

Research article

Correlation of hepatic transaminases with cortisol levels in type 2 diabetes

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Corresponding author: **Vinod Chandran**. Email: vinod.chandran@manipal.edu**ABSTRACT**

Introduction and Aim: Aminotransferases are the markers of liver function and cortisol is the hyperglycemic stress hormone, both have been associated with insulin resistance and type 2 diabetes. Hypothalamic pituitary adrenal axis is known to control many functions of the liver. This study was aimed to evaluate the correlation of cortisol with hepatic transaminases; AST and ALT also with fasting blood glucose (FBG) and HbA1c in type 2 diabetic patients. Also, the AST, ALT and cortisol levels of participants were compared based on their diabetic duration and gender.

Materials and Methods: This prospective study included patients with type 2 diabetes (n=89) with a mean diabetic duration of 7.66 ± 6.871 years, of which 66.3% were males and 33.7% were females. Data for the above parameters except cortisol were collected from the data management system of the central lab. Morning serum cortisol levels were estimated by enzyme-linked immunosorbent assay (ELISA) method. Karl Pearson's correlation coefficient and independent student's t-test were applied to find correlation and comparison of AST, ALT and cortisol levels of participants based on their diabetic duration and gender respectively.

Results: The comparison based on diabetic duration shows significant differences ($p < 0.005$) with AST while, not with ALT and cortisol. Also, they did not show a significant difference in either of the gender. Among hepatic transaminases, the probability of association of ALT with FBS levels and HbA1c levels was significant ($p < 0.05$). However, though a positive trend is seen in the AST association, there is no strong correlation observed. Likewise, the association of serum cortisol levels, with AST, ALT and HbA1c was not significant but the probability of association was significant with FBS levels.

Conclusion: Findings from the present study suggest that liver transaminases are positively correlated with serum cortisol levels in type 2 diabetic patients.

Keywords: Type 2 diabetes mellitus; hepatic transaminases; aspartate aminotransferase; alanine amino transferase; NAFLD; cortisol; subclinical hypercortisolism.

INTRODUCTION

Type 2 diabetes is a non-communicable, and common form of diabetes with high alarm rates in this most modern era and has a close relation with our lifestyle in all aspects including, diet and mental factors. This metabolic condition is characterized by hyperglycemia, where the body is insulin-deficient or resistant to insulin action, which can also reduce the latent period of developing various health complications ranging from the heart, kidney, brain, eyes, vasculature, and nerves. Also, it is related to elevations of liver enzymes in type 2 diabetes mellitus (T2DM) patients compared to the general population (1-3).

The elevated liver enzymes in patients with T2DM are an indication of liver injury and insulin resistance (IR) (4). Insulin resistance is a precursor pathophysiological mechanism of T2DM, thereby increasing obesity, hyperlipidaemia, increased glycogen lysis and gluconeogenesis in the liver, which will expand possibilities of risk to fatty liver/non-alcoholic fatty liver diseases (NAFLD; 5), a condition in which excess fat gets deposited in the liver in people who drink a small amount of alcohol or not. This can

evolve into steatohepatitis (NASH) which is a more severe form of NAFLD. The development of liver diseases is the major cause of death in patients with T2DM.

Elevation of hepatic aminotransferases; AST and ALT than the normal levels (5-40 and 6-40 IU/l) reflects the liver damage. Because when the liver gets injured, these enzymes start to leak out and make their way to the blood. But in chronic conditions of cirrhosis and hepatocellular carcinoma, these will be in a normal range. The conditions like incidents of oxidative stress (6), mitochondrial dysfunctions, lipid peroxidation, peroxisomal beta-oxidation and cytokine release will also lead to the elevation of transaminases in hyperglycaemia and IR states (7).

Cortisol is a hyperglycaemic steroid hormone, released with a diurnal cycle from the adrenal cortex in response to adrenocorticotrophic hormone (ACTH). Its release is increased in response to stress and low blood-glucose concentrations/IR, at which it induces the breakdown of protein and fat in muscles and adipose tissues respectively thus, gluconeogenesis occurs in the liver (In the extrahepatic tissues, they inhibit the uptake and utilization of glucose. The

overall effect will be the elevation of glucose again. Thus, severe T2DM may be associated with subclinical hypercortisolism (SH), which is distinguished by impaired ACTH/cortisol homeostasis without any classical signs or symptoms of Cushing's syndrome. The person with both these conditions; T2DM and SH may suffer from more severe diseases, such as hypertension, dyslipidaemia and the obligation for insulin treatment, all of which are well-established risk factors for diabetes complications (8).

Since, metabolism of hormones is one of the main functions of the liver and also, it's a synthetic storehouse for precursors of almost all the adrenal hormones as well as cortisol binding globulin (CBG), it is not surprising that the various endocrine disturbances are associated with liver diseases. The HPA axis controls many functions of the liver through neuroendocrine forward signaling pathways as well as negative feedback mechanisms. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and enhanced release of cortisol is crucial to a successful response to stress, but this homeostatic mechanism is disrupted in liver disease. In cirrhosis, impaired responsiveness of the adrenal to ACTH contributes to increased mortality with haemodynamic impairment (9). Replacement with low-dose hydrocortisone significantly improves resolution of shock and survival (10).

The cortisol which is synthesized in the adrenal gland circulates in free (5%, active) and is bound with CBG (90%, inactive) and albumin (11). Recently, several cases and studies showing adrenal dysfunction in the whole spectrum of liver diseases, include adrenal insufficiency in which there is an elevation of liver enzymes with cortisol (12,13).

As per the recent international surveys, 8.5% of the world's population was diagnosed with diabetes, of which 90-95% itself had T2DM. International Diabetes Federation it is now estimated that over 640 million will have diabetes by 2040. So, according to the facts, it is no wonder that T2DM is said to be a non-transmissible silent pandemic.

Since, elevated level of cortisol is associated with T2DM and increased or decreased cortisol levels can cause an elevation in liver enzymes as well as, the T2DM is a risk factor for liver diseases, it is very important to check if there is any linear relation

between hepatic transaminases with cortisol levels in type 2 diabetic patients. Hence T2DM raises the risk of liver diseases, finding of other factors associated with T2DM therefore liver diseases, will help in the early detection thereby lifestyle modifications and diet control will reduce the risk of disease burden for the patients from developing liver diseases.

MATERIALS AND METHODS

It was a prospective short-term study conducted based on lab reports of LFT and estimation of morning cortisol levels in 89 (59 males and 30 females) known T2DM patients with a mean diabetic duration of 7.66 ± 6.871 years, received at Kasturba Medical College Hospital (KMCH), Ambedkar Circle, Mangalore. The mean age of participants was 60 ± 11 years. This study was approved by the institutional ethics committee, Kasturba Medical College, Mangalore. (Protocol No: IECKMCMLR-12/2020/411). Informed consent was taken from patients.

Type 2 diabetes patients on insulin therapy and known cases of renal disorders, infective hepatitis and cirrhosis of the liver were excluded from the study. Details of diabetic duration and drug taken were obtained from patients. Data for AST, ALT, FBG and HbA1C were collected from the data management system from the central lab after the consent from authorized personnel. Leftover serum samples of the selected subjects were collected from the lab, stored at -20°C , and used for the estimation of cortisol levels by ELISA method using LISA PLUS ELISA reader according to manufacturer's instructions. Statistical analysis was done using SPSS software version 27.0. Results were summarized using mean and SD. Correlation of cortisol with AST and ALT, also with FBG and HbA1c was done by Karl Pearson's correlation coefficient. Independent student's t-test was applied to find the association of AST, ALT and cortisol in the gender in and participants with a diabetic duration of ≤ 10 and > 10 years. A p-value < 0.05 was considered as significant.

RESULTS

A total of 89 participants (66.3% males and 33.7% females) with a mean diabetic duration of 7.6 ± 6.8 years were included in the study (table 1). Even though the levels of transaminases were within the normal range, ALT (27.8 ± 14 U/L) levels were higher than AST (25.2 ± 12 U/L).

Table 1: Descriptive statistics of study participants (n=89)

Parameters	Mean \pm SD
Age (in years)	61 \pm 11
Duration of diabetes (in years)	7.6 \pm 6.8
AST (U/L)	25.2 \pm 12
ALT (U/L)	27.8 \pm 14
Cortisol ($\mu\text{g/dl}$)	15.5 \pm 6
FBS (mg/dl)	158 \pm 59
HbA1c concentration (%)	7.7 \pm 1.8

Table 2: Comparison of AST, ALT and cortisol in participants categorised based on the duration of T2DM

Parameters	Groups depending upon the duration of diabetes	Mean± SD	p-value
AST (U/L)	Group 1	24 ± 9.8	0.01
	Group 2	27 ± 15	
ALT (U/L)	Group 1	27 ± 15.4	0.296
	Group 2	28 ± 13	
Cortisol (µg/dl)	Group 1	15.6 ± 6.5	0.581
	Group 2	15.3 ± 5.5	

Group 1- diabetic duration of ≤5 years

Group 2- diabetic duration of >5 years

Participants were divided into two groups (table 2); those with a duration of diabetes less than or equal to 5 years (49 participants) and those with a duration of diabetes of more than 5 years (40 participants).

Descriptive data in table 2 shows both the groups show significant differences (p=0.01) with AST. However, ALT and cortisol levels were not significant in both the group (p=0.296 and p=0.581).

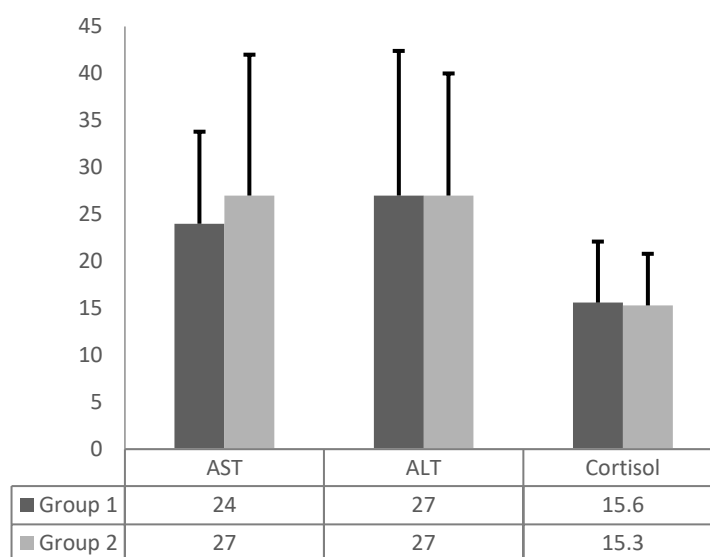
**Fig. 1:** Comparison of AST, ALT and cortisol in participants categorised based on the duration of T2DM.

Fig. 1 shows the change in AST, ALT and cortisol levels with an increase of duration of T2DM.

Table 3: Gender-wise comparison of AST, ALT and cortisol in T2DM participants

	Gender	Mean± SD	p-value
AST (U/L)	Male	26 ± 12	0.583
	Female	23.4 ± 11.4	
ALT (U/L)	Male	28.4 ± 13	0.409
	Female	26.6 ± 16	
Cortisol (µg/dl)	Male	15 ± 6	0.916
	Female	16.5 ± 6.15	

Table 3 shows among the whole set of 89 people, 59 were male and 30 were female. AST & ALT activities did not show any significance (p=0.583 and p= 0.409) in either of the genders. Cortisol levels also did not show any statistical significance (p=0.916) in any of the two genders.

Correlation of transaminases and cortisol with FBS and HbA1c

AST and ALT were significantly correlated to each other (r= 0.580, p< 0.001). Among hepatic transaminases, the association of AST with FBS levels

in the given set of samples is significant (p=-0.003). Likewise, the association of serum cortisol levels with AST (p=0.011), ALT (p=0.031) and FBS (p=-0.39) was significant. HbA1c was negatively correlated with AST (p=-0.038).

DISCUSSION

The present study was a prospective study with 89 participants with a history of 1 to 35 years of type 2 diabetes. Patients who were on insulin and with known liver diseases are excluded from the study. This study attended to examine the correlation of transaminases

with cortisol in type 2 diabetic patients by determining morning serum cortisol levels.

Studies showed there will be a significant difference between elevated ALT and diabetic duration.⁴⁷ In this study, although the elevation of AST and ALT levels increases with the duration of diabetes, ALT does not show a significant difference between the groups; who were diabetic for less than or equal to 5 years and more than 5 years. Surprisingly, AST levels showed a significant difference ($p=0.01$) in both groups.

There is an observable interrelation between the stress hormone cortisol and higher levels of blood sugar in people with T2DM. This is supported by several studies that demonstrated the elevated levels of cortisol in T2DM patients were associated with age-related cognitive changes and various micro and macro-vascular complications of diabetes (14,15). Chiodini *et al.*, have shown that; later complications and long-term T2DM, as well as gender, were significantly linked to the duration of diabetes (16). But in this study even though there is a small elevation in cortisol with increased duration of diabetes, no much significant difference between the groups of diabetic duration. In the current study cortisol levels also did not show any statistical significance in males and females.

The results from this study showed that there was no significant difference in levels of AST and ALT within the gender. These findings are similar to a retrospective, cohort study by Alzahrani *et al.*, which showed that higher AST and ALT levels were found in T2DM patients, but no statistically appreciable link was observed between the serum AST or ALT levels with the gender (17).

Although, both the hepatic transaminases are found in other body tissues, the activity of ALT outside the liver is very less. Therefore, this enzyme is considered more specific for hepatocellular damage (18) Several studies highlighted that; males were associated with an increased risk of elevated ALT (19,20). A similar trend was observed in this study, even though there was no significant difference, ALT levels were found to be high when compared with AST in males.

Dahman *et al.*, in their study on the Yemeni population, shown that AST is strongly correlated with ALT. In the current study also, we found that a strong positive correlation ($p<0.001$) between AST and ALT (21). Sunita *et al.*, and Bora *et al.*, showed AST and ALT were significantly correlated with FBS (22,23). Our study also revealed a significant positive correlation of AST with FBS. These similar results are commensurate with the previous study by Al Jameil *et al.*, (24). They also showed significant positive correlational statistics between HbA1c and ALT ($r=0.32$). In the present study, HbA1c was negatively correlated with AST ($p=-0.038$).

The role of cortisol in the pathophysiology of type 2 diabetes remains controversial. The findings from the present study show that; cortisol secretion has a significant correlation with AST and ALT, as well as FBS. Chiodini *et al.*, and Oltmanns found that in T2DM patients with normal HPA axis activity, HbA1c has a direct link with cortisol secretion (8,14).

In recent times, several studies and case reports have shown adrenal dysfunction in the whole spectrum of liver diseases. Because chronic T2DM, is a risk factor for 1) liver disease such as fatty liver/NAFLD and 2) the elevation of cortisol (a hyperglycaemic steroid hormone (12,25), it is important to know whether there is a link between liver function and cortisol in T2DM. Therefore, finding other factors associated with T2DM will help in the early detection of the root causes, and thereby modifications in lifestyle and diet control will reduce the risk of disease burden for the patients from developing liver diseases. To the best of our knowledge, no study has been done for this. In the present study, we correlated the markers of liver function, transaminases: AST and ALT with serum cortisol levels and we found that transaminases correlated positively with cortisol.

CONCLUSION

The present study found that liver transaminases are positively correlated with serum cortisol levels in type 2 diabetic patients. Although adrenal dysfunction and hepatic complications are considered a trivial factor in T2DM, current findings may encourage clinicians to pay more attention to screen T2DM patients with high serum cortisol, and to interlink the two organs in all clinical aspects. That will prevent further complications associated with the liver. Cortisol being a stress hormone clinicians can suggest meditations and lifestyle modification for T2DM as well as liver disease patients. In addition, even though the liver transaminases were within the normal range, we can see their elevation with FBS, HbA1c and, duration of diabetes. Hence, timely diagnosis and management of T2DM along with cortisol may help to minimize the elevation of liver enzymes, hence liver-related morbidity and mortality in the diabetic population.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Alhussona, A. J., Al-Musawi, A. H., Jalood, H. H., Hamzah, S. S. A study of ATPase gene variants of mitochondrial DNA in patients with Type 2 diabetes mellitus. *Biomedicine*. 2023 Feb 26;43(1):225-229.
2. Suvarna, R., Biswas, M., Shenoy, R. P., Prabhu, M. M. Association of clinical variables as a predictor marker in type 2 diabetes mellitus and diabetic complications. *Biomedicine*. 2023 Mar 28;43(01):335-340.
3. Galicia, G.U., Benito, V. A., Jebari, A., Larrea, S.A., Siddiqi, H., Uribe, K.B., et al., Pathophysiology of Type 2 Diabetes

- Mellitus. International Journal for Molecular Sciences. 2020 Aug;21(17):62-75.
4. Abro, M.U. R., Butt, A., Baqa, K., Waris, N., Khalid, M., Fawwad, A. Association of serum liver enzyme Alanine Aminotransferase (ALT) in patients with type 2 diabetes. Pak J Med Sci. 2018 Aug; 34(4):839-843.
5. Tanase, D.M., Gosav, E.M., Costea, C.F., Ciocoiu, M., Lacatusu, C.M., Maranduca, M.A., et al., The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease (NAFLD). Jia G, editor. Journal of Diabetes Research. 2020 Aug 4;2020:3920196.
6. Mohamed, J., Nazratun, N.A.H., Zariyantey, A.H., Budin, S.B. Mechanisms of Diabetes-Induced Liver Damage: The role of oxidative stress and inflammation. Sultan Qaboos Univ Med J. 2016 May;16(2):e132-e141.
7. Elizabeth, H.H. Elevated Liver Function Tests in Type 2 Diabetes. Clinical Diabetes. 2005 Jul;23(3):115-119.
8. Chiodini, L., Torlontano, M., Scillitani, A., Arosio, M., Bacci, S., Lembo, S.D., et al., Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. European Journal of Endocrinology. 2005 Dec;153(6):837-844.
9. Tsai, M.H., Peng, Y.S., Chen, Y.C., Liu, N.J., Ho, Y.P., Fang, J.T., et al., Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock Hepatology, 43 (2006), pp. 673-681.
10. Fernández, J., Escorsell, A., Zabalza, M., Felipe, V., Navasa, M., Mas, A., et al., Adrenal insufficiency in patients with cirrhosis and septic shock Hepatology, 44 (2006), pp. 1288-1295.
11. Cobbina, E., Akhlaghi, F. Non-Alcoholic Fatty Liver Disease (NAFLD) - Pathogenesis, Classification, and Effect on Drug Metabolizing Enzymes and Transporters. Drug Metabolism Reviews. 2017;49(2):197-211.
12. Kharb, S., Garg, M.K., Pankaj, P., Bhaskar, N., Karninder, S.B., Abhay, G., et al., Assessment of adrenal function in liver diseases. Indian Journal of Endocrinology and Metabolism. 2013 Jun;17(3):465-471.
13. Ari, L., Orna, Z. S., Ruth, F., John, G.L., Aron, W. Measuring cortisol in human psychobiological studies. Physiology and Behavior. 2007;90(1):43-53.
14. Oltmanns, K. M., Dodt, B., Schultes, B., Raspe, H. H., Schweiger, U. Cortisol correlates with metabolic disturbances in a population study of type 2 diabetic patients. European Society of Endocrinology. 2006 Feb;154(2):325-331.
15. Reynolds, R.M., Strachan, M. W. J., Labad, J., Lee, A.J., Frier, B.M., Fowke, G., et al., Morning Cortisol Levels and Cognitive Abilities in People With Type 2 Diabetes. Diabetes Care. 2010 Apr;33(4):714-720.
16. Chiodini, L., Adda, G., Scillitani, A., Coletti, F., Morelli, V., Lembo, S. D., et al., Cortisol secretion in patients with type 2 diabetes relationship with chronic complications. Diabetes Care. 2007 Jan; 30(1):83-88.
17. Alzahrani, S. H., Baig, M., Bashawri, J. I., Aashi, M. M., Shaibi, F. K., Alqarni, D. A. Prevalence and Association of Elevated Liver Transaminases in Type 2 Diabetes Mellitus Patients in Jeddah, Saudi Arabia. Cureus. 2019 Jul 18;11(7).
18. Mathur, S., Mehta, D. K., Kapoor, S., Yadav, S. Liver Function in Type-2 Diabetes Mellitus Patients. International Journal of Scientific Study. 2016 Jan; 3(10):43-47.
19. Meybodi, M. A., Ardekani, M. A., Rashidi, M. Prevalence of abnormal serum alanine transaminase levels in type 2 diabetic patients in Iran. Pakistan Journal of Biological Science. 2008;11(8):2274-2277.
20. Ko, S. H., Baeg, M. K., Han, K. D., Ahn, Y.B. Increased liver markers are associated with higher risk of type 2 diabetes. World J Gastroenterol. 2015 Jun 28;21(4):7478-7487.
21. Dahman, L. S. B., Humam, M. A., Musiaan, N. S., Daakik, A.M., Balfas, M. A. Elevated Liver Enzymes and its Association with Type Two Diabetes Mellitus: The Occurrence in Yemeni Population. Int J Endocrinol Metab Disord. 2021 Apr 15;7(1).
22. Bora, K., Borah, M., Chutia, H., Nath, C.K., Ruram, A. A., Das, D. Presence of concurrent derangements of liver function tests in type 2 diabetes and their relationship with glycemic status: A retrospective observational study from Meghalaya. J Lab Physicians. 2016 Feb 14;8(1):30-35.
23. Sunitha, S., Rajeev, G., Wilma, D.S.C.R., Rao, S. Evaluation of significance of liver enzymes as screening tests for the early detection of clinically asymptomatic non-alcoholic fatty liver disease in type 2 diabetes mellitus patients. International Journal of Biomedical and Advance Research. 2015;6(12):860-863.
24. Al-Jameil, N., Khan, F. A., Arjumand, S., Khan, M. F., Tabassum, H. Associated liver enzymes with hyperlipidemic profile in type 2 diabetes patients. Int J Clin Exp Pathol. 2014 Jun 15;7(7):4345-4349.
25. Joseph, J. J., Golden, S. H. Cortisol dysregulation: the bidirectional link between stress, depression, and type 2 diabetes mellitus. Annals of the New York Academy of Science. 2016;1391(1):20-34.