What is the normal serum alanine aminotransferase (ALT) value for Thai subjects with the low risk of liver diseases?

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Background	:	*It still remains unclear whether the currently used normal range for serum alanine aminotransferase (ALT) levels really reflects a healthy liver.*
Objective	:	*To determine the thresholds for healthy ALT values or the normal value for Thai subjects with the low risk of liver diseases who participate in the annual physical checkup at King Chulalongkorn Memorial Hospital (KCMH).*
Materials and Methods	:	*We retrospectively reviewed the medical records of annual health examination, including questionnaires conducted at KCMH, Thailand from January to December 2006. A group of the low risk of liver diseases was selected by excluding patients who showed any abnormalities of the risk factors that were significantly associated with the serum ALT level, including hepatitis B, hepatitis C, alcohol consumption, diabetes, hyperlipidemia and obesity.*

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Results   :   *The mean age of the 1,879 enrolled subjects was 41.7 ± 10.1 years, and 81.7% of them were female. The upper limit range of the ALT level of the group of subjects with the low risk of liver diseases (i.e. 95th percentile) was 33.6 IU/L for males and 32 IU/L for females. The upper thresholds of AST and ALT value of the subjects with the metabolic syndrome (METS) were statistically significantly higher than those in subjects without METS (AST 57.4 vs. 30IU/L and ALT 87.3 vs. 31.6 IU/L).*

Conclusion   :   *The ALT threshold of the group of Thai subjects with the low risk of liver diseases was clearly lower than the previously accepted threshold (<40IU/L). Metabolic syndrome significantly affects the ALT threshold level.*

Keywords   :   *Healthy ALT, metabolic syndromes, physical checkup.*

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ที่มาของงานวิจัย	:	*ในปัจจุบันยังคงมีคำถามว่าค่าที่เราใช้เป็นค่าปกติของระดับอะลานีนอะมิโนทรานสเฟอเรส (Alanine aminotransferase-ALT) ในเลือดเป็นค่าที่ปกติจริงหรือไม่*
วัตถุประสงค์	:	*เพื่อหาค่าปกติของระดับอะลานีนอะมิโนทรานสเฟอเรส (Alanine amino-transferase-ALT) ในเลือดจากการตรวจร่างกายประจำปีของบุคลากรไทยที่สุขภาพแข็งแรงที่ทำงานในโรงพยาบาลจุฬาลงกรณ์*
วิธีการวิจัย	:	*เป็นการศึกษาที่มาจากการทบทวนเวชระเบียนและข้อมูลการตรวจสุขภาพประจำปีย้อนหลังของบุคลากรที่สุขภาพแข็งแรงที่โรงพยาบาลจุฬาลงกรณ์ทั้งสิ้น 1,879 รายตั้งแต่เดือนมกราคม – ธันวาคม พ.ศ. 2549*
ผลการศึกษา	:	*จากผู้ที่เข้ารับการตรวจร่างกายประจำปีทั้งสิ้น 1,879 ราย ร้อยละ 81.7 เป็นเพศหญิง โดยมีอายุเฉลี่ย 41.7 ± 10.1 ปี เมื่อแยกผู้ที่เป็นพาหะโรคไวรัสตับอักเสบบี ซี การดื่มแอลกอฮอล์และผู้ที่อยู่ในกลุ่มโรคเมตาบอลิกออกพบว่าค่าเปอร์เซนไทล์ที่ 95 ของระดับ ALT ในเลือดสำหรับเพศชายและหญิงคือ 33.6 และ 32 IU/L ตามลำดับ โดยพบว่าค่าระดับแอสปาร์เตท ทรานสเฟอเรส (Aspartate transferase - AST) และ ALT ในเลือดของผู้ที่อยู่ในกลุ่มโรคเมตาบอลิกจะสูงกว่าอย่างมีนัยสำคัญทางสถิติ (AST 57.4 vs. 30IU/L และ ALT 87.3 vs. 31.6 IU/L).*
สรุปผล	:	*ระดับ ALT ในเลือดของผู้ที่มีสุขภาพแข็งแรงในปัจจุบันมีค่าต่ำกว่าในอดีต (<40IU/L). อย่างชัดเจน ความผิดปกติจากกลุ่มโรคเมตาบอลิกเป็นปัจจัยสำคัญที่มีผลต่อระดับ ALT ในเลือด*
คำสำคัญ	:	*ค่าปกติของ ALT ในเลือด, กลุ่มโรคเมตาบอลิก, การตรวจร่างกายประจำปี.*

Serum alanine aminotransferase (ALT) assay is the most common laboratory test for the detection of liver disease. [1] ALT is influenced not only by liver diseases, but also various medical conditions for example metabolic syndrome. Moreover, demographic determinants including age, sex, and body mass index also had effect on ALT level. The cut-off serum ALT value that discriminates between healthy livers and liver diseases has not yet been clearly defined. The currently upper normal limit of serum ALT in our laboratory (38IU/L) was determined principally from the studies performed before the introduction of anti–hepatitis C virus (HCV) testing, and prior to the development of the concept of nonalcoholic fatty liver disease (NAFLD). [2, 3] Prati et al. [4] recently performed a retrospective cohort study in the Italian population who had the lowest risk for liver diseases, and suggested a new upper limit of serum ALT level of 30 IU/L for males and 19 IU/L for females. However, it is uncertain whether this new range of serum ALT levels in young Italians could be generalized to the Thais. We aimed to find out the normal value of serum AST and ALT in Thai subjects with the low risk of liver diseases who had their annual physical checkup at King Chulalongkorn Memorial Hospital (KCMH).

Methods

1. Study population

A total of 4,790 subjects who visited King Chulalongkorn Memorial Hospital (KCMH), Thailand, for an annual physical checkup from January to December 2006 were included in this study.

2. Methods

All subjects completed self-administered questionnaires about demographic data such as age, gender, personal and family history of disease, cigarette smoking and alcohol consumption and underwent anthropometric measurements as well as blood testing. Of the 4,790 subjects, 2,911 of them (61.3%) were excluded because of the presence of the hepatitis B surface antigen (HBsAg), hepatitis C virus (Anti-HCV), a daily alcohol intake $\geq$ 60 gm/day, resulting in a final study population of 1,879 subjects (39.2%). Weight, height, and blood pressure (in the sitting position) were measured by nursing staff. Venous blood was sampled after an overnight fasting to measure the blood levels of AST, ALT, total cholesterol, triglycerides (TG) and fasting plasma glucose (FPG) were analyzed in a standardized manner at the biomedical laboratory of KCMH.

3. Definitions

The normal range of serum ALT levels was defined as less than 38 IU/L, according to the upper normal limit used at our institution. Obesity was defined as body mass index (BMI) $\geq$ 25 kg/m^2. Dyslipidemia was defined by serum lipid levels as follows: high total cholesterol (>200 mg/dL) and/or high triglyceride (>150 mg/dL). The subjects without metabolic syndrome (METS) are the subjects who had no criterion of the following characteristics: body mass index (BMI) $\geq$ 25 kg/m^2, high total cholesterol (>200 mg/dL) and/or high triglyceride (>150 mg/dL) and high fasting plasma glucose $\geq$ 100 mg/dl or impaired fasting glucose (IFG), based on the revised Adult Treatment Panel III of the National Cholesterol Education Program. [5]
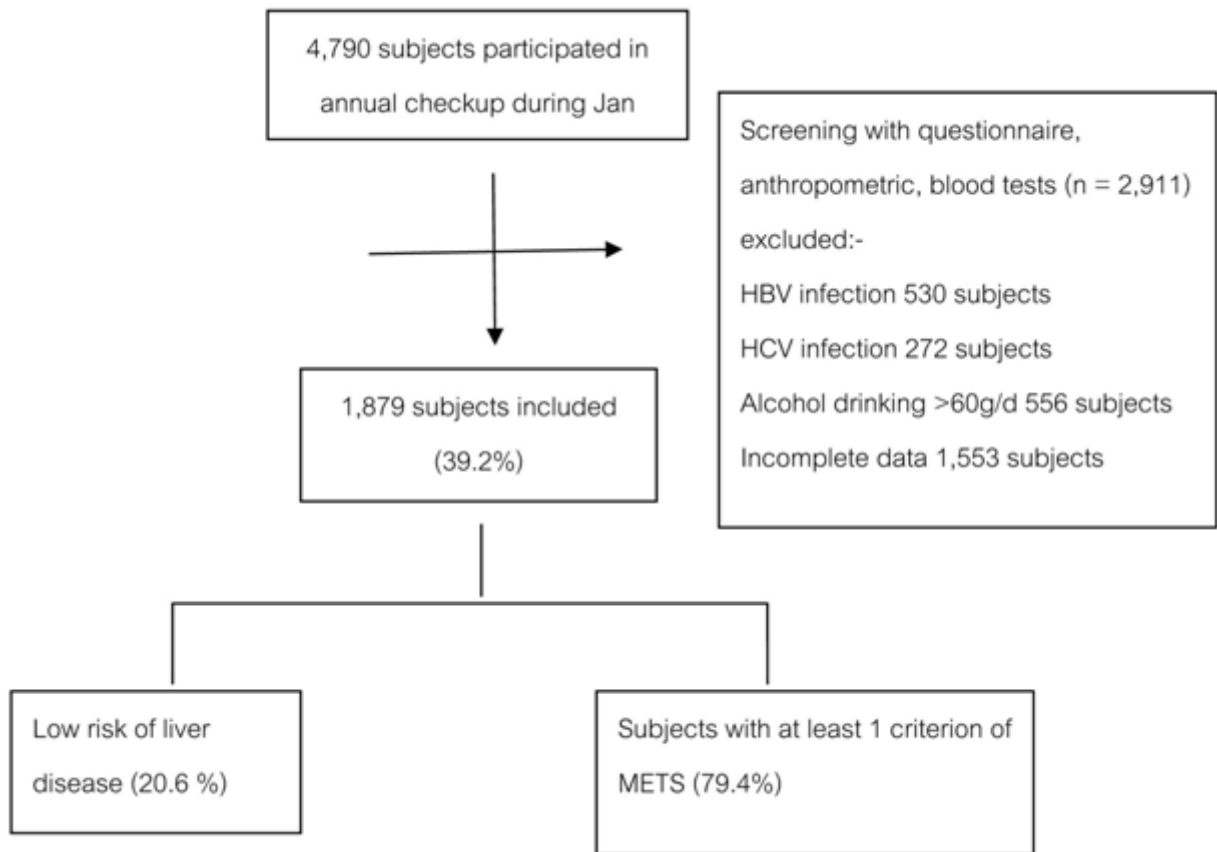
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Figure 1. Flowchart for selection of the study participants.

4. Statistical analysis

Data are presented as mean ± SD or frequency (%) values. Student's *t*-test and Chi-square test were performed to compare continuous variables and categorical variables between two groups, respectively. *P*-values of less than 0.05 was considered statistically significant. ANOVA was used to assess the significant difference among groups. We set the ALT level of the subjects with the low risk of liver disease to the 95th percentile [(4)] in the healthy population, as is commonly done for the distribution of a continuous variable in the normal population. All statistical analyses were performed with the SPSS statistical package for Windows, version 15.0 (SPSS, Chicago, IL, USA).

Results

Of the 1,879 subjects who met the inclusion criteria, 81.7% were female. The mean age of the enrolled subjects was 41.7 ± 10.1 years (range 15 - 73 years) as shown in Table1. Overall mean BMI was 24.0 ± 3.9 kg/m^2. There were 30 subjects (1.6%) who met all of the criteria for metabolic syndrome and 387 subjects (20.6%) who had no criterion for the metabolic syndrome in our study. Table 2 shows the correlation between serum ALT and qualitative and quantitative factors in male and female subjects. ALT was significantly correlated with BMI, serum fasting plasma glucose, total cholesterol and triglyceride in both genders.

Table 1. Baseline characteristics of the study population.

Variables [number (%) or mean ± S.D.]	N = 1879
Sex (%female)	1,533 (81.6%)
Age (years)	41.7 ± 10.1
BMI (kg/m^2)	24.0 ± 3.9
No. of Obesity	362 (34.7%)
Subjects with impaired fasting glucose (IFG) or DM	205 (11%)
Subjects with hypercholesterolemia	998 (53.1%)
Subjects with hypertriglyceridemia	279 (14.9%)

Table 2. Correlation (in univariate analysis) between serum ALT and qualitative and quantitative factors in male and female subjects.

Variable	Male (n = 346)		Female (n = 1533)	
	Pearson correlation	p-value	Pearson correlation	p-value
BMI	0.27	< 0.01	0.34	< 0.01
Age	0.085	0.62	0.06	0.44
Serum FBS	0.24	< 0.01	0.21	< 0.01
Serum triglyceride	0.23	< 0.01	0.17	< 0.01
Serum total cholesterol	0.37	< 0.01	0.27	< 0.01

We compare the baseline characteristics between the subjects with and without metabolic syndrome (METS) and found the statistically significant difference of the mean BMI, fasting plasma glucose, total cholesterol, triglyceride, AST and ALT as shown in Table 3 - 4.

We separated the baseline characteristic data between male and female and compared the subjects without any criterion of METS and those with at least one criterion of METS. We found that there were statistically significant difference between female group with and without at least 1 criterion of

METS for serum total cholesterol, triglyceride. To find out the "true" normal ALT for the subjects with the low risk of liver diseases, we analyzed the characteristic, BMI, metabolic profile, AST and ALT in the subjects without any characteristics of METS and had negative results of hepatitis B and C serology. The mean BMI of the subjects was 21.5 ± 2.0 kg/m^2 in male and 21.4 ± 2.0 kg/m^2 in female subjects. The mean AST was 20.6 ± 4.3 IU/ml in male and 20.4 ± 5.5 IU/ml in female. The mean ALT was 16.9 ± 7.6 IU/ml in male and 16.6 ± 7.9 IU/ml in female. For the 95th percentile, we found that the AST was 30.1IU/ml in male and

30 IU/ml in female, respectively. And the 95th percentile for ALT was 33.6IU/ml in male and 32IU/ml in female, respectively. There were statistically significant difference of serum AST and ALT between male and female only in the group of subjects with at least 1 criterion of METS.

Table 3. Comparison of baseline characteristics between the subjects with and without metabolic syndrome (METS).

Variables [number (%) or Mean ± S.D.]	Group 1 Subjects without METS (n = 387)	Group 2 Subjects with 1 - 2 criteria of METS (n = 1462)	Group 3 Subjects with METS (n = 30)	*p*-value
% female	355 (91.7%)	1,154 (78.9%)	24 (80%)	
Age (year)	48.2 ± 6.4	49.7 ± 6.0	46.8 ± 8.4	0.62
BMI (kg/m^2)	21.4 ± 1.9	24.1 ± 5.5	29.7 ± 3.4	<0.01
No. of obese subjects	0 (0%)	622 (42.6%)	30 (100%)	
FPG (mg/dl)	84.6 ± 7.0	90.4 ± 14.8	111.2 ± 12.4	<0.01
No. of cases with IFG or DM	0 (0%)	178 (12.4%)	27 (90%)	
Total cholesterol (mg/dl)	172.9 ± 19.1	215.2 ± 37.9	262.0 ± 47.9	<0.01
Triglyceride (mg/dl)	69.6 ± 26.6	110.1 ± 87.8	260.4 ± 182.5	<0.01
AST (IU/L)				
- Mean ± S.D.	20.40 ± 5.4	22.7 ± 9.5	27.9 ± 11.7	<0.01
- 95th percentile	30	36	57.4	
- 97.5th percentile	34.3	43.9	64.0	
ALT (IU/L)				
- Mean ± S.D.	16.60 ± 7.8	22.9 ± 12.1	35.5 ± 19.1	<0.01
- 95th percentile	31.6	50	87.3	
- 97.5th percentile	40.0	54.0	83.0	

Table 4. Comparison of baseline characteristics between the subjects with and without metabolic syndrome (METS).

Variables [number (%) or Mean ± S.D.]	Subjects without METS (n = 387)			Subjects with at least 1 criteria of METS (n = 1,492)		
	Male (n = 32)	Female (n = 355)	p-value	Male (n = 314)	Female (n = 1,178)	p-value
% Female	32 (8.3%)	355 (91.7%)		314 (21%)	1,178 (79.0%)	
Age (year)	48.1 ± 6.6	48.1 ± 6.6	0.83	49.2 ± 8.3	49.8 ± 9.2	0.73
BMI (kg/m^2)	21.5 ± 1.9	21.3 ± 1.9	0.6	25.0 ± 3.8	24.6 ± 4.1	0.13
No. of obese	0 (0%)	0 (0%)		145(46.2%)	622 (42.6%)	
FPG (mg/dl)	85.3 ± 6.5	84.6 ± 7.0	0.58	91.8 ± 15.3	90.6 ± 15.0	p = 0.23
No. of IFG or DM	0 (0%)	0 (0%)		46 (14.9%)	159 (13.8%)	
Total cholesterol	173.6 ± 18.2	172.9 ± 19.2	0.83	210.6 ± 37.8	217.6 ± 38.7	<0.01
Triglyceride	77.4 ± 28.5	69.6 ± 26.6	0.83	126.5 ± 96.1	109.5 ± 88.8	<0.01
AST(IU/L)						
- Mean ± S.D.	20.6 ± 4.3	20.4 ± 5.5	0.84	23.5 ± 8.5	22.4 ± 8.1	0.03
- 95th percentile	30.1	30		36.3	37	
- 97.5th percentile	32.0	34.3		43.3	44.1	
ALT(IU/L)						
- Mean ± S.D.	16.9 ± 7.6	16.6 ± 7.9	0.84	25.1 ± 14.7	21.3 ± 13.2	<0.01
- 95th percentile	33.6	32		52	50	
- 97.5th percentile	35.0	40.0		61.0	60.0	

Discussion

Because of the progression of the liver disease despite the normal level of serum ALT resulting in the question that the previous normal value of AST and ALT is the 'true' normal. We analyzed the data of AST and ALT in the subjects who participated in their annual physical checkup at King Chulalongkorn Memorial Hospital. Our study shows that the normal value of AST and ALT was lower than that currently in use. The upper thresholds of serum ALT in our populations with the low risk of liver diseases, using the 95th percentile [4] was 33.6 IU/L for male and 32 IU/L for female, respectively. We found the progressive increment of the AST and ALT value from the group of subjects with the low risk for liver disease through the group of subjects with at least one criterion of METS and the greatest ALT value in the group of subjects with fulfill criteria of METS. This results was not much different from several previous reports proposing the updated upper normal limit (ULN) of serum ALT, however, the ULN varies slightly in different reference populations with different ethnic variations, for example Prati et al. [4] suggested ULN values of 30 IU/L for male and 19 IU/L for female in an

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Italian population, whereas Kang *et al.* [6] proposed 31 IU/L for male and 23 IU/L for female (Table 5). The higher proposed ULN of ALT values of our study are likely due to the higher mean age of the patients and maybe the higher proportion of female subjects. Whether the use of the 95th percentile as in Prati *et al.* [4] or the 97.5^{th} percentile for ULN values of ALT as described by the American Association of Gastroenterology[7] was still questionable. Nevertheless, our study used 95th percentile as the reference value because it was commonly used in previous studies. Body mass index and at least one criterion of the metabolic syndrome have the statistically significant influence to serum ALT. Base

on the results from several study [2,4,6,8], ALT levels were significantly modified by several factors including age, gender, the presence of metabolic syndrome. The interaction among these variables has to be considered to set up the normal ALT level for general population. Our study has some limitations; first, our data is the retrospective review and questionnaire without repeating the viral serology in all subjects. Some asymptomatic subjects may have the pre-existing unknown chronic liver disease. However, if calculated the AST and ALT only in the subjects without any metabolic abnormalities and history of chronic viral hepatitis B and C, the value is much less than those we currently used at our hospital. Second,

Table 5. Shows the characteristics of subjects with low risk of liver disease between our study and other study

	Prati *et al.* [4]	Kang *et al.* [6]	Our study
% female	2,970 (43.5%)	1,041 (59.7%)	1,178 (79.0%)
Age (year)	29.8 ± 9.5	47.8 ± 12.4	48.2 ± 6.4
BMI (kg/m^2)	23.1 ± 3.2	23.4 ± 2.8	21.3 ± 4.0
No. of obese			0 (0%)
No. of diabetes		331 (5.4)	0 (0%)
FPG (mg/dl)	91.9 ± 10.1	90.1 ± 16.7	84.6 ± 7.0
Total cholesterol (mg/dl)	179.0 ± 36.1	182.4 ± 32.6	172.9 ± 19.1
Triglyceride (mg/dl)	83.6 ± 54.4	122.0 ± 77.8	69.6 ± 26.7
AST			
- Mean ± S.D. (IU/L)		19.5 ± 4.5	M = 20.6 ± 4; F = 20.4 ± 5.5
- 95th percentile (IU/L)			M = 30.1; F = 30
- 97.5^{th} percentile (IU/L)			M = 32; F = 34.3
ALT			
- Mean ± S.D. (IU/L)	-	16.9 ± 5.7	M = 16.9 ± 7.6; F = 16.6 ± 7.9
- 95th percentile (IU/L)	M = 30; F = 19	M=30; F=23	M = 33.6; F = 32
- 97.5^{th} percentile (IU/L)	-	-	M = 35; F = 40

the majority of our participants were female. We supposed that the characteristics of the metabolic syndrome play an important role in this issue. However, we found the influence of gender to the ALT level had been found in only female subjects with at least one criterion of the metabolic syndrome. This finding may be resulted from the low proportion of male subjects in our study. Currently, the incidence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide and has closed association with the metabolic syndrome. Moreover, the recent study reveal that the subjects with the highest risk of having NAFLD were those with a BMI >25 kg/m[(2)] with odds ratio of 4.3. Abdominal obesity, impaired fasting plasma glucose >100 mg/dL or elevated homeostatic model assessment of insulin resistance were the risk factors.[(9-10)] Additionally, there was an evidence showing that obese healthy subjects have higher liver fibrosis score measured by transient elastrography compared with subjects with normal BMI.[(9-10)] Thus, the new normal ALT level of the Thai subjects without metabolic syndrome components or subjects with the low risk of liver diseases must be used with the new cut-off value of 33 IU/L in male and 32 IU/L in female and the further prospective studies are required for the additional result for confirmation.

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