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Prevalence and Risk Factors of Elevated Alanine Aminotransferase among Korean Adolescents: 2001-2014

한국 청소년에서 알라닌 아미노전이효소 상승의 유병률 및 위험 인자: 2001-2014

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서울대학교 대학원
의학과 소아과학 과정
김주휘

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The Department of Medicine
Seoul National University Graduate School
Ju Whi Kim

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Ju whi Kim

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Professor _____ Vice chairman

Professor _____

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위 원 장 _____ (인)

부위원장 _____ (인)

위 원 _____ (인)

ABSTRACT

Introduction: An elevated alanine aminotransferase (ALT) level is a surrogate marker of non-alcoholic fatty liver disease (NAFLD), the most common liver disorder in adolescents. The majority of previous NAFLD studies in adolescents were performed in selected obese populations or had a cross-sectional design without a time-trend analysis. The purpose of this study was to estimate the prevalence and time trends of elevated ALT levels in a general adolescent population and to identify factors associated with ALT elevation.

Methods: We analysed data on adolescent participants (aged 10–18 years) in the Korean National Health and Nutrition Examination Survey 2001–2014, a representative sample of the general population in South Korea. Suspected NAFLD was defined by ALT elevation (>30 U/L) without hepatitis B surface antigen. In all the statistical analyses, sampling weight- and design-based data were used.

Results: ALT was elevated in 5.3% (standard error: 0.3%) of the study population of adolescent participants (N=8455). No significant trends were found from 2001-2014 in the

prevalence of elevated ALT among male and female adolescents. In the multiple logistic regression analysis, elevated ALT was independently associated with sex (odds ratio [OR] male versus female 4.5; 95% CI, 3.3-6.2), obesity (OR 7.6; 95% CI, 5.3-11.0), and truncal obesity (OR 2.5; 95% CI, 1.8-3.5). Furthermore, male sex, obesity, truncal obesity and high household income level were associated with log transformed ALT levels in multiple regression analysis.

Conclusions: In Korean adolescents, the prevalence of elevated ALT levels was stable from 2001 to 2014 in adolescents of both genders. This study revealed that sex, obesity, truncal obesity and household income level are associated with paediatric NAFLD.

Keywords: Alanine aminotransferase, Prevalence, Fatty liver

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CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ALT; Alanine Aminotransferase

NAFLD; non-alcoholic fatty liver disease

OR; odds ratio

ULN; upper limit of normal

KCDC; Korean Centers for Disease Control and Prevention

KNHANES; Korean National Health and Nutrition Examination Survey

BMI; Body mass index

logeALT; log transformed ALT level

CIs; confidence intervals

NHANES; National Health and Nutrition Examination Survey

INTRODUCTION

Four decades ago, the first cases of paediatric non-alcoholic fatty liver disease (NAFLD) were reported. NAFLD is one of the most common causes of chronic liver disease in children in the developed world, and its prevalence is increasing in the developing world (1, 2). Paediatric NAFLD is associated with numerous serious health conditions, such as cardiovascular disease and metabolic syndrome, which includes dyslipidemia and hypertension (1). A recent systematic review based on 20 surveys in different populations reported that the prevalence of NAFLD in the general population is 7.6%, and there is no evidence that the prevalence has changed over time (3).

Despite controversies regarding the upper limit of normal (ULN) in children, an elevated ALT level is a common diagnostic criterion for NAFLD, especially in studies of the general population (1). ALT levels are influenced not only by NAFLD but also by various factors such as viral infection, alcohol consumption and drug use. However, liver biopsy, the gold standard for diagnosing NAFLD, is invasive, expensive and impractical as a population-level screening test. Ultrasound imaging, which is non-invasive and relatively inexpensive, is used for the diagnosis of NAFLD in the general population; however, this imaging method is too expensive and not feasible to utilize to determine the NAFLD prevalence in a nationwide survey (3). Based on ALT levels, the prevalence of NAFLD in adolescents in the United States increased over the past 20 years (4); in Korea, the prevalence was 6.5% in the Korean National Health and Nutrition Examination Survey (KNHANES) 2007-2009 (5).

In addition, it has been proposed that factors other than obesity and metabolic syndrome are associated with NAFLD. The prevalence of NAFLD is higher in countries with higher

economic status among adults; however, socioeconomic status is inversely associated with elevated ALT levels among United States adolescents (6). There have been few studies of the associations between NAFLD and socioeconomic factors such as household income level and parental education level. The purpose of this study was to estimate NAFLD prevalence and its trend among Korean adolescents and to identify risk factors, such as socioeconomic factors, to use for NAFLD screening using national data from 2001 to 2014.

MATERIALS AND METHODS

This study was based on data from the KNHANES conducted in South Korea by the National Center for Health Statistics of the Korean Centers for Disease Control and Prevention (KCDC). It consisted of a cross-sectional interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample representative of the general Korean population (7).

We analysed data on adolescent participants (aged 10-18 years) in KNHANES 2001-2014 (wave 2-6), a representative sample of the general Korean population. We excluded data from KNHANES wave 1 (1998), which had several limitations such as overestimated rates of diabetes mellitus due to sampling error. Sample weights were used to account for differential probabilities of selection and nonresponse and were included in the estimation process for all of the analyses. To analyse the annual prevalence and its trend, the weighted data were subsequently adjusted to represent the resident Korean population for ages 10 to 19 years, as estimated by the Korea Census in 2005. Informed consent was obtained from all of the participants, and the protocols for the KNHANES and this study were approved by the Institutional Review Board of the KCDC.

The health interview questionnaire is based on information provided by an adult respondent aged 19 years or older from a sampled household and includes income and demographic information on all members of the sampled household. Data were collected on sex, residency (e.g., urban or rural), age (i.e., years), household income and parental education level to define the subgroup at high risk for ALT elevation. We merged data for each parent to ascertain the parental education level, which was included in the KNHANES protocol from

2007.

According to standardized protocols, all health examinations were performed by trained medical staff who followed standardized procedures. Body weight, height, and waist circumference were measured to the nearest 0.1 kg or 0.1 cm. Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in metres squared (kg/m^2). Using Korean National Growth Charts (8), we defined the cutoff point for obesity as a BMI at the 95th percentile (25 kg/m^2). The cutoff point for truncal obesity was defined as the 90th percentile.

Serum samples were subsequently analysed at a central certified laboratory. Plasma concentrations of ALT and other parameters were measured with an autoanalyser. An elevated ALT level was defined as >30 U/L, which is the value used in previous studies on adolescents (6). We also conducted a repeat analysis using the 97.5^{th} percentile for ALT (33 U/L for boys and 25 U/L for girls), as suggested by a recent report based on KNHANES data (5). The presence of hepatitis B surface antigen was assessed using an electrochemiluminescence immunoassay.

Statistical analysis

Using the R statistical programming language, we generated figures for the time trend of elevated ALT prevalence and log transformed ALT level [$\log_e$ALT] by survey wave. We present P values for linear time trends using survey regression analysis after taking into account primary sampling units, stratification, and sample weights for time trends. Odds ratios (ORs) and 95% confidence intervals (CIs) for the prevalence of elevated ALT were

calculated by univariate survey logistic regression analyses using adjusted sample weights for the study population. A multiple logistic regression was used to estimate the OR associated with an elevated ALT level while controlling for all of the predictors that showed a significant association in the univariate analysis. In addition, survey regression analysis was used to assess the association of factors with $\log_e$ALT as a continuous variable. Factors thought to contribute to $\log_e$ALT were analysed after adjusting for age and sex in a stepwise multiple linear regression. Sample weights were included in the estimation process for all of the analyses to reflect the differential probabilities of selection, nonresponse, and noncoverage. A P value <0.05 was considered statistically significant, and all statistical analyses were conducted using SAS version 9.3 (SAS institute Inx, Cary, NC).

RESULTS

Of 17,093 adolescents who participated in the survey, 8,522 provided blood samples and formed our study population. Adolescents who were positive for hepatitis B surface antigen (n=20) were excluded. Additionally, we excluded 47 persons because of missing data on any of the factors according to the exclusion criteria (Table 1). The weighted and standardized prevalence of elevated ALT levels (defined as ALT >30 U/L) was 5.3%, and the median ALT level was 12.0 U/L (interquartile range, 10-16) in the study population. The prevalence was 2.1% among female adolescents and 8.0% among male adolescents (P<0.001). Density plots of the time trends of ALT levels are presented in Figure 1. No significant trend was found in the prevalence of elevated ALT among male and female adolescents from 2001-2014 (Table 2). NAFLD was present in 2.6% of non-obese children and 24.2% of obese children. Using higher ULN (defined as ALT >40 U/L), the prevalence of elevated ALT levels was 2.8%. We repeated the analysis using gender-specific ULNs (>33 U/L for boys and 25 U/L for girls), and the resulting prevalence was 5.4%.

Table 1. Characteristics of adolescents with and without elevated alanine aminotransferase

Characteristic	Number (%)	
	ALT≤30U/L (N=8031)	ALT>30U/L (N=424)
Age (mean±SD)	13.7±2.5	14.2 ±2.8
Sex		
Female	3897 (98.1)	75 (1.9)
Male	4134 (92.2)	349 (7.8)
Obesity	717 (75.8)	229 (24.2)
Truncal Obesity	556 (76.1)	175 (23.9)
Residential area		
Urban	6617 (94.8)	361 (5.2)
Rural	1414 (95.5)	63 (4.5)
House income		
First quartile	965 (94.8)	53 (5.2)
Second quartile	1987 (95.6)	92 (4.4)
Third quartile	2491 (95.6)	115 (4.4)
Fourth quartile	2411 (93.7)	152 (6.3)

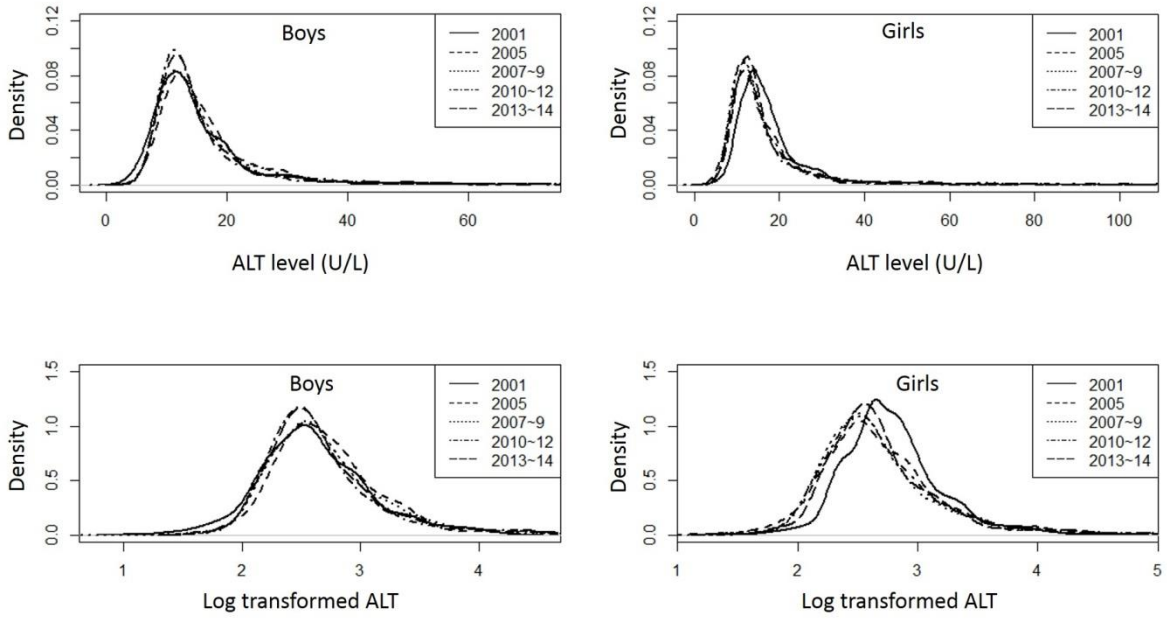

Figure 1 Density plot of ALT level and log transformed ALT in adolescents between 2001 to 2014 by gender

Table 2. Time trend for elevated ALT prevalence by gender group: 2001~2014

Prevalence% (SE)		Wave 2 (2001)	Wave 3 (2005)	Wave 4 (2007-9)	Wave 5 (2010-2)	Wave 6 (2013-4)	Total	P for trend
ALT>=30	M	6.9(1.1)	6.4(1.2)	9.5(1.0)	7.8(0.9)	7.9(1.1)	8.0(0.5)	0.1563
ALT>=30	F	1.6(0.6)	2.0(0.7)	1.9(0.4)	1.9(0.5)	1.4(0.5)	2.1(0.2)	0.9343
	Total	4.4(0.7)	4.4(0.8)	6.0(0.6)	5.1(0.5)	4.8(0.7)	5.3(0.3)	0.2694

In the univariate logistic regression analysis, elevated ALT levels were significantly associated with male sex, age, residency, obesity and truncal obesity. In the age- and sex-adjusted analysis, residency, obesity and truncal obesity were significantly associated with elevated ALT levels. In the multiple logistic regression analysis, male sex, obesity, and truncal obesity were independent predictors of elevated ALT (Table 3). A comparison of the college graduate group and the other groups showed that neither maternal nor paternal education level was significantly associated with elevated ALT.

Table 3. Logistic regression analysis by elevated ALT

	Univariate		AgeSex adjust		Multivariate	
variable	OR (95% C.I.)	P-value	OR (95% C.I.)	P-value	OR (95% C.I.)	P-value
Sex	4.5(3.4-6.0)	<0.001	4.5(3.4-6.0)	<0.001	4.5(3.3-6.2)	<0.001
Age (year)	1.1(1.0-1.2)	<0.001	1.1(1.0-1.2)	<0.001	1.1(1.0-1.1)	0.0684
Town (urban vs. rural)	1.4(1.0-2.0)	0.036	1.4(1.0-2.0)	0.041	1.0(0.9-1.9.)	0.1422
Obesity	15.2(11.8-19.7)	<0.001	11.2(8.8-14.4)	<0.001	7.6(5.3-11.0)	<0.001
Truncal obesity	9.1(7.2-11.5)	<0.001	11.0(8.6-14.1)	<0.001	2.5(1.8-3.5)	<0.001
Income	1.1(0.8-1.6)	0.5214	1.1(0.6-1.7)	0.675	-	-
Edu* F (quartile)	0.8(0.7-1.0)	0.63	0.9(0.7-1.1)	0.1786	-	-
M (quartile)	0.9(0.7-1.0)	0.1312	0.9(0.7-1.1)	0.3564	-	-

* the parental education level was included in the KNHANES protocol from 2007.

Log_eALT was associated with male sex, obesity, truncal obesity, older age group, and high household income level (Figure 2). In the univariate regression analysis, log_eALT was significantly associated with male sex, obesity, truncal obesity and high household income level. After adjusting for age and sex in the multiple regression analysis, these factors remained significantly associated with log_eALT (Table 4). Neither maternal nor paternal education level was significantly associated with log_eALT. Multivariate logistic regression analyses in subgroups showed a gender disparity in risk factor; urban residence was significant in only the female subgroup (OR=2.6; 95% CI, 1.2-5.9; P=0.0174).

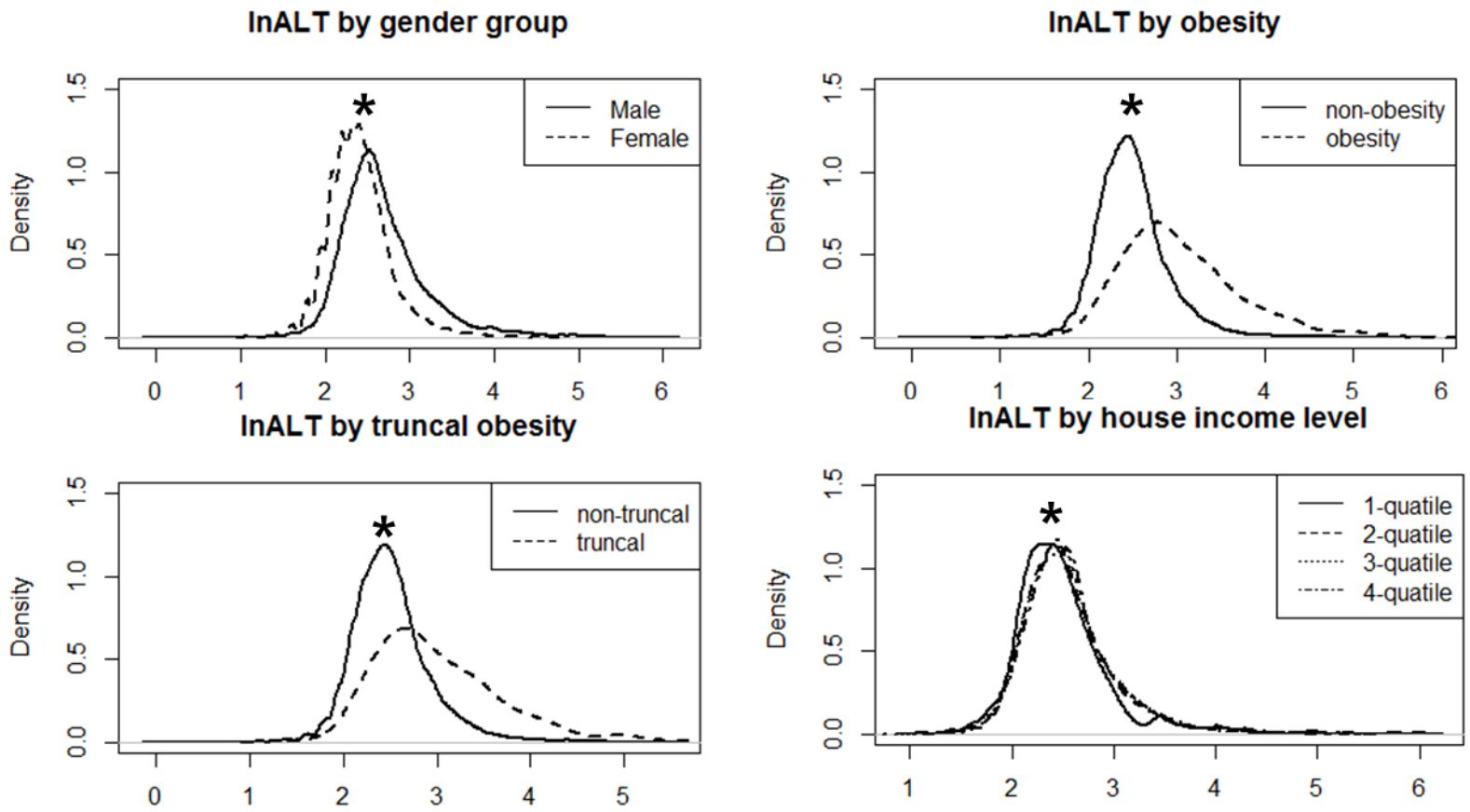

Figure 2. Log transformed alanine aminotransferase in adolescents by risk factor (* P<0.05)

Table 4. Regression analysis by ln ALT

	Univariate		AgeSex adjust		Multivatiate	
variable	Exp(B)	p	Exp(B)	P	Exp(B)	p-value
Sex (M vs F)	0.29 (0.26~0.31)	<0.001	0.29 (0.26~0.31)	<0.001	0.26 (0.24~0.29)	<0.001
Age (year)	0.00 (-0.01~0.00)	0.8247	0.00 (-0.01~0.00)	0.6493		
Town	0.03 (-0.01~0.06)	0.1703	0.02 (-0.01~0.06)	0.3297		
Obesity	0.57 (0.52~0.62)	<0.001	0.54 (0.49~0.58)	<0.001	0.43 (0.37-0.49)	<0.001
Truncal obesity	0.48 (0.43~0.54)	<0.001	0.50 (0.45~0.55)	<0.001	0.16 (0.09-0.22)	<0.001
Income (quartile)	0.03 (0.02-0.04)	<0.001	0.03 (0.01-0.04)	<0.001	0.03(0.01-0.04)	<0.001
Edu* F (quartile)	0.00 (-0.03~0.03)	0.9647	0.00 (-0.03~0.03)	0.9926		
M (quartile)	0.00 (-0.03~0.02)	0.7972	0.00 (-0.03~0.02)	0.8636	-	-

* the parental education level was included in the KNHANES protocol from 2007.

DISCUSSION

The aim of this study was to examine the prevalence, time trends and risk factors of an elevated ALT level, a surrogate marker of NAFLD, among Korean children aged 10–18 years from 2001 to 2014. Our major findings were as follows. First, in the study population, the prevalence of elevated ALT levels was 5.3% (S.E. 0.3), and this prevalence plateaued from 2001 to 2014 in both gender groups of adolescents. Second, obesity, male sex, truncal obesity and high household income level were associated with NAFLD. Taken together, our findings suggest that trends in the prevalence of NAFLD are strongly associated with obesity and that this risk factor could be utilized to identify adolescents with NAFLD, thus potentially preventing disease progression at an early age.

Our first major finding is that the prevalence of an elevated ALT level was 5.3% (S.E. 0.3) in the study population. In an epidemiologic survey, ALT ≥30 U/L was a surrogate marker of NAFLD that was closely correlated with hepatic fat accumulation demonstrated by sonography in obese children (6). The prevalence of an elevated ALT level differed from that in other studies using the same cutoff level. In the NHANES (National Health and Nutrition Examination Survey), the prevalence of elevated ALT levels, defined as >30 U/L, was 2.3% (n=2748, 1994 to 1998), 8.0% (n=5586, 1999 to 2004), and 6.9% (n=2138, 2007 to 2010) among 12- to 19-year-old adolescents and 1.6% (n=249, 2004) and 2.1% (n=288, 2007) in Japanese junior high school students (4, 9). Possible explanations for these differences include race, sample size and study year. There was no statistical evidence from the meta-regression that NAFLD prevalence differed by diagnostic method (ALT versus

ultrasonography) (3). However, elevated ALT levels may overestimate NAFLD in normal weight children and underestimate it in obese children (10). The actual prevalence of NAFLD in Korean adolescents would be higher than that estimated based on elevated ALT level; the prevalence of histologically proven NAFLD in adolescents (11.3% to 17.3%) was higher than that reported in the NHANES study (8%) with a five-year overlap (11). The trend in the prevalence of elevated ALT plateaued from 2001 to 2014 in adolescents of both genders. A meta-analysis revealed that the prevalence of NAFLD in children and adolescents has not changed over time (3). As expected, these results are consistent with a study that reported a plateau in childhood obesity, which is tightly associated with NAFLD (12). This finding could be explained by an awareness of the obesity epidemic in children and efforts at both the personal and public levels. Our results differed from those of NHANES, which demonstrated that the prevalence of suspected NAFLD has risen substantially among US adolescents over the previous 20 years (4). However, excluding the prevalence of 3.9% in NHANES III (1988-1994), the prevalence in each NHANES was 9.1%, 10.4%, and 10.7% in NHANES IV, V, and VI, respectively. Further studies based on general populations are needed to examine trends in the prevalence of elevated ALT levels in adolescents.

Our second major finding was that obesity, truncal obesity, male sex and high household income level were associated with NAFLD. In this study, obesity was the most significant independent risk factor for the development of NAFLD; this finding is consistent with those of numerous studies (13). We used KCDC age- and gender-specific BMI values and defined the 95th percentile, or 25 kg/m^2, as the cutoff value for “obesity”; this cutoff is lower than other criteria, such as those in CDC 2000 (Centers for Disease Control and Prevention criteria in 2000). Asians have a higher body fat percentage compared with Europeans at the same

BMI and an associated increased health risk at lower BMI values (14). Screening for NAFLD in high risk groups has been recommended for children. In the US, the American Academy of Pediatrics recommends screening for NAFLD in children who are ≥10 years and overweight with risk factors such as familial clustering, drinking beverages with a high fructose content and waist circumference greater than the 95th percentile for age and sex. In Europe, the European Society for Paediatric Gastroenterology Hepatology and Nutrition recommends that NAFLD should be suspected in children who are ≥3 years and overweight or obese, especially if they have a high waist circumference and/or a family history of NAFLD (15).

The second purpose of this study was to identify risk factors, especially those that are non-invasive. Most children with obesity (75.8%, 717 of 946) did not have NAFLD, suggesting that obesity and NAFLD are not interchangeable (2). Furthermore, a high percentage (15-21%) of Asia-Pacific NAFLD subjects have been reported to be non-obese, despite using strict ethnic-specific criteria (16). As a part of metabolic syndrome, the independent OR (2.5; 95% CI, 1.8-3.5) of truncal obesity supports previous guidelines and indicates that a physician should check a child's waist circumference when their BMI is in the 85th percentile or higher (15, 17).

Previous studies have demonstrated that the prevalence of NAFLD varies according to sex and age in both paediatric and adult populations (10). NAFLD is more common in boys than in girls in both the general population and in clinical studies. The gender disparity in our study is consistent with previous findings, especially those of studies using ALT to assess NAFLD (13). Although the reason for this remains unclear, differences in muscle mass and

sex hormones between genders might be involved (18). In addition, several studies concluded that gender-specific normal limits for ALT should be applied (5, 18, 19), but in these studies, different cutoffs were used by clinical laboratories for the ULN of ALT in children.

Differences in NAFLD prevalence may also be influenced by environmental factors, location of residence and socioeconomic status. A recent review suggested that the prevalence of NAFLD is higher in countries with a higher economic status and is higher in urban settings than in rural settings (20). However, there have been few studies on these associations in a general paediatric population. The present study demonstrated that high household income level was associated with $\log_e$ALT in the general paediatric population, and the urban and rural gap was present in female adolescents. The results are partially consistent with a recent Korean study that reported that childhood obesity is more prevalent in boys with a high household income (21). However, these findings are in contrast with those of Fraser et al., who reported that socioeconomic status is inversely associated with elevated ALT levels based on the NHANES 1999–2004 data (6). Further studies based on the latest data are needed to examine the association between socioeconomic status and NAFLD in adolescents. The urban/rural gap may be explained by lifestyle, with less physical activity and a higher calorie diet being more common in urban environments (22). We also analysed the association between parental education and NAFLD but found no relationship.

The present study has several strengths. To the best of our knowledge, this is the first study to analyse trends in the prevalence of elevated ALT in Korea and outside the US. The main strength of this study is the relatively large sample size based on five sets of KNHANES data

within the last 14 years. It is one of the largest epidemiologic studies to determine the prevalence of and risk factors for NAFLD in a general paediatric population. Furthermore, we conducted the analysis using stratification, clustering and sample weights, which are more commonly used when analysing the KNHANES data to calculate correct standard errors (23). In addition, this is the first study in a general population to analyse the association between paediatric NAFLD and socioeconomic factors, including household income level and parental education level.

Our study has some limitations. First, since 2007, NHANES has become a continuous survey; thus, the methods used in the surveys were inconsistent, and each KNHANES wave was conducted with different subjects. Therefore, unintentional bias may have been introduced, especially when estimating the prevalence and trend of elevated ALT levels. Second, we could not exclude all causes of ALT elevation, such as hepatotoxic medications, daily alcohol ingestion and chronic diseases, because the survey questions for children are limited compared with those for adults. However, the KNHANES is the only available nationwide dataset that represents the health status of the general population.

In summary, this study found that the prevalence of elevated ALT levels was stable from 2001 to 2014 in adolescents of both genders and identified risk factors associated with childhood NAFLD. These findings suggest that trends in the prevalence of NAFLD are associated with those of obesity, and further studies are needed to identify risk factors for paediatric NAFLD.

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국문 초록

서론: 혈중 알라닌 아미노전이효소(alanine aminotransferase, ALT)의 상승은 청소년기의 가장 흔한 간질환인 비알코올성간질환(non-alcoholic fatty liver disease, NAFLD)의 임상지표이다. 청소년기 NAFLD에 대한 이전 연구들은 대부분 비만집단을 대상으로 이루어졌거나 시계열분석이 없는 단변조사연구였다. 본 연구의 목적은 일반적인 청소년 집단에서 ALT 상승의 유병률과 그 추이를 확인하고 이와 연관된 요인들을 확인하는 것으로 하였다.

방법: 한국 일반인구의 대표성을 가진 자료인 국민건강영양조사자료에서 2001 년부터 2014 년까지 참여한 만 10 세부터 18 세 청소년의 자료를 대상으로 하였다. B 형 간염 항원이 음성이고 ALT 가 30 U/L 이상인 경우 NAFLD 의심 환자로 정의하였다. 모든 통계분석은 가중치를 사용하였고, 조사설계에 기반한 분석기법을 사용하였다.

결과: 전체 8455 명의 연구대상 청소년 인구에서 ALT 상승의 유병률은 5.3% (표준오차 0.3%)로 확인되었다. 남자와 여자 모두에서 ALT 상승의 유병률은 2001 년부터 2014 년까지 통계적으로 유의한 변화를 보이지 않았다. 다중

로지스틱회귀분석에서 성별 (여성대비 남성의 비교위험도[Odds ratio, OR] 4.5; 95%신뢰구간[confidence interval, CI], 3.3-6.2), 비만 (OR 7.6; 95% CI, 5.3-11.0), 그리고 복부비만 (OR 2.5; 95% CI, 1.8-3.5)이 각각 독립적으로 ALT 상승과 연관관계를 보였다. 그리고 로그변환한 ALT 값은 다중회귀분석에서 성별, 비만, 복부비만 및 가구소득수준과 유의한 연관성을 가지고 있었다.

결론: 한국 청소년에서의 ALT 상승의 유병률은 2001 년부터 2014 년까지 남녀 성별 모두에서 안정화 단계에 있다. 본 연구에서 성별, 비만, 복부비만, 가구 소득 수준이 소아 NAFLD 와 연관인자로 확인되었다.

주요어: 알라닌 아미노전이효소; 유병률; 지방간

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