Original Article

DOI: 10.7860/NJLM/2022/51859.2574

Biochemistry Section

Levels of Serum Selenium and Zinc in Critically ill Type 2 Diabetics and Normal Healthy Individuals at Tertiary Care Hospital, Surat, India

SHEETALKUMARI PARESH PATEL[1], DVSS RAMAVATARAM[2], N CHANDRIKA[3], HASITKUMAR DALPATBHAI LAD[4]

ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM), accounting for 85-90% of diabetic subjects globally, is reported to be also caused by imbalance between pro-oxidant and anti-oxidant factors. This very fact necessitates exploring and evaluating the possibilities of role of various antioxidant trace elements like selenium and zinc, in further understanding the pathogenesis and appropriate applicable intervention required, if any for patients suffering from diabetes mellitus. The levels of trace elements like selenium and zinc, representing antioxidant capacity, might be implicated in development of type II diabetes and vice versa.

Aim: To evaluate the levels of serum selenium and zinc in critically ill type 2 diabetic patients and comparing them with healthy individuals.

Materials and Methods: This case-control study was conducted for a period of nine months from October 2016 to June 2017. Fifty critically ill type 2 diabetic patients and 150 apparently healthy age and gender matched controls were recruited into this study. Serum selenium and zinc levels were estimated in subjects of both the groups. Mean, standard deviation, Analysis of Variance (ANOVA) test, student t-test and correlation coefficient were statistical tools used to interpret the results.

Results: Fifty critically ill T2DM patients constituted the cases and 150 age and sex matched healthy adults were the second group controls. Mean Random Blood Sugar (RBS) in controls was 113.14±25.52 mg/dL while in that in cases was 246.48±98 mg/dL and the difference was significant (p-value<0.01). This study showed significant difference (p<0.01) in the level of serum selenium and zinc levels in critically ill diabetic patients compared to healthy individuals across all age groups i.e., <40, 40 to 55 and >55 years. The mean level of Selenium in cases and controls was 83.8±11.97 and 103.08±67.7 µg/dl (p-value<0.01) respectively. The mean level of Zinc amongst cases and controls was 40.83±21.19 and 103.08±67 (p-value<0.01) respectively.

Conclusion: Serum selenium and zinc levels are decreased in critically ill type 2 diabetic patients owing to the increased production of free radicals in them. Supplementation of selenium and zinc in these individuals could be beneficial and is therefore recommended.

Keywords: Anti-oxidant, Oxidative stress, Trace minerals, Therapeutic supplementation

INTRODUCTION

The T2DM, previously known as Non Insulin Dependent Diabetes Mellitus (NDDM) is commonest type of diabetes which accounts for 85 to 90 percent of diabetic subjects globally. It is one of the predisposing conditions for development of sepsis and septic shock. It is described as a syndrome characterised by insufficient synthesis of insulin or insulin resistance or both. The main aetiology of T2DM seems to be lack of an appropriate increase in circulating insulin levels following carbohydrate rich meal, leading to abrupt rise in blood glucose levels known as postprandial hyperglycaemia. Even in the presence of adequate insulin synthesis, the postprandial hyperglycaemia may exist and it may be due to insulin resistance, which features decreased hepatic sensitivity to insulin in some of the diabetic subjects [1].

Even after so many years, the pathogenesis of diabetes mellitus is not clear. Decreased production of insulin by β-cells of pancreas due to its destruction or decreased sensitivity of hepatic cells to insulin is considered among the primary aetiological factors for its pathogenesis. A number of reports suggested the role of oxyfree radicals in the causation of diabetes mellitus. Oxyfree radicals are produced by the action of xenobiotics or by autoimmune response and appear to play a role in destroying the β-cells. This condition that exists in diabetic patients makes it conducive for decrease in the concentration of antioxidants [2].

The generation of free radicals in most cases is a self-propagating process and the build-up of free radicals inside the cell leads to a condition called oxidative stress, in which cellular antioxidant defenses cannot control the amount of radicals being produced. An increase in oxidative stress will itself cause an increase in radical production by almost all the mechanisms.

Selenium (Se) a component of antioxidant system plays a crucial role in maintaining the structure and activity of glutathione peroxidase and has functional relationship with vitamin E. There are many findings which establish an association between selenium nutritional status and diabetes but this association is complicated and intriguing. There have been several studies done earlier to investigate the behavior of these trace elements in T2DM but no conclusive or quantitative relationship was established in any of these studies as they all were conducted in small number of samples [3,4] or special groups such as in metabolic syndrome [5], obesity [6,7] and Polycystic Ovary Syndrome (PCOS) patients [8]. Wang Y et al., have observed an association between dietary Se intake and insulin resistance in the large Complex Diseases in the Newfoundland Population: Environment and Genetics (CODING) study. The most important finding of this study was a negative association between dietary Se intake and insulin resistance in females and males [9]. Stratified meta-analysis demonstrated that serum Se concentration is lower in women with gestational diabetes mellitus both in second and third trimesters; however, the results were significant after the 33rd week of pregnancy [10].

Zinc (Zn) is the second most abundant trace element in the body. It has multiple biochemical roles. It binds to insulin and increases its

stability; Zinc also maintains the structural stability of Superoxide Dismutase (SOD) thus, being responsible for optimal activity of the enzyme. SOD is required to decrease oxidative stress as it neutralises superoxide radical effectively. Binding of zinc to insulin is important for the crystallization of the hormone [11] and it is believed that this ensures adequate insulin amounts to be stored in pancreatic β-cells to allow sufficient release after a meal [12]. Zn^{2+} ions which are co-secreted with insulin, suppress inherent amyloidogenic properties of monomeric insulin [13]. Zinc concentrated in the islet cells is related to the synthesis, storage and secretion of insulin [14]. In-vitro studies show that when insulin is co-administered with zinc, there will be less degradation of insulin [15]. When zinc concentration falls, there is a reduction in insulin secretion and peripheral insulin sensitivity, which if persists for long it leads to T2DM. Zinc has anti-inflammatory role and through this role, it abolishes effects of inflammatory proteins such as C-reactive protein. It also helps to get rid of substances that cause inflammation in cells, helping to preserve cell health and insulin sensitivity [16].

In the present study, levels of serum selenium and zinc have been compared between critically ill patients with T2DM and healthy controls. With reference to these elements, current study is a small attempt to add to the existing knowledge in the field of diabetology with the objective of contemplating about therapeutic supplementation of these trace elements in type 2 diabetic patients. The study will contribute to the field of research involving trace elements.

MATERIALS AND METHODS

The case-control study was carried out in the subjects admitted in the Intensive Care Unit (ICU) of Medicine and Surgery Department for treatment of complicated diabetes mellitus at Surat Municipal Institute of Medical Education and Research (SMIMER), Surat, Gujarat, India, from October 2016 to June 2017after obtaining the Ethics Committee Approval (No. IEC/OUT/No: 232; dated: 13/10/2017). The present study was conducted on a total of 200 subjects who were segregated into two groups. Fifty critically ill T2DM patients constituted the case group and 150 age and sex matched healthy adults constituted the second group controls group.

Inclusion criteria: All the subjects between the age group of 25 and 70 years, admitted to the Medicine or Surgical ICU of tertiary care hospital were included as case group. Healthy adults between 25 and 70 years of age were included as control group.

Exclusion criteria: Chronic Alcoholics, subjects taking supplements of Selenium and Zinc, known case of Human Immunodeficiency Virus (HIV) and Hepatitis B and patients diagnosed with malignancy were excluded from the study.

Sample size calculation: To calculate sample size and feasibility of the study, a small pilot scale study was conducted taking five samples in each group i.e. cases & controls. It was found that mean selenium levels in cases was 123.56 µg/L with standard deviation (SD) of 29.27 µg/L whereas the same for controls was 108.57 µg/L & 31.91 µg/L respectively. Considering this pilot study data, sample size was calculated using open epidemiologic (epi) software [17]. The ratio of case: control was taken as 1:3 to increase representation of control group. The calculated sample size was 42 for cases and 126 for controls which were rounded to 50 and 150 respectively. The pilot study samples were included in the final sample size.

Procedure

Blood samples of all the 200 participants of the study were collected in both plain and fluoride containers. A random venous blood sample was drawn from the fifty cases either on the first or second day of admission. Serum/plasma was separated through centrifugation and preserved for the analysis. Trace element study principle was based on the Atomic Absorption Spectrophotometer (AAS) of thermo-scientific 3500i series in which zinc estimation was done on flame mode using 10 ppm standard concentration and 1:10 sample dilution. Selenium estimation was done on furnace mode using same standard concentration as in zinc with dilution ratio1:3. Random Blood Glucose (RBG) estimation was carried out using standard enzymatic Glucose oxidase Peroxidase (GOD POD) method on ERBA XL-640 fully automated analyser.

Normal ranges of biochemical parameters measured are as below.

Random blood sugar: 70-140 mg/dL, serum selenium 70-150 µg/L and serum zinc 80-160 µg/dL.

STATISTICAL ANALYSIS

The statistical analysis was done by applying mean and standard deviation, ANOVA test, student t-test and correlation coefficient. The p-value<0.05 is considered significant.

RESULTS

The present study included a total of 200 subjects who were fulfilling inclusion criteria. Out of these subjects 150 were controls, 50 subjects were critically ill T2DM patients. In present study, both cases and controls were divided according to age groups of <40 years, 40-55 years and >55 years. [Table/Fig-1] shows age and gender wise distribution of participants in two groups. As enumerated in [Table/Fig-2] mean RBG levels were significantly higher (p<0.01) in cases than in controls across all the age groups. Increase in the mean blood glucose levels with increasing age was also noted in cases.

Groups	Based on gender		Based on age		
	Male	Female	<40 y	40-55 y	>55 y
Controls	72	78	67	60	23
Cases	32	18	8	18	24
p-value	**0.05**		p-value<0.001		

[Table/Fig-1]: Distribution of controls and cases based on gender and age.
* To know the association between groups (Cases & Controls) and age groups χ^2 test could not be applied as it does not follow the assumption of χ^2 test

Age group	RBS (mg/dL)		p-value
	Controls	Cases	
<40 years	95.46±19.51	196.87±26.47	**<0.01**
40-55 years	125.11±20.23	234.89±90.44	**<0.01**
>55 years	133.39±19.95	271.71±112.16	**<0.01**
All	113.14±25.52	246.48±98	**<0.01**

[Table/Fig-2]: Comparison of blood glucose levels in control and cases.
* RBS: Random Blood Sugar

The focus of study was to assess the status of selenium and zinc levels in critically ill patients with T2DM and to compare them with that of healthy controls. As per [Table/Fig-3], in the cases for the various age groups of less than 40, 40 to 55 and more than 55 years, the Mean±SD value of serum selenium were found to be 75.89±5.84 µg/L, 86.52±13.34 µg/L; 84.44±11.66 µg/L, respectively. The observed levels were significantly lower (p-value<0.01) than that estimated in corresponding age group of healthy control in whom Mean±SD value of serum selenium were 143.35±15.59 µg/L, 148.31±22.72 µg/l and 159.05±26.76 µg/L, respectively.

Age group (Years)	Selenium (µg/dL)		Zinc (µg/L)		p-value
	Controls	Cases (DM)	Controls	Cases (DM)	
<40	143.35±15.59	75.89±5.84	106.16±63.88	47.57±16.21	**<0.01**
40-55	148.31±22.72	86.52±13.54	109.94±74.79	39.24±22.72	**<0.01**
>55	159.05±26.76	84.4±11.66	76.2±53.7	39.78±21.83	**<0.01**
All	147.74±21.13	83.8±11.97	103.08±67.7	40.83±21.19	**<0.01**

[Table/Fig-3]: Comparison of serum selenium and zinc levels in controls and cases.

Again as per [Table/Fig-3], significantly lower level of zinc in cases compared to corresponding levels in controls across all age groups were found. Mean±SD value of serum zinc were 47.57±16.21 µg/dL, 39.24±22.72 µg/dL, 39.78±21.83 µg/dL for age group less

than 40 years, 40 to 55 years and more than 55 years respectively amongst diabetic patients, which was significantly ($p<0.05$, $p<0.01$, $p<0.01$) lower than that of respective healthy controls of the corresponding age group in which the values were 106.16±63.88 µg/dL, 109.94±74.79 µg/dL, 76.2±53.7 µg/dL, respectively. There are reports of significant excretion of urinary zinc in T2DM. This shows that T2DM is accompanied by hypozincaemia and hyperzincuria. It is evident from [Table/Fig-4] that the present study overwhelmingly supports the existence of hypozincaemia in T2DM as 98% of cases had serum zinc levels below 80 µg/dL, normal range being 80-160 µg/dL. Only 2% T2DM subjects fell within the normal range.

Range µg/L	Selenium		Range µg/dL	ZINC	
	Controls	Cases		Controls	Cases
<70	0 (0%)	4 (8%)	<80	84 (56%)	49 (98%)
70-150	93 (62%)	46 (92%)	80-160	28 (18.7%)	1 (2%)
>150	57 (38%)	0 (0%)	>160	38 (25.3%)	0 (0%)

[Table/Fig-4]: Percentage distribution across various levels of serum selenium and zinc amongst controls and cases.

Again as per [Table/Fig-4], among the diabetics, 8% of subjects had <70 µg/l of serum selenium levels where none of the controls had the deficiency of selenium. In addition to that as per [Table/Fig-3], there were consistent lower levels of selenium observed amongst cases compared to controls even though Se levels were within normal range in both the groups.

DISCUSSION

Diabetes mellitus is the leading cause of morbidity and mortality worldwide, with an estimated 346 million adults being affected every year. The prevalence is expected to be doubled between years 2025 and 2030. At present 80% of the world's population with diabetes live in low and middle income countries [16]. Diabetes is also associated with a host of life threatening and potentially disabling macro and micro-vascular complications [18].

As in the present study, the results of age and gender distribution showed non-significant association while the blood glucose levels showed significantly higher values in cases as compared to controls. Mean blood glucose levels showed significant association with increasing age amongst cases.

In study carried out by Karalis DT et al., it was observed that the administration of Se in the recommended dosages improves the values of fasting glucose, glycated haemoglobin (HbA1c), blood total cholesterol, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL). The study concluded that it enforces the claims concerning the multiple benefits of selenium as a dietary supplement in patients with type II diabetes under the prerequisite of following the Mediterranean diet as the recommended treatment method [19]. Many workers have attributed these low levels to increased urinary excretion of these trace elements in T2DM subjects [20].

A large number of studies were found reporting significantly low concentration of zinc, selenium and manganese in serum of diabetic subjects compared to non diabetics [21,22].

There are reports of significant excretion of urinary zinc in T2DM. This shows that T2DM is accompanied by hypozincaemia and hyperzincuria. In the present study also, existence of hypozincaemia was evident in 98% of T2DM subjects. This supports the earlier findings of the common zinc deficiency in the developing countries, where diabetes mellitus is also showing an exponential increase in its prevalence [23]. When we extrapolate the decreased zinc level to oxidative stress, it can be naturally expected that for the development of T2DM, low zinc levels play very significant role as it is an integral part of SOD enzyme, required for the neutralisation of superoxide radicals. In addition to that, zinc itself has an antioxidant potential through the non enzymatic stabilisation of bio structure in bio membranes [24].

There were consistent lower levels of selenium observed amongst cases as compared to controls even though Se levels were within normal range in both the groups. Experimental studies indicate that selenium mimics the effect of insulin, including glucose transport activity and enhancing the insulin receptor tyrosine kinase activity [25]. Present study clearly shows a negative association between serum selenium levels and diabetes mellitus when we compared with the corresponding age group of control subjects. Though, there are studies including ours, indicates an association between diabetes mellitus and low selenium levels, the biochemical reason behind this association will not be easy to explain as there are some germane points and questions regarding the role of selenium in development of insulin resistance. There are some studies showing a negative association between dietary selenium intake and insulin resistance in both males and females. Another possible explanation may be in the presence of low selenium levels, there may be decreased glutathione peroxidase enzyme activity which in turn leads to increased oxidative stress. It may affect pancreatic beta cell functions leading to the decreased synthesis of insulin. There may be a direct effect of Reactive Oxygen Species (ROS) in increasing insulin resistance. Both the above factors cumulatively may lead to the development of T2DM [26].

In present study, none of the subjects in the cases had serum zinc levels above 160 µg/dL, whereas 25.3% of the control subjects had level above 160 µg/dL. This shows the existence of lower levels of zinc in T2DM subjects. A number of studies have reported significantly lower levels of zinc, manganese and selenium in diabetic subjects compared to non diabetic control subjects [27,28]. Many workers attributed this to increased urinary excretion of these trace elements in diabetic subjects as hyperglycaemia interferes with the active transport of these elements back into the renal tubular cells [21]. Other workers have also reported significantly increased excretion of urinary zinc and manganese in both the types of diabetes compared to control subjects and a positive correlation between zinc excretion and HbA1c has been also reported [21].

Limitation(s)

The current study did not analyse pro-oxidants and antioxidant parameters in serum of healthy controls and critically ill type 2 diabetic patients. The antioxidant vitamins also were not analysed in the current study.

CONCLUSION(S)

Serum selenium levels and development of insulin resistance remains controversial, In the present study, we have observed decreased levels of both Serum selenium and zinc levels in critically ill T2DM patients compared to healthy adults. These findings reinforce the credibility of the statement that oxidative stress has a vital part to play in aetiology and progression of T2DM. Supplementation of trace elements like selenium and zinc can be contemplated considering that they increase the antioxidant capacity of the body.

Acknowledgement

I would like to acknowledge the technical contribution provided by Dr. Swati Mehta; Assistant Professor, Department of Preventive & Social Medicine, SMIMER. Her contribution has helped me to effectively utilize SPSS software for statistical data analysis purpose for my study.

REFERENCES

[1] The pharmacological treatment of hyperglycaemia in NIDDM. American Diabetes Association. Diabetes Care. 1995;18(11):1510-18. doi: 10.2337/diacare.18.11.1510. PMID: 8722084.
[2] Helmat Sies, Oxidative stress from basic clinical medicine in: Trace Elements and free radicals in oxidative dieses Editor Alain E, Jean Nave, Patrice Faure 1994: pp.1
[3] Kim HN, Song SW. Concentrations of chromium, selenium, and copper in the hair of viscerally obese adults are associated with insulin resistance. Trace Elem Res. 2014;158(2):152-57.

[4] Ozkaya M, Sahin M, Cakal E, Gisi K, Bilge F, Kilinc M. Selenium levels in first degree relatives of diabetic patients. Biol Trace Elem Res. 2009;128(2):144-51.
[5] Rotter I, Kosik-Bogacka D, Dołęgowska B, Safranow K, Lubkowska A, Laszczyńska M. Relationship between the concentrations of heavy metals and bioelements in aging men with metabolic syndrome. Int J Environ Res Public Health. 2015;12(4):3944-61.
[6] Azab SF, Saleh SH, Elsaeed WF, Elshafie MA, Sherief LM, Esh AM. Serum trace elements in obese Egyptian children: a case-control study. Ital J Pediatr. 2014;40:20. PMID: 24555483
[7] Alizadeh M, Safaeiyan A, Ostadrahimi A, Estakhri R, Daneghian S, Ghaffari A, et al. Effect of L-arginine and selenium added to a hypocaloric diet enriched with legumes on cardiovascular disease risk factors in women with central obesity: a randomized, double-blind, placebo-controlled trial. Ann Nutr Metab. 2012;60(2):157-68.
[8] Jamilian M, Razavi M, Fakhrie Kashan Z, Ghandi Y, Bagherian T, Asemi Z. Metabolic response to selenium supplementation in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf). 2015;82(6):885-91.
[9] Wang Y, Lin M, Gao X. High dietary selenium intake is associated with less insulin resistance in the Newfoundland population Editor: Pratibha V. Nerurkar, University of Hawai, 2017: 6-10. https://doi.org/10.1371/journal.pone.0174149
[10] Askaria G, Irajb B, Salehi-Abargoueic A, Fallahe AA, Jafari T. The association between serum selenium and gestational diabetes mellitus: A systematic review and meta-analysis. J Trace Elem Med Biol. 2015 Jan;29:195-201. doi: 10.1016/j.jtemb.2014.09.006. Epub 2014 Sep 16
[11] Dodson G, Steiner D. The role of assembly in insulin's biosynthesis. Curr Opin Struct Biol. 1998;8:189-94.
[12] Rutter GA. Think zinc. New roles for zinc in the control of insulin secretion. Islets. 2010;2:49-50.
[13] Noormagi A, Gavrilova J, Smirnova J, Tougu V, Palumaa P: Zn(II) ions cosecreted with insulin suppress inherent amyloidogenic properties of monomeric insulin. Biochem J. 2010;430:511-18.
[14] Zalewski P, Millard S, Forbes I, Kapaniris O, Slavotinek S, Betts W, et al. Video image analysis of labile Zn in viable pancreatic islet cells using specific fluorescent probe for Zn. J 288. Histochem Cytochem. 1994;42:877-84.
[15] Arquilla ER, Packer S, Tarmas W, Miyamoto S. The effect of zinc on insulin metabolism. Endocrinology. 1978;103:1440-49.
[16] Ortega RM, Rodríguez-Rodríguez E, Aparicio A, Jiménez AI, López-Sobaler AM, González-Rodríguez LG, et al. Poor zinc status is associated with increased risk of insulin resistance in Spanish children. British Journal of Nutrition. 2012;107:398-404.
[17] Open Source Epidemiologic Statistics for Public Health; 2013; http://www.openepi.com/Menu/OE_Menu.htm
[18] WHO Diabetes Fact Sheet. 2021; https://www.who.int/news-room/fact-sheets/detail/diabetes
[19] Karalis DT. The Beneficiary Role of Selenium in Type II Diabetes: A Longitudinal Study. Cureus. 2019;11(12):e6443. Published 2019 Dec 22. doi:10.7759/cureus.6443
[20] Rocourt CRB, Cheng WH. Selenium supranutrition: are the potential benefits of chemoprevention outweighed by the promotion of diabetes and insulin resistance? Nutrients. 2013;5:1349-65.
[21] El-Yazigi A, Hannan N, Raines D. Effect of diabetic state and related disorders on the urinary excretion of magnesium and zinc in patients. Diabet Res. 1993;22:67-75.
[22] Kazi TG, Afridi HI, Kazi N, Jamali MK, Arain MB, Jalbani N. Copper, chromium, manganese, iron, nickel, and zinc levels in biological samples of diabetes mellitus patients. Biol Trace Elem Res. 2008;122:1-18.
[23] Masood N, Baloch GH, Ghori RA, Memon IA, Memon MA, Memon MS. Serum zinc and magnesium in type-2 diabetic patients. J Coll Physicians Surg Pak. 2009;19:483-86.
[24] Pidduck HG, Wren PJ, Evans DA. Hyperzincuria of diabetes mellitus and possible genetical implications of this observation. Diabetes. 1970;19:240-47.
[25] Black RE. Zinc deficiency, infectious disease and mortality in the developing world. J Nutr. 2003;133:1485S-89S.
[26] Ezaki O. The insulin-like effects of selenate in rat adipocytes. J Biol Chem. 1990;265:1124-28.
[27] Szymańska-Chabowska A, Antonowicz-Juchniewicz J, Andrzejak R. The concentration of selected cancer markers in workers occupationally exposed to arsenic and some heavy metals during a two years of study, In: International Journal of Occupational Medicine and Environmental Health. 2007;20(3):229-39.
[28] Akinloye O, Ogunleye K, Oguntibeju OO. Cadmium, lead, arsenic and selenium levels in patients with type 2 diabetes mellitus. Afr J Biotechnol. 2010;9(32):5189-95.

PARTICULARS OF CONTRIBUTORS:
1. Tutor, Department of Biochemistry, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat, India.
2. Professor, Department of Biochemistry, Smt. B. K. Shah Medical Institute and Research Centre and Dhiraj Hospital, Vadodara, Gujarat, India.
3. Associate Professor, Department of Biochemistry, Chamarajanagar Institute of Medical Sciences, Chamarajanagar, Karnataka, India.
4. Associate Professor, Department of Biochemistry, Surat Municipal Institute of Medical Education and Research, Surat, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Hasitkumar Dalpatbhai Lad,
A-106, Department of Biochemistry, SMIMER Medical College, Opp. New Bombay Market, Umarwada, Surat: 395010, Gujarat, India.
E-mail: hasitlad@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 16, 2021
- Manual Googling: Oct 18, 2021
- iThenticate Software: Oct 20, 2021 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 10, 2021**
Date of Peer Review: **Aug 31, 2021**
Date of Acceptance: **Oct 20, 2021**
Date of Publishing: **Jan 01, 2022**