RELATIONSHIP BETWEEN THIAMINE LEVELS AND HEMATOLOGICAL PARAMETERS AMONG PATIENTS OF TYPE 1 DIABETES: A CROSS-SECTIONAL ANALYSIS

1. Adeeba Salahuddin Khan
MBBS, MD fellow
Resident, Emergency Medicine, Ziauddin University Hospital, Karachi
adeebakhan1001@gmail.com

2. Uzma Raza
M.Phil., PhD
Professor, Department of Biochemistry, Hamdard College of Medicine and Dentistry
Hamdard University Karachi

3. Ghazala Panhwar
MBBS, M.Phil
Associate Professor, Department of Biochemistry, Bahwalpur Medical College
dr.ghazala73@gmail.com

4. Fareena khan
MBBS, FCPS, FCAI
Senior Registrar, Anesthesia Baqai Medical University
dr.fareenakhan.rk@gmail.com

5. Ahsan Ali Siddiqui
MBBS, MSC Public Health
Specialist Family Medicine, Ministry of Health, Riyadh
drahsan77@hotmail.com

6. **Adnan Anwar** MBBS, M.Phil.
Associate Professor, Department of Physiology, Hamdard college of Medicine and Dentistry
anwaradnan32@gmail.com

***Corresponding author:**
Dr. Adnan Anwar.
Associate Professor,
Department of Physiology,
Hamdard college of Medicine and Dentistry,
Hamdard University, Karachi.
anwaradnan32@gmail.com

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Adeeba Salahuddin Khan[1], Uzma Raza[2], Ghazala Panhwar[3], Fareena khan[4], Ahsan Ali Siddiqui[5], Adnan Anwar[6]

[1]Department of Emergency Medicine Ziauddin University Hospital Karachi
[2]Department of Biochemistry Hamdard College of Medicine and Dentistry Hamdard University
[3]Department of Biochemistry, Bahwalpur Medical College
[4]Department of Anesthesia, Baqai Medical University
[5]Family Medicine, Ministry of Health, Riyadh
[6]Department of Physiology, Hamdard college of Medicine and Dentistry

ABSTRACT

Objective: Thiamine or vitamin B1 is a coenzyme involved in the carbohydrate metabolism. It is vital micronutrient that is required for the production and secretion of insulin, and its level drops in diabetes. Therefore, the aim of this study was to evaluate the biochemical changes related to different thiamine levels in patients with type I Diabetes Mellitus.

Methodology: This was a case-control study carried out in outpatient department (OPD) of Diabetes Department of Jinnah post graduate medical institute, Karachi. The duration of the study was about 6 months following approval of synopsis. A total of 30 participants with newly diagnosed type I Diabetes were selected; 18 participants had low/normal serum thiamine level while 12 participants had high serum thiamine level of both genders with age < 25 to > 46 years were included. Mann-Whitney U Test was applied to evaluate the association between thiamine levels and biochemical and hematological parameters in patients with type I diabetes.

Results: The study findings revealed the mean age of type 1 diabetes patients was 24.20±6.39 years whereas 22 (73.3%) of them were females. Comparison of hematological parameters among type 1 diabetic patients with different thiamine levels revealed that only mean red blood cell count was significantly different among them (p=0.048) where patients with low/normal thiamine level had higher red blood cell count than those with high thiamine level (4.58±0.72 vs. 4.12±0.36). Moreover, mean total cholesterol levels were also found to be higher among patients

with low/normal thiamine levels than those with high thiamine levels (210.06±41.22 vs. 190.42±14.24).

Conclusion: This study concluded that patients with low/normal thiamine level had significantly higher red blood cell count than those with high thiamine level. However, low/normal and high levels of thiamine were insignificantly associated with biomarkers related to diabetes such as glucose, high density lipoprotein, triglycerides and cholesterol, serum creatinine and urea.

Keywords: Blood sugar, hematological parameters, thiamine level, type I diabetes mellitus.

INTRODUCTION

Thiamine is also termed as Vitamin B1 which is water-soluble vitamin that cannot be made by the body and a coenzyme that involves in the metabolic reactions of branched-chain amino acids in addition to carbohydrates [1]. Thiamine is a fundamental micronutrient that is found in different food sources, while many factors can affect its serum level for instance elevated temperature and high pH, diuretics, calorie rich food having simple sugars, prolonged drinking of alcohol, pyrexia, unnecessary workout, pregnancy and milk secretion, trauma and distress. [2] Moreover, the half-life of thiamine in human ranges from 1–3 weeks. [3] Thiamine is a vital micronutrient in the body for energy metabolism, exactly 4400 kJ of energy can be generated by 0.33 mg of thiamine [4].

Thiamine di-phosphate (ThDP) is the basic active form of thiamine. It is a component that helps in numerous multi-enzyme complexes linked with glucose metabolic reaction, such as α-ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex (PDHC), and transketolase. Thiamine deficiency (TD) indicates an appropriate investigational system to comprehend the neurodegenerative illness wherein mitochondrial malfunction causes non-functioning of tri-carboxylic citric acid (TCA) cycle enzymes [5].

Diabetes mellitus (DM) is an important public health encumbrance because of its accompanied morbidity, high monetary expenses and mortality. The occurrence of diabetes is rising speedily all over the world, involving several Arab Gulf Kingdoms [6]. A community-based national epidemiological health analysis stated that total incidence of diabetes mellitus in Saudi adults has been reported 23.7% involving the age between 30-70 years [7]. Similarly, a research by Al-

Daghri et al. conducted in year of 2011 revealed that occurrence of diabetes mellitus in the Kingdom of Saudi Arabia (KSA) was 31.6% [8]. Type I diabetes [previously termed insulin-dependent diabetes mellitus (IDDM)], which is characterized by an irreparable autoimmune devastation of beta-cells of pancreatic islets [9]. It is most frequently occurs in children and young people that is described by insulin insufficiency and hyperglycemic state [9, 10]. The etiological factor of type I diabetes is not fully implicit, however it is documented that environmental and genetic factors are responsible for progression and development of disease [11].

It is also stated that many other organ systems and hematopoiesis might be affected by thiamine insufficiency. Additionally, human body possess erythrocytes that are most important blood cells. They transport oxygen to the cells in respiration [12]. Furthermore, hemoglobin (Hb) is oxygen-carrying protein in blood that reflects the ability of the blood to supply the oxygen to tissues in order to perform body functions along with transfer of carbon dioxide from the body [13]. Moreover, thiobarbituric acid reactive substance (TBARS) is the outcome of lipid peroxidation (LPO) that is a significant episode triggered by oxidative stress connected to the development of many diseases. Elevated reactive oxygen species (ROS) in deficient thiamine can stimulate cell membrane destruction together with LPO and trigger variations of transporters and ion channels [14].

Besides the effects of thiamine deficiency on hematopoiesis, thiamine is a cofactor that involves in sugar metabolism; [15] Thiamine is necessary for the preparation and release of insulin, and its level drops in diabetes. In thiamine insufficiency, glucose is digested and absorbed by metabolic pathways that can initiate insulin resistance and complications of diabetes [16]. Earlier researches have been stated that diabetes can be controlled by intake of thiamine supplements [17].

Use of diuretics for longer duration causes thiamine deficiency resulting a renal impairment [18]. The most severe complication of diabetes is Diabetic nephropathy that clinically obvious as existence of microalbuminuria eventually develops macroalbuminuria. Therefore, sufficient renal replacement therapy is needed for proper functioning of kidney at this stage [19]. The evidence of microalbuminuria is suggested to be diabetic nephropathy in diabetes and also indicates cardiac episodes [20]. Consequently, the development of diabetic nephropathy in type I diabetes patients could be stopped by regulating glycaemia and blood pressure with angiotensinogen-

converting enzyme (ACE) inhibitor treatment that decreases microalbuminuria [21]. It is observed that reduced thiamine level in diabetes is associated with increased renal clearance of thiamine [22]. Additionally, thiamine therapy is also advised to prevent renal and cardiac episodes in type II diabetes patients, thus enhancing worth of life and decreasing more complications [23]. Therefore, this study was intended to assess several biochemical parameters with low/normal and high serum thiamine levels in type I diabetes patients.

METHODOLOGY

This case-control study was conducted in outpatient department (OPD) of Diabetes Department of Jinnah post graduate medical institute, Karachi by using non-probability convenient sampling technique. The duration of study was about 6 months following synopsis approval. The ethical approval was accepted by the Ethical Review Board of concerned Department. A total of 30 participants with newly diagnosed type I diabetes were selected; 18 participants had low/normal serum thiamine level while 12 participants had high serum thiamine level of both genders with age < 25 to > 46 years were included in the study whereas those patients who were taking diuretics, had co-morbidities like Ischemic heart diseases, chronic liver diseases, those patients who experienced major transplant surgery, end phase renal disease and gastrointestinal disease were excluded from the study.

After receiving permission from the participants, data was documented from patients of diabetic clinics of Jinnah Post graduate Medical Center (JPMC) Karachi. Blood Samples were collected from the diabetic clinics of Jinnah Post graduate Medical Center (JPMC), Karachi and Dow University Ojha Campus, Karachi. Collected Blood was used to determine the hematological parameters like RBCs, hemoglobin (Hb), WBC count, and hematocrit value (HCT). The collected blood samples were centrifuged immediately at 2000 rounds/minute (rpm) for 20 minutes duration in non-heparinized tube. The clear supernatant serum was assessed for biochemical parameters including fasting blood sugar (FBS), random blood sugar (RBS), creatinine, urea, hemoglobin A1c (HbA1c), blood and urinary thiamine levels. Complete lipid profile such as triglycerides, high density lipoprotein [HDL]-cholesterol, total cholesterol was evaluated by using a biochemical analyzer.

The SPSS Statistics version 20 was used to analyze data. Biochemical parameters, blood sugar level, creatinine, urea, HbA1c, blood and urinary thiamine levels and cholesterol level were documented as Mean±S.D. Mann-Whitney U test was used to evaluate the association between thiamine levels and biochemical and hematological parameters in patients with type I diabetes. A p value less than 0.05 was reflected as statistically significant.

RESULTS

The mean age of type 1 diabetes patients was 24.20±6.39 years whereas 22 (73.3%) of them were females. Comparison of hematological parameters among type 1 diabetic patients with different thiamine levels revealed that only mean RBCs count was significantly different among them (p= 0.048) where patients with low/normal thiamine level had higher red blood cell count than those with high thiamine level (4.58±0.72 vs. 4.12±0.36). Moreover, mean total cholesterol levels were also found to be higher among patients with low/normal thiamine levels than those with high thiamine levels (210.06±41.22 vs. 190.42±14.24) whereas mean serum creatinine levels were found to be higher among patients with high thiamine levels than those with low/normal thiamine levels (0.82±0.21 vs. 0.71±0.12) though both these relationships were statistically insignificant, as shown in Table I.

Table I: Comparison of Hematological Parameters across Thiamine Levels

Variables	Thiamine Level		p*
	Low/Normal (n=18)	High (n=12)	
	Mean±S.D.	Mean±S.D.	
RBC Count	4.58±0.72	4.12±0.36	0.048
Hematocrit	41.78±3.81	40.67±3.08	0.602
Hemoglobin	11.49±1.26	11.15±0.95	0.325
WBC Count	7.13±2.58	7.41±2.16	0.439
Platelet Count	260.50±65.04	256.58±59.70	0.983
Fasting Blood Sugar	151.00±43.45	151.75±51.64	0.851
Random Blood Sugar	269.61±34.52	266.42±40.89	0.723
Urea	25.78±5.45	29.42±9.47	0.346
Creatinine	0.71±0.12	0.82±0.21	0.185
Sodium	133.67±2.19	133.83±2.62	0.917
Potassium	4.01±0.28	4.10±0.37	0.917
HbA1c	7.40±0.66	7.63±0.55	0.285
Triglycerides	180.28±62.91	153.17±45.19	0.391
LDL Cholesterol	117.89±15.84	118.50±17.21	0.95
HDL Cholesterol	39.78±6.51	41.33±7.17	0.602
Total Cholesterol	210.06±41.22	190.42±14.24	0.113

*Mann-Whitney U Test

DISCUSSION

Thiamine is an essential water-soluble vitamin and accessibility of this vitamin is necessary for usual cellular metabolism of the brain [24] and required for many other bodily functions. It works as a particular component of certain enzymes contributed in cellular metabolism to get energy and its insufficiency may disturb TCA cycle enzymes [25, 26]. Therefore, this study demonstrated the association between hematological and biochemical parameters, blood sugar level with different thiamine levels among type I diabetic patients.

The present study reported an insignificant difference between total cholesterol levels and high and low thiamine level among type I diabetes patients. These findings were not corroborated with another research that revealed a substantial reduction in total cholesterol amongst individual with adequate thiamine intake. The reported frequencies of patients with raised total cholesterol and LDL-C levels were lesser in adequate thiamine intake group, [27] that was consistent with another former research findings [28]. Furthermore, one of the studies demonstrated that regular administration of thiamine improves vascular functions and impedes atherosclerosis development [29], which was in agreement with further research that supported thiamine treatment for shorter duration restored vascular function in smokers [30].

Similarly, another research detected a robust relationship between blood thiamine levels and differs in biochemical factors in diabetes type I. These include blood glucose level ($p=0.008$), HDL ($p= 0.001$), and serum creatinine ($p= 0.001$). Their research statistics proved the part of thiamine and thiamine phosphate esters in averting the metabolic variations and probably the complications associated with

type I diabetes; thiamine and thiamine phosphate ester levels were associated with biomarkers related with diabetes such as HDL, LDL, blood glucose, triglycerides and cholesterol along with micro-albuminuria and urinary thiamine [31]. The present study findings were inconsistent with the above reported research and showed an insignificant association between HDL, blood glucose, triglycerides, cholesterol level, serum creatinine and thiamine level among type I diabetes patients ($p>0.05$).

Notably, another research reported that triglycerides and cholesterol levels were considerably increased in both types of diabetes patients in comparison with controls.[15] Their study findings further showed that HDL level was significantly decreased in both types of diabetes patients than control group.[15] Likewise, previous research performed in 2016 also observed significantly lower HDL levels in type I diabetes patients in comparison with controls ($p=0.005$). Furthermore, one of the studies has been found significantly higher level of triglycerides and cholesterol in type I diabetes patients in comparison with controls ($p= 0.008$) [23]. Similarly, one more research assessed the cholesterol level in type II diabetes revealed that significantly higher level of triglycerides in patients with type II diabetes as compared to controls ($p<0.001$) [32]. The present study did not supported the above mentioned researches as triglycerides level were

insignificantly decreased as well as HDL level were insignificantly increased with high thiamine level among type I diabetes patients ($p>0.05$).

Interestingly, findings of one research indicated that both RBS and FBS levels were significantly raised in both types of diabetes patients in comparison with controls. Additionally, their findings further revealed significantly higher HbA1c in both types of diabetes patients in comparison with controls [15]. In the same way, earlier study piloted in 2015 indicated significantly higher glucose levels in type I diabetes patients in comparison with controls ($p=0.001$) [31]. Likewise, one former research conducted in 2003 also revealed higher levels of HbA1c in patients with diabetes than individuals without diabetes ($p=0.002$). HbA1c has also been recommended to be a greatly particular and expedient investigative tool for diabetes [33]. The present study revealed confliction with the above researches by revealing an insignificant association between FBS, RBS and HbA1c and thiamine levels among type I DM patients.

Nonetheless, this study can have selection predisposition owing to a non-probability sampling technique and observer bias. Therefore, prospective researches along with a probability sampling technique are suggested for elucidation the relationship in bigger samples to acquire more accurate consequences.

CONCLUSION

This study concluded the positive impact of thiamine to prevent metabolic variations among patients with type I diabetes. It was revealed that patients with low/normal thiamine level had significantly higher red blood cell count than those with high thiamine level. However, low/normal and high levels of thiamine were insignificantly associated with biomarkers related to diabetes such as glucose, high density lipoprotein, triglycerides and cholesterol, serum creatinine and urea.

Ethical Consideration: Study was approved from the ERC of University.

Conflict of Interest: No Any

REFERENCES

1. Manzetti S, Zhang J, van der Spoel D. Thiamin function, metabolism, uptake, and transport. Biochemistry. 2014 Feb 11; 53(5):821-35. doi: 10.1021/bi401618y.
2. Kiela PR. Unraveling the pathophysiology of alcohol-induced thiamin deficiency. Am J Physiol Renal Physiol. 2010 Jul; 299(1):F26-7. doi: 10.1152/ajprenal.00266.2010.
3. Lonsdale D. A review of the biochemistry, metabolism and clinical benefits of thiamin(e) and its derivatives. Evid Based Complement Alternat Med. 2006 Mar;3(1):49-59. doi: 10.1093/ecam/nek009.
4. Smithline HA, Donnino M, Greenblatt DJ. Pharmacokinetics of high-dose oral thiamine hydrochloride in healthy subjects. BMC Clin Pharmacol. 2012 Feb 4; 12:4. doi: 10.1186/1472-6904-12-4.
5. Sharma A, Bist R, Bubber P. Thiamine deficiency induces oxidative stress in brain mitochondria of Mus musculus. Journal of Physiology and Biochemistry.2013;69(3): 539–546.
6. Abuyassin B, Laher I. Diabetes epidemic sweeping the Arab world.World J Diabetes. 2016 Apr 25; 7(8): 165–174. doi: 10.4239/wjd.v7.i8.165.
7. Naeem Z. Burden of Diabetes Mellitus in Saudi Arabia.Int J Health Sci (Qassim). 2015 Jul; 9(3): V–VI. doi: 10.12816/0024690.
8. Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Yousef M, Sabico SL, et al. Diabetes mellitus type 2 and other chronic non-communicable diseases in the central region, Saudi Arabia (Riyadh cohort 2): a decade of an epidemic. BMC Med. 2011 Jun 20; 9:76. doi: 10.1186/1741-7015-9-76.
9. Espe K, Galler A, Raila J, Kiess W, Schweigert FJ. High-normal C-reactive protein levels do not affect the vitamin A transport complex in serum of children and adolescents with type 1 diabetes. Pediatr Res. 2007 Dec; 62(6):741-5.
10. Chiang JL, Maahs DM, Garvey KC, Hood KK, Laffel LM, Weinzimer SA, et al. Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association. Diabetes Care. 2018 Sep; 41(9): 2026–2044. doi: 10.2337/dci18-0023.

11. Hirschhorn JN. Genetic epidemiology of type 1 diabetes. Pediatr Diabetes. 2003 Jun;4(2):87-100. doi: 10.1034/j.1399-5448.2001.00013.x.
12. Sharma A, Bist R. Alteration in MDA, GSH level and hematological changes due to thiamine deficiency in *Mus musculus.* Interdiscip Toxicol. 2018; 11(4): 321–325. doi: 10.2478/intox-2018-0032.
13. Thom CS, Dickson CF, Gell DA, Weiss MJ. Hemoglobin variants: biochemical properties and clinical correlates. Cold Spring Harb Perspect Med. 2013 Mar 01; 3(3):a011858.
14. Aguilar Diaz De Leon J, Borges CR. Evaluation of Oxidative Stress in Biological Samples Using the Thiobarbituric Acid Reactive Substances Assay. J Vis Exp. 2020 May 12;(159). doi: 10.3791/61122.
15. Anwar A, Ahmed Azmi M, Siddiqui JA, Panhwar G, Shaikh F, Ariff M. Thiamine Level in Type I and Type II Diabetes Mellitus Patients: A Comparative Study Focusing on Hematological and Biochemical Evaluations. Cureus. 2020 May 8; 12(5):e8027. doi: 10.7759/cureus.8027.
16. Rad MG, Sharifi M, Meamar R, Soltani N. The role of pancreas to improve hyperglycemia in STZ-induced diabetic rats by thiamine disulfide.Nutr Diabetes. 2022; 12: 32. doi: 10.1038/s41387-022-00211-5.
17. Luong KV, Nguyen LT. The impact of thiamine treatment in the diabetes mellitus. J Clin Med Res. 2012 Jun; 4(3):153-60. doi: 10.4021/jocmr890w.
18. Suter PM, Vetter W. Diuretics and vitamin B1: are diuretics a risk factor for thiamin malnutrition? Nutr Rev. 2000 Oct; 58(10):319-23. doi: 10.1111/j.1753-4887.2000.tb01827.x.
19. Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice. Nephropathy in patients with type 2 diabetes. N Engl J Med. 2002 Apr 11; 346(15):1145-51. doi: 10.1056/NEJMcp011773.
20. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, et al.: Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009 Aug; 20(8):1813-21. doi: 10.1681/ASN.2008121270.

21. Nix WA, Zirwes R, Bangert V, Kaiser RP, Schilling M, Hostalek U, et al. Vitamin B status in patients with type 2 diabetes mellitus with and without incipient nephropathy. Diabetes Res Clin Pract. 2015 Jan; 107(1):157-65. doi: 10.1016/j.diabres.2014.09.058.
22. Miyan Z, Waris N; MIBD. Association of vitamin B_{12} deficiency in people with type 2 diabetes on metformin and without metformin: a multicenter study, Karachi, Pakistan. BMJ Open Diabetes Res Care. 2020 May; 8(1):e001151. doi: 10.1136/bmjdrc-2019-001151.
23. Tai VML. A case report on the use of oral thiamine in a palliative care patient in the management of peripheral edema in a community setting in New South Wales, Australia. Int J Case Rep Images 2016; 7(1):15–17.
24. Liu D, Ke Z, Luo J. Thiamine deficiency and neurodegeneration: the interplay among oxidative stress, endoplasmic reticulum stress, and autophagy. Molecular Neurobiology.2017;54(7): 5440–5448.
25. Sharma A, Bis R. Thiamine deprivation disturbs cholinergic system and oxidative stress in liver of Mus musculus. Int J Pharmacol Pharm Sci.2014; 6(5):139–143.
26. Sharma A, Bist R, Bubber P. Thiamine deficiency induces oxidative stress in brain mitochondria of Mus musculus. Journal of Physiology and Biochemistry. 2013;69(3): 539–546.
27. Duc HN, Oh H, Yoon IM, Kim MS. Association between levels of thiamine intake, diabetes, cardiovascular diseases and depression in Korea: a national cross-sectional study. J Nutr Sci. 2021; 10(31): 1-11.doi: 10.1017/jns.2021.23.
28. Al-Attas O, Al-Daghri N, Alokail M, Abd-Alrahman S, Vinodson B, Sabico S. Metabolic Benefits of Six-month Thiamine Supplementation in Patients With and Without Diabetes Mellitus Type 2. Clin Med Insights Endocrinol Diabetes. 2014 Jan 23;7:1-6. doi: 10.4137/CMED.S13573.
29. Arora S, Lidor A, Abularrage CJ, Weiswasser JM, Nylen E, Kellicut D, et al. Thiamine (vitamin B1) improves endothelium-dependent vasodilatation in the presence of hyperglycemia. Ann Vasc Surg. 2006 Sep;20(5):653-8. doi: 10.1007/s10016-006-9055-6.

30. Stirban A, Nandrean S, Kirana S, Götting C, Veresiu IA, Tschoepe D. Benfotiamine counteracts smoking-induced vascular dysfunction in healthy smokers. Int J Vasc Med. 2012; 2012:968761. doi: 10.1155/2012/968761.
31. Al-Daghri NM, Alharbi M, Wani K,Abd-Alrahman SH, Sheshah E, Alokail MS. Biochemical changes correlated with blood thiamine and its phosphate esters levels in patients with diabetes type 1 (DMT1). Int J Clin Exp Pathol. 2015; 8(10): 13483–13488.
32. Waheed P, Naveed AK, Ahmed T. Thiamine deficiency and its correlation with dyslipidaemia in diabetics with microalbuminuria. J Pak Med Assoc. 2013 Mar; 63(3):340-5. PMID: 23914634.
33. Greci LS, Kailasam M, Malkani S, Katz DL, Hulinsky I, Ahmadi R, et al. Utility of HbA(1c) levels for diabetes case finding in hospitalized patients with hyperglycemia. Diabetes Care. 2003 Apr; 26(4):1064-8. doi: 10.2337/diacare.26.4.1064.