Potential role of liver enzymes for predicting elevated blood glucose levels

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Research article

Keywords: Liver enzyme, elevated blood glucose, risk factor

Posted Date: January 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-155346/v1

Abstract

Background

This study was to explore the potential effect of different liver enzymes on elevated blood glucose with the use of a more detailed blood glucose grouping.

Methods

This cross-sectional study enrolled 144,135 participants who had biochemical examinations from 2014–2018. Participants were classified by sex and different blood glucose levels (< 5.0 mmol/L, 5.0-5.5 mmol/L, 5.6–6.2 mmol/L, 6.3–6.9 mmol/L, and ≥ 7.0 mmol/L). The associations between liver function indicators and occurrence of type 2 diabetes (T2DM) were analyzed through multivariate linear regression and multiple logistic regression.

Results

There was a significant difference among the biochemical indices between different blood glucose groups in males and females. Liver enzymes such as alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT) were independent risk factors for raised blood glucose, and there were gender differences in the predictive performance of each liver enzyme to elevated blood glucose levels. In men, GGT was the most appropriate to predict progressive elevation of blood glucose or T2DM risk, and ALT and ALP may only be applicable to the prediction of impaired fasting glucose (IFG). By contrast, ALT and ALP were the most appropriate enzymes for the prediction of the risk of elevated blood glucose or T2DM in women, and AST and GGT may only be appropriate for the prediction of IFG.

Conclusions

Liver enzymes were independent risk factors for elevated blood glucose. There were gender differences in the role of each liver enzyme for elevated blood glucose. GGT was more suitable as a predictor for dynastic elevated blood glucose in men, whereas for women, ALT and ALP were more suitable.

Background

With our changing lifestyles, diabetes has gradually become one of the most important chronic diseases in humans. It is the third leading chronic fatal disease after cancer and cardiovascular disease. The World Health Organization predicts that more than 300 million people will suffer from diabetes worldwide by 2030[1]. Early diagnosis and intervention can significantly reduce the incidence of type 2 diabetes (T2DM)

[2]. Therefore, the whole population and the high-risk population of T2DM should be evaluated, to enable timely targeted prevention.

Recent diabetes studies have focused on identifying risk factors associated with a high risk of T2DM, to identify potential intervention targets and to understand the pathophysiological mechanisms. As the main site and target of insulin metabolism, the liver plays an important role in the pathogenesis of T2DM. Nonalcoholic fatty liver disease (NAFLD) is a liver disease characterized by excessive accumulation of fat in liver cells. Many studies have found that NAFLD is an independent risk factor for T2DM[3], and its most common characteristic is elevated liver enzyme levels. Studies have shown that liver enzyme levels, such as alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (GGT), reflect liver function and are closely related to the pathogenesis of T2DM[4–6]. However, the relationship between liver enzyme levels and T2DM remains controversial.

Due to gender and age differences in liver enzyme levels[7, 8], it has been speculated that the sensitivity of the four liver enzymes to increased blood glucose may also be different, so it is necessary to group the subjects by sex to accurately reflect the glucose status for gender. In addition, most of the current studies have focused on the prediction of T2DM by liver enzymes, and there is still a lack of studies involving the risk of prediabetic or elevated blood glucose levels. Based on a more detailed grouping of blood glucose, this study aimed to explore the role of different liver enzymes on elevated blood glucose levels in males and females.

Methods

Study Population

A population based cross-sectional study was conducted from 2014-2018 at the Sixth Affiliated Hospital of Kunming Medical University in Yuxi City, Yunnan Province, China. A total of 159244 (94328 men and 64916 women) local residents attending an annual physical examination at the People's Hospital of Yuxi City (Yunnan Province, P.R. China), aged 14-98 years, were initially enrolled in the study. According to the exclusion criteria, a total of 144135 (83828 men and 60307 women) participants were ultimately included in the study (Fig. 1). Biochemical information of all participants was collected.

All procedures in studies involving human participants were performed according to the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Review Board of the People's Hospital of Yuxi City.

Inclusion and Exclusion Criteria

This study included cases with complete datasets for blood glucose, ALT, AST, ALP, and GGT levels, and age. The subjects all participated in the initial health examination, but exclusion criteria were as follows: liver diseases (chronic viral hepatitis, autoimmune liver diseases, drug-induced liver injury/medications

that potentially affect liver enzyme levels, liver cirrhosis, genetic liver disease), Obstructive liver disease, Hematological disease, bone diseases that may affect ALP level, maglignant tumors, chronic kidney disease, nephrotic syndrome, pregnancy. The participants who had heavy drinking (≥40 g alcohol per day) were also excluded (Fig. 1).

Grouping and Laboratory Tests

The participants were categorized according to sex and blood glucose (< 5.0 mmol/L, 5.0-5.5 mmol/L, 5.6-6.2 mmol/L, 6.3-6.9 mmol/L, ≥ 7.0 mmol/L). In addition, the subjects were divided into four groups (Q1, Q2, Q3, Q4) according to the quartile of each liver enzyme for the different genders: ALT (male: ≤ 17, 18-25, 26-36, ≥ 37; female: ≤ 10, 11-14, 15-21, ≥ 22), AST (male: ≤ 17, 18-21, 22-27, ≥ 28; female: ≤ 15, 16-17, 18-22, ≥ 23), ALP (male: ≤ 60, 61-70, 71-84, ≥ 85; female: ≤ 49, 50-59, 60-74, ≥ 75), GGT (male: ≤ 24, 25-29, 30-35, ≥ 36; female: ≤ 21, 22-25, 26-31, ≥ 32).

Venous blood samples were collected from each participant after an overnight fast for at least 12 h. Serum and plasma were immediately separated by centrifugation and used directly or frozen at -80 °C until assay. Plasma glucose was measured by using a hexokinase enzymatic method. Serum liver enzymes (ALT, AST, ALP, GGT) were detected by colorimetric methodology. All of the above tests were performed using a Roche Cobas701 automatic biochemical analyzer (Roche, Basel, Switzerland).

Statistical Analyses

Statistical analyses were performed using SPSS software (version 21.0, Chicago, IL) and MedCalc 19.0.4 program where appropriate, and used Graphpad 8.0.2 to construct the chart.

Statistical Description and Intergroup Comparison

The Shapiro-Wilk test was used to determine the normality of distribution and skewed variables were log transformed. Continuous variables were expressed as the mean ± SD for normally distributed data or median (interquartile range) for skewed variables. Categorical variables were expressed as number of participants and percentage. Student's t-test was used to compare continuous variables. Pearson chi-square tests were used to compare categorical variables and a P-value of < 0.05 was considered statistically significant.

Correlation Analysis

The Pearson analysis was used for correlation testing. Generally, the correlation coefficient $0.8 \leq |r| < 1$ indicated that the variables had a strong correlation ($P < 0.05$). Coefficients of $0.5 \leq |r| < 0.8$ indicated that the variables had a moderate correlation. Values of $|r| < 0.5$ indicated that the variables had a weak or absent correlation.

Multivariate Linear Regression

According to the quartile of serum ALT, AST, ALP, GGT levels, participants were divided into four groups (Q1, Q2, Q3, and Q4). Liver enzymes were used as independent variables, and fasting blood glucose levels were used as dependent variables. Multiple linear regression was used to assess the relationship between liver enzymes and fasting blood glucose levels by regression coefficient (β) and 95% confidence interval (CI), for each liver enzyme quartile.

Multiple Logistic Regression

Liver enzymes were used as categorical or continuous variables (with risk expressed per SD change in the natural log of the marker), and the relationship between serum liver enzyme levels and fasting blood glucose levels was investigated by multivariate logistic regression analysis. Two separate logistic regression models were constructed for each liver enzyme: the first model consisted of unadjusted data. The second model included age and lipids. Odds ratios (ORs) and 95% confidence intervals (95% CI) for risk of elevated blood glucose level were estimated for each liver enzyme quartile.

Results

Baseline Characteristics

A total of 144,135 subjects (83,828 men, and 60,307 women) were included in this study and their gender specific biochemical characteristics are shown in Table 1.

The difference in age and biochemical characteristics between blood glucose groups was statistically significant in men when compared to women ($P < 0.001$). In men, liver enzyme levels basically increased with increasing blood glucose levels, but ALT, AST, and ALP was decreased with a blood glucose ≥ 7.0 mmol/L, when compared to 6.3-6.9 mmol/L. The levels of liver enzymes in women were positively correlated with blood glucose. In both genders, triglycerides (TG) was positively, and high density lipoprotein cholesterol (HDL-C) was negatively correlated with blood glucose.

Analysis of the Correlations Among the Eight Laboratory Indices

We subjected the eight clinical indexes to correlation analyses in men and women with SPSS and constructed a heatmap by Graphpad 8.0.2 (Fig. 2, 3). TC and low density lipoprotein cholesterol (LDL-C) were significantly and strongly correlated ($r = 0.716$ in men, $r = 0.826$ in women). ALT and AST were moderately correlated ($r = 0.696$ in men, $r = 0.698$ in women), as were TG and HDL-C ($r = 0.433$ in men, $r = 0.406$ in women). The remaining indices were extremely weakly correlated or uncorrelated.

Relationship Between Blood Glucose as Continuous Variable and Serum Liver Enzyme Levels

The results of multiple linear regression analysis by gender are shown in Table 2. Multiple linear regression analysis showed that high concentrations of liver enzymes corresponded to higher fasting blood glucose levels. Compared with the baseline group, the fasting glucose levels in the fourth quartile

for ALT, AST, ALP, and GGT in men were 0.192, 0.173, 0.064, and 0.184 mmol/L, respectively, and those in women were 0.195, 0.177, 0.180, and 0.030 mmol/L, respectively.

Relationship Between Blood Glucose as Categorical Variable and Serum Liver Enzyme Levels

In this study, the blood glucose subgroups belong to ordinal categorical variables, but the parallel regression assumption had been violated. Therefore, multiple logistic regression analysis of the unordered categorical was carried out, and the results are shown in Table 3.

As categorical variables, with or without factor adjustment, elevated levels of ALT, AST, and ALP in all groups (5.0-5.5 mmol/L, 5.6-6.2 mmol/L, 6.3-6.9 mmol/L, ≥ 7.0 mmol/L) were positively correlated with the risk of elevated blood glucose in both sexes. Like other indicators, GGT was positively correlated with the risk of increased blood glucose in the abnormal blood glucose groups (5.6-6.2 mmol/L, 6.3-6.9 mmol/L, ≥ 7.0 mmol/L). However, there were differences in the relationship between GGT levels and the risk of increased blood glucose in both genders in model two, with glucose levels of 5.0-5.5 mmol/L, but the relationship between the two is positively correlated in men (Q4：OR 1.197，95%CI：1.143-1.253) and negatively correlated in women (Q3: OR 0.939, 95% CI: 0.893-0.987; Q4: OR 0.927, 95% CI: 0.878-0.979).

The control group was replaced in turn to explore the contribution of liver enzymes in the dynamic increase of blood glucose. When the previous adjacent blood glucose level was the control, the relationship between serum liver enzymes and each blood glucose level grouping is shown in Table 4.

After adjusting for potential confounders (Model two), the contribution of liver enzymes to the continuous increase of blood glucose levels was found to be different between male and females. In men, there was no significant correlation between ALT, ALP, and the risk of blood glucose rising to 6.3-6.9 mmol/L or ≥ 7.0 mmol/L, which may indicate that ALT and ALP are not sensitive predictors for the risk of higher blood glucose. GGT appeared as a risk factor in elevated blood glucose, which may be used to predict the risk of elevated blood glucose or T2DM in men. The OR value of AST in men in the 6.3-6.9 mmol/L group was not statistically significant, but the OR value of blood glucose ≥ 7.0 mmol/L was < 1 and statistically significant, when compared with that in the IFG (5.6-6.9 mmol/L), suggesting that AST may not be suitable for predicting the risk of T2DM in men. For women, the OR of AST and GGT in the IFG (5.6-6.9 mmol/L) was > 1 and was statistically significant, and therefore, this may be suitable for predicting the risk of IFG. The contribution of ALT and ALP to the persistent elevation of blood glucose levels in women is similar, and both of them continue to present as risk factors in the elevation of blood glucose, and may be used to predict the risk of elevated blood glucose or T2DM.

Liver enzymes were separately added into Model two as continuous variables for multiple logistic regression analysis (Table 3). When a blood glucose level of < 5.0 mmol/L was used as the control, the increase in 1SD of four liver enzymes in all blood glucose subgroups (5.0-5.5 mmol/L, 5.6-6.2 mmol/L, 6.3-6.9 mmol/L, ≥ 7.0 mmol/L) for men was significantly correlated with the increased risk of high blood glucose. Females were similar to males except that the OR value of GGT in the 5.0-5.5 mmol/L group was not statistically significant.

Liver enzymes were incorporated into Model 2 as continuous variables (Table 3). Although there were also differences in the results of several indicators in specific blood glucose groups, liver enzymes were basically risk factors for increased blood glucose. In the male with 5.0-5.5 mmol/L, an OR value for ALT showed no statistical significance, and AST, ALP, and GGT were positively correlated with the risk of increased blood glucose. In males with ≥ 7.0 mmol/L, the OR value of AST was not statistically significant, but others were positively correlated with raised blood glucose. For women, in the 5.0-5.5 mmol/L group, GGT was found to be a protective factor, and ALT, AST, and ALP were all risk factors. In females from the 6.3-6.9 mmol/L and ≥ 7.0 mmol/L, OR values of AST were not statistically significant, while the OR values of other liver enzymes were all > 1 and statistically significant.

Discussion

Prospective and cross-sectional studies have previously explored the relationship between serum liver enzymes and T2DM, but the results remain controversial. The aim of this study was to investigate the relationship between serum liver enzymes and blood glucose levels and the predictive power of changes in serum liver enzymes to increase blood glucose levels in different genders.

Our study found that all four indicators of liver enzymes were independent risk factors for raised blood glucose. However, there were gender differences in the predictive performance of each index to elevated blood glucose levels. The multiple logistic regression analysis of unordered categorical data showed that the GGT level in the fourth quantile was related to elevated blood glucose levels and presented as a risk factor. Changing the control blood glucose group to further analyze the contribution of liver enzymes in the dynamic increase of blood glucose, we found that GGT was more suitable for predicting the risk of elevated blood glucose or T2DM in men, while in women, it may only be applicable for predicting the risk of IFG. GGT may be a useful biochemical indicator in clinical practice. Studies have suggested that GGT is involved in the catabolism of glutathione and is related to increased oxidative stress, which seems to play an important role in the development of insulin resistance and diabetes[9]. The role of GGT in the development of T2DM proposed in our study is consistent with others[10, 11].

The role of ALT and ALP for predicting elevated blood glucose was similar and increased ALT and ALP levels were positively correlated with the risk of elevated blood glucose in all blood glucose groups, in both men and women. When the previous adjacent blood glucose group is further changed to controls, we found that the contribution of ALT and ALP to the dynamic increase in blood glucose levels was different between ganders. In men, both indicators may also be used to predict abnormal blood glucose levels, but the prediction of T2DM may lack sensitivity. However, ALP and ALT performed better in women and were more suitable for predicting the risk of elevated blood glucose or T2DM.

AST was similar to ALT and ALP, but AST presented as a protective factor in the male ≥ 7.0 mmol/L group, when the adjacent blood glucose groups were successively changed to controls, which may reflect AST as not being linearly correlated with the risk of elevated blood glucose in men, and suggests that AST may not be suitable for predicting T2DM. Others have also proposed a lack of correlation between

AST and T2DM[12, 13]. However, AST behaved differently in women when compared to men and it may therefore, play a role in the prediction of T2DM in women.

A study on the correlation between serum liver enzymes and T2DM risk remains controversial. We believe that the reason for the difference between the results is the lack of gender analysis. The authors believe that the difference can be attributed to the lack of gender grouping analysis. Studies have pointed to the fact that there are gender and age differences in liver enzyme levels[7, 8], and differences in the sensitivity of liver enzyme levels to elevated blood glucose in different genders. This suggests that it is necessary to explore suitable serum liver enzymes for the predicting the risk of elevated blood glucose in specific genders. In addition, ethnicity, and insufficient understanding of the biological mechanisms of liver enzymes, and related confounding factors may also contribute to this difference. Therefore, there remains a need to further explore the mechanism of liver enzymes on T2DM, and to identify the predictive performance of each serum liver enzyme on IFG and T2DM using a larger prospective epidemiological study in specific races.

Recently, studies have estimated a potential causal relationship between liver enzymes and diabetes through Mendelian randomization studies but results remain controversial. Most studies reported strong evidence for a positive effect of ALT on T2DM but not for ALP or GGT[14, 15], while others negated it[16, 17]. Through genetic analysis, De Silva et al.[18] showed that higher ALT and AST levels in the circulation were related to an increased risk of T2DM, and there was a negative correlation between ALP and T2DM risk. However, there was no correlation found between GGT and T2DM risk. Nano et al.[19] proposed that the relationship between GGT levels and the risk of DM may be due to reverse causality or residual confounding factors. Therapies aimed at reducing GGT were unlikely to be effective in preventing T2DM. However, adherence to good lifestyle habits, including smoking cessation, weight control, exercise, moderate alcohol consumption, and a healthy diet, may delay the onset of T2DM or cardiovascular disease and increase life expectancy[20, 21]. The authors suggested that before it was clear whether causal relationship existed between liver enzymes and diabetes, monitoring liver enzyme levels and alerting patients to early interventions for diabetes through lifestyle improvements may be desirable.

Our study has several strengths. The main advantage is the inclusion of many subjects with clear exclusion criteria to avoid the effects of liver disease on liver enzyme levels. In addition, we also grouped the population by gender, to further explore the role of liver enzymes in specific genders. However, the limitations of our study should be acknowledged also. First, we only collected information on fasting blood glucose from patients once. Second, the influence of accidental factors on fasting blood glucose cannot be ruled out. Finally, the cross-sectional observational study failed to clarify the causality between laboratory indicators and T2DM. Based on the results of this study, we will consider further prospective studies to explore and verify the potential role of liver enzymes in elevated blood glucose.

Conclusion

Overall, our study confirmed that liver enzymes are independent risk factors for elevated blood glucose. There were gender differences in the role of each liver enzyme for elevated blood glucose. Currently, the correlation between serum liver enzymes and the risk of T2DM is still controversial, which may be due to the lack of understanding of the biological mechanism of liver enzyme levels, other related confounding factors, or a lack of detailed grouping of the subjects. Therefore, it is still necessary to further explore the mechanism of liver enzymes on T2DM, and to identify the predictive performance of each serum liver enzyme on IFG and T2DM, using a larger prospective epidemiological study for predicting elevated blood glucose levels.

Abbreviations

T2DM: Type 2 diabetes; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; GGT:γ-glutamyl transpeptidase; IFG: Impaired fasting glucose; NAFLD: Nonalcoholic fatty liver disease; ORs: Odds ratios; 95% CI: 95% confidence intervals; TG: triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol.

Declarations

Acknowledgments

We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

Authors' contributions

MN Wu and SY Nian researched data and contributed to/reviewed and edited the manuscript; L Feng contributed to/reviewed and edited the manuscript; WB Xu performed analyses and reviewed the manuscript; D Ye designed analyses and reviewed the manuscript. CT Zhang performed analyses and reviewed the manuscript; ZF Yan, QX Ma and C Shao researched the data. All authors have read and approved the manuscript

Funding

This work was partially supported by Yunnan Provincial Department of Science and Technology-Kunming Medical University Joint Special Project on Applied Basic Research: 2018FE001(-081), and the fund recipient Shiyan Nian researched data and contributed to/reviewed and edited the manuscriptas as co-first author. This study was also supported by Scientific Research Fund of Yunnan Education Department (2020Y0140, 2019J1307, 2019J1309) and the Postgraduate Innovation Fund of Kunming Medical University (2020S233), and the fund recipient Mengna Wu, Dan Ye and Chunting Zhang researched data, contributed to/reviewed and edited the manuscriptas and performed analysesas the first author and co-author.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics and consent to participate

All procedures in studies involving human participants were performed according to the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by Review Board of the People's Hospital of Yuxi City (2020kmykdx6f40).

Consent for publication

Not Applicable

Competing interests

The authors declare that they have no competing interest.

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Tables

Due to technical limitations, table 1, 2, 3, 4 is only available as a download in the Supplemental Files section.

Figures

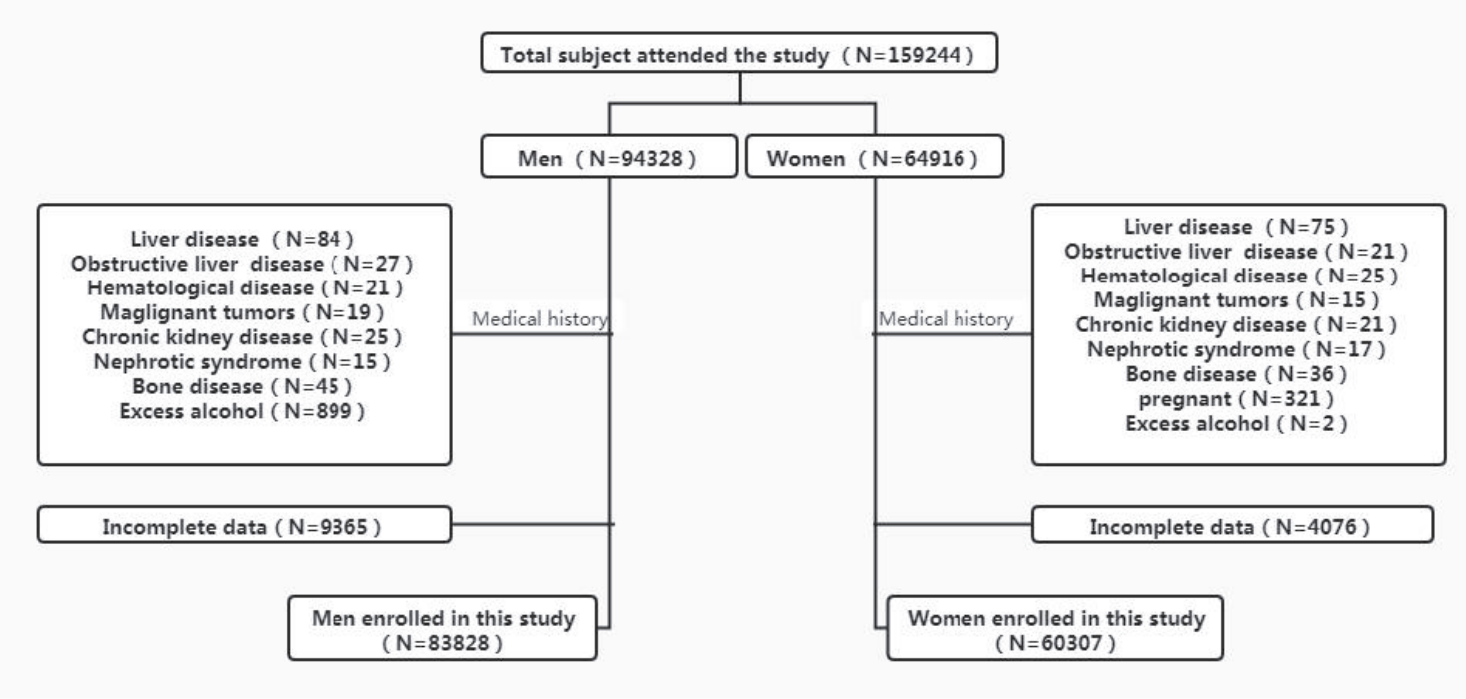

Figure 1

Flow chart of the study participants.

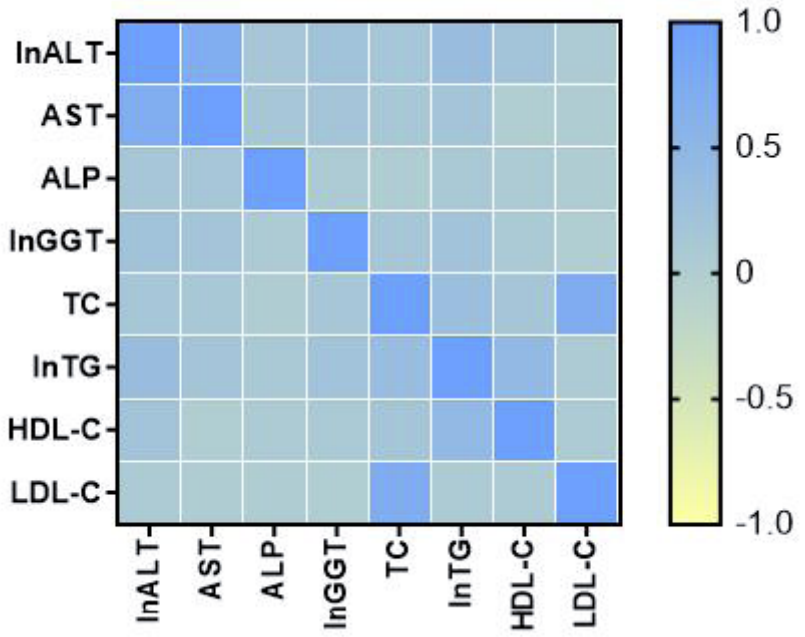

Figure 2

Correlations among the 8 laboratory index in men.

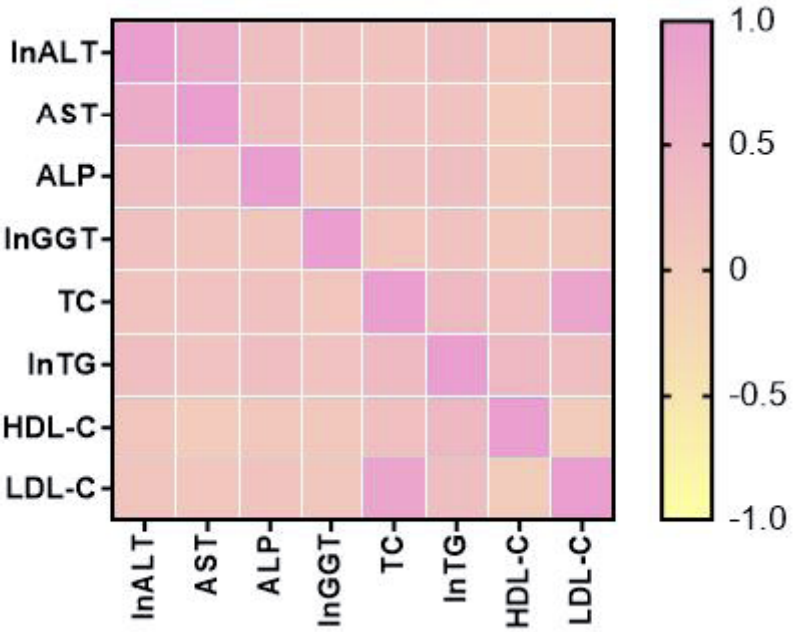

Figure 3

Correlations among the 8 laboratory index in women

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table14.pdf
- STROBEchecklistcrosssectional.doc