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Statistical Analyses for Gender Dependent Risk of Non-Alcoholic Fatty Liver in Non-Diabetic Patients

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Abstract

Background: Non-alcoholic fatty liver is a chronic lifestyle disease caused by low physical activity and high food intake, which exposes patients to obesity and diabetes mellitus. High incidences and serious consequences of the disease have attracted a great number of new researches. elucidating mechanism for gender dependent risk of the disease is the main endeavor of this study.

Methods: In the present study 286 male and 324 female individuals, aged 45±5 years with 13±1.5 and 8±2 mmHg (systolic/diastolic) blood pressure and BMI exceeding 22 were examined. The patients were non-diabetic with increased plasma concentrations of hepatic enzymes, their ratio of aspartate amino transferase (AST) to alanine amino transferase (ALT) was under unity.

Results: Except for AST/ALT ratios in both sexes which fell less than the normal range (<1), all other measured parameters including fast blood sugar, triglyceride, cholesterol, high density lipoprotein, low density lipoprotein, very low density lipoprotein, thyroid stimulating hormone, blood urine nitrogen and creatinine were within normal range (P-value>.05). Independent t-tests showed that triglyceride, high density lipoprotein, low density lipoprotein, thyroid stimulating hormone, blood urine nitrogen and creatinine were significantly different in both genders (P-value<.01), while fast blood sugar, cholesterol and very low density lipoprotein were not different (P-value>.05).

Conclusion: Path analysis output indicated that women with higher and negative cumulative effect on AST/ALT ratio were at higher risk for non-alcoholic fatty liver, since the lower AST/ALT ratio as previously reported correlates with more serious fatty liver consequences.

Keywords: Aspartate amino transferase/alanine amino transferase ratio; Non alcoholic fatty liver; Path analysis; Thyroid stimulating hormone

Introduction

Non-alcoholic fatty liver disease (NAFLD) affects more than 20 to 30 percent of human populations aged 40 to 60 years worldwide with higher prevalence rates in women than in men [1,2]. In type 2 diabetics and/or obese individuals, the rate of NAFLD prevalence is even higher exceeding seventy percent [3,4]. It is shown that accumulation of more than 5% of triglycerides in hepatocytes in NAFLD patients leads to serious complications including steatosis, lipid induced hepatitis, cirrhosis and eventually hepatocellular carcinoma [5,6].

The increases in serum alanine amino transferase (ALT), with a half-life of 36 hours, and serum aspartate amino transferase (AST), with a shorter half-life of 18 hours, are two major markers used for routine diagnosis of NAFLD liver damage [7-10]. However, ALT is used as a prolonged index for NAFLD monitoring [11]. The reliability of these two markers is affected by metabolic disorders such as hyperglycemia, hyperlipidemia and insulin resistance. Because of the shorter half-life of AST compared to ALT, the value of AST/ALT ratio in NAFLD disease becomes less than unity in NAFLD patients contrast to normal individuals having ratio of ~1. The ratio provides an extensive index for differential diagnosis of NAFLD as well as steatosis from other liver abnormalities [12,13]. For instance, the ratio of ≥2 is indicative for alcoholic fatty liver disease [14,15].

About 15.2 to 36.3 percent of NAFLD populations show increased thyroid stimulating hormone (TSH) or hypothyroidism, the condition coexists and probably predisposing NAFLD [16-18]. The disease of NAFLD in turn is also incriminated for kidney insufficiency and diabetic nephropathy onset with increased BUN in advanced state [19,20].

There are increasing evidences that show statistically significant correlations between sera levels of biochemical parameters of TSH, BUN, creatinine (Creat), TG, Chol, LDL, VLDL, HDL and FBS with AST and ALT activities in NAFLD patients [21-25].

Based on this introduction, we preformed multiple regression analysis as well as path analysis modeling on the data obtained for none-diabetic male and female patients having AST/ALT<1 ratio. In this study, TSH, BUN, creatinine (Creat), TG, Chol, LDL, VLDL, HDL and FBS were used as independent variables for modeling and AST/ALT<1 ratio as dependent variable for path

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analysis. For diagnostic and prognosis purposes, we decided to make causal models containing interactions between enrolled biochemical parameters and their effects on AST/ALT<1 ratio [26,27].

Methods and Materials

Subjects selection

The study was carried out on 286 males and 324 females of non alcoholic and non-diabetic patients having AST/ALT ratios less than unity and fasting blood sugar lower than 120 mg/dl. Participants were recruited from the outpatients referred to Atieh clinic, Tehran, Iran for hair and scalp problems. Participants, aged 45±5 years, had controlled blood pressure of 13±1.5 and 8±2 mmHg (systolic/diastolic) with BMI of more than 22. They were enrolled in the study upon prior informed consent. The study was carried out from 21st April to 23rd September 2017 in Shahid Chamran University of Ahvaz.

Biochemical measurement

Blood samples were collected from fasted subjects as a part of prescribed checkup tests. For each patient, serum was separated and biochemical factors including TG, HDL, LDL, VLDL, Chol, AST, ALT, FBS, Creat and BUN were measured using an auto analyzer system (COBAS MIRA System, Roche Diagnostics Corporation). TSH level was measured using TSH Elisa Kit, Padtan Gostar Isar Co. IRAN.

Statistical analysis

Independent t-test was used to compare the levels of biochemical factors in male and female groups. Two tailed Persons' test was performed to discover reasonable correlations between the determined factors in order to explore linear regression and path analysis models. The data was treated using SPSS software (Statistical Package for the Social Science version 21.0.Armonk, NY:IBM Corp. software). The differences were considered statistically significant at P-value < 0.05 throughout the tests.

Path analysis

A path analysis based on multiple linear regressions was performed using factors including FBS, TG, Chol, HDL, LDL, VLDL, TSH, BUN and Creat as independent variables and relative AST/ALT ratios as dependent variables as per our defined Path model. It is important to notice that in path analysis only those factors showing significant correlation (P value <0.05) with each other were used to construct the model. The variance of dependent variable (AST/ALT) was expected to be explained partly by independent variables. The rest of variance was taken to be introduced by an unknown variable not included in the model, referred to as the extraneous variable depicted by (e) and linked by one headed arrow to dependent variable. The standardized coefficients are shown over headed arrows representing the net and significant effect of that independent variable on the targeted variable. The positive value of the standardized coefficient conveys an increasing effect of the independent variables over the dependent one and *vice versa*. In addition to direct effect, the independent variables may affect the dependent variable indirectly via an intervening variable. This effect can be calculated by multiplying the coefficients of intermediate variables [28]. Amos (version 23.0) software was used for path analysis throughout this study. All equations were checked for significance at 0.05 levels.

Ethical approval

The study was conducted upon approval of Ethical Committee of Shahid Chamran University of Ahvaz, Iran.

Results

Independent t-test was performed to see if biological parameters were significantly different in both groups of patients. Table 1 summarizes, mean deference (mean±SD) tests in accordance with p-values, as well as 95% confidence interval of the difference for all parameters in both male and female groups. The table indicates that BUN, Creat, TG and VLDL were 14, 20, 27 and 26 percent higher in males than females respectively. While TSH and HDL were 34 and 3 percent higher in females than in male group. The AST/ALT ratios were also significantly lower in males. However, there was no significant difference in FBS, Chol and LDL between the two groups. The comparison of these values with normal ranges in healthy individuals (Table 1) indicates that except of TG and VLDL which tend to be at upper limits, the rest parameters fall within normal ranges. Nevertheless AST/ALT ratios as seen in table 1 were lower than unity for both groups, emphasizing the fact that fat deposition and consequent NAFLD may overwhelm the liver in people with normal lipid profiles.

Tables 2a and 2b represent the results obtained from two tailed Persons' tests done on all variables for male and female groups respectively. As highlighted in Table 2a, FBS does not show any significant correlation with the remaining variables, while in female group (Table 2b) all variables manifest significant correlations with each other. Accordingly, except for FBS in male group, all other variables were used for path analysis.

Assuming AST/ALT ratio as a dependent variable and the remaining as independent variables, we carried out stepwise multivariate regression analysis to extract different possible patterns through which independent variables affect the dependent variable. In addition to direct interaction, independent variables may interact indirectly with the dependent variable via certain variable in the model. Therefore, it was possible to have different models for variables interactions. These models were analyzed and optimized in Amos (version 23.0) software to construct path models.

Figures 1-A and 1-B show the best model extracted for male and female groups respectively. As shown, all variable enrolled in our models were putted in a rectangle and single headed arrows were drawn from independent variable toward dependent variables. The calculated standardized coefficients for direct relations were putted over these arrows. The error terms, shown by e (e1 to e5) were uncorrelated with variables of the model and with each other **and** putted over on headed arrows. In our models, TG plays central role in mediating independent

Table 1: Blood parameters comparison for male and female groups.

	Normal Range	Male	Female	Mean Difference	95% Confidence Interval of the Difference		p-value
					Lower	Upper	
TSH(mIU/L)	0.4-4.8	2.21±3.32	2.97±3.82	-0.76347	-1.33734	-0.1896	0.009
BUN(mg/dL)	8-21	13.52±3.16	11.80±3.12	1.72585	1.22472	2.22698	0.001
Creat(mg/dL)	0.6-1.2	0.89±0.14	0.74±0.13	0.14529	0.12251	0.16807	0.001
FBS(mg/dL)	65-110	89.46±12.14	88.83±11.62	0.6317	-1.25993	2.52333	0.512
TG(mg/dL)	40-150	170.00±103.03	133.50±78.76	36.50391	22.01191	50.99591	0.001
Chol(mg/dL)	<200	182.98±42.50	184.92±38.22	-1.93333	-8.3523	4.48564	0.554
HDL(mg/dL)	45-59	46.05±7.28	47.75±8.701	-1.70373	-2.98917	-0.41828	0.009
LDL(mg/dL)	100-129	106.86±39.26	109.88±33.37	-3.01209	-8.79381	2.76962	0.307
VLDL(mg/dL)	2-30	33.89±20.53	26.84±15.75	7.04737	4.15231	9.94244	0.001
AST/ALT	~1.14	0.73±0.15	0.80±0.13	-0.06761	-0.09051	-0.04471	0.001

Abbreviations: TSH, Thyroid Stimulating Hormone; BUN, Blood Urine Nitrogen; Creat, Creatinine; FBS, Fast Blood Sugar; TG, Triglyceride; Chol, Cholesterol; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; VLDL, Very Low Density Lipoprotein. The data are calculated by independent t-test and expressed as Mean ±SD, P values <0.05 are considered as significant.

Table 2a: Two-tailed Pearsons' correlation tests performed for all parameters determined in males (n=324).

Male	TSH	BUN	Creat	FBS	TG	Chol	HDL	LDL	VLDL
BUN	0.060 (0.309)								
Creat	0.172 (0.003)	0.305 (<0.001)							
FBS	-0.095 (0.111)	0.040 (0.500)	0.065 (0.272)						
TG	0.075 (0.203)	0.038 (0.525)	0.057 (0.334)	0.097 (0.102)					
Chol	0.045 (0.451)	0.114 (0.055)	0.022 (0.707)	0.029 (0.623)	0.381 (<0.001)				
HDL	-0.035 (0.556)	0.047 (0.433)	-0.043 (0.474)	0.070 (0.235)	-0.089 (0.135)	-0.006 (0.913)			
LDL	0.017 (0.770)	0.051 (0.387)	-0.003 (0.964)	-0.037 (0.531)	-0.041 (0.488)	0.784 (<0.001)	-0.157 (0.008)		
VLDL	0.080 (0.177)	0.030 (0.610)	0.049 (0.411)	0.084 (0.158)	0.993 (<0.001)	0.379 (<0.001)	-0.094 (0.112)	-0.046 (0.440)	
AST/ALT	0.038 (0.524)	-0.027 (0.653)	0.058 (0.332)	0.051 (0.388)	-0.127 (0.032)	-0.083 (0.163)	0.091 (0.123)	-0.063 (0.287)	-0.136 (0.022)

Abbreviations: TSH, Thyroid Stimulating Hormone; BUN, Blood Urine Nitrogen; Creat, Creatinine; FBS, Fast Blood Sugar; TG, Triglyceride; Chol, Cholesterol; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; VLDL, Very Low Density Lipoprotein. Correlation coefficient in accordance with P-value in parenthesis is shown for each pair of variables. P values <0.05 are considered as significant.

variables with the dependent variable of AST/ALT ratio. Table 3 summarizes the direct, indirect and total effect of each variable on AST/ALT ratios for both groups. The cumulative regression constant or total effect (Table 3), obtained by summation of all constants were -0.267 for the male and -0.341 for female groups. The negative sign indicates that increase in these variables decrease the ratio to lower values that seems to be compatible with NAFLD disease severity, from medical point of view.

It is noticeable that TSH and FBS play roles in NAFLD onset in the female group while their effects were absent or limited in the male group. The lower cumulative regression constant or the total effect for females (-0.341) contrasted that of males (-0.267). This may reflect the more serious condition for NAFLD progression in the female group compared with the male group.

Table 4 summarizes the model fit indices including Chi-Square test statistic, Degree of freedom (DF) and related p-value, Tucker Lewis index (TLI), Comparative Fit Index (CFI), Degrees of Freedom (DF) and Root Mean Square Error of Approximation (RMSEA) for our models of male and female groups. A model with good fit should have a bigger Chi-square value than zero or Chi-Square/DF ratio lower than 5 with P-value exceeding 0.05. The indexes of TLI and CFI more than 0.95 and RMSEA lower than 0.05 also show good fit for our models [29-30]. According to the parameters for our models of male and female groups in Table 4,

Table 2b: Two-tailed Pearsons' correlation test performed for all parameters determined for females (n=286).

Female	TSH	BUN	Creat	FBS	TG	Chol	HDL	LDL	VLDL
BUN	0.006 (0.914)								
Creat	0.087 (0.12)	0.498 (<0.001)							
FBS	-0.019 (0.733)	0.055 (0.321)	0.058 (0.294)						
TG	0.132 (0.017)	0.055 (0.324)	0.060 (0.280)	0.226 (<0.001)					
Chol	0.044 (0.426)	0.048 (0.389)	0.034 (0.544)	0.110 (0.048)	0.333 (<0.001)				
HDL	-0.053 (0.342)	-0.087 (0.118)	0.033 (0.556)	0.007 (0.899)	0.005 (0.936)	-0.042 (0.449)			
LDL	-0.080 (0.150)	0.012 (0.829)	-0.016 (0.780)	0.026 (0.639)	-0.023 (0.682)	0.755 (<0.001)	-0.263 (<0.001)		
VLDL	0.127 (0.023)	0.051 (0.356)	0.056 (0.314)	0.217 (<0.001)	0.989 (<0.001)	0.333 (<0.001)	0.003 (0.955)	-0.028 (0.621)	
AST/ALT	-0.046 (0.413)	-0.023 (0.677)	0.032 (0.567)	0.011 (0.841)	-0.159 (0.004)	-0.145 (0.009)	0.104 (0.061)	-0.086 (0.121)	-0.158 (0.004)

Abbreviations: TSH, Thyroid Stimulating Hormone; BUN, Blood Urine Nitrogen; Creat, Creatinine; FBS, Fast Blood Sugar; TG, Triglyceride; Chol, Cholesterol; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; VLDL, Very Low Density Lipoprotein. Correlation coefficient in accordance with P-value in parenthesis is shown for each pair of variables. P values <0.05 are considered as significant. Table-3: Direct, indirect and total effects of all determined parameters on AST/ALT ratio in path diagram (Figure 1A and 1B) for the male and female groups.

Table 3: Direct, indirect and total effects of all determined parameters on AST/ALT ratio in path diagram (Figure 1A and 1B) for the male and female groups.

	Indirect effect		Direct effect		Total effect	
	Males	Females	Males	Females	Males	Females
TSH	-.001	-.016	.000	.000	-.001	-.016
Creat	-.003	.000	.000	.000	-.003	.000
HDL	.013	-.001	.000	.000	.013	-.001
LDL	.008	.004	.000	.000	.008	.004
BUN	-.010	.000	.000	.000	-.010	.000
Chol	-.147	-.135	.000	.000	-.147	-.135
TG	.000	.000	-.127	-.158	-.127	-.158
FBS	.000	-.035	.000	.000	.000	-.035
Cumulative effects	-.140	-.183	-.127	-.158	-.267	-.341

Abbreviations: TSH, Thyroid Stimulating Hormone; BUN, Blood Urine Nitrogen; Creat, Creatinine; FBS, Fast Blood Sugar; TG, Triglyceride; Chol, Cholesterol; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; VLDL, Very Low Density Lipoprotein.

Table 4: Model fit parameter extracted for two models obtained for male and female groups using Amos (version 23.0) software.

Model Fit	Chi-square	P-value	DF	TLI	CFI	RMSEA
Male(n=286)	25.921	.467	26	1.000	1.000	<.001
Female (n=324)	11.734	.699	15	1.005	1.000	<.001

the models show very good fit with all indices. Therefore, these models were reliable for results interpretation.

Discussion

It is well known that decreased physical activity and sedentary lifestyle in most developed countries are basic underling factors for the most frequent chronic diseases such as obesity, diabetes mellitus, cardiovascular and lipid storage disease. Among these diseases, NAFLD affects up to 80 percent of obese people with incidence rate of 9-36 percent worldwide [33]. One of outstanding tools for diagnosis of this disorder is a panel including elevated hepatic enzymes of AST and ALT and especially their under unity ratio (AST/ALT <1) [15].

Increased lipids and lipoproteins (TG, LDL, VLDL, Chol and FBS), as well as increased TSH, creatinine and BUN in obese, insulin resistant and diabetic individuals constitute threatening

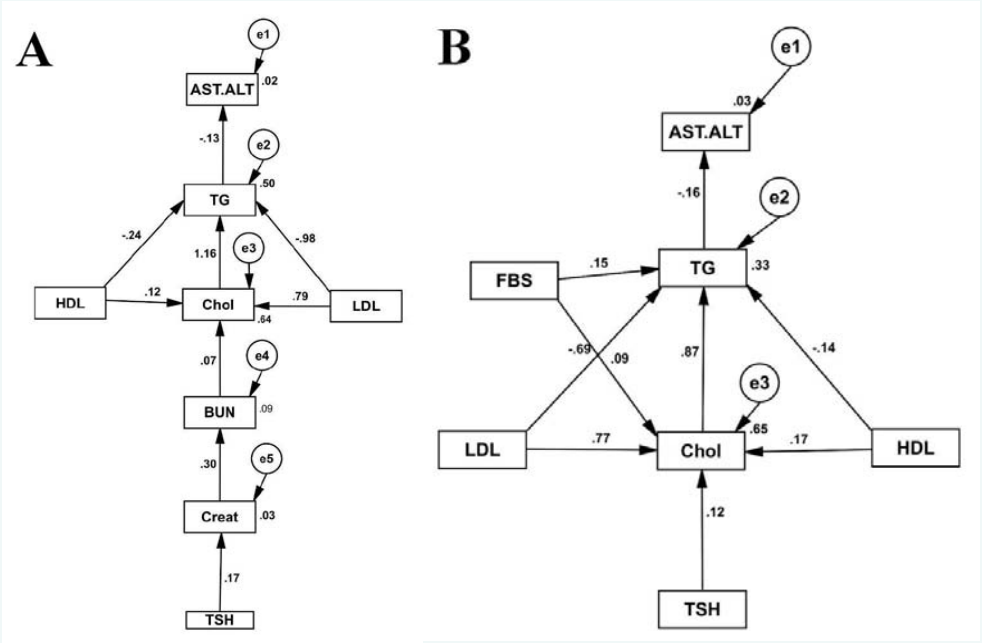

Figure 1 The best diagram extracted for the male (A) and female (B) groups. Dependent and independent variables are shown in rectangles. Variables not included in the models are shown in circles. Single headed arrows with standardized coefficients link independent variables to the dependent variable. The diagrams are plotted and optimized in Amos (version 23.0).

factors for fat deposition in liver and NAFLD establishment [9, 37].

Given the fact that a ratio of AST/ALT<1 serves as a criterion for NAFLD, a lower ratio means a more serious case of the disease. The Path analysis modeling for the causality relationship between measured factors and the AST/ALT ratio may be helpful to discover how those factors affect the ratio of AST/ALT and how to quantify their deleterious or protective effects on NAFLD disease.

Based on our results depicted in Table-1, the male group showed higher levels of TG of 170±103 mg/dL in contrast to females with 133.5±78.76 mg/dL concentration (p-value<.05). The VLDL level in males (33.89±20.53) was higher than that in females (26.84±15.7) (p-value<.05). However, the HDL levels in males (46.05±7.28) was lower than that of females (47.75±8.70). The same applies for AST/ALT ratios in both sexes. It is, therefore, reasonable to expect that the male group be at a higher risk to NAFLD. However, this contrasts scenario proposed by some authors [37-38] and faces opposition from others [1,2].

Therefore, we undertook the path analysis to shed light on this apparent paradox. The Path analysis output depicted in Figure 1 (A and B) and Table 3 shows different patterns or different mechanisms of interactions between suspected biochemical parameters in NAFLD for two groups in such a way that TSH and FBS in the female group negatively affect AST/ALT ratios leaving pathogenic effect on NAFLD. This means that increased concentration of TSH in hypothyroidism and increased level of glucose in diabetes mellitus especially in elderly facilitate NAFLD onset in females but not in males [16,31].

On the other hand, the significant increase of BUN concentrations and creatinine in males (Table 1), which were probably caused by mild chronic kidney insufficiencies (note regression coefficients of -0.003, for Creat and -0.01 for BUN in Table 3) contribute to NAFLD in male group but not in the female as previously reported by some authors [32-34].

In male group, indirect effects with pathogenic or protective effects on NAFLD are primarily exerted by Chol (-0.147) and HDL (+0.013) respectively (P-value<.05) (Table 3).

Taking into consideration the path analysis diagrams (Figure 1) and regression coefficients (Table 3), the overall effects of biochemical parameters determined in this study give more determinant indexes for their causative effects on NAFLD induction. As indicated, the cumulative coefficient for the female group is equal to -0.341 and for the male group is equal to -0.267. The higher coefficient for the female group conveys that concentrations of TG, VLDL, BUN and Creatinine are lower in females than in males. The female group is surprisingly at higher risk for NAFLD onset. This means that changes in independent variables (biochemical parameters) cause a more prominent decrease in AST/ALT ratio in females rather than in males. In fact, a more effective decrease in the ratio with aging leads to fat deposition and consequently to NAFLD. Figures 1 A and 1B represent schematically the interactions between variables and their causality relations with AST/ALT ratios. These figures show the same symmetry for both group except for BUN and creatinine which are absent from the female diagram and for FBS which is absent from the male diagram. This in turn means that kidney

problem plays role in NAFLD in males but not in females, while FBS and diabetes mellitus or even insulin resistance play the same role in females.

Conclusion

Despite the existence of lower AST/ALT ratios and higher concentrations of pathogenic lipids and lipoproteins in the male group, path analysis indicates that the female group is at higher risk for NAFLD. Path analysis provides better understanding of the disease and helps constructing reliable causality relations between variables to unravel the complicated relations between parameters. It also assist in interpretation of mechanisms by which NAFLD overwhelms.

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Authors' Contributions: Mohammad Reza Dayer designed the experiments and constructs the main idea of the project. Vahideh Sadat Nazemi performed statistical analysis and extract the PATH diagrams under supervision of Sayed Mohammad Reza Alavi in SPSS and AMOS environment. Mohammad Saaid Dayer took part in final analysis of the results and in discussion as well as the revision of the manuscript.

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