Observational Study

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Physical activity can reduce the prevalence of gallstone disease among males

An observational study

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Abstract

Several previous studies have reported that physical activity (PA) levels can independently affect the prevalence of gallstone disease (GD) in Western countries. However, this association has not been reported in Eastern countries. Therefore, this study aimed to determine whether PA is an independent determinant of GD prevalence in a Korean population, according to the World Health Organizations Global Recommendations on PA for Health.

A total of 8908 subjects who completed a questionnaire underwent medical examination and ultrasound scanning at the Health Promotion Center of the Jeju National University Hospital between January 2009 and December 2018. GD and fatty liver disease were diagnosed by abdominal ultrasound. Biochemical parameters and body mass index were determined, and metabolic syndrome status, age, and PA levels were extracted from medical records. Univariate and multivariate analyses were performed to identify independent factors affecting GD.

The estimated rates of PA and GD among male subjects were 23.7% and 4.6%, whereas the rates among females were 18.4% and 4.2%, respectively. Multivariate analysis suggested that no PA, old age, and higher aspartate aminotransferase level in males and nonalcoholic fatty liver disease status in females were independent factors affecting GD.

In our study, PA was associated with a reduction in GD among males but not females.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GD = gallstone disease, GGT = gamma-glutamyl transferase, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, PA = physical activity.

Keywords: gallstones, metabolic syndrome, nonalcoholic fatty liver disease, physical activity, risk factors

1. Introduction

Gallstone disease (GD) can cause acute abdomen, jaundice, and abnormal liver function due to stones deposited in the gallbladder or bile ducts. This disease is widespread and is one of the most expensive digestive diseases around the world.[1] It has been reported that GD comprises 13% to 50% of digestive diseases in Western countries, including the US and Europe, and 2% to 10% in Eastern countries, including South Korea.[2] The prevalence of GD is known to vary greatly by region and race. In particular, well-established risk factors for GD include old age, female gender, obesity, metabolic syndrome, weight loss, Crohn disease, and chronic liver disease.[3–5]

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease that is most common in developed countries where no drugs have been approved as a standard therapy.[6,7] NAFLD occurs in patients who do not qualify as having consumed excessive amounts of alcohol or as fulfilling other known risk criteria for chronic liver disease. NAFLD is associated with various histological features, ranging from simple steatosis to steatohepatitis. Furthermore, NAFLD can develop into severe hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma.[8–10] This disease is closely related to extrahepatic diseases, including type 2 diabetes mellitus, chronic kidney disease, and cardiovascular disease.[3] Qiao et al[10] recently reported a significantly high prevalence of GD among NAFLD patients. They also noted that the prevalence of NAFLD and GD was high

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among the same subjects because NAFLD and GD share risk factors, such as obesity, type 2 diabetes mellitus, and peripheral resistance to insulin.[10] Moreover, metabolic syndrome is also known as a risk factor for GD,[11,12] and metabolic syndrome, like NAFLD, shares risk factors with GD, including peripheral resistance to insulin, obesity, and dyslipidemia.[13] Therefore, metabolic syndrome, NAFLD, and GD share common risk factors.[9,14]

Regular physical activity (PA) reduces the incidence of chronic diseases, particularly cardiovascular diseases.[1] Furthermore, PA has been reported to play a role in preventing NAFLD among obese patients.[6] However, a lack of PA is associated with obesity, type 2 diabetes mellitus, and, accordingly, peripheral resistance to insulin as well as metabolic syndrome.[1] These associations suggest that PA can reduce the incidence of NAFLD and metabolic syndrome. The authors hypothesized that PA might reduce GD prevalence by mitigating the effects of GD risk factors. Thus, the primary objective of this study was to determine whether PA could be an independent determinant of GD development according to the World Health Organizations Global Recommendations on PA for Health.[15] The secondary objective was to determine whether there are any differences in clinical variables that are known to influence the prevalence of GD, including metabolic syndrome or NAFLD status, that vary by PA levels or gender.

2. Methods

2.1. Subjects

A total of 10,133 subjects visited the Health Promotion Center of Jeju National University Hospital for medical checkups between January 2009 and December 2018. Among them, 1225 subjects were excluded because they underwent cholecystectomy (n = 316) or hepatectomy (n = 4), because they did not complete their questionnaires or refused to consent (n = 581), or because they had hepatitis (n = 324). If a patient underwent more than 1 medical checkup during the study period, their initial data were used. Finally, 8908 subjects were included in this study. This study was reviewed and approved by the hospitals institutional review board (IRB number. JNUH 2019–06–009–001).

2.2. Questionnaire

Subjects were asked to complete a questionnaire and to declare clinical indicators and demographic data. The questionnaire was designed by the study investigators and included the following items and categories: address, telephone number, history of medical diseases (including, specifically, hyperlipidemia, diabetes mellitus and related medication history, hypertension, stroke, heart disease, and tuberculosis), smoking history, familial causes of death, alcohol consumption, and other medications.

2.3. Diagnosis of gallstone disease

Ultrasound examinations using IU22 (Koninklijke Philips Electronics N. V., Amsterdam, the Netherlands) high-resolution ultrasound equipment were performed by special radiologists. The abdominal scan was performed after subjects fasted for at least 8 hours. GD was diagnosed based on the presence of echogenic and acoustic shadows and echo movement within the gallbladder associated with position changes.[16]

2.4. Definition of physical activity

Subjects were asked to complete a questionnaire evaluating PA levels according to the World Health Organizations Global Recommendations on Physical Activity for Health 2010.[15] Subjects were defined as physically active if they performed moderate-intensity aerobic PA for at least 150 minutes, or vigorous-intensity activity for at least 75 minutes throughout the week with aerobic activity comprising at least 10 minutes duration.

2.5. Definitions of nonalcoholic fatty liver disease and metabolic syndrome

NAFLD was defined according to the revised definition provided by the Korean Association for the Study of the Liver in 2013.[17] NAFLD was characterized by fatty infiltration observed on the liver on biopsy or radiologic findings (brightness of the liver and the presence of diffuse echogenicity in the liver parenchyma on abdominal ultrasonography[18]), with no history of medication intake, other causes of fatty liver (for example, autoimmune hepatitis, positive hepatitis B antigen, or hepatitis C virus), or significant alcohol consumption (≥210 g/week for males; ≥140 g/week for females).

Metabolic syndrome was defined according to the revised National Cholesterol Education Program criteria. Subjects were diagnosed as having metabolic syndrome if they fulfilled 3 or more of the following criteria: waist circumference ≥90 cm in males or ≥80 cm in females using the International Obesity Task Force criteria for the Asian-Pacific population to determine waist circumference,[19] triglycerides ≥150 mg/dl, antidyslipidemic medication use, high-density lipoprotein (HDL)-cholesterol <40 mg/dl in males or <50 mg/dl in females, high blood pressure ≥130/85 mm Hg or antihypertensive medication use, high fasting blood glucose ≥100 mg/dl or diabetes medication use (insulin or oral hypoglycemic agents).

2.6. Physical examination

Height and weight were automatically measured (GL-150R, G-Tech International Co., Gyeong-gido, Korea) without shoes and with light clothing in each subject. Subject age and sex were extracted from medical records. Venous blood samples were taken after 8 hours of fasting. Fasting blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total cholesterol, triglycerides, HDL-cholesterol, and low-density lipoprotein (LDL)-cholesterol levels were measured using venous blood samples.

GD prevalence was calculated according to sex, PA level, and age. The subjects were divided into 4 groups according to age: the 20–49, 50–59, 60–69, and ≥70-year age groups. Body mass index (BMI) was calculated by dividing weight by the square of height and classified into 4 groups, according to the World Health Organizations BMI categories for Asian populations[20]: underweight, <18.5 kg/m^2; normal weight, 18.5–22.9 kg/m^2; overweight, 23.0–24.9 kg/m^2; and obese, ≥25.0 kg/m^2. Fasting blood glucose levels were classified into 3 groups based on the standard proposed by the American Diabetes Association in 2015[21]: normoglycemia, <100 mg/dl; impaired fasting glucose, 100–125 mg/dl; and diabetes, ≥126 mg/dl. Fasting was defined as no caloric intake for at least 8 hours. Total cholesterol levels were classified into 3 groups: <200 mg/dl, 200–239 mg/dl, and ≥240 mg/dl. Serum LDL-cholesterol levels were classified into 5 groups:

<100 mg/dl, 100–129 mg/dl, 130–159 mg/dl, 160–189 mg/dl, and ≥190 mg/dl. Serum HDL-cholesterol levels were classified into 3 groups: <40 mg/dl, 40–60 mg/dl, and ≥60 mg/dl. Serum triglyceride levels were classified into 4 groups: <150 mg/dl, 150–199 mg/dl, 200–499 mg/dl, and ≥500 mg/dl. Each lipid level was classified according to the 2015 Korean Guidelines for the Management of Dyslipidemia.[22] AST levels were considered elevated if they were over 32 IU/L for men and over 26 IU/L for women. ALT levels were considered elevated if they were over 34 IU/L for men and over 24 IU/L for women.[23] ALP and GGT levels were considered high if they were greater than 130 IU/L and 71 IU/L, respectively.

2.7. Statistical analysis

We compared clinical variables using Students *t* test for continuous variables and the Chi-Squared test for categorical variables, depending on the presence of GD. We performed binary logistic regression analysis, including age, sex, NAFLD, metabolic syndrome, BMI, fasting blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, ALT, AST, GGT, and ALP levels, as well as PA. Stepwise logistic regression was applied for the development of the fitted model estimating the predictive probability of GD when the factors were less than 0.1 on the univariate analysis by binary regression analysis. We considered a *P* value <.05 as statistically significant. All statistical analyses were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. GD prevalence and PA rates

Of the 8908 subjects, 4696 (53%) were males and 4212 (47%) were females. The estimated rates of GD and PA were 4.6% and 23.7% among male subjects and 4.2% and 18.4% among female subjects, respectively. There was no difference in GD prevalence between the genders. The estimated rates of PA according to gender and age group are shown in the Figure 1. The rates of PA among male subjects were significantly higher than those among female subjects in all age groups.

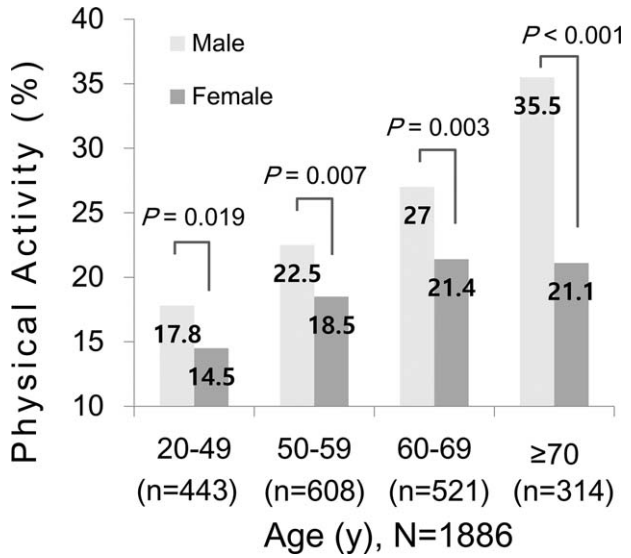

Figure 1. The rates of physical activity recommended by the World Health Organization according to age.

Table 1

Comparisons of the variables between 2 groups according to the presence or absence of gallstones in subjects who underwent medical check-up.

Variables	Subjects with GD (n = 394)	Subjects without GD (n = 8,514)	*P* value
Gender (%)			.353
Male	217 (55.1)	4479 (52.6)	
Female	177 (44.9)	4035 (47.4)	
Nonalcoholic fatty liver disease			<.001
Yes	205 (52.0)	3622 (42.5)	
No	189 (48.0)	4892 (57.5)	
Metabolic syndrome			<.001
Yes	124 (33.5)	1920 (24.8)	
No	246 (66.5)	5812 (75.2)	
Age (years)	59.4 ± 11.6	55.7 ± 11.3	<.001
Body mass index (kg/m^2)	25.5 ± 4.0	24.8 ± 3.4	<.001
Fasting blood glucose (mg/dl)	102.0 ± 27.7	98.7 ± 29.2	.031
Total cholesterol (mg/dl)	198.6 ± 37.1	199.0 ± 37.3	.813
LDL-cholesterol (mg/dl)	122.4 ± 34.6	121.3 ± 34.5	.534
HDL-cholesterol (mg/dl)	51.9 ± 13.5	54.1 ± 13.7	.002
Triglycerides (mg/dl)	123.8 ± 80.3	118.5 ± 93.9	.279
AST (IU/L)	29.7 ± 39.6	27.8 ± 52.9	.509
ALT (IU/L)	32.2 ± 37.7	29.9 ± 73.4	.543
GGT (IU/L)	47.3 ± 62.6	44.6 ± 78.1	.513
ALP (IU/L)	221.1 ± 82.5	208.2 ± 86.4	.008
Medication use for diabetes			.023
Yes	32 (8.1)	456 (5.4)	
No	362 (91.9)	8058 (94.6)	
Medication use for dyslipidemia			.375
Yes	13 (3.3)	375 (4.4)	
No	381 (96.7)	8139 (95.6)	
Medication use for hypertension			<.001
Yes	95 (24.1)	1434 (16.8)	
No	299 (75.9)	7080 (83.2)	
Physical activity			.165
Yes	72 (18.3)	1814 (21.3)	
No	322 (81.7)	6700 (78.7)	

Values are expressed as n (%) or mean ± standard deviation.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GD = gallstone disease, GGT = gamma-glutamyl transferase, HDL = high-density lipoprotein, LDL = lower density lipoprotein.

3.2. Comparisons of clinical variables between subjects with and without GD

Subjects were classified into 2 groups according to the presence or absence of GD. The mean age, BMI, fasting blood glucose, and ALP level were significantly higher among subjects with GD. The mean HDL-cholesterol level was significantly lower among subjects with GD. Subjects with GD had significantly higher rates of NAFLD and metabolic syndrome, as well as medication use for diabetes and hypertension than those without GD (Table 1). There was no statistical difference in GD prevalence between physically active and inactive subjects.

3.3. Univariate analysis of risk factors for GD

Table 2 shows the factors affecting GD according to gender. Age, NAFLD, metabolic syndrome, AST level, medication use for diabetes, and hypertension, and PA were significantly associated

Table 2

Univariate analysis of risk factors affecting for gallstone disease according to gender in subjects who underwent medical check-up.

	Male subjects				Female subjects			
Factors	**Number of subjects**	**Number of gallstone disease, n (%)**	**Odds ratio (95% Confidence interval)**	***P value**	**Number of subjects**	**Number of gallstone disease, n (%)**	**Odds ratio (95% Confidence interval)**	***P value**
Age (years)				<.001				.042
20–49	1486	44 (3.0)	1.000		1229	44 (3.6)	1.000	
50–59	1544	59 (3.8)	1.302 (0.875–1.937)	.193	1407	49 (3.5)	0.972 (0.642–1.471)	.892
60-69	1091	69 (6.3)	2.213 (1.503–3.257)	<.001	1054	54 (5.1)	1.454 (0.968–2.185)	.071
≥70	575	45 (7.8)	2.783 (1.815–4.266)	<.001	522	30 (5.7)	1.642 (1.020–2.643)	.041
Nonalcoholic fatty liver disease				<.001				<.001
Yes	2381	119 (5.0)	1.255 (0.905–1.565)		1446	86 (5.9)	1.904 (1.374–2.514)	
No	2315	98 (4.2)	1.000		2766	91 (3.3)	1.000	
Metabolic syndrome				.004				.023
Yes	1592	95 (6.0)	1.504 (1.136–1.991)		452	29 (6.4)	1.616 (1.068–2.444)	
No	2766	112 (4.0)	1.000		3292	134 (4.1)	1.000	
BMI (kg/m^2)								
<18.5	72	3 (1.4)	1.000	.234	110	2 (1.8)	1.000	.210
18.5–22.9	976	40 (4.1)	0.983 (0.297–3.258)	.978	1509	54 (3.6)	2.004 (0.482–8.331)	.339
23–24.9	1197	46 (3.8)	0.919 (0.279–3.030)	.890	1060	52 (4.9)	2.786 (0.669–11.596)	.159
≥25	2451	128 (5.2)	1.267 (0.394–4.081)	.691	1533	69 (4.5)	2.545 (0.616–10.523)	.197
Fasting blood glucose (mg/dl)								
<100	2741	115 (4.2)	1.000	.065	2877	111 (3.9)	1.000	.076
100–125	1172	63 (5.4)	1.297 (0.947–1.778)	.106	715	40 (5.6)	1.477 (1.019–2.140)	.040
≥126	510	32 (6.3)	1.532 (1.023–2.294)	.038	213	12 (5.6)	1.488 (0.806–2.745)	.204
Total cholesterol (mg/dl)								
<200	2274	119 (5.2)	1.000	.223	2053	83 (4.0)	1.000	.574
200–239	1528	68 (4.5)	1.441 (0.913–2.272)	.116	1271	61 (4.8)	1.197 (0.853–1.678)	.298
≥240	624	23 (3.7)	1.215 (0.750–1.968)	.429	465	21 (4.5)	1.123 (0.688–1.832)	.643
LDL-cholesterol (mg/dl)								
<100	1141	66 (5.8)	1.000	.186	1040	33 (3.2)	1.000	.131
100–129	1523	63 (4.1)	0.703 (0.493–1.001)	.051	1359	61 (4.5)	1.434 (0.932–2.208)	.101
130–159	1151	58 (5.0)	0.864 (0.601–1.242)	.431	941	45 (4.8)	1.533 (0.969–2.423)	.068
160–189	452	15 (3.3)	0.559 (0.316–0.990)	.046	320	16 (5.0)	1.606 (0.872–2.958)	.128
≥190	138	15 (3.3)	0.870 (0.391–1.937)	.734	102	8 (7.8)	2.597 (1.166–5.784)	.019
HDL-cholesterol (mg/dl)								.023
<40	831	50 (6.0)	1.000	.105	242	19 (7.9)	1.000	
40–60	2726	127 (4.7)	0.763 (0.545–1.069)	.116	1857	80 (4.3)	0.528 (0.314–0.888)	.016
≥60	882	34 (3.9)	0.626 (0.401–0.979)	.040	1706	67 (3.9)	0.480 (0.283–0.814)	.006
Triglyceride (mg/dl)								
<150	2988	145 (4.9)	1.000	.792	3301	135 (4.1)	1.000	.126
150–199	686	31 (4.5)	2.652 (0.364–19.319)	.336	288	18 (6.2)	1.563 (0.941–2.596)	.084
200–499	712	34 (4.8)	2.461 (0.329–18.391)	.380	210	12 (5.7)	1.421 (0.774–2.610)	.257
≥500	53	1 (1.9)	2.608 (0.350–19.432)	.350	6	1 (16.7)	4.690 (0.544–40.425)	.160
AST (IU/L)				.043				.018
≤32 for men	2648	114 (4.3)	1.000		3014	119 (3.9)	1.000	
> 32 for men	998	59 (5.9)	1.397 (1.011–1.929)		399	26 (6.5)	1.696 (1.095–2.627)	
ALT (IU/L)				.081				.029
≤34 for men	2029	84 (4.1)	1.000		2931	114 (3.9)	1.000	
>34 for men	2394	126 (5.3)	1.286 (0.970–1.707)		875	49 (5.6)	1.466 (1.040–2.067)	
GGT (IU/L)				.398				.744
≤71	3477	166 (4.8)	1.000		3721	155 (4.2)	1.000	
>71	1219	51 (4.2)	1.148 (0.833–1.582)		491	22 (4.5)	1.079 (0.683–1.704)	
ALP (IU/L)				.486				.659
≤130	146	5 (3.4)	1.000		372	14 (3.8)	1.000	
>130	4550	212 (4.7)	1.378 (0.559–3.398)		3840	163 (4.2)	1.134 (0.650–1.978)	
Medication use for diabetes				<.001				<.001
Yes	342	23 (6.7)	1.745 (0.989–2.417)		146	9 (6.2)	1.944 (0.763–3.045)	
No	4354	194 (4.5)	1.000		4066	168 (4.1)	1.000	
Medication use for dyslipidemia				<.001				<0.001
Yes	166	8 (4.8)	1.303 (0.508–2.159)		222	5 (2.3)	2.703 (0.795–4.807)	
No	4530	209 (4.6)	1.000		3990	172 (4.3)	1.000	
Medication use for hypertension				<.001				<.001
Yes	930	64 (6.9)	1.805 (1.292–2.358)		599	31 (5.2)	1.042 (0.871–1.929)	
No	3766	153 (4.1)	1.000		3613	146 (4.0)	1.000	
Physical activity				.030				.770
Yes	1112	38 (3.4)	0.673 (0.471–0.962)		774	34 (4.4)	0.945 (0.644–1.385)	
No	3584	179 (5.0)	1.000		3438	143 (4.2)	1.000	

Values are expressed as n (%) or mean ± standard deviation.

* This value was obtained using the binary regression test.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = gamma-glutamyl transferase, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 3

Multivariate analysis of risk factors for gallstone disease according to gender in subjects who underwent medical check-up.

Male subjects			
Factors	**Odds ratio**	**95% Confidence interval**	***P* value**
Age (years)			<.001
20–49	1.000		
50–59	1.147	0.894–2.277	.137
60–69	2.868	1.830–4.493	<.001
≥70	3.863	2.357–6.332	<.001
AST (IU/L)			.023
≤32 for men	1.000		
>32 for men	1.465	1.054–2.036	
Physical activity			.013
Yes	0.599	0.400–0.897	
No	1.000		

Female subjects			
Factors	**Odds ratio**	**95% Confidence interval**	***P* value**
Nonalcoholic fatty liver disease			<.001
Yes	1.712	1.004–2.408	
No	1.000		

AST = aspartate aminotransferase.

with GD among male subjects. Age, NAFLD, metabolic syndrome, HDL-cholesterol, AST level, ALT level, medication use for diabetes, and hypertension were significantly associated with GD among female subjects. Interestingly, PA did not show a significant association with GD among female subjects (Table 2).

3.4. Multivariate analysis of risk factors for GD

Binary logistic regression analysis was performed for clinical variables, including age, NAFLD, metabolic syndrome, AST level, and medication use for diabetes, and hypertension, as well as PA among male subjects, and age, NAFLD, metabolic syndrome, HDL-cholesterol, AST and ALT levels, medication use for diabetes, and hypertension among female subjects, were significantly associated with GD in the univariate analysis (Table 3). PA, old age, higher AST level among male subjects, and NAFLD among female subjects were independently associated with GD. GD prevalence significantly increased with age (odds ratio [OR], 1.147 in the 50–59 age group; OR, 2.868 in the 60–69 age group; and OR, 3.863 in the ≥70 age group; $P < .001$ for all). The factors independently associated with GD were PA (OR, 1.000 for no PA; OR, 0.599 for PA; $P = .013$) and AST >32 IU/L (OR, 1.465; $P = .023$) among male subjects, and NAFLD (OR, 1.712; $P < .001$) among female subjects.

3.5. Comparisons of clinical variables between the genders

To reveal why there was no difference in GD prevalence between the genders, we compared clinical variables according to gender. Male subjects had significantly higher rates of PA, NAFLD, metabolic syndrome, medication use for diabetes, and medication use for hypertension, as well as significantly higher mean values for BMI, fasting blood glucose, total cholesterol, triglycerides, AST, ALT, GGT, and ALP levels than female subjects. However, the mean HDL-cholesterol level and the proportion of subjects taking medication for dyslipidemia were significantly higher among female subjects (Table 4).

Table 4

Comparisons of the variables between 2 gender groups in subjects who underwent medical check-up.

Factors	**Male Subjects (n = 4,696)**	**Female Subjects (n = 4,212)**	***P* value**
Gallstone disease (%)			.353
Yes	217 (4.6)	177 (4.2)	
No	4479 (95.4)	4035 (95.8)	
Nonalcoholic fatty liver disease			<.001
Yes	2381 (50.7)	1446 (34.3)	
No	2315 (49.3)	2766 (65.7)	
Metabolic syndrome			<.001
Yes	1592 (36.5)	452 (12.1)	
No	2766 (63.5)	3292 (87.9)	
Age (years)	55.5 ± 11.3	55.9 ± 11.4	0.127
Body mass index (kg/m^2)	25.3 ± 3.3	24.3 ± 3.6	<.001
Fasting blood glucose (mg/dl)	102.5 ± 34.0	94.6 ± 21.3	<.001
Total cholesterol (mg/dl)	199.9 ± 37.8	198.0 ± 36.7	.022
LDL-cholesterol (mg/dl)	122.0 ± 35.5	120.5 ± 33.3	.054
HDL-cholesterol (mg/dl)	50.0 ± 12.2	58.7 ± 13.7	<.001
Triglycerides (mg/dl)	140.6 ± 108.3	93.2 ± 63.2	<.001
AST (IU/L)	30.4 ± 52.2	25.0 ± 52.5	<.001
ALT (IU/L)	35.3 ± 77.1	23.8 ± 65.4	<.001
GGT (IU/L)	61.6 ± 96.6	25.3 ± 38.0	<.001
ALP (IU/L)	214.4 ± 84.8	202.3 ± 87.6	<.001
Medication use for diabetes			<.001
Yes	342 (7.3)	146 (3.5)	
No	4354 (92.7)	4066 (96.5)	
Medication use for dyslipidemia			<.001
Yes	166 (3.5)	222 (5.3)	
No	4530 (96.5)	3990 (94.7)	
Medication use for hypertension			<.001
Yes	930 (19.8)	599 (14.2)	
No	3766 (80.2)	3613 (85.8)	
Physical Activity			<.001
Yes	1112 (23.7)	774 (18.4)	
No	3584 (76.3)	3438 (81.6)	

Values are expressed as n (%) or mean ± standard deviation.
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, HDL = high-density lipoprotein, LDL = lower density lipoprotein.

3.6. Comparison of clinical variables according to physical activity and gender

Physically active male subjects had a higher mean age, HDL-cholesterol level and a higher rate of medication use for hypertension, as well as significantly lower mean levels of total cholesterol, triglycerides and NAFLD than males who were not physically active. A significantly higher proportion of physically active than inactive female subjects were taking medication for diabetes. Physically active females also had the lower mean level of triglycerides (Table 5).

4. Discussion

In the last few decades, prevalence of GD in Korea has been reported as 2% to 3%.[24,25] Because the Westernized diet characterized by high calories and refined carbohydrates has become prevalent,[3,4] the GD prevalence in Korea has increased, according to reports from Western countries,[2,26] The GD prevalence in Korea has recently been estimated to be 4% to 5%, which is slightly higher than that reported by previous studies.[2,26] The present study found the overall prevalence of

Table 5

Comparisons of the variables according to physical activity in 2 gender groups according to gender in subjects who underwent medical check-up.

	Male subjects			Female subjects		
Factors	Subjects with PA (n = 1,112)	Subjects without PA (n = 3,584)	*P* value	Subjects with PA (n = 774)	Subjects without PA (n = 3,438)	*P* value
Gallstone disease (%)			.027			.766
Yes	38 (3.4)	179 (5.0)		34 (4.4)	143 (4.2)	
No	1074 (96.6)	3405 (95.0)		740 (95.6)	3295 (95.8)	
Nonalcoholic fatty liver disease			.012			.586
Yes	527 (47.4)	1854 (51.7)		259 (33.5)	1187 (34.5)	
No	585 (52.6)	1730 (48.3)		515 (66.5)	2251 (65.5)	
Metabolic syndrome			.268			.296
Yes	363 (35.1)	1229 (37.0)		89 (13.2)	363 (11.8)	
No	672 (64.9)	2094 (63.0)		583 (86.8)	2709 (88.2)	
Age (years)	57.9 ± 11.4	54.8 ± 11.2	<.001	57.4 ± 10.9	55.6 ± 11.5	.063
Body mass index (kg/m^2)	25.4 ± 3.2	25.2 ± 3.3	.095	24.3 ± 3.6	24.3 ± 3.6	.682
Fasting blood glucose (mg/dl)	103.4 ± 40.6	102.2 ± 31.7	.346	94.6 ± 19.4	94.6 ± 21.7	.566
Total cholesterol (mg/dl)	197.3 ± 35.2	200.7 ± 38.5	.012	195.5 ± 35.5	198.5 ± 36.9	.528
LDL-cholesterol (mg/dL)	121.2 ± 33.2	122.2 ± 36.2	.416	118.4 ± 31.4	121.0 ± 33.7	.098
HDL-cholesterol (mg/dL)	50.8 ± 12.3	49.7 ± 12.2	.013	59.6 ± 13.9	58.5 ± 13.7	.254
Triglycerides (mg/dl)	126.0 ± 83.1	145.1 ± 114.6	<.001	87.9 ± 49.9	94.4 ± 65.7	.001
AST (IU/L)	30.3 ± 39.4	30.4 ± 55.5	.930	26.1 ± 40.5	24.8 ± 54.7	.614
ALT (IU/L)	34.9 ± 90.6	35.5 ± 72.5	.846	25.0 ± 55.5	23.5 ± 67.4	.443
GGT (IU/L)	57.4 ± 93.1	62.9 ± 97.7	.108	23.5 ± 27.1	25.7 ± 40.0	.051
ALP (IU/L)	211.3 ± 94.8	215.4 ± 81.3	.198	202.1 ± 82.2	202.4 ± 88.8	.906
Medication use for diabetes			.113			.012
Yes	93 (8.4)	249 (6.9)		39 (5.0)	107 (3.1)	
No	1019 (91.6)	3335 (93.1)		735 (95.0)	3331 (96.9)	
Medication use for dyslipidemia			.137			.593
Yes	31 (2.8)	135 (3.8)		44 (5.7)	178 (5.2)	
No	1081 (97.2)	3449 (96.2)		730 (94.3)	3260 (94.8)	
Medication use for hypertension			.043			.649
Yes	244 (21.9)	686 (19.1)		114 (14.7)	485 (14.1)	
No	868 (78.1)	2898 (80.9)		660 (85.3)	2953 (85.9)	

Values are expressed as n (%) or mean ± standard deviation.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, HDL = high-density lipoprotein, LDL = lower density lipoprotein.

GD to be 4.4%, which is similar to previous results for Korean participants who recently underwent medical.[2]

A systematic review analyzing 22 studies evaluating PA reported that the proportion of subjects performing the recommended level of PA was highest among participants in their 60 seconds compared with other age groups, and the PA level among male subjects was significantly higher than that among female subjects in all age groups.[27] Additional reports present PA rates of approximately 0.8% to 21.4% and corroborate the observation that PA levels among male subjects are higher than among female subjects in this region.[28,29] The present study also found that PA levels among male subjects in all age groups were statistically significantly higher than those among female subjects, and PA levels were the highest for subjects in their 70 seconds or older compared with other age groups. The overall PA rates were approximately 23.7% and 18.4% for male and female subjects, respectively, and the PA rate for male subjects was approximately 5% higher than that of female subjects, which is similar to the results from other studies.[27,28]

A study conducted in Europe emphasized that PA plays a protective role against GD,[1,6] and other studies have shown that PA has an inverse association with GD prevalence.[30] The present study demonstrated that PA was independently and inversely associated with GD among male subjects only. To determine whether PA was independently associated with GD prevalence among male subjects, the present study investigated the difference between male and female subjects depending on PA and gender. The mean total cholesterol and triglyceride levels, as well as the NAFLD prevalence, were lower—and the mean HDL-cholesterol level—was higher among physically active men compared with physically inactive men. On the other hand, the mean triglycerides level was only lower among physically active females compared with inactive females. Moreover, values for NAFLD prevalence, as well as mean BMI, fasting blood glucose, total cholesterol, and triglyceride levels were lower—and mean HDL-cholesterol level was higher—among male subjects than among female subjects. These factors were previously known to be risk factors for GD, and their effects could be mitigated by PA. As reported by Qiao et al[10] and Jeong et al,[26] GD is caused by lithogenic factors, including peripheral resistance to insulin, high BMI, and low HDL-cholesterol levels in male subjects, and GD is caused by estrogen that is influenced by pregnancy and childbirth in female subjects. These explanations can be inferred from these results. For example, for male subjects, the frequencies of risk factors for GD that could be corrected by PA were relatively high, and 1 might infer that NAFLD and total cholesterol levels were ameliorated by PA, thereby reducing the GD prevalence. However, for female subjects, the frequencies of risk factors for GD that could be corrected by PA were relatively low, and GD in female subjects

occurs mainly due to estrogen levels that are not controlled by PA.

The proportions of physically active individuals among male subjects were higher in all age groups compared with the proportions among female subjects. Nevertheless, there was no significant difference in GD prevalence according to gender. This may be a paradoxical result considering the plausible explanation that GD was caused by uncorrectable estrogen levels in female subjects. However, this can be explained in the sense that male gender is associated with more risk factors that influence GD. In other words, there was no difference in GD prevalence between male and female subjects, although there was a higher proportion of physically active males because the male subjects were susceptible to more risk factors for GD that are correctable by PA, but some of these were offset by the increased PA level among males, which led to the lack of a statistically significant difference between the genders.

The mean age of the physically active participants of the present study was significantly higher than that of the inactive participants. This suggests that as people grow older, they become more interested in health and therefore engage in more exercise. In many studies, age has been shown to be the factor most strongly associated with GD prevalence.[9,11,26] Studies conducted on Korean populations have made the same observation.[2] It follows, then, that the prevalence of GD should be higher in the PA group with a higher mean age. However, the present study found that the prevalence of GD was lower in the PA group than among participants who were categorized as inactive. This finding suggests that PA is a protective factor in the incidence of GD.

PA has been reported to reduce the prevalence of GD.[1,30] PA reduces hyperinsulinemia and peripheral resistance to insulin, which are major contributors to the pathophysiology of GD. Further along the pathway, hyperinsulinemia promotes cholesterol absorption in the liver and increases the secretion of cholesterol in bile while reducing the secretion of bile acids. Regular PA reduces the levels of serum cholesterol and triglycerides and increases the HDL-cholesterol level. Apolipoprotein A1, which is a major component of HDL-cholesterol, has been reported to form and proliferate through PA.[31] Lecithin cholesterol acyltransferase, which plays an important role in the reverse cholesterol transport process together with apolipoprotein A1, is an enzyme that transports cholesterol esters to HDL-cholesterol, and the activation of lecithin cholesterol acyltransferase is reportedly increased by PA.[32,33] PA has also been reported to reduce the activation of cholesterol ester transfer proteins that transfer esters in HDL-cholesterol to other lipoproteins.[31–35] Thus, in line with the results of the present study, the increase of HDL-cholesterol levels by PA is induced by an increase in the concentration of apolipoprotein A1 as well as the migration and increase of peripheral tissue and intracellular cholesterol to HDL-cholesterol as a result of the enzymes mobilized during the reverse cholesterol transport process. The level of blood HDL-cholesterol increases in physically active individuals, and serum triglyceride levels, which are inversely associated with PA levels, play an important role in the production of cholesterol gallstones by influencing peripheral resistance to insulin as well as hyperinsulinemia.[1] Insulin stimulates the activation of hydroxyl-3-methylglutaryl-coenzyme A reductase and decreases the activation of 7a-hydroxylase, thereby increasing the secretion of cholesterol and reducing the secretion of bile acids[4,36]. The results of the present study are consistent with those of previous studies, reaffirming that HDL-cholesterol significantly increases among physically active men.

The World Health Organizations Global Recommendations on PA for Health in 2010 suggested that muscle-strengthening actives should be performed involving major muscle groups on 2 or more days a week.[15] However, unfortunately, the PA questionnaire developed for the present study did not inquire about this PA criterion because the criterion was recommended after the study had already begun. Moreover, previous studies investigated the relationship between PA and GD according to the previously recommended definitions, which were compared for this study. Thus, a prospective study that includes muscle-strengthening activities is required.

This study had some limitations. First, because this study retrospectively analyzed data recorded in the questionnaires rather than directly examining the PA during a set period, this study did not capture the length of time of PA required for an association with a reduction in GD. Second, this study was conducted at a single institution. Furthermore, because most of the subjects were living on Jeju Island, which is far from mainland South Korea, the results can differ slightly from populations living on the mainland. Thus, future multicenter prospective studies in South Korea are warranted. Third, this study did not collect and analyze other GD-related factors, including a history of alcohol consumption, viral hepatitis, or alcoholic fatty liver, as well as weight changes in association with GD. Fourth, this study was not able to compare risk factors according to gallstones constituents because ultrasound examinations are incapable of analyzing gallstones by their components.

Despite these limitations, this study analyzed the associations between PA and GD for South Koreans of both genders, and to the best of our knowledge, this was the first study to report on this subject in Asia. To accurately verify the results of this study in the future, a long-term, multicenter, prospective study will be required involving various South Korean institutions.

In conclusion, PA was independently and inversely associated with GD among males. Furthermore, physically active individuals differed from inactive individuals in terms of GD risk factors, such as triglyceride, total cholesterol, and HDL-cholesterol levels among males, and triglyceride levels among females.

Author contributions

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