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Increasing risk of diabetes mellitus according to liver function alterations in electronic workers

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ABSTRACT

Aims/Introduction: We sought to determine the association between change in fasting plasma glucose (FPG) and levels of liver enzymes, such as aspartate transaminase, alanine transaminase and gamma-glutamyltransferase, from health examinations.

Materials and Methods: A total of 9,393 health screen examinees with no evidence of viral hepatitis, liver diseases, abnormal liver function and diabetes in their past disease history were enrolled in the present study. All the participants underwent three health examinations. Group 1 and 4 were stationary groups of those with normal liver enzyme levels in the first and second health examinations (G1), and abnormal liver enzyme levels in the first and second health check-up (G4). Groups 2 and 3 were altered groups of those with abnormal liver enzyme levels in the first health examination, which became normal in the second health examination (G2), and from a normal liver enzymes level to an abnormal liver enzymes level (G3).

Results: FPG levels were elevated in male participants ($P < 0.01$), and were related to old age ($P < 0.01$), drinking ($P < 0.01$), smoking ($P < 0.01$) and so on. There was a strong relationship between FPG levels in the last health examination and altered liver function enzyme levels from the first health examination to the second check-up. In other words, group 4 had the highest level of FPG compared with the other groups (G1 < G2 < G3).

Conclusions: An association was observed between FPG levels and abnormal liver function in manufacturing workers. Abnormal liver function can be closely associated with the development of diabetes.

INTRODUCTION

According to a 2005 report from the World Health Organization, 170 million people are estimated to suffer from diabetes around the world[1]. This number is expected to rise to approximately 300 million by 2025[1,2]. The prevalence of diabetes was less than 1% in Korea in the 1970s. However, a total of 2,694,220 diabetes patients (7.75% of the people) were confirmed between the ages of 20 and 79 years in 2003. Nearly 10% of all patients with diabetes were new patients[3].

Increased activity of liver enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltranspeptidase (GGT), are indicators of hepatocellular injury, which are also associated with insulin resistance[4], metabolic syndrome[5,6] and type 2 diabetes[7,8]. In particular, serum GGT concentrations showed a strong dose–response relationship with incident diabetes in a study of healthy Korean men[9]. Serum GGT level was shown to be related to chronic diseases, such as hypertension, hyperlipidemia, obesity and diabetes, and metabolic syndrome, in Korea[10,11]. In a previous study, the results of Coronary Artery Risk Development in Young Adult (CARDIA) as a prospective cohort study among 20,000 participants in 2003 showed a strong association between GGT and fasting plasma glucose (FPG)[12,13].

However, although an increasing number of studies have been using indicators of liver function tests, correlation studies regarding FPG as a diabetes diagnostic indicator and liver

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function deterioration are still insufficient. The objective of the present study was to determine the association between altered levels of FPG and levels of liver enzymes, such as AST, ALT and GGT, after adjustment for potential risk factors including age, sex and so on from health examinations among semiconductor workers.

MATERIALS AND METHODS

Selection of Participants

Initially, 19,534 semiconductor workers (mean age 32 years, range 20–59 years) were recruited from a health examination center between January 2002 and December 2010. We then selected 9,907 semiconductor workers who underwent three cycles of clinical health examination (follow-up rate 50.7%). A total of 514 participants were excluded from the study if any of the following were detected from their self-questionnaire and clinical data: a history of hepatitis, the presence of abnormal liver function, diabetes, hepatitis B or hepatitis C virus-positive cases and FPG ≥126 mg/dL. A total of 9,393 people were selected as final participants. Follow-up duration between the first and last health examinations was 73 months (range 18–105 months).

Group 1 and 4 were stationary groups of those with normal liver enzyme levels in the first and last health examinations (G1), and abnormal liver enzyme levels in the first and last health check-up (G4), respectively. Groups 2 and 3 were altered groups of those with abnormal liver enzyme levels in the first health examination, which became normal in the last (G2), and from normal liver enzymes level to abnormal (G3), respectively. All participants gave written, informed consent, and the protocol was approved by the institutional review board committee of the Kangbook Samsung Hospital.

Analysis of Clinical Biomarkers

General factors that influenced the results of the examinations were used to analyze age, sex and body mass index (BMI), and the factors of liver function were used to analyze AST, ALT and GGT by an automatic analyzer. A diagnosis of diabetes was made for FPG ≥126 mg/dL by the Hexokinase method. Height, weight, waist circumference, systolic and diastolic blood pressure were measured, and BMI (kg/m^2) was calculated using body height and weight.

Total cholesterol (TC) and triglyceride (TG) were measured by the enzymatic calorimetric test, low-density lipoprotein cholesterol was measured with the homogeneous enzymatic colorimetric test, and high-density lipoprotein-cholesterol was measured with the selective inhibition method (Advia 1650, Bayer, Germany). Hepatitis B surface antigen (Isomedic, ICN, Costa, MA, USA) and hepatitis C antibody (Wizard 1470, Wallac, Finland) were measured using a radioimmunometric assay. Abdominal ultrasounds were carried out with a 3.5-MHz transducer (Logic Q700 MR; GE, Milwaukee, WI, USA) by 12 experienced radiologists who were unaware of the aims of the study and blinded to laboratory values. Images were captured in a

Table 1 | Geometric means and standard deviations of fasting plasma glucose levels by health-related characteristics in semiconductor workers

Categories	*n*	(%)	FPG levels in last health check-up			
			GM	GSD*	*P*-value*	Duncan
Sex						
Male	8,355	(88.9)	95.98	1.11		
Female	1,039	(11.1)	92.07	1.10		
Total	9,394	(100)	95.54	1.11	<0.01	
Age (years)						
26 – 39	5,985	(63.7)	95.10	1.10		A
40 – 49	3,292	(35.0)	96.24	1.12		A/B
50 – 59	117	(1.2)	98.53	1.12		A/B
Total	9,394	(100)	95.54	1.11	<0.01	
Drinking frequency						
Non-drinkers	1,665	(18.0)	93.80	1.10		A
Two to three times/month	4,696	(50.9)	95.26	1.11		A
One to two times/week	2,473	(26.8)	96.75	1.12		A/B
Three to four times/week	359	(3.9)	97.87	1.11		B/C
Every day	38	(0.4)	98.80	1.09		C
Total	9,231	(100)	95.59	1.11	<0.01	
Smoking status						
Non-smokers	3,228	(37.4)	94.30	1.11		A
Ex-smokers	2,238	(25.9)	96.07	1.11		A
Smokers	3,176	(36.8)	96.21	1.11		B
Total	8,642	(100)	95.59	1.11	<0.01	
Duration of smoking						
Less than 5 years	857	(16.4)	95.18	1.11		A
5 –10 years	1,238	(23.7)	95.85	1.11		A/B
10 –20 years	2,707	(51.9)	96.09	1.11		A/B
20 –30 years	412	(7.9)	97.28	1.11		A/B
>30 years	5	(0.1)	101.62	1.13		B
Total	5,219	(100)	95.59	1.11	<0.01	
Diet pattern						
Vegetarian	325	(3.5)	93.23	1.10		A
Balanced diet	7,282	(78.3)	95.44	1.11		A
Meat eater	1,692	(18.2)	96.37	1.12		B
Total	9,299	(100)	95.59	1.11	<0.01	
Liver status						
Fatty liver	2,656	(28.6)	98.32	1.13		
Non-fatty liver	6,634	(71.4)	94.46	1.10		
Total	9,290	(100.0)	95.49	1.11	<0.01	
Sweated exercise						
Non-exercise	3,625	(42.1)	95.01	1.11		A
One to two times/week	3,339	(38.8)	95.64	1.11		A/B
Three to four times/week	1,416	(16.5)	96.25	1.11		A/B/C
Five to six times/week	139	(1.6)	94.13	1.10		B/C

Table 1 | (*Continued*)

Categories	*n*	(%)	FPG levels in last health check-up			
			GM	GSD*	*P*-value*	Duncan
Almost every day	82	(1.0)	97.39	1.17		C
Total	8,601	(100)	95.59	1.11	<0.01	
Past disease history (excluding hepatitis, liver disease and diabetes mellitus)						
Tuberculosis	383	(20.6)	93.98	1.11		A
Hypertension	226	(12.1)	102.06	1.16		A/B
Heart disease	24	(1.3)	94.55	1.09		B
Stroke	7	(0.4)	97.63	1.08		B
Cancer	20	(1.1)	94.17	1.07		B
Other	1203	(64.6)	94.70	1.10		B
Total	1,863	(100)	95.58	1.11	<0.01	

*Statistical analysis by Student's *t*-test or ANOVA test, Duncan's post-hoc test. GM, geometric mean; GSD, geometric standard deviation. A, B and C represent the same group by each variable.

Table 3 | Multiple linear regression for fasting plasma glucose levels by liver function biomarkers, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltranspeptidase

Variable	Parameter estimate (β)	Standard error	*P*-value
Intercept	3.497	0.062	<0.01
AST	0.013	0.006	0.03
ALT	0.010	0.004	<0.01
GGT	0.016	0.002	<0.01
Sex	0.009	0.004	0.04
Age	0.001	0.000	<0.01
BMI	0.096	0.011	<0.01
Diet pattern	0.000	0.003	0.97
Drinking frequency	0.006	0.002	<0.01
Smoking status	0.002	0.001	0.16
Systolic BP	0.135	0.011	<0.01

n = 8,379. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; GGT, gamma-glutamyltranspeptidase.

standard manner with the patient in the supine position with the right arm raised above the head[14]. An ultrasonographic diagnosis of fatty liver was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma[15]. Ultrasonographic diagnosis of fatty liver was determined by the radiologists using live images.

Statistical Analysis

All results were calculated using the mean value and standard deviation for each of the parameters considered, and were checked for statistical significance using analysis of variance (ANOVA) and Student's *t*-test for FPG levels and liver function status (normal vs abnormal) by sex. The differences were confirmed using the Duncan's post-hoc test by ANOVA.

Estimates of elevation to FPG at the last health screening, covariates including sex, age, BMI, diet pattern, drinking frequency, smoking status, physical activity and systolic blood pressure were determined by deriving the parameter estimate (β) and its *P*-value using multiple linear regressions. For all tests, a two-sided $P < 0.05$ was considered statistically significant. Data analyses were carried out using the SAS 9.2 statistical software package (SAS Inc., Cary, NC, USA).

Table 2 | Geometric means and geometric standard deviation of biomarkers in blood from physical examinations

Variables	First check-up			Second check-up			Third check-up		
	n	GM	GSD	*n*	GM	GSD	*n*	GM	GSD
FPG	9,394	91.68	1.09	9,394	94.16	1.09	9,394	95.54	1.11
AST*	9,393	23.68	1.35	9,394	22.84	1.36	9,394	22.92	1.39
ALT†	9,394	25.58	1.71	9,394	24.61	1.71	9,394	24.09	1.73
GGT‡	9,393	23.95	1.93	9,394	26.72	1.96	9,394	28.51	2.04
TC	9,394	193.01	1.19	9,394	188.87	1.19	9,394	197.52	1.19
TG	9,394	119.54	1.67	9,394	121.10	1.68	9,394	119.79	1.70
HDL-C	9,394	51.81	1.23	9,394	51.46	1.22	9,394	51.66	1.25
LDL-C	9,394	112.13	1.30	9,394	110.20	1.30	9,394	117.51	1.30
BMI	9,391	23.59	1.13	9,391	23.82	1.13	9,384	24.02	1.13
SBP	9,392	114.79	1.11	9,394	114.43	1.11	9,393	116.02	1.11
DBP	9,392	73.98	1.14	9,394	74.23	1.13	9,393	74.10	1.12

*Alanine aminotransferase (ALT): normal is <40 IU/L for men and <35 U/L for women, and abnormal is ≥40 IU/L for men and ≥35 IU/L for women. †Aspartate aminotransferase (AST): normal is <40 IU/L for men and <35 IU/L for women, and abnormal is ≥40 IU/L for men and ≥35 IU/L for women. ‡Gamma-glutamyltranspeptidase (GGT): normal is <63 IU/L for men and <35 IU/L for women, and abnormal is ≥63 IU/L for men and ≥35 IU/L for women. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 4 | Odds ratios for fasting plasma glucose elevation by alteration of liver function enzyme levels from first to last health examination

Categories	First check-up → last check-up	*n*	FPG ≥126			FPG ≥100		
			OR	95% CI	*P**	OR	95% CI	*P**
ALT	G1: Normal → normal	6,994	1	–		1	–	
	G2: Abnormal → normal	796	1.78	1.00 – 3.18		1.11	0.94 – 1.30	
	G3: Normal → abnormal	685	2.68	1.52 – 4.71		1.38	1.17 – 1.64	
	G4: Abnormal → abnormal	919	4.82	3.14 – 7.39	<0.01	1.50	1.29 – 1.75	<0.01
AST	G1: Normal → normal	8,661	1	–		1	–	
	G2: Abnormal → normal	317	2.79	1.61 – 4.82		1.33	1.05 – 1.68	
	G3: Normal → abnormal	275	4.14	2.42 – 7.09		1.43	1.11 – 1.83	
	G4: Abnormal → abnormal	140	2.97	1.47 – 6.01	<0.01	1.36	0.96 – 1.92	<0.01
GGT	G1: Normal → normal	8,163	1	–		1	–	
	G2: Abnormal → normal	213	1.58	0.67 – 3.73		1.08	0.81 – 1.45	
	G3: Normal → abnormal	483	3.90	2.42 – 6.29		1.66	1.37 – 2.01	
	G4: Abnormal → abnormal	534	3.87	2.52 – 5.96	<0.01	1.91	1.59 – 2.29	<0.01

*Statistical analysis by logistic regression (adjusted for age, body mass index and sex) and *P* for trend.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FPG, fasting plasma glucose; GGT, gamma-glutamyltranspeptidase.

RESULTS

The present study surveyed a total of 9,393 semiconductor workers comprising of 8,354 men (88.9%) and 1,039 women (11.1%). The participants' age range was from 20 to 39 years (63.7%), and the frequency of drinking was to two to three times a month (50.9%). A total of 36.8% of the participants were smokers, and 63.3% were current non-smokers. The period of smoking was mostly 5–10 years (23.7%). A total of 78.3% had balanced eating (regular) habits. Fasting plasma glucose (FPG) levels at the last health check-up were related to sex ($P < 0.01$ by Student's *t*-test), age (<0.01 by ANOVA), drinking frequency (<0.01), smoking status (<0.01), duration of smoking (<0.01), diet pattern (<0.01) and liver status (<0.01) in the univariate analysis. FPG levels were related to sweat exercise status (Table 1; $P < 0.01$ by ANOVA). In past diseases history, the FPG level with hypertension was the highest, and then stroke and heart disease (<0.01 by ANOVA; Table 1).

The geometric mean ± geometric standard deviation of FPG was 91.68 ± 1.09, 94.16 ± 1.09 and 95.54 ± 1.11 mg/dL in the first, second and last medical examinations, respectively. The health outcomes from general clinical examinations, such as cholesterols, triglyceride, blood pressure and so on, are described in Table 2. FPG was associated with AST ($P = 0.03$), ALT (<0.01) and GGT (<0.01) after adjustment for sex (men vs women), age (26–39, 40–49 and 50–59 years), BMI (weight [kg] / height $[m]^2$), diet pattern (vegetarian, balanced diet and meat eater), drinking frequency (non-drinkers, two to three times/month, one to two times/week, three to four times/week and every day), smoking status (non-smokers, ex-smokers and smokers) and systolic blood pressure in multiple linear regression ($n = 8.379$; Table 3).

Table 4 shows the odds ratios for FPG by alteration of liver function enzymes, such as ALT, AST and GGT, from the first to last health check-up. All odds ratios for liver function enzymes were elevated from G1 (reference) to G4 after adjusting for age, BMI and sex (*P* for trend <0.01; Table 4). The levels of FPG at last health examination were increased from G1 to G4 ($P < 0.01$ for ALT, AST and GGT by ANOVA test; Figure 1).

DISCUSSION

The present study used the data of participants who had three cycles of health check-ups from 2002 to 2010 to study the impact of changes of enzymes levels on liver function. The highest abnormal liver function value in the first test was shown as the same highest abnormal liver function value in the second test in semiconductor workers. Therefore, the present study shows quantitatively that people with abnormal liver function levels can be diabetics, and the FPG level of recovered liver function is lower than the level of existing bad liver function or newly worse liver function. The FPG levels at the last check-up were the highest in the G4 group for each liver marker as shown in Figure 1. The meaning of this result is the absolute values of glucose in each group. The odds ratios for FPG >126 were the highest in G3 for AST and GGT, or in G4 for ALT, as shown in Table 4. The result represents the risk of prevalence of over 126 FPG, but we could explain the highest odds ratios in G3 for AST and GGT as being by chance.

In a previous study, the Bogalusa Heart's Study showed that diabetes ($n = 80$) and prediabetes ($n = 101$) were significantly associated with ALT and GGT in healthy adults (average age 41.3 years)[16]. A previous prospective community-based study found an association between ALT and type 2 diabetes in an Asian population[17]. We also showed the independent predictive value of AST, ALT and GGT activity in diabetes after adjustment for risk factors including age, BMI, alcohol drinking frequency and blood pressure. The results of the present study

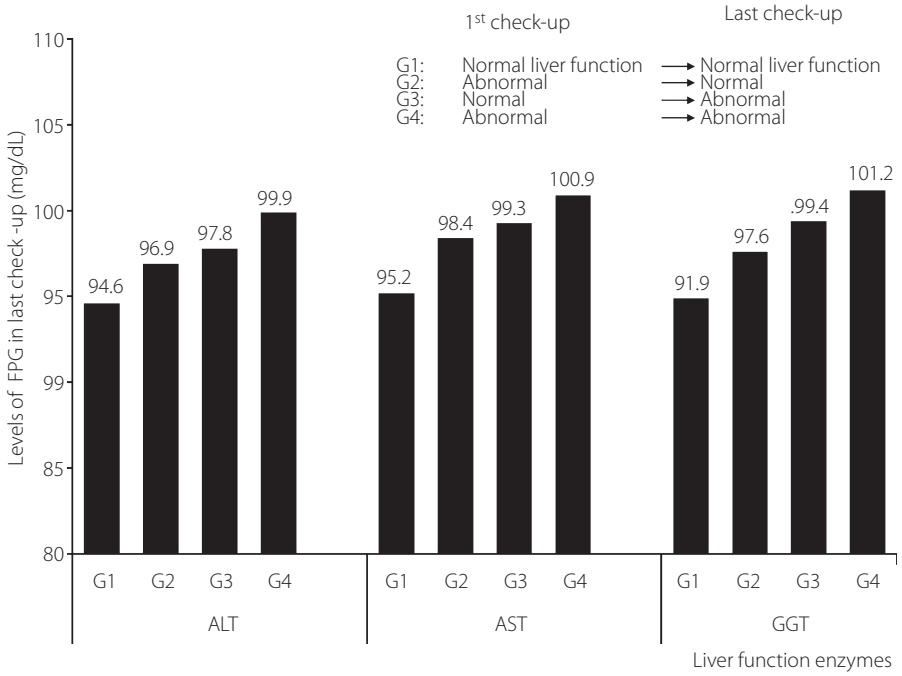

Figure 1 | Changes of fasting plasma glucose (FPG) levels at last health check-up depending on liver function from the first to second health examinations. *P*-values were <0.01 for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma (γ)-glutamyltranspeptidase (GGT) levels by ANOVA test.

support previous longitudinal follow-up studies reporting an association between abnormal liver function and diabetes. However, epidemiological studies on FPG levels through alterations of liver function from continuous monitoring are limited. Scientists have shown that oxidative stress is related to liver function enzymes[8] and diabetes[18]. An animal model study showed that oxidative damage is associated with insulin resistance or insulin sensitivity[19] and diabetic patients[20]. Increased oxidative stress serves to facilitate transport of glutathione in the cell, increased glutathione is related to diabetes[21]. In particular, GGT is used as an indicator of oxidative stress, and is also associated with diabetes in a previous study[22].

The benefits of the present study, first of all, are that the study was able to more precisely identify the FPG level related to changes of liver function from the check-up data collected from participants who underwent all three check-ups. Second, all of the existing studies have focused on the consequential occurrence of chronic disease according to the level of liver function, but in the present study, the risk of FPG level was confirmed through a regression model. Finally, our analysis of a large number of participants gave more statistically significant results and removed selection bias.

In conclusion, an association was observed between FPG levels and abnormal liver function in manufacturing workers. Abnormal liver function can be closely associated with the development of diabetes. In order to prevent further diabetes burden in people with abnormal liver enzyme levels, healthcare professionals should monitor them carefully.

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