 2.73	< 0.001	22.29 ± 2.84	22.34 ± 2.73	0.616
Fasting glucose, mg/dL	91.67 ± 5.26	91.42 ± 5.31	0.185	90.39 ± 5.56	90.12 ± 5.56	0.175
Triglycerides, mg/dL	138.39 ± 91.63	128.97 ± 80.13	0.003	93.98 ± 60.49	91.60 ± 50.48	0.248
Total cholesterol, mg/dL	187.75 ± 33.18	182.66 ± 32.16	< 0.001	178.87 ± 31.73	176.41 ± 32.37	0.033
LDL-C, mg/dL	112.94 ± 26.13	108.12 ± 38.15	0.002	103.42 ± 28.42	103.29 ± 31.62	0.512
Weekly alcohol consumption, g/wk	69.08 ± 106.58	72.97 ± 119.46	0.356	6.26 ± 27.69	7.98 ± 32.68	0.125
Hypertension, %	6.2	5.7	0.082	2.5	3.5	0.071
Dyslipidemia, %	7.5	4.9	0.781	1.5	1.7	0.812
Current smoker, %	20.9	14.9	0.002	1.4	1.0	0.552
ALT, IU/L	38.10 ± 32.19	26.45 ± 13.99	< 0.001	22.52 ± 15.20	16.30 ± 6.79	< 0.001
Delta ALT level	−14.81 ± 27.15	13.76 ± 28.90	< 0.001	−7.46 ± 12.50	9.38 ± 16.17	< 0.001
Follow-up period of longitudinal ALT-change assessment, yr	9.58 ± 3.51	9.69 ± 3.61	0.400	8.88 ± 3.37	10.09 ± 3.54	< 0.001

Values are presented as mean ± standard deviation.
ALT = alanine aminotransferase, LDL-C = low-density lipoprotein cholesterol.

Table 2. Baseline characteristics of subjects as the serum GGT level was increased or decreased at the end of follow-up

Characteristics	Male (n = 3,598)		*P* value	Female (n = 3,275)		*P* value
	Decreasing serum GGT (n = 1,658)	Increasing serum GGT (n = 1,940)		Decreasing serum GGT (n = 1,360)	Increasing serum GGT (n = 1,915)	
Age, yr	56.38 ± 8.67	54.05 ± 8.00	< 0.001	53.67 ± 9.18	54.01 ± 8.36	0.282
Body mass index, kg/m^2	23.73 ± 2.85	22.96 ± 2.69	0.734	22.33 ± 2.93	22.29 ± 2.72	0.674
Fasting glucose, mg/dL	91.75 ± 5.34	91.46 ± 5.23	0.348	90.34 ± 5.57	90.26 ± 5.67	0.663
Triglycerides, mg/dL	146.13 ± 97.33	126.57 ± 79.02	< 0.001	92.51 ± 58.59	93.53 ± 55.89	0.615
Total cholesterol, mg/dL	190.46 ± 33.62	182.63 ± 1.96	< 0.001	178.13 ± 32.16	177.85 ± 31.88	0.807
LDL-C, mg/dL	113.94 ± 31.17	109.88 ± 28.88	< 0.001	104.46 ± 29.31	104.32 ± 28.62	0.911
Weekly alcohol consumption, g/wk	68.66 ± 98.67	71.60 ± 119.82	0.427	6.3 ± 30.60	7.25 ± 28.92	0.418
Hypertension, %	6.9	5.6	0.095	2.6	3.2	0.260
Dyslipidemia, %	7.3	4.6	0.686	1.8	1.8	0.967
Current smoker, %	21.9	15.6	< 0.001	1.2	0.8	0.756
GGT, IU/L	40.03 ± 29.03	30.50 ± 20.94	< 0.001	17.23 ± 13.15	14.27 ± 8.03	< 0.001
Delta GGT level	−11.54 ± 17.02	20.20 ± 44.39	< 0.001	−3.91 ± 8.39	8.12 ± 0.00	< 0.001
Follow-up period of longitudinal GGT-change assessment, yr	9.84 ± 3.55	9.43 ± 3.54	0.803	9.24 ± 3.44	9.39 ± 3.52	0.259

Values are presented as mean ± standard deviation.
GGT = gamma-glutamyl transferase, LDL-C = low-density lipoprotein cholesterol.

HRs assessed by unadjusted analysis and multivariate analysis after adjusting for age, BMI, and log-transformed weekly alcohol consumption, age, hypertension, dyslipidemia, and current smoking were 1.13 (95% CI, 0.97–1.32; $P = 0.095$), 1.20 (95% CI, 0.99–1.46; $P = 0.054$), and 1.20 (95% CI, 0.99–1.46; $P = 0.064$), respectively, which were not statistically significant. Also in females, the HRs were not statistically significant on both univariate and multivariate analyses. **Table 4** shows the multivariate regression analysis for the occurrence of new-onset IFG when the delta GGT levels were increased during follow-up compared to the case in which the level was decreased. The results of the multivariable Cox proportional hazard model revealed that, in males, the HRs were 1.52 (95% CI, 1.31–1.77; $P < 0.001$), 1.76 (95% CI, 1.45–2.13; $P < 0.001$), and 1.76 (95% CI, 1.45–2.12; $P < 0.001$), respectively, on both univariate and multivariate analyses after adjusting for the other covariates, which were statistically significant. On the other hand, in females, the HR was 1.41 (95% CI, 0.75–2.64; $P = 0.284$) and 1.38 (95% CI, 0.74–2.63; $P = 0.328$), respectively, on multivariate analysis after adjusting for confounding factors, which was not statistically significant.

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Table 3. Hazard ratio of new-onset impaired fasting glucose when the serum ALT level was increased compared to decrease in the serum ALT level over time

Models	Male (n = 3,598)		Female (n = 3,275)	
	95% CI	*P* value	95% CI	*P* value
Unadjusted	1.13 (0.97–1.32)	0.095	1.01 (0.81–1.26)	0.898
Adjust I	1.20 (0.99–1.46)	0.054	1.20 (0.99–1.46)	0.064
Adjust II	0.96 (0.53–1.74)	0.902	0.94 (0.51–1.73)	0.851

Adjust I, after adjustment for age, body mass index, and log-transformed weekly alcohol consumption; Adjust II, Adjust I plus after adjustment for hypertension, dyslipidemia, and current smoking.
ALT = alanine aminotransferase, CI = confidence interval.

Table 4. Hazard ratio of new-onset impaired fasting glucose when the serum GGT level was increased compared to decrease in the serum GGT level over time

Models	Male (n = 3,598)		Female (n = 3,275)	
	95% CI	*P* value	95% CI	*P* value
Unadjusted	1.52 (1.31–1.77)	< 0.001	1.32 (1.05–1.66)	0.017
Adjust I	1.76 (1.45–2.13)	< 0.001	1.41 (0.75–2.64)	0.284
Adjust II	1.76 (1.45–2.12)	< 0.001	1.38 (0.74–2.63)	0.328

Adjust I, after adjustment for age, body mass index, and log-transformed weekly alcohol consumption; Adjust II, Adjust I plus after adjustment for hypertension, dyslipidemia, and current smoking.
GGT = gamma-glutamyl transferase, CI = confidence interval.

DISCUSSION

In the present longitudinal study, we followed up the serum ALT or GGT levels of individuals according to sex and evaluated the occurrence of new-onset IFG in subjects whose follow-up values were increased compared to those whose levels were decreased from baseline. When we followed up serum GGT levels from baseline in males, we found that male subjects with increased serum GGT levels compared to male subjects with decreased serum GGT levels showed a statistically significant association with new-onset IFG on univariate analysis. This association was maintained even after adjusting for multivariate confounding variables. However, in females, the relationship between serum GGT and IFG incidence was not statistically significant. In addition, the relationship between serum ALT and incidence of IFG was not statistically significant in both males and females. Thus, these findings demonstrate that an increase in only the GGT level over time is a reliable marker for the development of IFG before onset of overt diabetes in males, and not females.

Our study results are consistent with previous longitudinal studies in males that showed a positive relationship between baseline serum GGT concentration and IFG or diabetes occurrence. In a longitudinal study by Yu et al.,[19] 83% (561/663) were male subjects, and as a result of follow-up for 7 years, an odds ratio (OR) of 3.685 (95% CI, 1.40–9.66) for borderline elevation of γ-GTP after adjustment for potential confounding variables was found. In a study by Nakanishi et al.,[20] in a longitudinal analysis of 2,918 Japanese male office workers followed for more than 7 years, the relative risk for IFG compared with serum GGT in the 1st quartile was 2.54 (95% CI, 1.29–5.01) for the 2nd quartile, 2.64 (95% CI, 1.33–5.23) for the 3rd quartile, and 3.44 (95% CI, 1.69–6.70) for the 4th quartile. In addition, in a longitudinal study conducted by our research team that included both male and female subjects, the IFG probability increased gradually with an increase in the circulating levels of GGT.[16] However, longitudinal studies on the occurrence of IFG according to baseline ALT levels have not shown consistent results. Yu et al.[19] demonstrated that, in the incidence of IFG or DM, the OR of borderline elevation of ALT was 2.664 (95% CI, 1.21–5.84), which was statistically significant. On the other hand, Nakanishi et al.[20] showed that the OR of ALT in the top quartile compared to the bottom fourth quartile was 1.19 (95% CI, 0.84–1.69), which was not

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statistically significant. As described above, longitudinal analytical studies performed to date have not shown consistent results, which may be due to limitations as previous longitudinal studies did not actually observe the changes in individual serum ALT or GGT levels over time and analyzed without distinguishing between males and females. In other words, retrospective longitudinal analytical studies that simply hypothesize that baseline values will be maintained during follow-up tests are not suitable for the real world, and observation of changes in serum levels considering the time changes of an individual according to the sex is the best way to evaluate actual patients. Therefore, in a situation where a long-term prospective blood follow-up study cannot be conducted in reality, our study, which longitudinally observed the changes in individual blood tracking compared to the baseline, can be said to be closer to the real world. Thus, our results suggest that the serum GGT level is a reliable marker that can predict the occurrence of IFG in males.

Although the exact mechanism of GGT in IFG development is not yet known, it might be explained as follows: Recent research studies suggest that GGT is an index for oxidative stress in connection with glutathione.[21] Since the pancreas lacks antioxidant enzymes more than any other organ in our body,[22] increased oxidative stress can lead to decreased pancreatic function. The pancreas is a body organ responsible for secretion of insulin, and an increase in the GGT level, which means an increase in oxidative stress,[23] leads to a decrease in pancreatic beta cell function, which may contribute to the development of IFG.

Our study has several limitations and strengths. First, our data were obtained from an analysis performed in non-randomly selected subjects from one center; thus, these results may not be representative of the entire population. Second, we did not include some confounding factors that are more closely related to insulin resistance, such as visceral fat or fasting insulin levels.[24,25] Last, covariates in the multivariate analysis were based on baseline values, with no follow-up data to account for time-dependent changes. This may have led to an underestimation of their impact. Similarly, since IFG was determined only at the last visit, earlier diagnoses could have been missed, potentially underestimating the true HRs in our Cox analysis.

However, despite these limitations, to the best of our knowledge, this study is significant as it is the first large-scale longitudinal analysis close to the real world in which the serum ALT and GGT levels of patients were followed up and compared with baseline values.

In conclusion, the current study shows that the serum GGT level, and not the ALT level is associated with an increased risk of IFG in males, and longitudinal elevation of the serum GGT level seems to help predict future incidence of IFG. Therefore, physicians should carefully observe the occurrence of IFG in male patients in order to ultimately prevent cardiovascular disease events when the serum GGT level is increased during follow-up examination compared to the baseline.

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