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EDITORIAL

Unmasking the Mysteries of Uncontrolled Diabetes Mellitus: "Why the Pharmacotherapeutic Advances are Not Competently Enough?

Asim Zulfiqar

Since the IDF's most recent figures were released in 2019, the prevalence of diabetes in Pakistan has dramatically increased. 33 million adults in Pakistan had diabetes in 2021, a 70% rise from 2019. After China (141 million) and India (74 million), Pakistan presently has the third-highest number of persons with diabetes worldwide. Diabetes caused 400,000 fatalities in the nation in 2021, more than any other disease in the Middle East and North Africa. In Pakistan, an extra 11 million persons have impaired glucose tolerance (IGT), putting them at a high risk of getting type 2 diabetes. Pakistan has the highest national prevalence of diabetes in the world, with a frequency of one in four persons (26.7%) almost a quarter.[1]

Diabetes is a chronic illness with several underlying factors: insulin resistance, beta cell failure, incretin deficiency/resistance and inadequate renal tubular handling of filtered glucose are few of them.[2] Number of pharmaco therapeutic agents like metformin, TZD, Sulphonylurea, glinides, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors along with various types of exogenous insulins are available to tackle these various pathogenic mechanisms.[3] Even in the presence of so many advanced therapeutic options, achievement of glycemic/metabolic targets along with improving quality of life of our diabetic patients seems to be very difficult. There is something somewhere that is not working for our diabetic patients. Control over the disease still seems remote and very challenging. This fact leads to the search of various non-pharmacological factors that can contribute to poor disease control. One of them can be allostatic load. Allostatic load refers to the cumulative burden of chronic stress and life events. It involves the interaction of different physiological systems with environmental stress. When environmental challenges exceed the individual's ability to cope then the allostatic overload ensues.[4] Stress has an important role in the glycemic control of a diabetic patients. Diabetic patients not only have to face the stressors regarding their disease like frequent blood sugar checks, diet restrictions, strict exercise routine but have also to face anxiety regarding glycemic variations as well as must live with continuous fear of having acute or chronic complications of the disease.[5,6] This is in addition to concerns regarding their work, family or finances that are not directly related to their illness. In a number of studies this has been documented that stress or allostatic load leads to increased inflammatory/oxidative damage thus contributing to poor glycemic control and increased incidence of complications in diabetic patients.[7,8] So health care providers must address the allostatic load management like provision of the services of psychotherapists/support groups for the holistic care of our diabetic patients. There is a significant link between psychological stress and glycemic control. Psychological stress affects the action of the pituitary gland and the sympathetic nervous system, which causes an increase in the levels of circulating catabolic hormones and a suppression of the anabolic hormones. People with Type 1 diabetes experience elevated blood glucose levels because of this. Stress results in behavioral modifications that can interfere with self-care. For instance, time constraints make it impossible to monitor blood glucose, which disrupts metabolic control. Additionally, comfort-seeking, or coping behaviors, such as increased food consumption and decreased physical activity, may be brought on by stress. People with diabetes who engage in these behaviors run the risk of having their metabolic regulation disturbed.

Another factor that can play a limiting role in the control of disease of a diabetic patients is a dysbiosis of gut microbiota. Insufficient glycemic control has been attributed to dysbiosis of gut microbiota that has significant impact on host metabolism specially glucose hemostasis. Dysbiosis has been revealed to affect short chain fatty acid synthesis and result in

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alteration of insulin signaling pathways, consequently developing inadequate glycemic control.[10]

The potential risk factors for type 2 diabetes include obesity, an unhealthy lifestyle, and gut microbial dysbiosis. Low intake of dietary fibers and consumption of meals high in fat and sugar have both been linked to a decrease in the diversity and abundance of the gut microbial community. The metabolic and functional pathways in the gut that are implicated in the onset of type 2 diabetes may be impacted by gut microbial dysbiosis. The production of short-chain fatty acids (SCFAs) and the composition of the gut microbiota are both significantly influenced by diet. The colony of commensal bacteria in the colon performs fermentation on the carbohydrates that are not digested and absorbed in the small intestine.[11] So for achieving metabolic/glycemic targets, minimizing acute/chronic complications, improving quality of life of our diabetic patients, health care providers will have not only to prescribe appropriate pharmacotherapeutic agent but also need to address some other less considered but important non pharmacological contributing factors like allostatic load, dysbiosis etc. This fact necessitates a multidisciplinary approach that not only involve physicians, nurses but also psychotherapist, counsellors, dieticians, and patient support group. This holistic approach by recognizing the non-pharmacological missing links, is the need of the time for achieving control of our diabetic patients.

REFERENCES

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional, and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes research and clinical practice. 2022;183:109119.
2. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nature reviews Disease primers. 2015;1(1):1-22.
3. Esposito K, Chiodini P, Bellastella G, Maiorino M, Giugliano D. Proportion of patients at HbA1c target< 7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. Diabetes, Obesity and Metabolism. 2012;14(3):228-33.
4. Kolesnikova VA, Clarke PJ, Mukherjee B, Sen S, Mezuk B. Psychosocial Stress and Hypothalamic-Pituitary-Adrenal Axis Stress Reactivity: Variations by Race and Socioeconomic Status Among Adults at Risk of Diabetes. Psychosomatic Medicine. 2022;84(7):813-21.
5. Juanamasta IG, Aungsuroch Y, Gunawan J, Suniyadewi NW, Wati NMN. Holistic care management of diabetes mellitus: An integrative review. International Journal of Preventive Medicine. 2021;12.
6. Mustafa M, Jahan S, Waseem M, Ramzan T, Latif D. Comparing Fasting Homocysteine Levels Among Healthy Adults, Diabetic and Non-Diabetic Cardiac Patients: JRCRS. 2018; 6 (2): 63-66.
7. Sharma VK, Singh TG. Chronic stress and diabetes mellitus: interwoven pathologies. Current diabetes reviews. 2020;16(6):546-56.
8. Jahan S, Parveen S, Barnabas S, Mehreen A. Restless Leg Syndrome and Sleep Quality in Diabetic Patients with and without Neuropathy.
9. Riazi A, Pickup J, Bradley C. Daily stress, and glycaemic control in Type 1 diabetes: individual differences in magnitude, direction, and timing of stress-reactivity. Diabetes Research and Clinical Practice. 2004 Dec 1;66(3):237-44.
10 Bielka W, Przezak A, Pawlik A. The role of the gut microbiota in the pathogenesis of diabetes. International journal of molecular sciences. 2022;23(1):480.
11. Ojo O, Feng QQ, Ojo OO, Wang XH. The role of dietary fibre in modulating gut microbiota dysbiosis in patients with type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Nutrients. 2020 Oct 23;12(11):3239.

CONFLICT OF INTEREST

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ORIGINAL ARTICLE

Association of Serum Gamma-Glutamyl Transferase and C-Reactive Protein as a Biomarkers of Oxidative Stress in Patients of Type 2 Diabetes Mellitus

Ammar ul Hassan, Zujaja Hina Haroon, Sobia Irum Kirmani, Muhammad Anwar, Muhammad Younas, Muhammad Usman Munir

ABSTRACT

Objective: To compare Serum gamma-glutamyl transferase and serum C-reactive protein as biomarker of oxidative stress in patients of type 2 Diabetes Mellitus.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: The study was conducted at Armed Forces Institute of Pathology, department of Chemical Pathology and Endocrinology Rawalpindi. The duration of study was 6 months i.e., 17 Nov 2021 – 17 May 2022 after approval from Institutional Review Board FC-CHP21-12/Read-IRB/22/846.

Materials and Methods: An analytical, cross-sectional research was carried out at Armed Forces Institute of Pathology Rawalpindi. An overall 300 diabetic patients were included between ages of 45 – 65 years. Group I had 100 nondiabetic individuals of 45 – 65 years of age with HbA1c < 5.7 %. Group II and III included 100 patients each of DM of matched age with HbA1c 6.5 – 7 % and greater than 7 % respectively, without any other chronic disease. Serum gamma-glutamyl transferase, HbA1c, Serum C-Reactive Protein were analyzed. Moreover, some more biochemical investigations such as serum liver enzymes were measured to rule out any liver disease. One-way ANOVA was followed up by post-hoc Tukey analysis for intergroup comparison.

Results: Mean serum gamma-glutamyl transferase levels were markedly increased in group III patients followed by group II and normal in group I. The mean of serum gamma-glutamyl transferase in group I was (9.38±4.05U/l), group II (34.27±15.07 U/l) and group III (47.08±20.56 U/l). The mean of Serum C-Reactive Protein in group I was (11±6.02 mg/l), group II (62.07± 26.94 mg/l) and group III (107.73±57.03 mg/l). Pearson correlation revealed prominent positive correlation between HbA1c, serum gamma-glutamyl transferase and Serum C-Reactive Protein with r value of serum gamma-glutamyl transferase (0.838367) and Serum C-Reactive Protein (0.684722). One-way ANOVA and post-hoc Tukey analysis had *p* value of < 0.05 which was statistically significant.

Conclusion: Serum gamma-glutamyl transferase is better marker of oxidative stress in patients of type 2 diabetes mellitus as compared to Serum C-Reactive Protein. The r value of serum gamma-glutamyl transferase is (0.838367) and Serum C-Reactive Protein is (0.684722) indicating strong positive correlation of serum gamma-glutamyl transferase with HbA1c. Therefore, Serum gamma-glutamyl transferase can be used for the prevention and monitoring of complications of type 2 Diabetes Mellitus.

Key Words: *Armed Forces Institute of Pathology (AFIP), C Reactive Protein (CRP), Diabetes Mellitus (DM), Gamma Glutamyl Transferase (GGT), Institutional review board (IRB).*

Introduction

Diabetes Mellitus (DM) is a collective term for several metabolic conditions that all exhibit the hyperglycemia phenotype. The disease's most recognizable symptoms and long-term problems are caused by hyperglycemia, which also serves as the disease's definition. The main objectives of diabetes mellitus research have been to comprehend the pathophysiology and prevent long-term consequences. Unquestionably, one of the most difficult health issues of the twenty-first century is diabetes. Recent studies have established role of inflammation and oxidative stress in pathophysiology of complications of DM. [1,3]

Serum GGT is a cell-surface enzyme that contributes to glutathione's extracellular degradation (GSH). The

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enzyme is produced in numerous tissues, although most of the Serum GGT are synthesized in the liver.[2] The role of Serum GGT in controlling extracellular glutathione (GSH) transport system serves as basis of intracellular antioxidant defenses. Several pathogenic diseases, including aging, carcinogenesis, inflammation, reperfusion injury and atherosclerosis relate to oxidative stress. Additionally, oxidative stress might also be a contributing factor to the development and pathophysiology of diabetes.[4,5] The majority of research examines the part oxidative stress plays in the development of cardiovascular problems in diabetic individuals.[3] In addition, increased levels of Serum GGT is linked with increased body weight and a liver disease called nonalcoholic fatty liver disease "NAFLD". It is caused when excessive fat is deposited in a liver. NAFLD is believed to be main contributory factor responsible for hepatic insulin resistance and ultimately development of hyperinsulinemia and systemic insulin resistance.

Thus, Serum GGT may reflect metabolic changes and may serve as diagnostic for the syndrome of insulin resistance. Several potential explanations explain the link between elevated Serum GGT levels and glycemic control in patients with type 2 diabetes with excellent and poor control.[5,18] In the pathophysiology of diabetes, Serum GGT may therefore play the role of the insulin resistance syndrome marker. Moreover, Serum GGT may leak into the serum due to regular cellular turnover and cellular stressors. There are multiple putative reasons for Serum GGT leakage, including oxidative stress, protein degradation, glycosylation, and endothelial cell injury. Thus, elevated Serum GGT levels may identify individuals with a minimal but constant increase in oxidative and other cellular stress.[16,17] Serum GGT is an upcoming biomarker of oxidative stress monitoring in disease progression from very beginning. The rationale of study is to evaluate Serum GGT as an early marker of oxidative stress in patients of type 2 Diabetes Mellitus. The main objective of this study is to compare Serum Gamma-Glutamyl Transferase and Serum C-Reactive Protein as biomarker of oxidative stress in patients of type 2 Diabetes Mellitus.

Materials and Methods

An analytical, cross-sectional research was carried out at Armed Forces Institute of Pathology Rawalpindi. The duration of study was 6 months. An overall 300 diabetic patients were included between ages of 45 – 65 years. Nonprobability convenient sampling technique was used. The study started after the approval of Ethical Review Committee i.e., 17 Nov 2021 – 17 May 2022 (FC-CHP21-12/Read-IRB/22/846.) Group I had 100 nondiabetic individuals of 45 – 65 years of age with HbA1c < 5.7 %. Group II and III included 100 patients each of DM of matched age with HbA1c 6.5 – 7 % and greater than 7 % respectively, without any other chronic disease.

We excluded patients with deranged liver enzymes and chronic disorders, as they could interfere with our results by falsely altering the concentration of Serum GGT. The patients taking hepatotoxic drugs were also excluded.

All eligible participants in this study were informed of the study's goals. Detailed history was taken in endocrine clinic department of chemical pathology and endocrinology AFIP. Group I included 100 nondiabetics individuals with 45 – 65 years of age with HbA1c < 5.7 %. Group II and III included 100 patients each of DM of matched age with HbA1c 6.5 – 7 % and greater than 7 % respectively, without any other chronic disease. Detailed history was followed up by review of patient's past medical reports from Laboratory Information Management System (LIMS). For participation in research groups and venipuncture, informed written agreement was obtained from all study participants. The emphasis was placed on the voluntary nature of participation in this study. During a standardized interview, the questions also focused on sociodemographic variables and the characteristics in the background diabetes has (length and type of DM, mode of treatment used for DM, and any complications). In addition, each participant got a comprehensive, standardized medical checkup, which included blood collection. Under fasting conditions, 5 ml of each participant's venous blood was collected using a disposable vacutainer equipment (Plain and EDTA). Serum and plasma were separated within a half-hour and kept at 2-8°C for analysis of Serum CRP and Plasma HbA1c. Samples were analyzed in multiple batches.

Glycosylated hemoglobin (HbA1c) was analyzed by Turbidimetric Inhibition Immunoassay (TINIA)

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method on Sebia Capillary Octa-3. Carboxy substrate kinetic method was used to determine the activity of Serum GGT on Chemistry Analyzer Advia 1800.

One-way ANOVA was conducted among three group for comparison of means. Post-hoc Tukey analysis was used to compare the intergroup mean. Pearson linear correlation was used to study correlation between HbA1c, Serum GGT and Serum CRP. Statistically speaking, *p*-value of < 0.05 and r value of > 0.75 was considered as significant.

Results

Mean of serum GGT were strikingly increased in the patients of group III followed by group II and normal in group I. The mean of Serum GGT in group I was (9.38±4.05U/l), group II (34.27±15.07 U/l) and group III (47.08±20.56 U/l). The mean of Serum CRP in group I was (11±6.02 mg/l), group II (62.07± 26.94 mg/l) and group III (107.73±57.03 mg/l). Pearson correlation revealed prominent positive correlation among HbA1c, Serum GGT and Serum CRP with r value of Serum GGT (0.838367) and Serum CRP (0.684722). One-way ANOVA and post-hoc Tukey analysis was conducted to compare the mean. Statistically speaking, *p*-value of < 0.05 was significant.

Table I: Mean Serum GGT and Serum CRP among Study groups (N = 300)

Group		Serum GGTT U/l	Serum CRP mg/l
I	(HbA1c < 5.7 %)	9.38±4.05	11±6.02
II	(HbA1c 6.5 – 7 %)	34.27±15.07	62.07± 26.94
III	(HbA1c > 7%)	47.08±20.56	107.73±57.03

Table II: Comparison of Serum GGT among Groups (N = 300)

Groups	Comparision	Mean Difference	p-Value
Group I (HbA1c < 5.7 %)	Group II (HbA1c 6.5 – 7 %)	119±80	< 0.001*
Group I (HbA1c < 5.7 %)	Group III (HbA1c > 7%)	199±99	< 0.001 *
Group II (HbA1c 6.5 – 7 %)	Group III (HbA1c > 7%)	145±70	< 0.001 *

**p* value < 0.05 considered as Statistically Significant

Table III : Comparison of Serum CRP among Groups (N = 300)

Group	Comparison	Mean Difference	p-Value
Group I (HbA1c < 5.7 %)	Group II (HbA1c 6.5 – 7 %)	150±90	< 0.001*
Group I (HbA1c < 5.7 %)	Group III (HbA1c > 7%)	250±110	< 0.001 *
Group II (HbA1c 6.5 – 7 %)	Group III (HbA1c > 7%)	190±95	< 0.001 *

**p* value < 0.05 considered as Statistically Significant

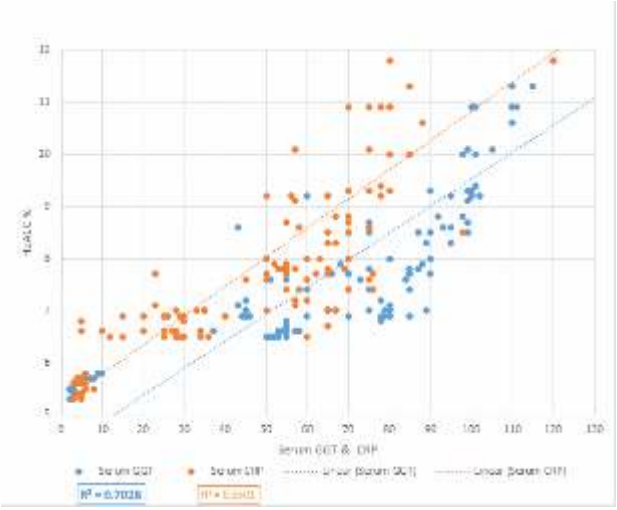

Figure 1: Pearson Correlation Scatterplot of Serum GGT & Serum CRP (N = 300)

Discussion

Patients of type 2 DM having poor glycemic control have considerably higher concentrations of Serum GGT and HbA1c compared to healthy individuals and those with tightly regulated glycemic control. In addition, we found a substantial positive linear correlation between Serum GGT and HbA1C. These results imply a correlation between oxidative stress (as evidenced by a higher serum GGT) and glycemic management with type 2 diabetic patients and associated comorbidities. This shows that oxidative stress and chronic inflammation have a major role in the pathogenesis of type 2 diabetes.[19-21]

Mean of Serum GGT was lowest in control group i.e individuals with normal glycemic control (HbA1c < 5.7 %) and significantly increased in group II (HbA1c 6.5 – 7 %) and Group III (HbA1c > 7 %). The mean of Serum GGT in group I was (9.38 U/l), group II (34.27 U/l) and group III (47.08 U/l). r value of Serum GGT was (0.838367) indicating positive correlation between Serum GGT and HbA1c. A serum GGT elevation may be indicative of nonalcoholic fatty liver disease, which is characterized by an excessive accumulation of fat in the liver. It is believed that a fatty liver results into hepatic insulin resistance leading to hyperinsulinemia.[22]

Serum CRP is a well-known marker of inflammation, however its role in oxidative stress secondary to type 2 diabetes mellitus has not been established. The mean of Serum CRP in group I was (11 mg/l), group II (62.07 mg/l) and group III (107.73 mg/l). However,

Pearson correlation revealed insignificant correlation of Serum CRP and HbA1c with r value of (0.684722).

There are other studies supporting our results and findings. R Sharma et al. demonstrate a strong correlation of Serum hsCRP and Serum GGT in diabetic with poor glycemic control, which may be due to oxidative stress and inflammation in diabetes.[9]

The findings of Thamer C et al. and Andre P et al. seconds a correlation between high serum GGT, uncontrolled diabetes and metabolic syndrome. Elevated levels of GGT are associated with increased insulin resistance, an increased risk of developing type 2 diabetes, and inadequate glycemic control. Moreover, Serum GGT may leak into the serum due to regular cellular turnover and cellular stressors. There are multiple putative reasons for Serum GGT leakage, including oxidative stress, protein degradation, glycosylation, and endothelial cell injury. [23,24]

Marchesini G et al. and Silventoinen K et al. determined that the close affiliation of serum GGT activity with other metabolic disorders related to DM, such as atherosclerosis, cardiovascular diseases, and dyslipidemia. Increased oxidative stress, fatty liver and insulin resistance may be responsible for the pathogenesis of disease increased activity of serum GGT. Increasing evidence suggests that Serum GGT is a measure of both fatty liver and oxidative stress. [12,13] Study revealed that Serum GGT plays a crucial role in the maintenance of intracellular antioxidant defenses by mediating the transport of extracellular glutathione into most cell types. It is an enzyme generally found on the outside of the cell membrane whose major job is to maintain intracellular concentrations of glutathione (GSH), the cell's most important antioxidant defense. Growth in Serum GGT activity may be a reaction to oxidative stress, allowing for an increase in the GSH precursors' movement into cells.[25]

Our research had numerous limitations. First, this was a cross-sectional study that reports no causal effect. In addition, serum GGT levels in the follow-up were not included in the analysis. In addition, some confounding variables, such as fasting insulin concentration and markers other than Serum CRP that can assess the inflammatory status of the patient in correlation with Serum GGT, could not be included in this study.

Conclusion

It can be concluded that serum GGT is a better and more specific marker of oxidative stress in patients of type 2 DM as compared to serum CRP. Serum GGT can be used for prevention and monitoring of complications of type 2 Diabetes Mellitus.

REFERENCES

1. Powers AC, Niswender KD, Evans-Molina C. Diabetes mellitus: diagnosis, classification, and pathophysiology. Harrison's principles of internal medicine. 2018;2:2399-407. bookid=2129&sectionid=192288322
2. Bandara D, Thennakoon S, Dias P, Withanage N. Association of serum gamma glutamyltransferase with diabetes mellitus, random blood sugar and body mass index in selected Sri Lankan subjects. Ceylon Journal of Medical Science. 2022 Dec 28;57(1). DOI: 10.4038/cjms.v57i1.4970
3. Ohiagu FO, Chikezie PC, Chikezie CM. Pathophysiology of diabetes mellitus complications: Metabolic events and control. Biomedical Research and Therapy. 2021 Mar 31;8(3):4243-57. DOI : 10.15419/bmrat.v8i3.663
4. Oyakhire F, Emokpae MA, Ogie E, Valentine EE. Effect of Diabetes Mellitus on the Excretory Function of the Liver. Medical Laboratory Technology Journal. 2021 Dec 31;7(2):155-63. DOI: https://doi.org/10.31964/mltj.v0i0.416
5. Sharmin F, Junaed MT. Association of Obesity and Serum Gamma Glutamyl Transferase with Impaired Fasting Glucose in Adults at a Tertiary Level Hospital of Bangladesh. Mymensingh Medical Journal: MMJ. 2022 Jul 1;31(3):614-21.
6. Darenskaya MA, Kolesnikova LI, Kolesnikov SI. Oxidative stress: pathogenetic role in diabetes mellitus and its complications and therapeutic approaches to correction. Bulletin of experimental biology and medicine. 2021 May;171(2):179-89. DOI: 10.1007/s10517-021-05191-7
7. Wan JY, Yang LZ. Liver Enzymes are Associated with Hyperglycemia in Diabetes: A Three-Year Retrospective Study. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2022 Feb 23;15:545-55. DOI https://doi.org/10.2147/DMSO.S350426
8. Rösen P, Nawroth PP, King G, Möller W, Tritschler HJ, Packer L. The role of oxidative stress in the onset and progression of diabetes and its complications: asummary of a Congress Series sponsored byUNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. Diabetes/metabolism research and reviews. 2001 May;17(3):189-212. doi: 10.1002/dmrr.196.
9. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001 Aug 1;50(8):1844-50. DOI: 10.2337/diabetes.50.8.1844
10. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M,

Blomhoff R, Jacobs DR. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. Diabetologia. 2003 Mar;46(3):359-64. DOI: 10.1007/s00125-003-1036-5
11. Sharma R, Sharma S, Kaushik GG. Gamma-glutamyltransferase (GGT)–a novel marker of endothelial dysfunction. JIACM. 2010;11(1):26-30.
12. Thamer C, Tschritter O, Haap M, Shirkavand F, Machann J, Fritsche A, Schick F, Häring H, Stumvoll M. Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intrahepatic lipids. Hormone and metabolic research. 2012 Apr;37(04):246-51. DOI: 10.1055/s-2005-861411
13. André P, Balkau B, Born C, Charles MA, Eschwège E. Three-year increase of gamma-glutamyltransferase level and development of type 2 diabetes in middle-aged men and women: the DESIR cohort. Diabetologia. 2015 Nov;49(11):2599-603. DOI: 10.1007/s00125-006-0418-x
14. Marchesini G, Avagnina S, Barantani EG, Ciccarone AM, Corica F, Dall'Aglio E, Dalle Grave R, Morpurgo PS, Tomasi F, Vitacolonna E. Aminotransferase and gamma-glutamyl transpeptidase levels in obesity are associated with insulin resistance and the metabolic syndrome. Journal of endocrinological investigation. 2005 Jun;28(6):333-9. DOI: 10.1007/BF03347199
15. Lee DH, Silventoinen K, Jacobs Jr DR, Jousilahti P, Tuomileto J. γ-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. The Journal of Clinical Endocrinology & Metabolism. 2004 Nov 1;89(11):5410-4. DOI: 10.1210/jc.2004-0505
16. Krishnamurthy V, Patted AS, Kumar A, Jayaram SK, Magaji BS. Evaluation of serum gamma-glutamyl transferase and highly sensitive C-reactive protein as biomarkers of oxidative stress and inflammation in type 2 diabetes mellitus patients with good and poor glycemic control. Int J Adv Med. 2019 May;6(3):650. DOI: https://doi.org/10.18203/2349-3933.ijam20191494
17. BS M, Patted DA, Krishnamurthy DV, Dak T, Jayaram DS. PDB9 Serum Ggt And hscrp: Early Predictors of Oxidative Stress and Inflammation in Type 2 Diabetes Mellitus Patients With Good And Poor Glycemic Contorl. Value in Health. 2019 Nov 1;22:S573. DOI: 10.1186/2251-6581-12-56
18. Elimam H, Abdulla AM, Taha IM. Inflammatory markers and control of type 2 diabetes mellitus. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2019 Jan 1;13(1):800-4. DOI: 10.1016/j.dsx.2018.11.061
19. Lee JH, Lee HS, Lee YJ. Serum γ-glutamyltransferase as an independent predictor for incident type 2 diabetes in middle-aged and older adults: Findings from the KoGES over 12 years of follow-up. Nutrition, Metabolism and Cardiovascular Diseases. 2020 Aug 28;30(9):1484-91. DOI: 10.1016/j.numecd.2020.04.027
20. Nagalakshmi CS, Savadi B, Santhosh NU, Shaikh SB, Javarappa D. Can Gamma Glutamyl Transferase Serve as a Marker to Predict the Risk of Metabolic Syndrome in Patients with Type 2 Diabetes Mellitus?. Indian Journal of Medical Biochemistry. 2019 Sep;23(3):347-9. DOI: 10.5005/jp-journals-10054-0116
21. Neuman MG, Malnick S, Chertin L. Gamma glutamyl transferase–an underestimated marker for cardiovascular disease and the metabolic syndrome. Journal of Pharmacy & Pharmaceutical Sciences. 2020 Apr 19;23:65-74. DOI: 10.18433/jpps30923
22. Mohapatra E, Priya R, Nanda R, Patel S. Serum GGT and serum ferritin as early markers for metabolic syndrome. Journal of Family Medicine and Primary Care. 2020 Jul;9(7):3458. doi: 10.4103/jfmpc.jfmpc_570_20
23. Dai H, Zhu L, Pan B, Li H, Dai Z, Su X. The relationship between serum γ-glutamyltransferase (GGT) and diabetic nephropathy in patients with type 2 diabetes mellitus: a cross-sectional study. Clinical and Experimental Medicine. 2023 Jan 11:1-2. DOI: 10.1007/s10238-023-00991-9
24. Shibabaw T, Dessie G, Molla MD, Zerihun MF, Ayelign B. Assessment of liver marker enzymes and its association with type 2 diabetes mellitus in Northwest Ethiopia. BMC research notes. 2019 Dec;12:1-5. DOI: 10.1186/s13104-019-4742-x Agarwal H, Jha OP, Meena PK. Role of Serum γ-Glutamyl Transpeptidase (GGT) Level as a Marker for the Detection of Type-2 Diabetes Mellitus.

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

A Morphological and Biochemical Study of Ethanolic Fruit Extract of Berberis Vulgaris Against Gentamicin Induced Renal Damage in Albino Rats

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ABSTRACT

Objective: To analyze the reno protective potential of berberis vulgaris on renal function by measuring renal biomarkers (serum urea and serum creatinine).

Study Design: Experimental lab-based study.

Place and Duration of Study: Study was done in Baqai Medical & Dental University 4th July 2017 to 3rd Aug 2017.

Materials and Methods: Forty adult healthy male laboratory animals were randomly divided into four groups. Group A was treated as control group. Group B were administered with Berberis vulgaris fruit extract 100 mg /kg/body wt. single oral dose for 21 days. Group C were administered with gentamicin 100 mg/kg/day intraperitoneally single dose for 21 days. Group D, animals received gentamicin intraperitoneally 100mg/kg/day along with berberis vulgaris fruit extract orally for 21 days. Both kidneys were dissected, all sections obtained were stained with two dyes hematoxylin and eosin and periodic acid schiff stain for histomorphology. Standard error of mean was used to express results. Numerical data obtained from different groups were analyzed using SPSS version 21. P-value of 0.05 or less than 0.05 was considered statistically significant.

Results: This study revealed that body weight, kidney weight has been reduced in gentamicin group whereas biomarkers and relative weight of kidney have shown significant increase in group D as compared to control group.

Conclusion: Berberis vulgaris fruit extract ameliorates functional abnormalities along with biochemical parameters associated with gentamicin induced nephrotoxicity.

Key Words: *Berberis vulgaris, Gentamicin, Nephrotoxicity, Serum creatinine, Serum Urea.*

Introduction

Kidneys play an important role for the removal of waste products, for maintenance of balanced body chemical and acid content of the body. Substances produced by different metabolic reactions that occur in the body are excreted through kidneys include ammonia, bilirubin and creatinine in muscles and also drugs and other xenobiotics.[1] Life threatening infections caused by different microorganisms such as Proteus, E.coli, Klebsiella, Citrobacter species and Staphylococcus species is most commonly treated by broad spectrum antibiotic gentamicin.[2] Clearance of gentamicin first rapidly by renal excretion but partially reabsorbed and accumulation occurred mostly within the proximal convoluted tubules, which are main site for renal toxicity. Therefore, gentamicin has always been a restriction in clinical use for long term. Renal insufficiency including renal end stage disease takes place in 30% of patients treated with gentamicin.[3] Aminoglycoside has the potential to generate acute kidney failure due to tubular cell necrosis confined to proximal convoluted tubules by raising serum biomarkers creatinine and urea. Additionally reactive oxygen species(ROS)e.g., hydroxyl radicals (OH), hydrogen peroxide (H2O2), and superoxide anion (O2-) which are the most important mediators of tissue damage are produced by gentamicin. Gentamicin renal toxicity also decreases the activity of renal tissue antioxidant agents like catalase, superoxide dismutase content.[4] Tissue damage induced by gentamicin mainly caused by mitochondrial dysfunction as mitochondria are

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main sites of ROS production.[5] It is proved that gentamicin renal accumulation facilitates nephrotoxicity.[6] Toxicity induced by gentamicin is mainly due to oxidative stress and this condition could be antagonize by dietary antioxidant.[7]

Berberis vulgaris medicinal herb belongs to the family Berberidaceae found abundance in European countries, Northwest Africa and in few Asian regions. Fruit of Berberis vulgaris commonly called Barberry, (Zereshk) in local language in Iran are edible,they contain large amount of vitamin C.[8] Barberry of both types dried and fresh have increased antioxidant activity and are rich in phenolic and anthocyanin compounds, intake of both is recommended.[9,10] Berberis vulgaris also contains large percentage of ascorbic acid which is antioxidant.[11] Fruit of Berberis vulgaris is approved by FDA and it is safe for humans.[12]

Considering reported therapeutic medicinal uses of berberis vulgaris fruit extract, the present study was conducted based on experiments to evaluate the probable protective role of berberis vulgaris fruit extract on renal parenchyma and to analyze the ameliorative potentials of berberis vulgaris fruit extract on renal function by measuring renal biomarkers (serum urea and serum creatinine).[13]

Materials and Methods

This experimental study was performed at Baqai Medical & Dental University in Anatomy department jointly with Animal house of BM & DU after ethical approval of experimental protocol (Ref: BMU-EC/2016-04) from Board of Advanced Research and Studies (BAS&R) Baqai Medical University 4thJuly 2017 to 3rd Aug 2017. Inclusion criteria for this study used were forty healthy male adult albino rats aged 10-12 weeks and weighted 180-250gms. Exclusion criteria for this study used were any diseased rat or rat died during study. Total four groups were made for this experimental study each having ten rats (n=10).Group A required laboratory food and water, no drug or treatment was given to this group. Group B animals were given fruit extract of berberis vulgarisorally100mg/kg rat bodywt./dayfor 21 consecutive days. Gentamicin was injected intraperitoneal route to group C at a single dose of 100mg/kg rat body wt./day daily for 21 consecutive days to induce nephrotoxicity. Group D were given gentamicin 100mg/kg rat body wt./day intraperitonially daily once as company with berberis vulgaris Ethanolic fruit extract 100 mg/kg rat body wt. daily once through gastric gavage for 21 days. Before the commencement of this procedure all animals were weighted by using digital electronic balance, tagged, and kept in segregated cages in animal house of BM&DU and allowed free access for fresh water& concentrated food (pellets) ad libitum.

Berberis vulgaris was purchased from local herbal market of Karachi and authenticated by pharmacognosy department of Karachi University. Berberis vulgaris fruit obtained was dried to make it free from bacteria, fungus then it was chopped into small pieces to make refine powder. The grounded sample was retained in a sealed jar and then reserved for further extraction. Grinded powdered fruit (1000g) was soaked in adequate volume of ethanol: water 70:30 ratio, stirred in a circular shaker at room temperature. The extract was kept for 7 days for further extraction. The decoction then separated from the remainder by filtration through whatmanno.1 filter paper. The remainder solvent of the concentrate removed by using rotary evaporator[14]. After completion of dosing, all animals were anesthetized and then sacrificed. All animals weight was recorded at the beginning and at the time of sacrifice.

Effects of gentamicin related nephrotoxicity in albino rats was measured by kidney weight/100g rat body weight [15], biomarkers serum creatinine and serum urea concentration in rats.

5ml whole blood samples were carefully collected at the end from each experimental rat by intracardiac puncture in a 10 ml capacity bottles for detailed estimation of biomarkers urea and creatinine levels. Abdominal cavities were exposed by giving midline incisions. Kidneys of both sides were obtained and divided into two equal-size length wise halves and were fixed for 24h in10% formalin (BFN). All fixed specimen of both kidneys were dehydrated with ascending grades of ethanol cleared in xylene solution and embedded in paraffin wax blocks.5um thick tissue sections were made. The architecture of all four groups slides A to D was observed.

Four randomly selected sections from each kidney were observed under a light microscope at 10 and 40X. Two basic stains routine hematoxylin and eosin (H&E) and periodic acid Schiff (PAS) were used to

notice the overall tissue architecture of both kidneys. Standard error means (SEM) was used to express results. Numerical data obtained from different groups were analyzed using SPSS version 21.P-value of 0.05 or less than 0.05 was considered statistically significant. The obtained data was analyzed by one way ANOVA.

Results

Normal control mean for initial and final body weight were recorded as 207±4.26 and 210 ± 3.09 respectively. Data showed highly significant increased (p-value 0.003) in the mean of final rat body weight of normal control group A (Table I). Berberis received group initial and final body weight were recorded as 196.50± 2.66 and 210.80±2.84 respectively. Significant increase (p-value0.0001) in the mean of final rat body weight of Group B was noticed. (Table I).Group C mean value for initial and final rat body weight were recorded as 196.2±2.26 and 183.8±1.93 respectively. Significant decrease (p-value 0.0001) (Table I) in the mean of final rat body weight of Group C was noticed.

Group D mean value for initial and final body weight were recorded as 203.30 ± and2.07 217.90 ± 2.09 respectively. Data showed significant increase (p-value0.0001) in the mean of final body weight of Group D. (Table I).

The mean value of weight of rat kidneys (gm) in group A and B were .614±.018 and .639±.013 respectively. Mean value of weight of rat kidney (gm) in gentamicin group was .962±.010 and mean value of weight of kidney in gentamicin along with berberis vulgaris treted group was .660±.009 (Table II).

It was noticed in this study data revealed highly significant increament in the mean value of weight of kidneys (p-value 0.00) in gentamicin treated group.962±.010 when compared with normal control group.614±.018.

The data of this study also showed highly significant increas in the mean of rat kidneys in gentamicin group (p-0.00) when compared with berberis group.639 ± .013.

Experimental data showed significant increment in the mean value of rat kidneys of group C .962 ±.010 (p-0.00) when compared with group D .660 ±.009.

The mean values of relative weight of kidneys in normal group, berberis vulgaris fruit exract group, gentamicin treated group, and gentamicin along berberis vulgaris group are shown in (Table III A).

Significant increase was observed in the mean value of relative kidneys weight (p-0.000) in group C when compared with control normal group A, B and D (Table IIIb).

Interstingly our data showed highly significant increased (p-0.00) in the mean of biochemical parameters serum urea level (mg/dl) of gentamicin treated group in comparision with normal control group A. Additionaly gentamicin along with berberis vulgaris treated group showed not much raised level of urea as compared to control group which revealed nephroprotective result of berberis vulgaris fruit extract against nephrotoxic drug gentamicin.(Graph no 1).

Mean value of serum creatinine level (mg/dl) in group A and B were 0.655±.011, mean.635±.007 respectively. Mean of serum creatinine level (mg/dl) in group C and D were 5.35±.186 and .688±.009. respectively (Graph No 2). Results of our study showed significant increament in the mean value of serum creatinine level (p-0.00) in gentamicin group 5.35±.186when compared with normal control group 0.655±.011.(Graph No 2).

The data showed significant increased in the mean value of serum creatinine level (p-0.00) in gentamicingroup C 5.35±.186 when compared with group D.688±.009.

Additionally, highly significant increase was observed in the mean value of serum creatinine level (p-0.00) in comparison with gentamicin group5.35±.186 when compared with berberis group .635±.007.

In contrast, tha data revealed no remarkable change in the mean value of serum creatinine level (p-0.869) in gentamicin treated along with berberis vulgaris fruit extract groupin comparision with control group A.

Table I : Mean Rat Body Weight (Gm) In Different Treated Groups

Groups n=10 in each group	Treatment received	Initial weight	Final weight	P-value
A	No experiment done	207±4.26	216±3.09	0.003*
B	Ethanolic Berberis vulgaris fruit extract (100mg/kg rat	196.5±2.66	210±2.84	0.000*

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	body wt/day)for 21 consecutive days orally			
C	Gentamicin (100mg/kg rat body wt /day) single dose i.p for 21days	196.2±2.66	183±1.93	0.000*
D	Gentamicin i.p (100 mg/kg rat body wt /day)+with berberis vulgaris orally for 21 days	203±2.07	217±2.09	0.000*

Table II: Mean Rat Kidney Weight (gm) in Study Groups n=40

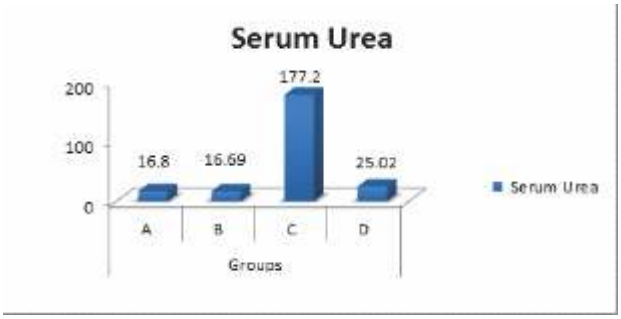
Groups	Treatment Received	Rats' Kidney Weight
A	No experiment done	.614±.018
B	Ethanolic Berberis vulgaris fruit extract (100mg/kg rat body wt/day)for 21 consecutive days orally	.639±.013
C	Gentamicin (100mg/kgrat body wt /day) single dose i.p for 21days	.962±.010
D	Gentamicin i.p (100 mg/kg rat body wt /day)+with berberis vulgaris orally for 21 days	.660±.009

Table III a : Mean Relative Weight of Kidney In Different Groups

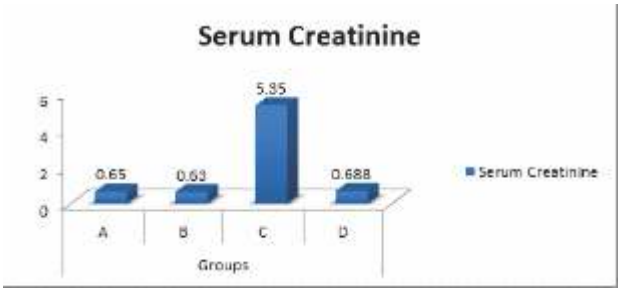
Groups	Treatment received	Relative weight of kidneys
A	No experiment done.	2.13±..063
B	Ethanolic Berberis vulgaris fruit extract (100mg/kg rat body wt /day)for 21 consecutive days orally	2.22±..067
C	Gentamicin (100mg/kg rat body wt /day)single dose i.p for 21 consecutive days	3.34±.064
D	Gentamicin i.p (100 mg/kg rat body wt /day)+with berberis vulgaris orally for 21 consecutive days	2.29±..069

Table III b Analysis of Differences in Relative Weight of Kidneys between Different Groups.

Comparision of groups.	Difference between treated groups	P-VALUE
A and B	-.086±.093	.361
A and C	-1.209±.093	.000
A and D	-.156±.093	.104
B and C	-1.12±.093	.000
B and D	-.096±.093	.464
D and C	-1.052±.093	.000



Graph No 1. Serum Urea Mean Values Comparision of Different Experimental Groups.



Graph No 2. Serum Creatinine Mean Values Comparison of Different Experimental Groups.

Discussion

Aminoglycoside brand Gentamicin is one of an important and effective antibiotic due to its strong bactericidal properties, lower resistance rate and cost effectivness. Aminoglycosides accounts for 10%-20% of nephrotoxicity which is its one of major complication.[16]

Gentamicin can be used both in humans as well as for animals in treating gram negative bacterial infections.[17] Gentamicin induced nephrotoxicity is commonly used to study acute kidney failure in animal model for research based experiments.[18] Gentamicin induced nephrotoxicity results in acute kidney failure.[19] AKF is a complex series of event indicated by elevated serum creatinine level and blood urea including proximal tubular cell necrosis resulting in renal failure.[20] Production of ROS in mitochondria is directly increased by gentamicin as a result cellular damage occurred, decreased production of ATP, apoptosis stimulating factor released from mitochondria, lipid per oxidation all these lead to cell hypertrophy and cell death by apoptosis thus resulting in decreased body weight. Sawardekar et al.[21] showed same results which was observed in this study. Berberis vulgaris fruit (BVF) can be used as an alternative medicine or as additive supplement food against nephrotoxicity generated

by gentamicin.

Berberis vulgaris (BV) and its important compound berberine have been used since for a long period in indigenous medicine. Antioxidant results of berberis vulgaris are greater due to synergy of phenols and berberine compounds.[22]

The most specific indicator for measuring adverse effects of divergent xenobiotics is the body weight,therefore it is considered as a principle parameter to test toxicity . Significant decline in rat body weight gain was noted in group C.Renal failure leads to acidosis, accompanied by anorexia and decreased food intake which later on results in body weight loss by gentamicin induced nephrotoxicity. Similar findings have been stated by Erdem et al.[23] In this study it was noted in berberis vulgaris protected group increase to some extent in body weight as compared to gentamicin treated group.[24] Tamilarasan et al also confirmed these findings.[25] Same energy levels were found in Group D animals when compared with normal group. This is because Berberis vulgaris fruit extract which has a potential to reduce oxidative stress, results in decline of free radicals scavenging activity. Berberis vulgaris possess strong antioxidantal effects which help to improve physical strength consequently increased body weight. This was in accordance with previously done study by Laamech et al.[26] Marked increase in relative weight of kidney was observed in gentamicin treated group C as compared to control group due to decreased prostaglandinE2 production which causes sodium retention resulting in renal hypertrophy and interstitial edema produced by gentamicin induced tubular necrosis resulted in significant increased kidney weight as similar to Noorani et al.[27]

Prominent increased level of serum urea and creatinine concentrations are good signs of concentrated glomerular filtration and significant kidney failure. Significant rise in levels of serum urea and creatinine concentrations resulted in powerful renal destruction produced by gentamicin nephrotoxicity.[28] Serum creatinine is more authentic biomarker in the mechanism of pathogenesis of renal disease as compared to urea.[29] Further more concentration of urea starts to develop right after injury of renal parenchyma. Antioxidantal properties of tissue are decreased by gentamicin which is revealed by prominent decrease in enzymatic activity of superoxide dismutase and marked increase in per oxidation of lipids. Due to this it generates oxidative stress to different organs. Antioxidant agent can alter majority of the modifications in histological tissue sections of renal parenchyma generated by gentamicin related nephrotoxicity.

The mechanism due to which serum urea and creatinine levels raised are because of the reason that gentamicin causes the Ca+2 to enter more into the mesangial cells resulting in decreased glomerular filtration rate.[30] Similar finding was observed by W Hozayen et al.[31]

It was clearly evident through results of our study that gentamicin at a dose of 100 mg/kg rat body wt/day generates nephrotoxic effects which was obvious by marked increase in p- value (0.000) in serum urea and blood creatininelevel as compared to normal control group.

Berberis vulgaris fruit extract has strong antioxidant potential leading to nephroprotective effects (Jyothilakshmi et al., 2013).[32] No significant increase in serum urea and blood creatinine concentration was found in Berberis vulgaris treated group when compared with normal control group. In the light of above statistical analysis, figures, and facts.

Conclusion

It is concluded that Gentamicin produces oxidative nephrotoxic effects on renal parenchyma which can be limited and prevented by protective antioxidative effect of Berberis vulgaris that restored histomorphological changes in renal tissue induced by gentamicin toxicity.

Limitations of Study

There will be no doubt if herbs will be used in future that will significantly benefit human beings. However sample size of this study is too small ,animal studies are time consuming and there will be chance of high failure in development of new drug.

REFERENCES

1. Hall AM, Trepiccione F, Unwin RJ. Drug toxicity in the proximal tubule: new models,methods, and mechanisms. Paediatric Nephrology. 2022 May;37(5):973-82. https://doi.org/10.1007/s00467-021-05121-9.
2 Veljković M, Pavlović DR, Stojiljković N, Ilić S, Jovanović I, Poklar Ulrih N, et al. Bilberry: Chemical Profiling, in Vitro and in Vivo Antioxidant Activity and Nephroprotective Effect against Gentamicin Toxicity in Rats. Phytotherapy Research.

 https://doi.org/10.57234/jiimc.june23.1584

2017;31(1):115-23. DOI:10.1002/ptr.5738.
3. Adil M, Kandhare AD, Dalvi G, Ghosh P, Venkata S, Raygude KS, et al. Ameliorative effect of berberine against gentamicin-induced nephrotoxicity in rats via attenuation of oxidative stress, inflammation, apoptosis and mitochondrial dysfunction. Renal failure. 2016;38(6): 996-1006.DOI: 10.3109/0886022X.2016.1165120.
4. Tavafi M, Ahmadvand H, Tamjidipour A, Rasolian B. Effect of normobaric hyperoxia on gentamicin-induced nephrotoxicity in rats. Iranian journal of basic medical sciences. 2014;17(4):287.
5. Chen Q, Cui Y, Ding G, Jia Z, Zhang Y, Zhang A, et al. PEA3 protects against gentamicin nephrotoxicity: role of mitochondrial dysfunction. American journal of translational research. 2017;9(5):2153.
6. Yousef FM, Alkreathy H. Effect of Licorice Extract against Gentamicin-Induced Nephrotoxicity in Male Rats. Life Science Journal. 2016;13(2). DOI: 10.7537/marslsj13021615.
7. Mahmoud YI. Kiwi fruit (Actinidia deliciosa) ameliorates gentamicin-induced nephrotoxicity in albino mice via the activation of Nrf2 and the inhibition of NF-κB (Kiwi & gentamicin-induced nephrotoxicity). Biomedicine & Pharmacotherapy. 2017;94: 206-18.DOI: 10.1016/j.biopha.2017.07.079.
8. Minaiyan M, Ghannadi A, Mahzouni P, Jaffari-Shirazi E. Comparative study of Berberis vulgaris fruit extract and berberine chloride effects on acetic acid-induced colitis in rats. Iranian journal of pharmaceutical research: IJPR. 2011;10(1):97.
9. SHARİFİ F, POORAKBAR L. The survey of antioxidant properties of phenolic compounds in fresh and dry hybrid Barberry fruits (Berberis integerrima× vulgaris). Cumhuriyet Science Journal. 2015;36(3):1609-17.
10. Yildiz H, Ercisli S, Sengul M, Topdas EF, Beyhan O, Cakir O, et al. Some physicochemical characteristics, bioactive content and antioxidant characteristics of non-sprayed Barberry (Berberis vulgaris l.) fruits from Turkey. Erwerbs-Obstbau. 2014;56(4): 123-9.DOI: 10.1007/s10341-014-0216-4.
11. Rahimi-Madiseh M, Lorigoini Z, Zamani-gharaghoshi H, Rafieian-kopaei M. Berberis vulgaris: specifications and traditional uses. Iranian Journal of Basic Medical Sciences. 2017;20(5): 569.DOI: 10.22038/IJBMS.2017.8690.
12. Abushouk A, Salem AMA, Abdel-Daim MM. Berberis vulgaris for cardiovascular disorders: a scoping literature review. Iranian Journal of Basic Medical Sciences. 2017;20(5): 503.DOI: 10.22038/IJBMS.2017.8674.
13. Al-Khamas AJ, Kadhim ZH, Al-Charak AG, Faris JK. BIOCHEMICAL AND HISTOLOGICAL STUDY OF RAT LIVER TOXICITY INDUCED BY GENTAMICIN AND PROTECTIVE ACTION OF BERBERINE.Plant Archives 2020; 20 (1);3073-3078.
14. Saki K, Bahmani M, Rafieian-Kopaei M, Hassanzadazar H, Dehghan K, Bahmani F, et al. The most common native medicinal plants used for psychiatric and neurological disorders in Urmia city, northwest of Iran. Asian Pacific Journal of Tropical Disease. 2014;4:S895-S901.DOI: 10.1016/S2222-1808(14)60754-4.
15. Amjad Z, Iqbal M, Shoro A. Lead-Induced Reduction in Body and Kidney Weight of Wistar Albino Rats Ameliorated by Ginkgo biloba Extract (EGb 761). Biochem Physiol. 2013;2(113): 2.DOI: 10.29052/IJEHSR.v8. i4.2020.202-211.
16. Mehan S, Dudi R, Kalra S. Renoprotective Effect of Corosolic Acid in Gentamicin-Induced Nephrotoxicity and Renal Dysfunction in Experimental Rats. Ann Pharmacol Pharm 2017; 2 (12).1065.
17. Bag AK, Mumtaz SF. Hepatoprotective and nephroprotective activity of hydroalcoholic extract of Ipomoea staphylina leaves. Bangladesh Journal of Pharmacology. 2013;8(3): 263-8.DOI**:** 10.3329/bjp.v8i3.14845.
18. Dubey T, Srivastava AK, Nagar H, Mishra BK, Mishra SS. Nephroprotective activity of nelumbo nucifera gaertn. roots, leaves and flowers in gentamicin induced nephrotoxicity. 2014.
19. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine 18E Vol 2 EB: McGraw Hill Professional; 2012.DOI: dl.iem.iums.ac.ir/handle/Hannan/123.
20. Nasri H. Ameliorative effects of metformin on renal histologic and biochemical alterations of gentamicin-induced renal toxicity in Wistar rats. Journal of Research in Medical Sciences. 2013;18(7):627.
21. Sawardekar SB, Patel TC. Evaluation of the effect of Boerhavia diffusa on gentamicin-induced nephrotoxicity in rats. Journal of Ayurveda and integrative medicine. 2015;6(2): 95.DOI: 10.4103/0975-9476.146545.
22. Tavafi M, Ahmadvand H, Toolabi P. Inhibitory effect of olive leaf extract on gentamicin-induced nephrotoxicity in rats. Iranian Journal of Kidney Diseases. 2012;6(1):25.
23. Erdem A, Gündogan NÜ, Usubütün A, Kılınç K, Erdem ŞR, Kara A, et al. The protective effect of taurine against gentamicin-induced acute tubular necrosis in rats. Nephrology Dialysis Transplantation. 2000;15(8): 1175-82.DOI: 10.1093/ndt/15.8.1175.
24. Hozayen W, Bastawy M, Elshafeey H. Effects of aqueous purslane (portulaca oleracea) extract and fish oil on gentamicin nephrotoxicity in albino rats. Nature and Science. 2011;9(2):47-62.
25. Tamilarasan B, Karthikeyan P, Kannan P, Periandavan K, Manchanda R, Khurana A, Nayak D, Palainivelu S. Understanding the role of homoeopathic preparation of Berberis vulgaris in mitigation of sodium oxalate-induced hyperoxaluria: An experimental approach. Indian Journal of Research in Homoeopathy. 2020;14(4):251-9.DOI: 10.4103/ijrh.ijrh_44_20.
26. Laamech J, El-Hilaly J, Fetoui H, Chtourou Y, Tahraoui A, Lyoussi B. Nephroprotective Effects of Berberis Vulgaris L. Total Extract on Lead Acetate-induced Toxicity in Mice. Indian Journal of Pharmaceutical Sciences. 2016;78(3):326-33.DOI: 10.4172/pharmaceutical-sciences.1000122.
27. Noorani AA, Gupta K, Bhadada K, Kale M. Protective effect of methanolic leaf extract of Caesalpinia bonduc (L.) on gentamicin-induced hepatotoxicity and nephrotoxicity in rats. Iranian Journal of Pharmacology & Therapeutics (IJPT). 2011;10(1):21-5.
28. Dubey T, Srivastava AK, Nagar H, Mishra BK, Mishra SS.

Nephroprotective activity of nelumbo nucifera gaertn. roots, leaves and flowers in gentamicin induced nephrotoxicity. 2014.
29. Kore KJ, Shete RV, Kale BN, Borade AS. Protective role of hydroalcoholic extract of Ficus carica in gentamicin induced nephrotoxicity in rats. International Journal of Pharmacy & Life Sciences. 2011;2(8).
30. Javed S, Khan JA, Khaliq T, Javed I, Abbas RZ. Experimental evaluation of nephroprotective potential of Calotropis procera (Ait) flowers against gentamicin-induced toxicity in albino rabbits. Pak Vet J. 2015;35:222-6.
31. Hozayen W, Bastawy M, Elshafeey H. Effects of aqueous purslane (portulaca oleracea) extract and fish oil on gentamicin nephrotoxicity in albino rats. Nature and Science. 2011;9(2):47-62.
32. Jyothilakshmi V, Thellamudhu G, Kumar A, Khurana A, Nayak D, Kalaiselvi P. Preliminary investigation on ultra-high diluted B. vulgaris in experimental urolithiasis. Homeopathy. 2013 Jul;102(03): 172-8.DOI: 10.1016/j.homp.2013.05.004.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Serum Phosphate Level in Patients with Severe Acute Malnutrition at Nutrition Stabilization Centre, Children Hospital, and Institute of Child Health Multan

Saadia Khan[1], Reema Arshad[2], Saliha Gillani[3], Sundas Irshad[4], Tehseen Ikram[5], Nazia Batool[6]

ABSTRACT

Objective: To evaluate the serum phosphate level of children with severe acute malnutrition and effect of therapeutic feeds (F75 and F100) on serum phosphate levels.

Study Design: Prospective Observational Study.

Place and Duration of Study : The study was conducted at Stabilization center of Children's Hospital and Institute of Child Health Multan from 1st March 2018 to 30th March 2019.

Materials and Methods: The total 270 children with severe acute malnutrition, who were under 5 years of age and admitted to the stabilization center for complicated SAM during study duration were included in the study. Initial management of the patients were started by following WHO protocols for Severe Acute Malnutrition management and the baseline labs along with serum phosphate levels were sent for evaluation. Patients were admitted at Stabilization Centre for the management plan as per guidelines. Once the patients were stabilized in one week approximately the transition towards rehabilitation phase of severe acute management started. Serum phosphate levels were assessed at admission, at stabilization (day 7 of admission) and at the time of discharge. Data was analyzed using SPSS version 21.

Results: The mean age of our patients was 22 ± 2 months. The male to female ratio were 1:2. Hypophosphatemia was documented in 180 (66%) patients with mean 0.96 ± 0.40 mmol/ltr < (1.45 – 1.78mmol/ltr) serum phosphate levels at the time of admission. During transition phase the phosphate levels were 1.1± 0.45 mmol/l and after rehabilitation phase 1.45 ± 0.45 mmol/l on average of 15 days of management. After using F75 and F100 therapeutic feeds in stabilization, transition, and rehabilitation phase 178 (98.9%) children were treated and had normal serum phosphate level at the time of discharge.

Conclusion: Hypophosphatemia is commonly present in SAM children. Introduction of therapeutic feeds F75 and F-100 during stabilization phase and rehabilitation phase significantly improves phosphate levels in SAM children with low phosphate levels.

Key Words: *Hypophosphatemia, Nutrition Rehabilitation, Phosphorous, Severe Acute Malnutrition, Serum phosphate levels, Therapeutic Feeds.*

Introduction

Early childhood less than five years of age is an important period for child survival, growth, and development. Adequate nutritional intake currently is necessary for normal growth and development of children. According to National Nutrition Survey of Pakistan (NNS) 2018, percentage of underweight children was 28.9% (almost one in three children), stunting was seen in 40.2% (almost 4 in 10 children) and wasting in 17.7%.[1,2] Therapeutic feeds as per WHO guidelines for management of SAM are F75; which provides 75 kcal/100ml and F-100 which provides; 100 kcal/100 ml. F-75 is starter feed and F-100 is the growth catch-up formula.[3] Malnourished children during initial stabilization phase are particularly at risk of developing re-feeding syndrome and electrolyte imbalances as hypokalemia, hypomagnesemia, hypophosphate that increases the risk of mortality.[4] During refeeding the body converts from catabolism to anabolism and a shift occurs from fat to carbohydrate metabolism which elicits insulin release and increased cellular

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uptake of electrolytes, including phosphate (i.e., natural occurring form of mineral phosphorous). If the diet contains insufficient amounts of phosphorous this may exacerbate phosphorous depletion. Serum electrolytes are not routinely monitored; therefore, adequate phosphorous content in the diet is essential to prevent depletion. To prevent refeeding syndrome, the WHO's guidelines on in patient management of SAM includes a stabilization phase with a low energy formula i.e., F-75 as well as gradual transition from stabilization phase (F-75) to rehabilitation phase (F-100). F75& F100 Therapeutic Feed by WHO Provided about 35mg/kg/dl of phosphorus on 130ml/kg/day feed from F75 to 156mg/kg/day of phosphorus during rehabilitation phase from 200ml/kg/day 0f F100.[5] In previous studies frequency of phosphate levels in children with SAM varies from 72.9% - 93% with limited local data.[6,7] Studies on hypophosphatemia in SAM children are usually focused on stabilization phase and at first day of admission. Hence it was planned to document phosphorous levels in SAM children and to evaluate improvement in phosphate levels after using therapeutic feeds i.e., F75 and F-100. Hence this study was aimed to evaluate the base line serum phosphate levels in children with SAM and monitoring levels during transition and after rehabilitation phase for improvement after using WHO therapeutic feeding formulas.

Materials and Methods

A prospective observational study was conducted at Stabilization center of Children's Hospital and Institute of Child Health Multan Pakistan from 1st March 2018 to 30th March 2019.

Simple random sampling technique was used and 270 the children whose parents/guardians gave consent and were less than five years and admitted to the Stabilization center with a diagnosis of uncomplicated SAM i.e., weight/height or length <-3SD or Mid Upper Arm Circumference (MUAC) < 11.5cm were included in the study [8]. After taking ethical board IRB letter (CHM-19-13, 03.01.2019) & informed written consent 290 patients fulfilling the inclusion criteria were enrolled during the study duration with SAM admitted to Stabilization Centre. After explaining the risks and benefits of this research, written informed consent was taken from the children's parents/guardians. The children whose guardian refused consent or had chronic illness or secondary malnutrition were excluded from the study.

A questionnaire was designed by the lead researcher and filled by the nursing staff of stabilization center.

All children were managed according to WHO guidelines.[8] During initial stabilization phase F75 i.e 75 kcal/100 ml, 0.9 gm protein /100 ml was used to stabilize the patients orally or through Nasogastric tubes 130 ml/kg/ day depending on the condition of patient. A child feeding 130 ml/kg/day F75 during stabilization phase gets 31mg/kg/day phosphorous. Stabilization phase lasts for upto 7 days usually. During rehabilitation phase a child gets 210ml/kg/day feed of F-100 which contains 152mg phosphorous/kg/day.

After initial registration and admission baseline labs were sent to the clinical laboratory of CH & ICH. Patients were daily monitored for vital signs, weight, height, and edema. Serum phosphate levels were measured at the time of admission, during the transition phase from stabilization to rehabilitation approx. at 7th day of admission according to WHO protocols of SAM management and during rehabilitation prior to discharge. Data was analyzed using SPSS version 21, mean and averages of frequency was calculated and significant value <5 was considered significant.

Operational Definition:

Serum phosphate level (1.45 – 1.78mmol/dl) were normal and <1.45mmol/dl were hypophosphatemia[9].

Results

The total 270 children with Severe Acute Malnutrition up to 5 years of age were included in the study. The mean age of the children included in the research was 22 ± 2 months. The male to female ratio was 1:2 (Table I). Hypophosphatemia was documented in 180 (66%) patients with mean serum phosphate levels at the time of admission was 0.96 ± 0.40 < (1.45-1.78mmol/Ltr) (Table II). After using F75 and F100 therapeutic feeds during transition phase of the management of SAM patients the mean serum phosphate levels were improved to 1.1 ± 0.45 and after rehabilitation phase on an average of 15 days of management serum phosphate levels raised to 1.45 ± 0.45 mmol/lit. Out of 270 children suffering from

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SAM, who were treated with F75 and F100 therapeutic feeds in transition and rehabilitation phase 178 (98.9%) children improved with a normal serum phosphate levels. only two patients still had hypophosphatemia and were further investigated and diagnosed to be suffering from Fanconi syndrome (Table II).

Table I: Baseline Characteristics, Anthropometry, and Complications of SAM Children (n=270)

Characteristics	(n= 270) mean ± SD
Age (mo.)	22.2 ± 2
Males (%)	175 (65.22)
Females	95 (35.78)
Weight (kg)	7.5 ± 1.46
Height / Length (cm)	78.52 ± 10.21
Edema (%)	38 (20)
Mid Upper Arm Circumference (MAUC)	10.49 ± 0.92
Length/Height for age (Z score)	1.94 ± 1.35
Weight for length/ height (Z score)	3.06 ± 1.01

Table II: Serum Phosphate Levels of SAM Children (n=270)

Blood profile	Stabilization Phase (Day 1)	Transition Phase (Day 7)	Rehabilitation Phase (Day 15)
Hypophosphatemia	188 (66%)	96 (35.5%)	2 (0.7%)
Serum Phosphate levels (1.45-1.78m mol/L)	0.98 ± 0.40	1.1 ± 0.45	1.45 ± 0.45

Discussion

This study shows that hypophosphatemia is very common in children with SAM as supported by similar result in other study. [6,10-12] Use of therapeutic feeds (F75 and F100) as per WHO guidelines significantly improves serum phosphate levels; mean 0.96 ± 0.4 to 1.45 ± 0.45 mmol/ltr after an average of 15 day stay.

In our study frequency of hypophosphatemia among SAM children was 66% during stabilization phase, 35.5 % during transition phase and only 0.7 % during rehabilitation phase. This prevalence is significantly lower than reported by the previous studies.[6,10] Data suggest that prevalence of hypophosphate in critically ill children at ICU was 71.6% which prolonged the hospital stay but was not directly linked to increased mortality.[13] However, in the present study we did not include the critically ill children in need of emergency care or on ventilators.

Study by Menezs et.al., also reported significant association between malnutrition and hypophosphatemia.[10] At the time of discharge phosphate levels in our study was 0.7% while in another study it was found to be 17% or more. [5] Higher prevalence in the study by Kimutai et al could be explained by difference in study population as they enrolled only children with edematous malnutrition. Prevalence of edema was 20% in our study which was higher than the study done by Kimutai et al which reported 12.3%.[14]

Early detection and monitoring of serum phosphate levels are mandatory in SAM children to prevent re-feeding syndrome.[15-17] Out of total about 66% children had hypophosphatemia in the present study. It also shows that malnourished children (SAM) must be treated as per WHO guidelines and phosphorous supplementation in stabilization and rehabilitation phase is mandatory using therapeutic feed for better treatment outcome and to reduce Re-feeding syndrome.[18,19] The therapeutic feeds prepared by WHO recipes for Sam children proves to be effective for correcting the phosphate levels of SAM children. Similar results were documented by Menezes et al. [10,16,20]

The study was conducted in a public sector territory care hospital, the findings represent a wide range of population and can therefore be generalized for all SAM children with medical complications during stabilization, transition, and rehabilitation phases. There are a few limitations of the study. Post-discharge phosphate levels were not assessed in these children. A multicenter study with large sample size needs to be conducted in future to evaluate the association of hypophosphatemia among SAM children with other factors.

Conclusion

Hypophosphatemia is commonly present in SAM children. Introduction of therapeutic feeds F75 and F-100 during stabilization phase and rehabilitation phase significantly improved phosphate levels in SAM children with poor phosphate levels.

REFERENCES

1. Bhutta Z, Soofi S, Zaidi S, Habib A. Pakistan national nutrition survey, 2018.
2. Bhutta Z, Berkley J, Bandsma R, Kerac M, Trehan , et. al, A Severe childhood malnutrition. Nat Rev Dis Primers. 2019;3(1):17067-69. doiI: 10.1038/nrdp.2017.67

3. World Health Organization, updates on the management of severe acute malnutrition in infants and children. [Internet]. 2019. http://apps.who.int/iris/bitstream/10665/95584/1/9789241506328_eng.pdf Date of citation, May,2012.
4. Irena A, Mwambazi M, Mulenga V. Diarrhea is a major killer of children with severe acute malnutrition admitted to inpatient set-up in Lusaka, Zambia. J Nutr. 2021;10(1):110. doi: 10.1186/1475-2891-10-110.
5. Selvaraj A, Sinha R, Singh P, Jain A, Seth A, Kumar P. Serum phosphate profile of children with severe acute malnutrition treated with locally prepared therapeutic feeds: A prospective observational study. World J. Clin. Pediatr. 2021.doi: https://doi.org/10.14740/ijcp458
6. Shazly A, Soliman D, Assar E, Behiry E, Gad A. Phosphate disturbance in critically ill children: Incidence, associated risk factors and clinical outcomes. Ann Med Surg (Lond). 2017;21:118-123. doi: 10.1016/j.amsu.2020.07.079.
7. Kalra K, Mital VP, Pal R, Goyal RK, Dayal RS. Serum electrolyte studies in malnutrition. Ind Peds. 2019;12(11):1135-40. PMID: 819367
8. Ahmed S, Ejaz K, Mehnaz A, Adil F. Implementing WHO feeding guidelines for inpatient management of malnourished children. J Coll Physicians Surg Pak. 2014;24(7):493-7. PMID: 25052973
9. Shah S, Irshad M, Gupta N, Kabra S, Lodha R. Hypophosphatemia in Critically Ill Children: Risk Factors, Outcome and Mechanism. Indian J Pediatr. 2019;83(12-13):1379-1385. doi: 10.1007/s12098-016-2188-x.
10. Menezes F, Leite H, Fernandez J, Benzecry S, Carvalho W. Hypophosphatemia in children hospitalized within an intensive care unit. J Intensive Care Med. 2018;21(4):235-9. doi: 10.1177/0885066606287081.
11. Yoshimatsu S, Hossain M, Islam M, Chisti M, Okada M, et al. Hypophosphatemia among severely malnourished children with sepsis in Bangladesh. Pediatrics International. 2019;55(1):79-84. doi: 10.1111/j.1442-200X. 2012. 03724. x.
12. Hother A, Girma T, Rytter M, Abdissa A, Ritz C, et al. Serum phosphate and magnesium in children recovering from severe acute undernutrition in Ethiopia: an observational study. BMC pediatrics. 2019;16(1):1-9. https://doi.org/10.1186/s12887-016-0712-9
13. Bandsma R, Voskuijl W, Chimwezi E, Fegan G, Briend A, et al. A reduced-carbohydrate and lactose-free formulation for stabilization among hospitalized children with severe acute malnutrition: A double-blind, randomized controlled trial. PLoS medicine. 2019;16(2):e1002747. doi: 10.1371/journal.pmed.1002747.
14. Kimutai D, Maleche-Obimbo E, Kamenwa R, Murila F. Hypophosphataemia in children under five years with kwashiorkor and marasmic kwashiorkor. East Afr Med J. 2020;86(7):330-336. doi: 10.4314/eamj.v86i7.54147.
15. Dakshayani B, Divyashree P, Sabpathi S, Kariyappa M. Changes in serum phosphorous level during inpatient treatment of children with severe acute malnutrition. Int J Contemp Pediatr 2020;6:1080-4.
16. Walsh K, Delamare V, McGurk J et al. Development of a legume-enriched feed for treatment of severe acute malnutrition. Wellcome Open Research 2021, 6:206 https://doi.org/10.12688/wellcomeopenres.16771.1.
17. Namusoke H, Hother AL, Rytter MJ, Kaestel P, Babirekere-Iriso E, Fabiansen C, Girma T, et al. Changes in plasma phosphate during in-patient treatment of children with severe acute malnutrition: an observational study in Uganda. Am J Clin Nutr. 2016;103(2):551-558.
18. Manary M, Hart C, Whyte M. Severe hypophosphatemia in children with kwashiorkor is associated with increased mortality. J Paediatr. 2018;133(3): 789–791. doi: 10.1016/s0022-3476(98)70153-2.
19. Ahmed Ny, Doaa S, Effat H, Eman B, Ibrahim A, et. al. Phosphate disturbance in critically ill children: Incidence, associated risk factors and clinical outcomes. Ann Surg.2017; 210 (2):118-123. https://doi.org/10.1016/j.amsu.2017.07.079.
20. Arunpandiyan S, Rajesh S, Preeti S, Anju J, Anju S, et. al. Serum Phosphate Profile of Children with Severe Acute Malnutrition Treated with Locally Prepared Therapeutic Feeds: A Prospective Observational Study**.** Int J Clin. 2021; 10(2): 35-42.doi: https://doi.org/10.14740/ijcp458.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

To Study the Histomorphological Changes in Cerebellar Purkinje Cells after Exposure to Fine Particulate Matter in C57BL/6J Mice

Saima Saleem[1], Shabnam Hamid[2], Abdul Basit Jilani[3], Sana Malik[4], Saima Mumtaz Khatak[5]

ABSTRACT

Objective: To study the histomorphological changes in cerebellar Purkinje cells after exposure to fine particulate matter in C57BL/6J mice.

Study Design: Laboratory based experimental study.

Place and Duration of Study: The study was conducted in the Anatomy department of the Army Medical College, Rawalpindi, from 15 June to 15 September 2020, in coordination with the Military Hospital, Rawalpindi, and the National Institute of Health (NIH), Islamabad.

Materials and Methods: Thirty male and female C57BL/6 mice, 8 weeks of age, weighing 37± 2 gm were obtained from NIH, Islamabad. The animals were divided in two groups, 15 mice in each group (8 male and 7 female) Group A were marked as control, received regular diet and water ad libitum. Group B (experimental group) received dynamic inhalation of 3mg/m³ fine particles (soot) through air circulation for 6h/d for 12 weeks, in plastic cabin measuring 2x2x2 feet fitted with two small fans for evenly distribution of Particulate Matter. After exposure period, the animals were sacrificed. After sectioning the tissue and staining, the microscopic analysis was carried out. Purkinje cell margins were evaluated. Number of Purkinje cells and changes in Purkinje cell size were noted. Data was collected, analyzed with the statistical package for social sciences version 23. A p value ≤ 0.05 was considered significant.

Result: The Purkinje cell margins were observed to become irregular and corrugated in the experimental groups B when compared with control group A. The number and size of Purkinje cells also showed difference when compared to the control group A.

Conclusion: The present study concluded that fine particulate matter induces changes in histomorphological features of mice cerebellar tissue including Purkinje cells.

Key Words: *Air Pollution, Cerebellum, Fine Particulate Matter, Purkinje Cells.*

Introduction

Air pollution is a major public concern that has adverse health and economic effects. Fine particulate matter containing many chemical components within these gradients, which can differ dynamically with time and space and with an aerodynamic diameter of < 10µm, is often associated with air pollution in large cities. The presence of particulate matter is responsible for more damage to human health as compared to ground level ozone.[3,4] Aerodynamic diameter is usually known as particulate matter (PM), ranging from coarse (between 2.5 and 10µm PM10) to fine (<2.5µm PM2.5) to ultrafine (<100nm or 0.1µm; UFP). Ambient UFPs, which result mainly from ignition processes, include the burning of fossil fuels, has primary source in the form of automobile emissions.[5,6] In several parts of the world, atmospheric air quality remains a most important concern, despite attempts to regulate atmospheric pollutant pollution. Total percentage of world's population exposed to pollutant concentrations above the recommended level of the World Health Organization (WHO) is more than eighty percent and from household related sources it accounts for about 4 million and about 3.6 million deaths can be due to environmental air pollution. In addition, air pollution can alter habitats, destroy constructions and

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memorials, as well as affect the energy balance of the planet and thus causes change in climate.[7] PM can be released directly into the atmosphere, called primary PM or it can be produced from gaseous precursors known as secondary PM. The scale of PM ranges from groups of molecules with a diameter of a few nanometers up to abrasion products of a micrometer. In the varying composition and characteristics of PM measured at source and receptor sites, this large dimensional range is expressed. Particulate Matter species are important atmospheric components and play a role in the climate system of the Earth. Some components of PM species absorb visible light and make the atmosphere warm i.e. black carbon, while other species, i.e. organic substances and sulphates reflect sunlight back into space and cool the environment.[8]

Air pollution is a multidimensional environmental toxin which through various pathways can attack the CNS. Inflammation and oxidative stress have been recognized as the common and essential mechanisms by which air pollution causes harm, including adverse effects in the CNS. It is known that black carbon can cause inflammation or that exposure to particulate matter in mice induces the development of pro-inflammatory cytokines (IL1-b, TNFa, and IFNg) in olfactory bulbs.[9,10] When neuroinflammation has started, it causes neuron damage and loss, stimulates microglia, leading to cytokine and ROS production, and causes damage and dysfunction of the blood brain barrier. Both of these events contribute to lipid peroxidation, astrogliosis, and damage to DNA and CNS diseases.[11] Epidemiological studies have linked air pollution with cognitive impairments reduced mental development index and IQ scores, attention-related disorders, anxiety/depression , nonverbal reasoning deficits, autism spectrum disorder (ASD) and delayed psychomotor development. Programmed cell death, or apoptosis, is an evolutionarily conserved process triggered by a variety of stimuli.[12] Exposure to PM has been associated with neuronal shrinkage, micro abscesses, and cerebellar edema.[1]

Studies have focused the histological effect of fine particulate matter on multiple organs for example lungs, heart, nasal mucosa, maternal exposure, and some components of brain. Despite considerable literature there is still a need for studies, which should investigate the histomorphological changes in brain because of rapidly increasing rate of dispersion of air pollutants, especially in the developing country like Pakistan. So, a research was planned to study the histomorphological changes in cerebellar Purkinje cells after exposure to fine particulate matter in C57BL/6J mice.

Materials and Methods

This study was conducted in Rawalpindi, Department of Anatomy, Army Medical College, in collaboration with the National Institute of Health (NIH), Islamabad, from June 2020 to September 2020, after getting approval by the Army Medical College, Rawalpindi, and the National University of Medical Sciences, Islamabad, Ethical Review Committee (ERC/ ID/ 10). Laboratory based experimental study was carried out and non-probability convenience sampling technique was used. Thirty male and female C57BL/6 mice, 8 weeks of age, weighing 37± 2 gram were procured from NIH, Islamabad. They were kept in separate cages in animal house of NIH under standard laboratory conditions with temperature 22 ± 2° C and 12-hour light/dark cycle. The animals were fed on standard laboratory rat chow and water *ad libitum.* Mice with any obvious injury and disease were excluded. The animals were divided in two groups, 15 mice in each group (8 male and 7 female).

Group A served as control. They received standard diet and water *ad Libitum.*

Group B (experimental group). Mice in experimental group B received dynamic inhalation of 3mg/m³ fine particles in the form of carbon soot through air circulation for 6h/d for 12 weeks.[13,14] 15 mice (8 males and 7 females) in two separate cages were placed in a plastic cabin measuring 2x2x2 feet fitted with two small fans opposite each other in NIH Islamabad. Air circulation was maintained by fan running at moderate speed. The particulate matter was evenly dispersed in the cabin through fan.[15, 16] The dose of particulate matter was calculated in mg/number of breaths in one minute. The dose was weighed by using digital precision balance. Fine particulate matter was purchased from Amazon.com. The particle name was Carbon powder with normal sensitivity and refractive index of 2.4. The size of the particle ranged from 0.020 to 2000.000µm with specific surface area of 0.555m^2/g. At the end of 03 months, after 18hrs of last exposure the animals

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were euthanized by placing the animals in the jar with cotton soaked in ether.[17] The animals were positioned on a dissecting board and decapitated by cutting the neck close to the head with the help of a sharp blade. Skin of the skull was removed by giving a longitudinal incision in the midline of the head. With the help of a bone cutter the cranium was opened along the sagittal suture and the bones were cracked open by using a forceps in the center. Brain was exposed and carefully lifted at its anterior end. Optic nerves were identified, and brain was separated from them and removed from the cranium by detaching from the spinal cord. The brain was placed on the dissection board and the cerebellum was identified. The cerebellum was separated from the cerebrum by locating and cutting through the layer of duramater (tentorium cerebelli) between the two. The middle cerebellar peduncle was identified, and the cerebellum was separated from the brain stem by cutting through this peduncle.

After washing the specimens with normal saline, the entire cerebellum was put into 10% formalin enough to cover all the tissue (about 3times the volume of tissue). From each cerebellum, splitting it into upper and lower halves, three transverse sections were obtained. All parts have been stored in tissue tek cassettes and processed in the automated tissue processor LEICA TP 1020. Sections were processed and cleared in xylene through the rising concentration of alcohol from 70 percent to 100 percent. For penetration and embedding, paraffin wax was used with a melting point of 58oC. LEICA EG 1160 Paraffin Embedding Center was used for this purpose. The blocks were allowed on a cold plate to solidify.[18] The rotary microtome (Leica rm 255) was used to cut 5µm thick cross sections. At 45˚C, pieces were floated in a hot water bath and then placed on glass slides. For 30 minutes, the slides were held in a slanting position to remove excess water and sections were dried at 65°C in a hot air oven for 60 minutes. Identification details were inscribed using the diamond tip pencil at the extreme corner of the glass slides. With the Leica auto-Stainer X, the sections were stained. Hematoxylin and Eosin (H&E) stains have been used to study cerebellum histology. Purkinje cell margins were observed in complete Purkinje cell layer in one slide per specimen at 40X magnification. The cell margins were recorded as regular (having normal pyriform somata with pale nuclei and prominent nucleoli) or irregular (having shrunken Purkinje cell bodies with irregular outline, deeply stained cytoplasm and hardly identified nuclei).[19] Number of cells was counted at high power field in complete Purkinje cell layer in one slide per specimen.[20] Size of Purkinje cells was measured by taking ten consecutive high-power fields from left to right and three cells per field were considered. Both length and width of Purkinje cell was calculated with the help of micrometry and mean was taken. It was compared with the control.[21] Micrometry is a technique to measure microscopic organisms and parameters using calibrated scale i.e., ocular micrometer and stage micrometer. The linear unit of measurement in micrometry is micron. One micron is equal to 1/1000mm. With the help of the stage micrometer, the eyepiece scale was calibrated, and the former was then used for measurements. By comparing the ocular micrometer scale with a calibrated stage micrometer, the eyepiece micrometer was calibrated. Once calibrated the ocular micrometer was used for measurement. 0.25 micrometer calibration factor was obtained for 40X and was valid for the optical combination. The stage micrometer was removed and on the microscope stage, slides of the cerebellum were placed. For the Purkinje cell size, the number of eyepiece divisions was counted and multiplied by 0.25. Using the eyepiece of the Olympus DP22 light microscope, the Sony digital camera (16 megapixels) was used. The zoom of camera was 3X. The images were corrected and modified by Photo Scape software. The magnification was calculated according to the formula below:

Magnification Power of eye piece (10) x Power of objective (10&40) x Camera zoom (3x)

Statistical package for data analysis SPSS version 23 was used to analyze data. Intergroup comparison for quantitative variables was done by independent sample t-test. A p value ≤ 0.05 was considered significant. Results were represented as mean ± standard deviation (mean ± SD). Qualitative variables were presented by frequency and percentage. Chi-square test was applied for comparison of qualitative variables

Results

Between the periods of 15 June 2020 to 15 September 2020, 15 out of 30 mice with average weight of 37±2 gram were given dynamic inhalation of 3mg/m³ fine particles through air circulation for 6h/d for 12 weeks. The mice were placed in a plastic cabin measuring 2x2x2 feet fitted with two small fans opposite each other in NIH Islamabad. Air circulation was maintained by fans running at moderate speed. The particulate matter was evenly dispersed in the cabin through fans. Till the end of the experiment, all the animals remained alive. The purkinje cells in control group A showed regular margins i.e., irregularity ratio was 0%.Whereas in experimental group B 73% of purkinje cells had irregular and distorted margins and 27% had regular margins (Fig l). The intergroup comparison between A and B was done by Fisher's exact test which showed significant results with p-value 0.000 (Table I).

Mean ± SD number of Purkinje cell number in control group A was 392 ± 62 whereas in experimental group B the mean ± SD of Purkinje cell number was 328 ± 67 (Fig. ll). The intergroup comparison between group A and B was done by independent sample t-test which yielded significant result with p-value 0.012 (Table ll). Mean ± SD size of Purkinje cells in control group A was 6.0 ± 0.4 µm whereas in experimental group B the mean ± SD size of Purkinje cells was 3.2 ± 0.36 µm (fig III). The intergroup comparison between group A and B was done by independent sample t-test which showed significant result with p-value 0.000 (Table ll).

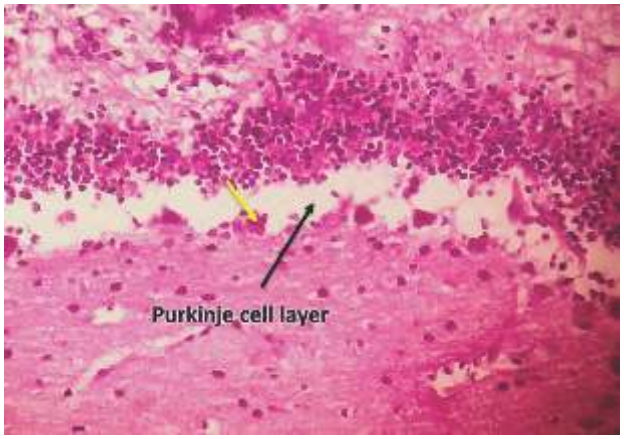

Fig. 1: Photomicrograph of Histological Section of Cerebellum in B2F Showing Purkinje Cell Layer (black arrowhead). Purkinje Cell Margin is Shown by Yellow Arrowhead. H&E 1200X

Table l Frequency of Purkinje Cell Margin Among the Control Group A and Experimental Groups B.

Parameter	Finding	Group A n=15	Group B n=15	P-value A v B
Margins of Purkinje cell	Regular	100%	4(27%)	0.000**
	Irregular	0%	11(73%)	

p-value ≤0.05Significant*
p-value <0.001Highly significant**

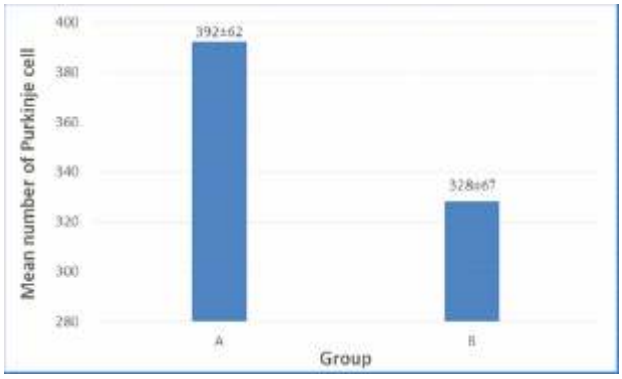

Fig. 2 : Bar Chart Showing Intergroup Comparison of Mean Number of Purkinje Cells among Control Group A and Experimental Group B (P- Value 0.012)

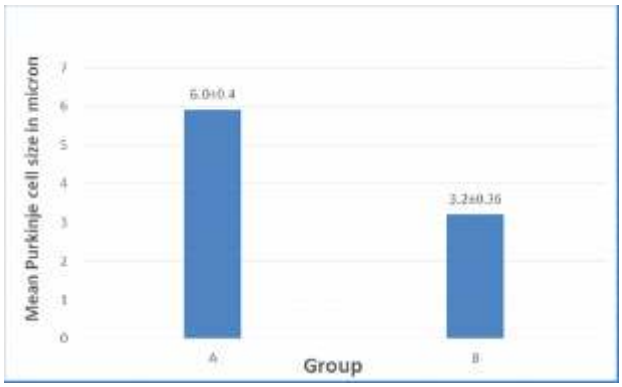

Fig. 3 : Bar Chart Showing Intergroup Comparison of Mean Size of Purkinje Cells Among Control Group A And Experimental Groups B (P-Value 0.000)

Table ll: Mean Cell Count and Cell Size of the Control Group A and Experimental Groups B.

Parameter	Group A n=15	Group B n=15	P- value
Number of Purkinje cell	392 ± 62	328 ± 67	0.012*
Size of Purkinje cell	6.0 ± 0.4µm	3.2 ± 0.36µm	0.000**

P value < 0.05 significant*
P value < 0.01 highly significant**

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Discussion

The aim of this study was to assess the effects of fine particulate matter exposure on the histomorphology of mice cerebellar Purkinje cells for which thirty C57BL/6 mice of 8 weeks of age were selected. All animals remained alive during the experimental period. Regarding the histomorphological examination the Purkinje cell margins were found to be smooth and regular in control group A, whereas in experimental groups B they were found to be highly irregular and corrugated, shrunken with deeply stained cytoplasm ($p<0.05$). These results were similar to a study conducted by El-Dien[19-22] in which the purkinje cell margins were irregular after exposure to fluoride which has same mechanism of action as particulate matter i.e. oxidative stress leading to neurodegenerative diseases. There was decreased number of Purkinje cells in experimental group B as compared to control group A with P-value 0.012. The decrease in number of Purkinje cells is most probably due to degenerative changes and stress imposed by exposure to FPM and also due to process of apoptosis stimulated by exposure to fine particulate matter as documented by Xiaozheng Zhu[23]. Also, there is an assumption that due to presence of spongiosis the Purkinje cells might have displaced from their normal place creating empty spaces in Purkinje cell layer. These results are in correlation with a study conducted Wallauer[20] in which there is decreased number of Purkinje cells after exposure to tobacco smoke. In another study done by Kivrak[21-24] in which there was reduced number of Purkinje cells after exposure to radiation which has similar mode of action as particulate matter. The size of Purkinje cells was decreased in experimental group B as compared to control group A with P-value 0.000. This is most probably due to degenerative changes in cells and stress imposed by exposure to particulate matter and due to development of spongiosis which compresses the cells. The results are similar to a study in which there is decrease in size of cells after exposure to radiation[21] with P-value <0.01 and also to a study conducted to find out quantitative analysis of purkinje cells in nude mice[25].

Conclusion

The present study concluded that fine particulate matter in the form of carbon soot induces changes in histomorphological features of mice cerebellar tissue. The major effects of exposure included both neurodegenerative and neuroinflammatory changes along with decreased size and number of Purkinje cells, which were presented by irregular and distorted margins.

Ethics statement

The rules and regulations regarding the handling and care of animal set forth by the ethics committee of the Army Medical College / National University of Medical Sciences were followed for the research (Dated: 2nd Feb 2020, NO: ERC/ID/10).

Author contribution

SH designed the project, SM & SMK helped in experimental procedure, ABJ analyzed the data. All authors approved the final version of manuscript.

Conflict of interest

Author has no conflict of interest to declare

Disclosure

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REFERENCES

1. Ku T, Ji X, Zhang Y, Li G, Sang N. PM2. 5, SO2 and NO2 co-exposure impairs neurobehavior and induces mitochondrial injuries in the mouse brain. Chemosphere. 2016;163:27-34. doi.org/10.1016/j.chemosphere.2016.08.00.
2. Lin C-H, Nicol CJ, Wan C, Chen S-J, Huang R-N, Chiang M-C. Exposure to PM2. 5 induces neurotoxicity, mitochondrial dysfunction, oxidative stress and inflammation in human SH-SY5Y neuronal cells. NeuroToxicology. 2022;88:25-35. doi.org/10.1016/j.neuro.2021.10.009.
3. Kim K-H, Kabir E, Kabir S. A review on the human health impact of airborne particulate matter. Environment international. 2015;74:136-43. doi.org/10.1016/j.envint.2014.10.005.
4. Brauer M, Amann M, Burnett RT, Cohen A, Dentener F, Ezzati M, et al. Exposure assessment for estimation of the global burden of disease attributable to outdoor air pollution. Environmental science & technology. 2012;46(2):652-60. doi.org/10.1021/es2025752.
5. Morris-Schaffer K, Merrill A, Jew K, Wong C, Conrad K, Harvey K, et al. Effects of neonatal inhalation exposure to ultrafine carbon particles on pathology and behavioral outcomes in C57BL/6J mice. Particle and fibre toxicology. 2019;16(1):10. doi.org/10.1186/s12989-019-0293-5.
6. Umezawa M, Onoda A, Korshunova I, Jensen AC, Koponen IK, Jensen KA, et al. Maternal inhalation of carbon black nanoparticles induces neurodevelopmental changes in mouse offspring. Particle and Fibre Toxicology. 2018;15:1-18. doi.org/10.1186/s12989-018-0272-2.

7. Rao S, Klimont Z, Smith SJ, Van Dingenen R, Dentener F, Bouwman L, et al. Future air pollution in the Shared Socio-economic Pathways. Global Environmental Change. 2017;42:346-58. doi.org/10.1016/j.gloenvcha.2016.05.012.
8. Klimont Z, Kupiainen K, Heyes C, Purohit P, Cofala J, Rafaj P, et al. Global anthropogenic emissions of particulate matter including black carbon. Atmospheric Chemistry and Physics Discussions. 2017;17(14):8681-723. doi.org/10.5194/acp-17-8681-2017.
9. Morris-Schaffer K, Sobolewski M, Allen JL, Marvin E, Yee M, Arora M, et al. Effect of neonatal hyperoxia followed by concentrated ambient ultrafine particle exposure on cumulative learning in C57Bl/6J mice. Neurotoxicology. 2018;67:234-44. doi.org/10.1016/j.neuro.2018.06.006.
10. Morris-Schaffer K, Merrill A, Jew K, Wong C, Conrad K, Harvey K, et al. Effects of neonatal inhalation exposure to ultrafine carbon particles on pathology and behavioral outcomes in C57BL/6J mice. Particle and fibre toxicology. 2019;16(1):1-15. doi.org/10.1186/s12989-019-0293-5.
11. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends in neurosciences. 2009;32(9):506-16. doi.org/10.1016/j.tins.2009.05.009.
12. Qin G, Wu M, Sang N. Sulfur dioxide and benzo (a) pyrene trigger apoptotic and anti-apoptotic signals at different post-exposure times in mouse liver. Chemosphere. 2015;139:318-25. doi.org/10.1016/j.chemosphere.2015.06.05.
13. Onoda A, Takeda K, Umezawa M. Dose-dependent induction of astrocyte activation and reactive astrogliosis in mouse brain following maternal exposure to carbon black nanoparticle. Particle and fibre toxicology. 2017;14(1):4. doi.org/10.1186/s12989-017-0184-6.
14. Zhang S, Meng P, Cheng S, Jiang X, Zhang J, Qin X, et al. Pregnancy exposure to carbon black nanoparticles induced neurobehavioral deficits that are associated with altered m6A modification in offspring. Neurotoxicology. 2020;81:40-50. doi.org/10.1016/j.neuro.2020.07.004.
15. Li D, Zhang R, Cui L, Chu C, Zhang H, Sun H, et al. Multiple organ injury in male C57BL/6J mice exposed to ambient particulate matter in a real-ambient PM exposure system in Shijiazhuang, China. Environmental pollution. 2019;248:874-87. doi.org/10.1016/j.envpol.2019.02.097.
16. Li H, Zhao Z, Luo X-S, Fang G, Zhang D, Pang Y, et al. Insight into urban PM2. 5 chemical composition and environmentally persistent free radicals attributed human lung epithelial cytotoxicity. Ecotoxicology and Environmental Safety. 2022;234:113356. doi.org/10.1016/j.ecoenv.2022.113356.
17. Takehara H, Makita M, Tanaka R, Tsuchiya M, Naya M, Hayashi M. Lung toxicity assessment using bronchoalveolar lavage fluid and pleural lavage fluid cytology by intratracheal treatment in rats. The Journal of toxicological sciences. 2014;39(1):141-5. /doi.org/10.2131/jts.39.141.
18. Suvarna KS, Layton C, Bancroft JD. Bancroft's Theory and Practice of Histological Techniques E-Book: Elsevier Health Sciences; 2018.
19. El-Dien S, El Gamal DA, Mubarak HA, Saleh SM. Effect of fluoride on rat cerebellar cortex: light and electron microscopic studies. Egypt J Histol. 2010;33:245-6.
20. Wallauer MM, Huf F, Tortorelli LS, Rahmeier FL, Carvalho FB, Meurer RT, et al. Morphological changes in the cerebellum as a result of ethanol treatment and cigarette smoke exposure: A study on astrogliosis, apoptosis and Purkinje cells. Neuroscience letters. 2018;672:70-7. doi.org/10.1016/j.neulet.2018.02.047.
21. Kivrak EG, Altunkaynak BZ, Alkan I, Yurt KK, Kocaman A, Onger ME. Effects of 900-MHz radiation on the hippocampus and cerebellum of adult rats and attenuation of such effects by folic acid and Boswellia sacra. Journal of microscopy and ultrastructure. 2017;5(4):216-24. doi.org/10.1016/j.jmau.2017.09.003.
22. Lopes GO, Martins Ferreira MK, Davis L, Bittencourt LO, Bragança Aragão WA, Dionizio A, et al. Effects of fluoride long-term exposure over the cerebellum: global proteomic profile, oxidative biochemistry, cell density, and motor behavior evaluation. International journal of molecular sciences. 2020;21(19):7297. doi.org/10.3390/ijms21197297.
23. Zhu X, Ji X, Shou Y, Huang Y, Hu Y, Wang H. Recent advances in understanding the mechanisms of PM2. 5-mediated neurodegenerative diseases. Toxicology Letters. 2020. doi.org/10.1016/j.toxlet.2020.04.017.
24. Hasan I, Jahan MR, Islam MN, Islam MR. Effect of 2400 MHz mobile phone radiation exposure on the behavior and hippocampus morphology in Swiss mouse model. Saudi Journal of Biological Sciences. 2022;29(1):102-10. doi.org/10.1016/j.sjbs.2021.08.063.
25. Bakalian A, Delhaye-Bouchaud N, Mariani J. Quantitative analysis of the Purkinje cell and the granule cell populations in the cerebellum of nude mice. Journal of neurogenetics. 1995;9(4):207-18. doi.org/10.3109/01677069509084157.

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Seroprevalence of Dengue Virus by Detection of IgG Antibodies: A Tertiary Care Hospital Study in Rawalpindi

Muhammad Ali Rathore, Memoona Arif, Eijaz Ghani, Saifullah Khan Niazi, Faraz Ahmed, Hammad Hussain

ABSTRACT

Objective: To determine the seroprevalence of dengue virus infection by detecting IgG antibodies in a tertiary care hospital in Rawalpindi.

Study Design: Cross sectional study.

Place and Duration of Study: Virology department, Armed Forces Institute of Pathology Rawalpindi, July 2021 to December 2021.

Materials and Methods: A total of one hundred and fifty healthy general population of Rawalpindi aged 15 – 45 years were included in this study. Enzyme Linked Immunosorbent Assay (ELISA) was performed for the detection of dengue immunoglobulin G (IgG) antibody in serum samples of patients. Statistical Package for Social Sciences (SPSS) version 25 was used to analyze the data.

Results: Among 150 patients, 71 (47.3%) were males and 79 (52.7%) were females. Out of total patients, 50 (33.3%) were positive and 100 (67.7%) were negative for dengue IgG antibodies. Majority of dengue IgG positive patients were 25-40 years of age. Acute febrile illness was present among 37 (24.6%) patients and was absent in 113 (75.3%) patients. Participants provided history of presence of waste points and stagnant water in surrounding areas of 84 (56%) patients.

Conclusion: This study shows that there was a high exposure of dengue virus in Rawalpindi population. This can be problematic from public health point of view in future as sensitized population against dengue virus is more prone to dengue fever and serious effects of dengue virus reinfection.

Key Words: *Dengue Fever, Dengue Virus, Enzyme Linked Immunosorbent Assay, Immunoglobulin G, Seroprevalence.*

Introduction

Dengue fever (DF) is a significant public health issue worldwide, affecting millions of individuals annually including Pakistan.[1] In Pakistan last major outbreak occurred in 2019, resulting in 53000 cases and 95 reported deaths.[1] Outbreaks of DF in Rawalpindi region became more frequent after 2011 outbreak.[2]

The World Health Organization (WHO) classified DF in 1997 and revision of this classification was done in 2009 to make it more inclusive. DF was divided into three categories in 1997 as DF, undifferentiated fever, and Dengue hemorrhagic fever (DHF).[3] Dengue was categorized later in 2009 as with warning signs or without warning signs and severe dengue. Fever and at least two clinical symptoms or any warning signs are required for dengue diagnosis.[4] More than 350,000 people have been admitted to hospitals across Asia since 1956, with nearly 12000 reported deaths.[5] After 2006, epidemics of dengue occurred each year which has increased populations of infected people with this virus in different cities of Pakistan. In upcoming years, it is expected to become a health concern in Asia including Pakistan.[6]

DF spreads by mosquitos mainly in tropical and sub-tropical regions because of its peri-domestic breeding. Dengue virus is caused by the Aedes aegypti, which also causes yellow fever. The growth and reproduction of this vector is associated with freshwater reservoirs. International travelers were one of the main facilitators in the global spread of this disease.[7]

Dengue cases have increased up to 30 folds in past 50 years and approximately half of the world's population in over 100 countries is affected by this disease. The first confirmed and reported cases of dengue fever took place in Asia, North America, and Africa consecutively in 1779-1780. According to WHO, an expected 1.3 billion number of cases DF were reported between 1996 to 2005.[8] Global travel was mainly responsible for rapid spread of this

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disease. The total number of cases of dengue virus infection according to WHO gradually increased from 505,430 in 2000 to more than 2.4 million in 2010 and 5.2 million in 2019. This increase occurred during the previous 20 years and 960 fewer deaths were reported in 2000 as compared to 4032 in 2015.[9]

The basis for the laboratory diagnosis of dengue infection is by detection of glycoprotein dengue NS1 antigen, dengue anti-IgM, anti-IgG, and polymerase chain reaction (PCR) for the detection of DENV. The production of antibody against DENV infection depends on the immune status of the host. Patients with early-stage dengue infection have significant amounts of the nonstructural protein (NS1) in their sera, and this presence is persistent from day 1 to day 9 after the onset of symptoms. In cases of dengue infection, IgM may become detectable on days 4–5 of illness and last for 12 weeks, but IgG develops by day 14 and may last a lifetime. The IgG rises within 1 to 2 days following the development of symptoms in secondary dengue infection, along with the IgM antibodies.[10]

The four DENV serotypes are 1, 2, 3, and 4. Secondary infection caused by another serotype leads to increased chances of severe dengue due to antibody dependent enhancement.

Several studies have been conducted on dengue virus seroprevalence globally and locally, there is still a lack of data on the prevalence of the virus in the Rawalpindi region of Pakistan. This article aims to fill this research gap by conducting a study on the seroprevalence of dengue virus by detection of IgG antibodies in a tertiary care hospital in Rawalpindi.

Therefore, this study was conducted to establish the exposure of Rawalpindi population to previous dengue infection by detecting IgG. Previous exposure of dengue infection determines the seroprevalence and burden of the disease. Individual with positive IgG is more vulnerable for severe dengue reinfection due to antibody dependent enhancement. Reinfection with dengue should be prevented by prompt management.

Materials and Methods

This cross-sectional study was carried out in the Virology department of the Armed Forces Institute of Pathology Rawalpindi, Rawalpindi, from July 2021 to December 2021. Approval from Institutional Review Board (IRB) (BS AHS/VIR-2/READ-IRB/21/625) was taken. The sampling technique was non-probability consecutive sampling. Sample size was calculated by confidence interval of 95%, a margin of error of 5%, and a reported prevalence of dengue IgG of 18% from a prior local study of Pakistan.[11] The sample size of 150 was estimated by the WHO sample size calculator.

Patients of either gender, aged between 15 to 45 years and resident of Rawalpindi were included in this study. Patients with autoimmune diseases, acute febrile illness or those who were not willing were excluded. Patients were informed about the study's purpose and written consent was taken.

The demographics information of the participants included age, gender, and history of febrile illness during last one-year, previous history of dengue virus infection and environmental surroundings such as presence of waste points and stagnant water were recorded. Participants were selected from general population of Rawalpindi.

Blood specimen of participants was drawn at Armed Forces Institute of Pathology, Rawalpindi and was transported to Virology department. Specimen was centrifuged at 3500 rpm for 4 minutes to separate serum. Indirect manual ELISA with dengue ELISA IgG kit of Vircell Spain was used for the detection of IgG antibody against dengue virus and optical density was analyzed by ELISA plate reader.[12]

The Statistical Package for the Social Sciences (SPSS) version 25.00 was used to analyze the data. For continuous variables, mean and SD were determined. Categorical variables were calculated by using frequency and percentages. P-value of ≤ 0.05 considered statistically significant.

Results

Among total 150 patients, 71 (47.3%) were males and 79 (52.7%) females. Dengue IgG antibodies were detected in 50 (33.3%) patients. Patients of different age groups showed positive seroprevalence, however middle age group showed higher frequency of dengue IgG detection as shown in figure 1. Age group (26-35 years) showed the highest prevalence of 25 (59.5%) cases whereas age group (15-25 years) showed the least prevalence of 10 cases (37%). About 37 (24.7%) patients had a history of acute febrile illness during the last 1 year, whereas 113 (75.3%) had no such history. The presence of waste points and stagnant water within 400 meters among

seropositive individuals was observed in 84 (56%).

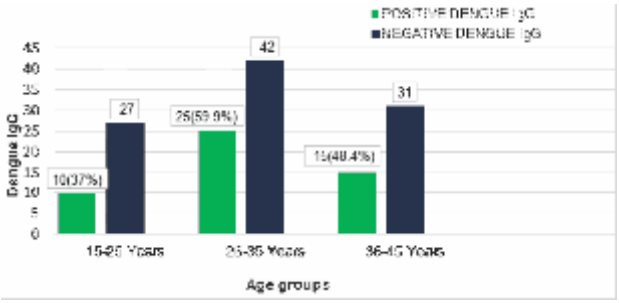

Fig. 1: IgG Seropositivity in Relation with Different Age Groups

Discussion

Dengue fever is a major public health concern worldwide, and seroprevalence studies are essential in understanding the spread and impact of the diseases.

Pakistan is one the countries with highest incidence of dengue fever according to WHO. Our study determined seroprevalence of dengue IgG in Rawalpindi. Dengue seroprevalence determine the percentage of individuals in population who have been infected with a dengue virus.

In our study, 150 samples were collected to determine the seroprevalence of dengue virus. There were 47.3% males and 52.7% females. The IgG antibody was detected using enzyme linked immunosorbent assay. Dengue IgG antibody was found in 33.3% patients. According to our results, out of 50 positive samples, 35.2% were males and 31.6% were females. This showed that prevalence of infection among males was approximately equal to females. Age group (26-35 years) showed the highest prevalence and 59.5% were positive for IgG antibodies against dengue virus. The age group (15-25 year) showed the least prevalence of 37%. In majority of cases waste points and stagnant water was present near the homes of people which also indicate to the problem of DF in urban and semi urban regions. These waste and stagnant water help in the propagation of mosquitoes which in turn help in spreading DENV. A study was conducted by Jyothi *et al* in India.[13] Five hundred and twenty serum samples were collected from clinically suspected dengue fever cases. A total of 11.9 % of the total tested serum samples were positive for one or more of the three serological markers (NS1, IgM, and IgG). Among 62 positive serum samples, 62.9% were positive for NS1, 11.3% were positive for dengue IgM, and 4.9% cases were positive for dengue IgG. This study shows low seroprevalence of Dengue IgG in comparison with our study.

A study was conducted by Eshetu D *et al* in 2016, in Ethiopia on dengue seropositivity and related risk factors.[14] In this study, risk factors associated with prevalence of DENV were evaluated. A total of 529 samples of patients having acute febrile illness were taken in 2016 and tested for dengue IgG and IgM antibodies. The prevalence of IgG and IgM antibody was 25.1% and 8.1% respectively which is lower in comparison with our study. Overall, people of age group 15-35 years accounted for 47.45 % of cases whereas 19.86% of cases were seen in age group 31-45 years. This showed that age group of young adults was more frequently infected by this virus as compared to other age groups.

A study conducted in Multan, Pakistan by Mukhtar et al, shows that out of 689 dengue suspected cases, 54.1% were positive for dengue IgG (27.6%) and IgM (54.7%). These results show high seroprevalence of dengue infection in comparison with our study.[15]

A study conducted in Lahore, found that seroprevalence of dengue IgG was 55.8% in the general population. This study also found that the prevalence was higher in males 62.2% than in females 49.3%. This study shows high seroprevalence of Dengue IgG in comparison with our study.[16]

In a study conducted in the district of Mardan in Khyber Pakhtunkhwa in 2017, a total number of 1978 patients were studied who were infected with DENV.[17] A total of 302 were positive (208 males and 94 females) for antibodies against DENV. Number of cases of dengue virus infection was higher in males 10.5% than in females 4.75%. The low prevalence in comparison with our study was found in this study of IgG and IgM antibodies was 23.84% and 53.9% respectively. The maximum amount of positivity of 47 % was in patients of age group 15 to 35 years.

There has been a variation in seroprevalence of dengue among different age groups and gender in previous studies. [18] Dengue viral infection prevalence is not similar but is different in various cities across Pakistan.[19] Our study showed that a considerable proportion of population of Rawalpindi might be exposed to DENV in the past which was detected by

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IgG antibodies. The population is especially at risk in future but to an outbreak by a different serotype of DENV. It is crucial to carry out extensive seroprevalence studies to ascertain the true scale of the issue. Timely identification can aid in reducing the morbidity and mortality rates. Neglecting the matter could result in significant dengue-related complications.

Limitations

The study was based on single center data in Virology department of the Armed Forces Institute of Pathology Rawalpindi. Sample size was small, and the duration of study was short which could have affected the results.

Conclusion

In this study it is concluded that there is a high exposure of DENV in Rawalpindi population. This can be problematic from public health point of view in future as sensitized population against dengue virus is more prone to serious effects of dengue virus reinfection with a different serotype.

Recommendations

Both large-scale epidemiological studies and vector control initiatives are urgently required. It is a concerning scenario, and if it is not handled by taking precautions, dengue will probably become a much bigger health issue in the years to come.

REFERENCES

1. Ali L, Gul Z, Ijaz A, Khalid N, Zeb F, Afzal S, et al. An overview of dengue viral infection circulating in Pakistan. J Vector Borne Dis 2022; 59:109-14.
2. Hussain AB, Muhammad Ali Rathore MA, Khan FA. Seasonal and demographic aspects of dengue outbreak of 2012 in Northern Pakistan. Pakistan Journal of Pathology 2011;22(3):112-117
3. World Health Organization. Dengue hemorrhagic fever: Diagnosis, treatment, prevention and control, 2nd edition. WHO, Geneva 1997. http://apps.who.int/iris/bitstream/10665/41988/1/9241545003_eng.pdf
4. World Health Organization. Dengue: Guidelines for diagnosis, treatment, prevention and control, new edition. WHO: Geneva 2009. http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf?ua=1.
5. Gubler DJ. Dengue and dengue hemorrhagic fever: its history and resurgence as a global public health problem. In: Gubler DJ, Kuno G, editors. Dengue and dengue hemorrhagic fever. Oxford: CAB International; 1997. p. 1-22.
6. Khan J, Khan I, Ghaffar A, Khalid B. Epidemiological trends, and risk factors associated with dengue disease in Pakistan (1980-2014): a systematic literature search and analysis. BMC Public Health. 2018 Jun 15;18(1):745. doi: 10.1186/s12889-018-5676-2. PMID: 29907109; PMCID: PMC6003098.
7. Liebig J, Jansen C, Paini D, Gardner L, Jurdak R. A global model for predicting the arrival of imported dengue infections. PLoS ONE 2019;14(12): e0225193. https://doi.org/10.1371/journal.pone.0225193.
8. Zeng Z, Zhan J, Chen L, Chen H, Cheng S. Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017. E Clinical Medicine. 2021 Jan 6; 32:100712. doi: 10.1016/j.eclinm.2020.100712.
9. World Health Organization. Dengue and severe dengue. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
10. Raafat N, Blacksell SD, Maude RJ. A review of dengue diagnostics and implications for surveillance and control. Trans R Soc Trop Med Hyg. 2019 Nov 1;113(11):653-660. doi: 10.1093/trstmh/trz068.
11. Raza FA, Ashraf S, Hasnain S, Ahmad J, Iqbal M. Dengue seroprevalence and its socioeconomic determinants in Faisalabad, Pakistan: a cross-sectional study. Revista da Sociedade Brasileira de Medicina Tropical. 2018 Aug;51(4):503–7.
12. Domingo C, Alves MJ, de Ory F, Teichmann A, Schmitz H, Müller R, Niedrig M. International external quality control assessment for the serological diagnosis of dengue infections. BMC Infect Dis. 2015 Apr 1; 15:167. doi: 10.1186/s12879-015-0877-0.
13. Jyothi P, Metri BC. Correlation of serological markers and platelet count in the diagnosis of Dengue virus infection. Adv Biomed Res. 2015 Jan 30; 4:26. doi: 10.4103/2277-9175.150396.
14. Eshetu D, Shimelis T, Nigussie E, Shumie G, Chali W, Yeshitela B, et al. Seropositivity to dengue and associated risk factors among non-malarias acute febrile patients in Arba Minch districts, southern Ethiopia. BMC Infectious Diseases. 2020 Aug 31;20(1).
15. Mukhtar, M.U., Mukhtar, M. and Iqbal, N. (2018), Dengue fever is an emerging public health concern in the city of Multan, Pakistan: its seroprevalence and associated risk factors. Microbiol Immunol, 62: 729-731.
16. Mahmood, Shahid, et al. "Seroprevalence of Dengue IGG Antibodies among Healthy Adult Population in Lahore, Pakistan." *International Scholarly Research Notices*, Hindawi, 12 Sept. 2013,
17. Anwar F, Ahmad S,Haroon M, Haq IU,Khan HU, Khan J et al. Dengue virus epidemics: A recent report of 2017 from district Mardan, Khyber Pakhtunkhwa province, Pakistan. International Journal of Mosquito Research 2019; 6(1): 46-49.
18. Prattay KMR, Sarkar MR, Shafiullah AZM, Islam MS, Raihan SZ, Sharmin N. A retrospective study on the socio-demographic factors and clinical parameters of dengue disease and their effects on the clinical course and recovery of the patients in a tertiary care hospital of Bangladesh. Ngondi JM, editor. PLOS Neglected Tropical Diseases. 2022 Apr 4;16(4):e0010297.
19. Khan J, Adil M, Wang G, Tsheten T, Zhang D, Pan W, et al. A

cross-sectional study to assess the epidemiological situation and associated risk factors of dengue fever, knowledge, attitudes, and practices about dengue prevention in Khyber Pakhtunkhwa Province, Pakistan. Frontiers in Public Health. 2022 Jul 29;10.

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ORIGINAL ARTICLE

Depression, Anxiety, and Stress Among Frontline Healthcare Workers During COVID-19

Goolam Hussein Rassool, Kalsoom Nawaz, Sara Latif, Umair Mudassar

ABSTRACT

Objective: To determine the frequency of depression, anxiety, and stress during COVID-19 among frontline healthcare workers (doctors vs. rescuers) in Pakistan.

Study Design: Cross-sectional online questionnaire survey.

Place and Duration of Study: Centre for Islamic Psychology, Riphah International University, Lahore Campus from 25th April 2020 to 20th June 2020.

Materials and Methods: A total of 364 frontline healthcare workers (n=182 doctors and n=182 rescuers) were included in the final analysis. The Depression, Anxiety, Stress Scale (DASS-21) was used to collect online data via Google form through convenience sampling. Statistical data analysis was done using the Statistical Packages for Social Sciences (SPSS-23), and the frequencies, percentages, mean, and standard deviation were calculated. Independent samples-*t* test was employed to identify differences between doctors and rescuers on depression, anxiety, and stress scale.

Results: The mean age of the participants was 28.79 ± 5.46 years. The study identified highly significant difference in depression (t (363) = 11.10, p<.01), anxiety (t (363) = 7.30, p<.01), and stress (t (363) = 10.21, p<.01) between doctors and rescue workers during COVID-19. The majority of doctors reported a moderate level of depression (41%), extremely severe anxiety (30%), and a moderate level of stress (22%), while the majority of rescue workers reported a moderate level of depression (21%), moderate anxiety (14%) and extremely severe stress (10%).

Conclusion: The frequency of depression, anxiety, and stress is higher among doctors as compared to rescuers. The study has manifold implications for healthcare workers and psychological health professionals to implement preventive and intervention programs to combat psychological problems.

Key Words: *Anxiety, Covid-19, Depression, Frontline Workers, Stress*.

Introduction

A constant threat of confronting both natural and man-made disasters is faced by healthcare workers. From swine flu pandemics in 2009 to the earthquake, tsunami in Northern Japan, and the recent Corona Virus cases initially reported in Wuhan have changed healthcare workers, especially doctors and rescue workers perception of disaster preparedness. From Wuhan, China a fatal respiratory disease (COVID-19) started and became a major physical and mental health threat for almost 160 countries.[1] In 2020, the World Health Organization (WHO) declared COVID-19 as a fatal respiratory disease with a public health emergency of global concern. WHO provided some guidelines to manage this novel virus at the primary level COVID-19 is the third pandemic after SARS and MERS.[2] Evidence from these epidemics also indicates that the sudden onset and life-threatening disease exposed healthcare professionals to long-lasting mental health problems.[3] To prevent the rapid transmission rate of this disease, one of the major guidelines is social distancing. However, doctors and rescuers were the only volunteers who instead of distancing themselves provided first-hand treatment to the sufferers.

Doctors are front-line workers treating patients with a transmittable pathogen, COVID-19 positive, and those who are suspected cases. Dealing with the mass quarantine of patients is also a causal factor of stress and anxiety among healthcare workers. During the outbreak of severe acute respiratory syndrome,

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it was identified that healthcare workers experienced anxiety, fear, depression, and frustration.[4,5] All healthcare professionals were involved, directly and indirectly, in working with patients during the COVID-19 epidemic. The Rescue 1122 Team was formulated specially to work as a rapid-response crisis management team to combat the crisis and traumatic events. Providing pre-hospital services during the pandemic eventually increases their vulnerability to stress and other psychological or emotional problems among healthcare professionals.[6] Many studies found that without safeguarding their mental health and receiving adequate training in the medical and psychosocial management of this pandemic, healthcare workers experienced many mental health problems.[7]

To the patients, the quality of healthcare services may be affected by the psychological problems faced by healthcare workers because of a prolonged and high level of work-related stress. For healthcare workers to ensure psychological well-being, a planned strategy is thus required. Mental health problems and the risk of infections are highest for the people working in hospitals[8]. Globally, the pervasiveness of depression, anxiety, and stress during the pandemic varied among various frontline workers. The reason may be an active number of cases and available resources to combat the COVID-19 pandemic.[9] A Chinese study reported almost half of the health care workers experienced depression 50.4%, anxiety 44.6%, insomnia 34% and 71.5% reported distress.[10] The healthcare workers are life saviors for their nation to care for and manage the pandemic COVID-19. Frontline healthcare workers who ultimately save human lives, their own physical and psychological health is most important.[11]There is limited literature available in Pakistan on psychological issues faced by frontline health care workers (doctors vs. rescuers) and likewise, there is the unavailability of any evidence-based training manual/ guide for disaster preparedness of health care workers and their psychological well-being. Therefore, there is a need to assess the psychological health of workers (doctors vs. rescuers) who were serving at their official locations during an epidemic situation in Pakistan. The present study was conducted to examine the incidence of psychological disorders i.e., depression, anxiety, and stress among frontline healthcare workers and rescuers in the peak times of COVID-19 in Pakistan. For this purpose, the two groups, doctors and rescuers, were selected to measure the levels of depression, anxiety, and stress. This study has manifold implications such as it will guide the importance of the development of a manual for disaster preparedness for healthcare workers and psychological intervention at the primary level. The objective of this present study was to determine the incidence of depression, anxiety, and stress among frontline healthcare workers and rescuers in Pakistan during COVID-19.

Materials and Methods

In the present study, a cross-sectional online questionnaire survey design was employed. It was conducted between 25th April 2020 to 20th June 2020, in different sectors such as Services Hospital, Jinnah Hospital, Lahore; District Health Authority, Sialkot, Coronavirus Field Hospital Hockey Stadium, Sialkot to collect data from doctors. Whereas the different rescue stations from Lahore, Sheikupura, Kasur, Sialkot, Gujranwala, and Gujrat were targeted to collect data from rescuers during the strict lockdown due to COVID-19 in Pakistan. The 364-sample size of both groups doctors and rescuers were gathered online on Google software form through Whatsapp and Emails by using convenience sampling and 360 valid responses were gathered (Response Rate = 72%).

The present research was conducted by following all ethical principles. Foremost, Ethical Committee Approval was sought from The Departmental Academic & Research Committee (DARC) which works as an Institutional Review Board (IRB). After that, informed consent was taken from every participant by adding it at the beginning of the Google software form. The aim and nature of the research were clarified to them. Further, a demographic sheet was attached along with the depression, anxiety, and stress scale after the informed consent. Participants were assured of the provision of secrecy and confidentiality of data, and the significance of the current study. The participants' anonymity was reserved by giving the code to every response sheet.

The participants included in the study were medical doctors who were providing tertiary care to patients

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diagnosed with COVID-19 in Coronavirus wards and emergencies. In addition, some rescuers work to bring people out of harm after a disaster, such as receiving the patients from their doors, giving emergency treatments, and caring for them on their way to treatment centers and hospitals. The exclusion criteria of this study participants were doctors and rescuers not directly dealing with the patients diagnosed with COVID-19 and not available round the clock in emergency settings.

Besides the demographic sheet, to measure depression, anxiety, and stress levels, DASS Questionnaire was used. It is developed by Loviband and it consists of 21 items.[12] It includes three self-reported subscales i.e., depression, anxiety, and stress. Every subscale comprised of 7 items with a 0 to 4-point Likert scale from (0) did not apply to me, (3) applied to me very much to rate the level of severity that an individual experienced in every state from the past week. The reliability coefficient is 92. The subscale depression measures the dysphoric mood, depreciation of life, desperation, self-criticism, anhedonia, and inertia while the subscale anxiety evaluates autonomic stimulation, muscular effects, a feeling of anxiousness, and anxiety from situations. The subscale stress assesses chronic unspecified arousal, being disturbed, perplexed, nervousness, impulsiveness, irritability, being spontaneous, and impatient. The cumulative score can be obtained by the sum of each subscale. A high score showed a high level of respective construct and vice versa. This measure provides the range of scorers from normal to mild, moderate to severe, and extremely severe.

Subsequently, data entry, data analysis, and data reporting were accomplished fairly. The data was analyzed on Statistical Packages for Social Sciences (SPSS-23). The frequency of depression, anxiety, and stress were measured through descriptive statics including frequencies, percentages, mean and standard deviation of demographic variables represented in tabular as well as graphical form. Further, t-test analysis was used to see the differences among doctors and rescue workers on depression, anxiety, and stress.

Results

The mean age of the participants in this study was 28.79 $\pm$ 5.46 years. A total of 254 (69.8%) participants were less than 30 years, 95 (26%) were of age range 30 – 40 years and 15 (4%) were above 40 years. A total of 250 (68.7%) participants were male and 114 (31%) were female and majority of the participants 153 (42%) reported the major source of information regarding COVID-19 to be TV News. Furthermore, t test revealed highly significant difference in depression (t (363) = 11.10, p<.01), anxiety (t (363) = 7.30, p<.01), and stress (t (363) = 10.21, p<.01) between doctors and rescue workers during COVID-19.

As also illustrated in figure 1, the majority of doctors' responses depict that they experience different levels of depression, anxiety, and stress during COVID-19. The responses of doctors showed that the average level of depression, anxiety, and stress experienced was (10.4%: 14.8%: and 28.6% respectively). Furthermore, the mild level of depression, anxiety, and stress was (15.9%: 15.4%: 15.9% respectively) and the moderate level of depression, anxiety, and stress was reported to be (40.7%: 18.1%: 26.4% respectively). Severe levels of depression, anxiety, and stress experienced by the doctors emerged to be (12.1%: 22.0%: and 15.4% respectively). The participant responses indicate that the extremely severe level of depression, anxiety, and stress was (20.9%: 29.7%: and 13.7% respectively). The responses of the doctors indicated that participants could manage stress during COVID-19, and the results of the participants show a greater degree of depression and anxiety over COVID-19.

Figure 2 illustrates the number of rescue workers experiencing different levels of depression, anxiety, and stress during COVID-19. The majority of participants' rescue worker's responses showed that the average level of depression, anxiety, and stress was (50.5%: 42.9%: and 75.3% respectively). The results of the participants showed that mild level of depression, anxiety, and stress was (21.5%: 19.8%: and 5.5% respectively). The result of moderate depression anxiety and stress was (21.5%: 13.7%: and 7.7% respectively). The participants' responses indicate that the levels of severe depression, anxiety, and stress were (2.7%: 13.2%: and 7.1% respectively). The ratio of extremely severe depression, anxiety, and stress was (3.8%: 10.4%: and 4.4% respectively). The results of rescue workers showed that participants manage their depression,

anxiety, and stress in a better way during COVID-19. The psychometric properties of the questionnaire revealed Cronbach's Alpha reliability coefficient *r*= .88 for the depression subscale, anxiety *r*=.78, and stress *r*=.88.

Table I: Descriptive Statistics of Demographic Variables of the Sample (N=364)

Variables	f	%	M ± SD
Age			28.79 ± 5.46
< 30	254	69.8	
31-40	95	26.1	
> 40	15	4.1	
Gender			
Male	250	68.7	
Female	114	31.3	
Profession			
Doctors	182	50.0	
Rescuers	182	50.0	
Main Source of Information COVID-19			
TV News	153	42.0	
Whatsapp	98	26.9	
Facebook	34	9.3	
Newspaper	33	9.1	
Friends	33	9.1	
Twitter	13	3.6	

Note. F = Frequency, % = Percentage, M = Mean

Table II: Differences between Doctors and Rescuers in the Study Variables (N = 364).

Variable	Profession								
	Doctors		Rescue Workers						
	(*n*=182)		(*n*=182)				95 % CL		Cohen's
	M	*SD*	*M*	*SD*	*t*(363)	*p*	*LL*	*UL*	*D*
Depression	9.51	4.46	4.74	3.67	11.10	.00	3.92	5.60	1.16
Anxiety	7.95	4.19	4.96	3.58	7.30	.00	2.18	3.79	0.76
Stress	10.58	4.57	5.66	4.59	10.21	.00	3.96	5.85	1.07

Note. ***p<.001*, LL = lower limit, UL = upper limit CI = Confidence Interval*

Discussion

The findings of the current study depict that frontline health care workers (both doctors and rescue workers) experienced depression, anxiety and stress during covid-19 outbreak. Highly significant difference in depression, anxiety, and stress between

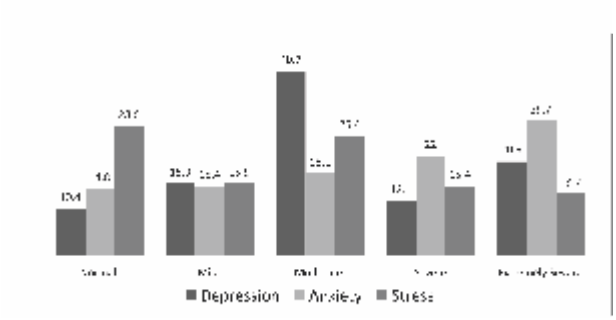

Fig. 1: Doctors Experiencing Depression, Anxiety, and Stress During COVID-19 (n=182).

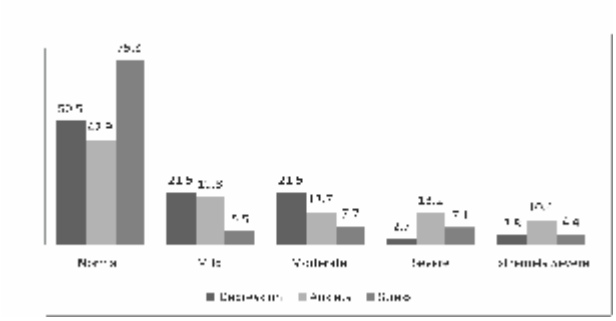

Fig. 2: Rescue Workers Experiencing Depression, Anxiety, and Stress During COVID-19 (n= 182)

doctors and rescue workers emerged which further indicates that doctors are more likely to experience it comparatively. The results of the present study are in congruence with the studies that highlight differences between frontline health care workers i.e. doctors vs. rescue workers experiencing psychological problems. The findings of the study by Elbay et al. (2020) indicate that the frontline workers are more prone to mental health problems due to increased working hours, and increased no of covid-19 patients cared for. It was found that 64.7% of doctors reported depressive symptoms, anxiety 51.6%, and 41.2% stress-related symptoms. [13, 14] In another study that was conducted by Vagni, Maiorano, Giostra, and Pajardi (2020), the findings showed that healthcare workers were more prone to stress and arousal than other workers in emergency settings. Furthermore, the medical professionals dealing directly with the patients of COVID-19 and are involved in their treatment were experiencing more levels of stress and were more susceptible to developing secondary trauma.[15]

The findings of the study also revealed that the majority of the doctors experienced moderate levels of depression. Whereas few doctors also reported

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severe anxiety and an extremely severe form of stress. The results are consistent with the findings by Amin et al. (2022) in which the prevalence rate of depression/anxiety was (43%) reported among frontline physicians in Pakistan.[16,17] Ullah et al. (2022) reported one-third of healthcare workers had depression while half had anxiety during this outbreak of covid-19.[18] Salman et al. (2022) also supported the current study by reporting the higher level of depression in frontline healthcare workers including doctors, nurses, and pharmacists.[19] Its evident from the literature also that major threat to COVID-19 were the speculations regarding rapid transmission and unavailability of prevention protocols and vaccination and subsequently the development of psychological problems.[16]

In the current study majority of the rescuers also reported moderate level of depression. Few rescuers also had reported severe anxiety and extremely severe stress. The findings of the existing study are in line with the findings by Ahmad et al. (2015), the rescue workers experienced severe and extreme severe levels of depression and anxiety symptoms during their daily life.[20]A study conducted by Sandesh et al. (2020) provides similar findings such as the highest levels of depression, anxiety and stress levels of healthcare employees emerge from the pandemic and in emergencies.[21]

The findings showed 32.6 and 45.7 percent of the participants were experiencing severe and extremely severe levels of depressive and anxiety symptoms respectively.

Moreover, the source of information regarding COVID-19 was requested from respondents. The majority of the sample (42%) relied on television news and others take an update from social media networks including WhatsApp, Facebook, Twitter, and also from newspapers, TV programs, and friends. The media coverage created more distressing consequences during the outbreak of SARS.[15, 22] Hence, the intensity of depression, anxiety, and stress may increase because of consistent exposure to media.

Limitations

Firstly, a total of 182 doctors and 182 rescue workers' data was retained (Response Rate = 72%). The dropout rate was high due to doctors' and rescuers' hectic routines, responsibilities, and time constraints. Secondly, the research was based on a self-administered questionnaire and thus, could not confidently depend on self-reported data on depression, anxiety, and stress. Also, the participant's engagement in dealing with Coronavirus was not directly observed and assessed. Thirdly, this study couldn't differentiate the specialization among doctors that work with joint hands in this pandemic phase. Fourthly, it doesn't include the other health care workers such as nurses, and paramedical staff.

Recommendations

During pandemics and emergency settings, healthcare workers (doctors, nurses, and paramedical staff) and rescuers are the frontline employees that provide essential services to the general public. Therefore, it was a dire need to design a study that targets the assessment of mental health risks among these groups. Thus in addition to this study, qualitative research (Interviews and case studies) can generate more rich data that would further guide the need of developing crisis intervention strategies at the national level.[16] It is further recommended that outcome-based studies should be designed that investigate the efficacy of psychological treatment programs among healthcare workers.

Conclusion

Both doctors and rescuers are always on the front line in face of any calamity. Both professions are associated with a risk of mental health problems. However, doctors are more prone to experience depression, anxiety, and stress as compared to rescuers. Almost half of the doctors experienced moderate levels of depression, one-third had anxiety and stress whereas the 1/4th of rescuers experienced moderate levels of depression and only few had experienced severe anxiety and severe stress.

REFERENCES

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New England journal of medicine. 2020 Jan 29; 382(13):1199-207. doi: 10.1056/NEJMoa2001316
2. Jiloha RC. COVID-19 and mental health. Epidemiology International (E-ISSN: 2455-7048). 2020 Mar 25; 5(1):7-9. doi: 10.24321/2455.7048.202002
3. Liua X, Kakadeb M, Fullerb CJ, Fanb B, Fangc Y, and Kongc J,

et al. Depression after Exposure to Stressful Events: Lessons Learned from the SARS Epidemic. Compr Psychiatry. 2012 Jan; 53(1):15-23. doi: 10.1016/j.comppsych.2011.02.003
4. Chong MY, Wang WC, Hsieh WC, Lee CY, Chiu NM, Yeh WC, et al. Psychological impact of severe acute respiratory syndrome on health workers in a tertiary hospital. The British journal of psychiatry. 2004 Aug; 185(2):127-33. doi: 10.1192/bjp.185.2.127.
5. Goulia P, Mantas C, Dimitroula D, Mantis D, Hyphantis T. General hospital staff worries, perceived sufficiency of information and associated psychological distress during the A/H1N1 influenza pandemic. BMC infectious diseases. 2010 Dec; 10(1):1-1. doi: 10.1186/1471-2334-10-322.
6. Drapeau A, Marchand A, Beaulieu-Prévost D. Epidemiology of psychological distress. Mental illnesses-understanding, prediction, and control. 2012 Jan 5; 69:105-6. doi:10.5772/30872
7. Greene T, Harju-Seppänen J, Adeniji M, Steel C, Grey N, Brewin CR, et al. Predictors and rates of PTSD, depression and anxiety in UK frontline health and social care workers during COVID-19. European Journal of Psychotraumatology. 2021 Jan 1; 12(1):1882781. doi: 10.1080/20008198.2021.1882781
8. Xing LQ, Xu ML, Sun J, Wang QX, Ge DD, Jiang MM, et al. Anxiety and depression in frontline health care workers during the outbreak of Covid-19. International Journal of Social Psychiatry. 2021 Sep; 67(6):656-63. doi: 10.1016/j.heliyon.2021.e08570
9. Rana W, Mukhtar S, Mukhtar S. Mental health of medical workers in Pakistan during the pandemic COVID-19 outbreak. Asian journal of psychiatry. 2020 Jun; 51:102080. doi: 10.1016/j.ajp.2020.102080
10. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA network open. 2020 Mar 2; 3(3):e203976. doi: 10.1001/jamanetworkopen.2020.3976
11. Chen Q, Liang M, Li Y, Guo J, Fei D, Wang L, et al. "Mental health care for medical staff in China during the COVID-19 outbreak": Correction. doi: 10.1016/S2215-0366(20)30078-X.
12. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behaviour research and therapy. 1995 Mar 1; 33(3):335-43. doi: 10.1016/0005-7967(94)00075-u.
13. Elbay RY, Kurtulmuş A, Arpacıoğlu S, Karadere E. Depression, Anxiety, Stress Levels of Physicians and Associated Factors In COVID-19 Pandemics. Psychiatry Research. 2020 May 27:113130. doi: 10.1016/j.psychres.2020.113130.
14. Tang L, Bie B, Park SE, Zhi D. Social media, and outbreaks of emerging infectious diseases: A systematic review of literature. American journal of infection control. 2018 Sep 1; 46(9):962-72. doi: 10.1016/j.ajic.2018.02.010.
15. Vagni M, Maiorano T, Giostra V, Pajardi D. Hardiness, Stress and Secondary Trauma in Italian Healthcare and Emergency Workers during the COVID-19 Pandemic. Sustainability. 2020; 12(14):5592. doi: 10.3390/su12145592.
16. Li S, Wang Y, Xue J, Zhao N, Zhu T. The impact of COVID-19 epidemic declaration on psychological consequences: a study on active Weibo users. International journal of environmental research and public health. 2020 Jan; 17(6):2032. doi: 10.3390/ijerph17062032.
17. Amin F, Sharif S, Saeed R, Durrani N, Jilani D. COVID-19 pandemic-knowledge, perception, anxiety and depression among frontline doctors of Pakistan. BMC psychiatry. 2020 Dec; 20(1):1-9. doi: 10.1186/s12888-020-02864-x.
18. Ullah I, Khan KS, Ali I, Ullah AR, Mukhtar S, de Filippis R, et al. Depression and anxiety among Pakistani healthcare workers amid COVID-19 pandemic: a qualitative study. Annals of Medicine and Surgery. 2022 Jun 1; 78:103863. doi: 10.1016/j.amsu.2022.103863.
19. Salman M, Mustafa ZU, Raza MH, Khan TM, Asif N, Tahir H, et al. Psychological effects of COVID-19 among health care workers, and how they are coping: a web-based, cross-sectional study during the first wave of COVID-19 in Pakistan. Disaster Medicine and Public Health Preparedness. 2023; 17:e104. doi: 10.1017/dmp.2022.4
20. Ahmad S, Arshad T, Kausar R. Psychological correlates of distress in rescue 1122 workers in Pakistan. International Journal of Emergency Mental Health and Human Resilience. 2015; 17(2):486-94. doi: 10.15537/smj.2016.7.15004
21. Sandesh R, Shahid W, Dev K, Mandhan N, Shankar P, Shaikh A, et al. Impact of COVID-19 on the Mental Health of Healthcare Professionals in Pakistan. Cureus. 2020 Jul; 12(7). doi: 10.7759/cureus.8974.
22. Ho CS, Chee CY, Ho RC. Mental health strategies to combat the psychological impact of COVID-19 beyond paranoia and panic. Ann Acad Med Singapore. 2020 Jan 1; 49(1):1-3. https://pubmed.ncbi.nlm.nih.gov/32200399/.

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

To Compare the Effectiveness of Platelet Rich Plasma vs Steroid Injection in the Management of Planter Fasciitis

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ABSTRACT

Objective: The study was done to compare the effectiveness of Platelet Rich Plasma (PRP) vs steroid injections in the management of planter fasciitis.

Study Design: It was a comparative study.

Place and Duration of Study: This study was conducted for the duration of one year from October 2021 to September 2022 in Pakistan Railway General Hospital, Rawalpindi.

Materials and Methods: The study was conducted on 500 patients that visited tertiary care unit for a period of one year. Two groups were made based on random sampling technique and type of treatment given for plantar fasciitis (Platelet Rich Plasma and steroid). After the preparation of platelet rich plasma by centrifugation method that separates the red blood cells from plasma and obtain the final volume of plasma with high concentration of platelets. A total of 3ml of platelet rich plasma was injected after all aseptic measures around the area of maximal tenderness in group A patients. 40 mg injection of triamcinolone acetonide was given to the all the participants in group B patients after doing all aseptic measures around the area of maximal tenderness after clinical examination

Results: There were 250 patients in each group including both male and females. The average age of patients in our study was 45.9 ± 5.6 years and 45.9±4.5 years in both groups respectively. Patient in group A had more effective pain relief in long term follow up than patients in group B. The Visual Analog Scale (VAS) score values gradually decreased as the duration of treatment increased with the lowest value obtained as 0.68 ± 0.65* and 0.60 ± 0.69* for steroid and PRP group respectively. There was no post injection problem in either group.

Conclusion: Our study concludes that PRP administration for the treatment of plantar fasciitis can be more effective as compared to steroid as it gives positive results even after 12 months of follow-up.

Key Words: *Plantar Fasciitis, Steroid Injections, And Platelet-Rich Plasma (PRP), Foot Function Index (FFI), Visual Analog Pain Scale.*

Introduction

Plantar fasciitis also known as plantar fasciosis is an orthopedic condition characterized by pain and tenderness in the heel and bottom of the foot. It results from the inflammation and micro tears in the plantar fascia. This condition affects daily activities such as walking and standing and can be paralyzing. There are several treatment options available for plantar fasciitis, including rest, medications, shockwave therapy, tapping and injections. Two highly known injection therapies used for plantar fasciitis are platelet-rich plasma (PRP) and steroid injections. In PRP therapy, the affected area is injected [1-2] with a concentrated solution of platelets and growth factors from the patient's own blood. This solution is believed to promote healing and reduce inflammation with no adverse effect on the plantar fasciitis. Steroid injections, on the other hand, involve the injection of a corticosteroid into the affected area to reduce inflammation. Recent

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studies suggest the use of steroid injection if the pain is persistent for more than 6 weeks despite use of noninvasive modalities[3]. There is ongoing debate among medical professionals about the effectiveness of these two treatments for plantar fasciitis. Some studies suggest that PRP may be more effective than steroid while others suggest the opposite. A meta-analysis [4-6]found that PRP was more potent than placebo injections in reducing pain, the effect was not statistically significant. Several studies have investigated the effectiveness of steroid injections for the therapy of plantar fasciitis. In addition to the meta-analysis, several other studies have also provided evidence for the effectiveness of PRP. The purpose of the following study was to determine the differences between the effectiveness[7-8] of platelet-rich plasma (PRP) injection and steroid injection in the management of plantar fasciitis. Plantar fasciitis is most seen in people between the ages of 40 and 60 and is more common in women than men. PRP is a relatively new treatment for plantar fasciitis and more research is needed to determine its long-term effectiveness.

It is important to note that PRP is not suitable for everyone and should be avoided in cases of platelet dysfunction or bleeding disorders. Steroid injections have been used for decades to treat a variety of conditions, including plantar fasciitis. They are well-established treatment option and are effective in reducing pain and inflammation.[9] They can have side effects, such as thinning of the skin or changes in skin color, especially if used repeatedly. They should not be used in patients who have an infection or skin condition at the injection site [10]. They should also be avoided in patients who are diabetic or have poor circulation to the feet. The study aimed to evaluate the safety and tolerability of both treatments, as well as their impact on quality of life.

Materials and Methods

The aim of this comparative study was to evaluate the effectiveness of platelet rich plasma vs steroid in patients with planter fasciitis. This study was conducted in the Department of orthopedics, Pakistan Railway General hospital, Rawalpindi from October 2021 to September 2022 on 500 patients who visited tertiary care unit for a period of one year. Methodology was designed after permission from ethical review board. Two groups were made based on type of treatment given for plantar fasciitis (PRP and steroids). Participants were equally and randomly divided into 2 groups by lottery method and after recruitment of the participants, the nature of the research, as well as its goals, was explained to each participant and written informed permission was acquired from patients or their families. There were 250 patients in each groups. The average age of patients in our study was 45.9 ± 5.6 years and 45.9±4.5 years in both groups respectively.

Patients with age 18 to 65 years old, diagnosed with the planter fasciitis and pain of more than 4 on a visual analog scale who failed to respond for conservative management were included in the study. Exclusion criteria included previous trauma/surgery on the affected heel, pregnancy, active infection, previous injections, and bleeding disorders. All participants had heel pain for at least 6 months and had failed previous conservative treatment. The injection of triamcinolone acetonide (40mg) was given to the all the participants in the steroid group. The injection of autologous platelet-rich plasma (3ml) was given to all the patients in the PRP group. For preparation of PRP, an initial method of centrifugation that separated the red blood cells from plasma followed by second centrifugation to concentrate platelets and ultimately obtain the final smallest volume of plasma with high concentration of platelets .The Statistical Package for the Social Sciences (SPSS) version 23 was used throughout the data analysis process. Descriptive statistics was used to outline the demographic and analytic characteristics of the participants. The primary outcome measured the change in pain score measured on a VAS after the injection. Secondary outcome measured functional improvement measured by the Foot Function Index (FFI), patient satisfaction, and adverse effects.

Results

There were 100 males and 150 females in PRP group and 118 males and 132 females in the steroid group. In the PRP group there were 130 patients whose right foot was affected, and 120 patients had left foot affected. In the Steroid group there were 120 patients with right and 130 with left foot affected as shown in table no. I.

Visual analogue scale score was compared for patients. The data was collected after 1, 6 and 12

Table I: Characteristic Features of Patients

Features	PRP group (number of patients=250)	Mean ±SD	Steroid group (Number of patients=250	Mean ±SD	P value
Age (year)		45.9 ± 5.6		45.9±4.5	0.005
Gender (male/female)	(100/150)		(118/132)		0.003
Affected foot (right/left)	(130/120)		(120/130)		0.005

months of treatment. It was found as per VAS scores that the statistically significant improvement was observed in pain after 1, 6 and 12 months of treatment in case of both PRP and steroid groups. Table II shows the VAS score values gradually decreases as the duration of treatment increases with the lowest value obtained as 0.68 ± 0.65* and 0.60 ± 0.69* for steroid and PRP group respectively. The VAS scores for Steroid group are lower than PRP group in the initial duration of treatment but after a follow-up of 12 months. The mean VAS score of steroid group and PRP group was compared. The PRP VAS scored was better than steroid group.

Table II: VAS Scores Comparison of Both Treatment Groups for Pretreatment and Post Treatment at 1, 6 and 12 Months

	Pretreatment	1 Month	6 Months	12 Months
Steroid Group				
VAS	7.60 ± 0.82	4.00 ± 1.00*	2.80 ± 1.00*	0.68 ± 0.65*
PRP Group				
VAS	7.72 ± 0.84	6.44 ± 0.92*	3.92 ± 0.91*	0.60 ± 0.69*
*Significant at ρ < 0.05 Comparison of 1 month, 6 months & 12 months to pretreatment scores Mean ± SD				

The statistical analysis was conducted. For equality of mean the T test, for equality of variance the Levene's Test and degree of freedom was calculated. It was found that the data was significant statistically.

Table III: Statistical Analysis of the Results

Pairs			t-test				
	Levene's Test for Equality of Variances		t-test for Equality of Means	Degree of Freedom	Sig. (2-tailed)	95% Confidence Interval of the Difference	
Steroid PRP	F Stats	Sig.				Lower	Upper
VAS0	0.006	0.940	-0.511	48	0.611	-0.592	0.352
VAS1	0.023	0.880	-8.994	48	0.000	-2.985	-1.895
VAS2	0.003	0.953	-4.143	48	0.000	-1.663	-0.577
VAS3	0.072	0.790	-0.423	48	0.674	-0.460	0.300

Discussion

Despite the introduction of multiple non-surgical methods for the effective treatment of plantar fasciitis, there is still needed to determine the ideal procedure and there is utmost need to do the long term follow up of patients to determine the single modality that is efficient, cost effective with less complication compared to different surgical techniques that put more burden on patients and associated with higher complications. Recently the PRP use has gained attention for the treatment of foot and ankle pathologies[11]. The corticosteroid injection help to relieve inflammation, promote fibrosis that ease pain and rapid healing with less complexity.[12] This study was designed for the comparison of the results of steroid injection and PRP for the plantar fasciitis treatment.

Our study has suggested that during the initial stages of treatment and after 1, 6 months of treatment the steroid injection had more functional outcomes than single dose of PRP for plantar fasciitis but after a follow-up of 12 months the mean VAS score was less for PRP as compared to steroid injection which suggest that long term effectiveness can be obtained by using PRP. Studies have shown that because of mechanical loading plantar fasciitis is caused by the inflammatory reaction to micro tears [12]. Steroid injections are in use for treatment of plantar fasciitis, but it only gives short term positive results [13]. In our study we compared the Visual analogue scale scores for patients before treatment and after 1, 6 and 12 months of treatment for both groups. It was found as per VAS scores that there was a significantly noticeable improvement in pain after 1, 6 and 12 months of treatment in case of both PRP and steroid groups. Our study is in accordance with the previous reports where there was gradual reduction in VAS score after steroid and PRP treatment.

Table II shows the VAS score values that gradually decreases as the duration of treatment increases with the lowest value obtained as 91.05%(0.68 ± 0.65)* and 92.27%(0.60 ± 0.69*) for steroid and PRP group respectively. The average pain reduction for Steroid group is lower than PRP group after 1 and 6 months of treatment but after 12 months the values were calculated, and data revealed that the mean VAS score of PRP was less than the mean VAS score of steroid group which suggest that steroid injection can give better results for short term pain relief, but PRP dose can be used as a long-term treatment. Steroid injections have been used for decades to treat a variety of conditions, including plantar

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fasciitis[13]. They are well-established treatment option and are effective in reducing pain and inflammation. They act quickly and the relief of pain is usually noticed within a few days [14]. Another study also explains the anti-inflammatory activity of steroid injections and PRP dose [15]. As per studies growth factors and proteins like vitronectin, fibronectin and thrombospondin found in PRP play an important role in the healing of tissue and for the regeneration of bones [16]. PRP with the assistance of growth factors stimulates stem cells to fasten the repair of cells and improves the circulation of blood.[17] As per studies it was found that PRP also enhances the tenocyte proliferation for the fast recovery of tendon as it has growth factors that provides revascularization thereby increasing the expression of collagen in the tenocytes.[18-20] The statistical analysis was conducted. For equality of mean the T test, for equality of variance the Levene's Test and degree of freedom was calculated. It was found that the data was significant statistically. Our study shows the anti-inflammatory response of PRP dose after 1, 6 and 12 months and the long-term results were significantly better than steroids. In our study before treatment the VAS score in steroid group was 7.60 ± 0.82 and after treatment an average pain reduction was found to be 47.36%(4.00 ± 1.00)*, 36.48%(2.80 ± 1.00)* and 91.05%(0.68 ± 0.65)* for 1, 6 and 12 months respectively. Meanwhile the VAS score for PRP before treatment was 7.72 ± 0.84 and after 1,6 and 12 months of treatment by PRP dosage the average pain reduction was found to be 16.58%(6.44 ± 0.92)*,49.22% (3.92 ± 0.91)* and 92.27%(0.60 ± 0.69)* respectively. That explains the gradual decrease in VAS score and slight difference in the VAS scores for PRP and steroid groups. Previous studies have reported that PRP has better outcomes than steroid for plantar fasciitis, our results showed that despite low VAS score in steroid group, PRP is better option as it gives long term results[20-21]. It is important to note that PRP is not suitable for everyone and should be avoided in cases of platelet dysfunction or bleeding disorders.

Conclusion

Being an elective procedure, patient satisfaction following injection remains an important factor for the surgeon when recommending this procedure for treatment. Our study concludes that PRP administration for the treatment of plantar fasciitis can be more effective as compared to steroid as it gives positive results even after 12 months of follow-up, therefore it can be considered as a long-term treatment as compared to steroid injections. However, more studies need to be done by using larger sample size and longer follow-up period so that a more elaborate and precise result can be made to better understand the efficacy of PRP.

REFERENCES

1. Seth I, Bulloch G, Seth N, Lower K, Rodwell A, Rastogi A, Gibson D, Bedi H. The Role of Corticosteroid Injections in Treating Plantar Fasciitis: A Systematic Review and Meta-Analysis. The Foot. doi: 10.1016/j.foot.2023.101970.
2. Ahadi T, Cham MB, Mirmoghtadaei M, Raissi GR, Janbazi L, Zoghi G. The effect of dextrose prolotherapy versus placebo/other non-surgical treatments on pain in chronic plantar fasciitis: a systematic review and meta-analysis of clinical trials. Journal of Foot and Ankle Research. doi: 10.1186/s13047-023-00605-3.
3. Syed Qasim Mehmood, Johar Ali, Asif Saeed, Muhammad Nawaz, Rifat Latif ,Efficacy of Intrasheath Steroid Injection in Treating DeQuervain's Disease, JIIMC Vol. 7 No. 2 (2012): December ISSN No: 1815-4018
4. Rabadi D, Seo S, Wong B, Chung D, Rai V, Agrawal DK. Immunopathogenesis, early detection, current therapies, and prevention of plantar fasciitis: A concise review. International Immunopharmacology. DOI: 10.1016/j.intimp.2022.109023.
5. Nayar SK, Alcock H, Vemulapalli K. Surgical treatment options for plantar fasciitis and their effectiveness: a systematic review and network meta-analysis. Archives of Orthopaedic and Trauma Surgery. 2023 Jan 3. doi: 10.1007/s00402-022-04739-0.
6. Beydoğan E, Yalçın A. Is 2D SWE sufficient as clinical diagnosis in patients with plantar fasciitis? *Acta Radiol*. 2023;64(1):147-152 doi: 10.1177/02841851211058928.
7. Tognolo L, Giordani F, Biz C, Bernini A, Ruggieri P, Stecco C, Frigo AC, Masiero S. Myofascial points treatment with focused extracorporeal shock wave therapy (f-ESWT) for plantar fasciitis: an open label randomized clinical trial. Eur J Phys Rehabil Med. 2022 Feb 1;58(1):85-93. doi: 10.23736/S1973-9087.21.06814-3.
8. Rhim HC, Kwon J, Park J, Borg-Stein J, Tenforde AS. A Systematic Review of Systematic Reviews on the Epidemiology, Evaluation, and Treatment of Plantar Fasciitis. Life. 2021 Nov;11(12):1287. DOI: 10.3390/life11121287.
9. Gamba C, Sala-Pujals A, Perez-Prieto D, Ares-Vidal J, Solano-Lopez A, Gonzalez-Lucena G, Ginés-Cespedosa A. Relationship of plantar fascia thickness and preoperative pain, function, and quality of life in recalcitrant plantar fasciitis. *Foot Ankle Int*. Aug;39(8):930-934. doi: 10.1177/1071100718772041.
10. Sheikh, S.I, Ahmed, A., Javaid, S., Basit, A., Sohail Sheikh, I.,

Sohail Sheikh, S. and Sohail Sheikh, Z. (2012). Comparison of Suprascapular Nerve Block & Intra-articular Injection in the treatment of Frozen Shoulder. Journal of Islamic International Medical College, pp.76-81.
11. Chen CM, Lee M, Lin CH, Chang CH, Lin CH. Comparative efficacy of corticosteroid injection and non-invasive treatments for plantar fasciitis: a systematic review and meta-analysis. Scientific Reports. 2018 Mar 5;8(1):1-9. doi: 10.1038/s41598-018-22402-w.
12. Aggarwal P, Jirankali V, Garg S. Evaluation of plantar fascia using high-resolution ultrasonography in clinically diagnosed cases of plantar fasciitis. Polish Journal of Radiology. 2020 Jul 24;85:e375-e380. doi: 10.5114/pjr.2020.97955.
13. Adnan.R.A, Iqbal.S.S, Sabir.N. Comparison between Hydro Dilatation and Intra Articular Steroid Injection in Patients with Frozen Shoulder in Term of Pain Relief and Range of Movement, JIIMC 2019 Vol. 14, No.3
14. Menon NA, Jain J. Plantar fasciitis: A review. Indian Journal of Pain. 2018 Jan 1;32(1):24. DOI:10.4103/ijpn.ijpn_3_18
15. Uğurlar M, Sönmez MM, Uğurlar ÖY, Adıyeke L, Yıldırım H, Eren OT. Effectiveness of four different treatment modalities in the treatment of chronic plantar fasciitis during a 36-month follow-up period: a randomized controlled trial. The Journal of Foot and Ankle Surgery. 2018 Sep-Oct;57(5):913-918. doi: 10.1053/j.jfas.2018.03.017.
16. Bildik C, Kaya O. Platelet-rich plasma vs autologous blood injection to treat plantar fasciitis: A prospective randomized, double-blinded, controlled trial. Foot & Ankle International. 2022 Sep;43(9):1211-1218. doi: 10.1177/10711007221114122.
17. Lim ST, Kelly M, O'Neill S, D'Souza L. Assessing the quality and readability of online resources for plantar fasciitis. The Journal of Foot and Ankle Surgery. 2021 Nov-Dec;60(6):1175-1178. doi: 10.1053/j.jfas.2021.02.014.
18. Trojian T, Tucker AK. Plantar fasciitis. American family physician. 2019 Jun 15;99(12):744-750.
19. Latt LD, Jaffe DE, Tang Y, Taljanovic MS. Evaluation, and treatment of chronic plantar fasciitis. Foot & Ankle Orthopaedics. 2020 Feb 13;5(1):2473011419896763. doi: 10.1177/2473011419896763.
20. Nakale NT, Strydom A, Saragas NP, Ferrao PN. Association between plantar fasciitis and isolated gastrocnemius tightness. Foot & ankle international. 2018 Mar;39(3):271-277. doi: 10.1177/1071100717744175.
21. Welte L, Kelly LA, Kessler SE, Lieberman DE, D'Andrea SE, Lichtwark GA, Rainbow MJ. The extensibility of the plantar fascia influences the windlass mechanism during human running. Proceedings of the Royal Society B. 2021 Jan 27;288(1943):20202095. doi: 10.1098/rspb.2020.2095.
22. Ersen Ö, Koca K, Akpancar S, Seven MM, Akyıldız F, Yıldız Y, Özkan H. A randomized-controlled trial of prolotherapy injections in the treatment of plantar fasciitis. Turkish journal of physical medicine and rehabilitation. 2018 Mar;64(1):59-65. doi: 10.5606/tftrd.2018.944
23. Caner ÖC, Güneş S, Gökmen D, Ataman Ş, Kutlay Ş. The efficacy and safety of extracorporeal shock wave therapy on plantar fasciitis in patients with axial spondyloarthritis: a double-blind, randomized controlled trial. Rheumatology International. 2022 Apr;42(4):581-589. doi: 10.1007/s00296-022-05098-0.

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Correlational Link of Work Family Conflict and Religiosity with Mental Well-Being Among Medical Doctors

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ABSTRACT

Objective: The present study aimed to measure correlational link of bidirectional work family conflict (work to family conflict & family to work conflict) and religiosity with mental well-being among medical doctors.

Study Design: The design of present study was correlational research design.

Place and Duration of Study: Study was conducted under research supervision of University of Gujrat. Gujranwala Hospitals including DHQ Hospital, Med care International, Gondal Medical Complex, Chattha Hospital, Jinnah Memorial Trust Hospital, Social Security hospital were approached for the data collection. Duration of the study March 2020 to October 2020.

Materials and Methods: Population of the present study included medical professionals of Gujranwala hospitals. Sample of 130 medical doctors were selected through simple random sampling technique. Questionnaires involved Work Family Conflict Scale to measure work to family conflict & family to work conflict, Religious Commitment Inventory-10 to measure religiosity and Warwick Edinburgh's Mental Well-being Scale to measure mental well-being. Artificial neural network model and multiple regression analysis was run to analyze the data.

Results: Analyses of artificial neural network revealed the predictive relationship between the independent variables and the mental well-being. Regression analysis revealed that work to family conflict & family to work conflict both are the negative predictors and religiosity is the positive predictor of mental wellbeing.

Conclusion: Present study revealed the association between the variables which were under consideration. Based on findings it can be concluded that work family conflict may negatively impact mental health of a professional and religiosity can reduce that influence and improve mental health. Study identified the need of organizational and individual level strategic plans and interventions to reduce the work life imbalance problem and to raise the mental wellbeing of medical professionals.

Key Words: *Family to Work Conflict, Mental Well-being, Religiosity, Work Family Conflict, Work to Family Conflict.*

Introduction

Work Family Conflict construct was originated from "Role Theory" and "Role Strain Hypothesis".[1] Greenhaus and Beutell explained work family conflict is the incompatibility of the roles of work and family domains and is a form of inter role conflict.[2] It is bidirectional in nature. Family can be the root of interference in the work-related responsibilities (work role) or work can be the source of interference in the family related responsibilities (family role). Interference caused by family in the work role is called "Family to Work Conflict(F-WC)"and if work hinders family role it is called as the "Work to Family Conflict(W-FC)".[3]

Influence of work family conflict on individuals' mental wellbeing is well established. Mental wellbeing, a state of persons in which they realize their own abilities and can deal with normal stressors of life, they can work fruitfully and productively contribute to the community.[4]

Religiosity has been studied in relevance to work family conflict. It is a complicated term because every discipline views it from different angle. It is considered in terms of faith, devotion, holiness, piousness and sometimes it refers to religious commitment.[5]

Literature revealed that people with high level of work family conflict reported lower level of

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wellbeing.[6] A longitudinal research revealed the negative relationship between work family conflict and wellbeing.[7] Other research also revealed significant positive relationship between religiosity and wellbeing.[8] Moreover, a research reported the positive relationship between religious commitment and wellbeing.[9] Khelak and Tekke's[10] research also revealed similar findings. To the best of our knowledge, most of the previous studies on work family conflict measured work family conflict as a unidirectional construct.[11] So due to this the effects and management of work family conflict has not been fully understood. So, there was the need to investigate it more.

Work, family, health, and religion are crucial aspects of human life, and they all have some direct and indirect effects on each other. Disturbance or conflict between work life and family life may affect other aspects of life such as person's health. With the passage of time person roles, values, organizational dynamics, and family dynamics have changed, now people must face bulk of challenges and pressures from both sides that lead towards disequilibrium and causing deterioration of organizational as well as family setups by affecting the individuals.[12]

To deal with this global issue of professionals, research is focusing on the effective ways to reduce them and one of them is religion. It is being focused in research that religious copying is very much effective for decreasing the negative influence of work family conflict especially in those cultures where religious healing is considered as an important de-stressor.[13] And Pakistani culture is one of those where religious practices are perceived a vital source of psychological wellbeing.[14] So here the present study aimed to examine these vital sides of life: religiosity, work family conflict and mental wellbeing. It inquired the bifacial construct of work family conflict and investigated the correlational link between W-FC, F-WC and religiosity variable with mental wellbeing among medical professionals. Based on theoretical framework, hypothesis was formulated that W-FC, F-WC would be the negative predictors and religiosity would be the positive predictor of mental wellbeing. Findings of the present study identified the need for interventions at organizational level to enhance professionals' mental wellbeing. It generated the knowledge vital for organizations that the work family conflict among professionals may affect their wellbeing and religious or meditation-based strategies may work to enhance their mental wellbeing. Present study is also a valuable contribution to the research literature relevant to the problems of medical professionals.

Materials and Methods

Correlation research design was used. Study was conducted under research supervision of University of Gujrat and data collection done in Gujranwala hospitals (DHQ Hospital, Medcare International, Gondal Medical Complex, Chattha Hospital, Jinnah Memorial Trust Hospital, Social Security hospital. Study duration was March 2020 to October 2020. Population of the study was medical doctors and sampling was done at two stages. Firstly, hospitals of Gujranwala city were selected randomly and at next stage the sample size of 130 doctors working in those selected hospitals were chosen through Simple Random Sampling.

The study was conducted after approval of the ethical review committee of the Department of Psychology, University of Gujrat (Ref no: Psy/UOG/21/2710 on 12th April 2021). And all other concerned authorities of the institutes where data was collected, were approached for permission.

Medical doctors working in Gujranwala hospitals (government or private or both) either in morning shifts or regular day schedules were included in the sample. Medical doctors working at night shifts were excluded from the sample because majority of previous research on same topic have already revealed the higher level of work family conflict among night shift professionals and present study tried to investigate the phenomena differently by including new participants those work in morning shifts or in regular day schedules.[15]

A scale battery was used for the data collection which includes inform consent form, demographic form, three questionnaires named as Work Family Conflict Scale, Religious Commitment Inventory-10, and Warwick Edinburgh Mental Wellbeing Scale.

Work Family Conflict Scale [16] was used to measure W-FC and F-WC. Religious Commitment Inventory-10 [17] was used to measure religiosity. Warwick Edinburgh Mental Wellbeing Scale [18] was used to measure mental wellbeing.

Data was scored, analyzed, interpreted, and

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tabulated with the help of IBM SPSS version 21. Type of data was parametric. To analyze the data multiple linear regression was used to measure the predictive relationship (correlation not cause-&-effect) and p-value less than 0.05 was considered significant. The unstandardized Beta (B coefficient) used to denote direction of predictive link (positive/negative relationship) present between the variables.

Another standardized statistical analysis named Artificial Neural Network(ANN) was used.

The present study run artificial neural network analysis to drive clearer picture of the relationships between variables. In ANN through synaptic weights, model summary and independent variable importance analysis (sensitivity analysis) the inferences were drawn.

Results

Present research run the multiple linear regression analysis before developing the Artifical neural network strucutre because literature evidences have been suggested that regression analysis could be a good preliminary step for generating more sophisticated relationship models[21].

Table I:Multiple Linear Regression Analysis for Predicting Effect of W-FC, F-WC and Religiosity on Mental Wellbeing

Predictors	Model 1	Outcome: Mental Wellbeing	
		B	P-value
W-FC		-0.15	0.12
F-WC		-0.28	0.01
Religiosity		0.26	0.00
F	8.70		
R^2	0.17		
ΔR^2	0.15		

Note: W-FC=Work to family conflict, F-WC=Family to work conflict, B==Unstandardized Beta, P-value=level of statistical significance

**p < .01, *p < .05

Table I. shows that F-WC was significant negative predictor and religiosity was significant positive predictor of mental well-being among medical doctors. W-FC were negative non-significant predictor of mental wellbeing. From the value of R square and adjusted R^2 (ΔR^2=.15) it can be said that variance (17%) in data was acceptable, and the model was fit for the hypothesis testing. This statement was further supported by significant F ratio (F = 8.70, p = .001).

Additionally, artificial neural network model named 'multilayer perceptron(MLP) was used to test relationship of W-FC, F-WC and religiosity with mental wellbeing. Artificial neural network models are of different types. Among these types one is called Multi-Layer Feed-forward Neural network. Multi-layer Feed-forward neural network is another name of Multilayer Perceptron(MLP). This type of ANN is consisting of multiple layers including input layer, one or more hidden layer and 1 output layer. Input layer comprises of independent/predictor variables and output layer displays dependent/outcome variable. Hidden layer (located mid of input layer and output layer) consists of hidden nodes which are vital elements of ANN because these nodes reveal information about relationships present among input and output variables.[21]

Developing the appropriate relationship model by designing the optimal MLP structure is not an easy task [22] so some crucial steps were focused before developing the MLP network structure. These included number of input and output nodes, number of hidden layers, number of hidden nodes in each hidden layer and activation functions.[21]

Present study run this analysis based on following structure: Number of input nodes were 3(W-FC, F-WC & religiosity) and 1 node in output layer (mental wellbeing) that were determined on basis of previous knowledge.[22]As reported by Guerrero Lazaro[22] this method of selection is known as model free approach. Best results of the present model were retrieved by performing several iterations with different configurations.

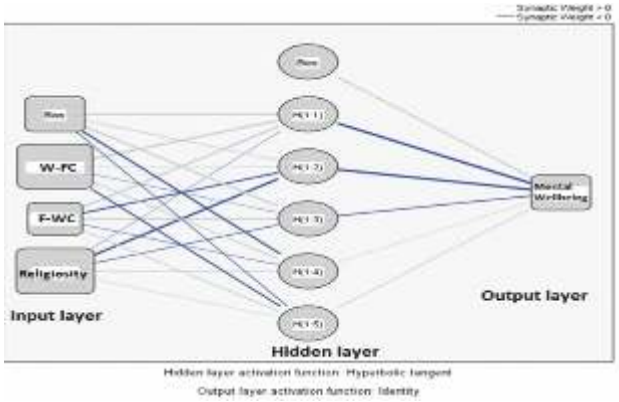

Fig. 1: Artificial Neural Network Model Diagram

As displayed in Figure 1. type of network structure of the present model is feed forward neural network. The input layer contained 3 nodes/predictors (W-FC, F-WC & religiosity) and yield node (output node) contained mental wellbeing as dependent variable. The present relationship model was consisted on one hidden layer with five nodes. Mostly one hidden layer is considered enough by the researchers for correlation purpose. To comprehend strength of relationship, present between network's input variables and output variables, magnitude of synaptic weights and sensitivity analysis are analyzed. Synaptic weights (parameter estimates) which seized and perform further from node of one layer to the node of another layer are considered high synaptic weights.[21]

First and foremost, in Figure 1. high synaptic weights (synaptic weight<0) showing the significant strength of the relationship between variables. As Figure 1 exhibited high synaptic weights for religiosity node and F-WC node because these nodes are connected to hidden nodes which are further connected to mental wellbeing node.

Table II: Artificial Neural Network Model Summary

Training	Sum of Squares Error	34.803
	Relative Error	.773
	Stopping Rule Used	1 consecutive step(s) with no decrease in error[a]
	Training Time	0:00:00.03
Testing	Sum of Squares Error	19.455
	Relative Error	.772

In SPSS before running the ANN model it is required to set partition of data into two sections named training and testing based on literature guidance. Partition of data were set 70% (91 cases) training and 30% (39 cases) testing from the sample. Table II. elaborated the sum of square errors and relative errors of training and testing. Through the values of sum of squares error and relative error values model fitting can be analyzed. In ANN training intends to minimize the error value so here the accuracy of estimation in the present model proves because sum of square value reduced from 34.80(in training) to 19.45(in testing). Relative error values of training (0.77) and testing (0.77) both are constant that gives the confidence that the present model is best fit to data and not over estimated. [23]

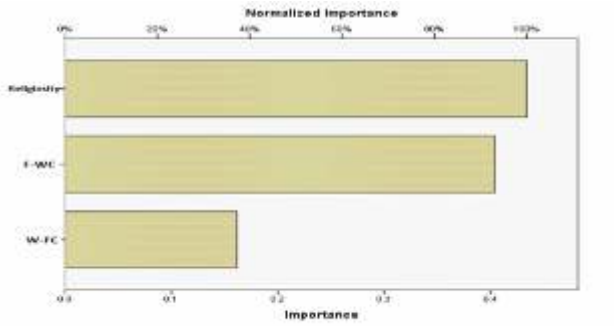

Fig. 2: Independent Variable Importance Analysis

Another important measure in ANN is Independent Variable Importance Analysis (sensitivity analysis). Figure 2. showed the results this sensitivity analysis which indicated the religiosity as the highest important predictor with 100% normalized importance. Further results revealed F_WC as the second important predictor with 93% normalized importance and W-FC as the third most important predictor of the mental wellbeing with 37% normalized importance value. Both analysis (regression & artificial neural network) revealed the similar results that supported the hypothesis of the present study.

Discussion

Primary goal of the study was to explore the both directions of work family conflict named as W-FC and F-WC and examine the relationship of these with mental well-being. Regression analysis revealed the non-significant negative relationship between W-FC & mental well-being and significant negative relationship between F-WC & mental wellbeing. ANN analysis also highlighted these as the important predictors of mental wellbeing through synaptic weights and normalized importance values. These findings are in line with the previous study which concluded the negative influence of work family conflict on the psychological wellbeing.[24]

Another objective was to explore the religiosity link with mental wellbeing. Independent variable importance analysis (sensitivity analysis) in ANN model revealed the clearer evidence that the religiosity as the highest important predictor of the mental well-being. Regression analysis revealed similar results and it is strongly supported by the empirical evidence provided by Zawawi.[9] Majority of previous studies indicated that religiosity contributes to the wellbeing of the people. Because

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religious practices help people to cope with stressors and people with high religious beliefs mostly have the healthier lifestyle.[10]

Previous research gaps which viewed work family conflict as a unidirectional construct were avoided. It was important to view both types of work family conflict because if the relationship found out between one type of work family conflict and wellbeing it would be difficult to infer the effects of other type of work family conflict on well-being and to manage it.[11]

Present study elucidates the knowledge about the work family imbalance issue and highlighted its consequences on mental wellbeing. Work family conflict has negative consequences it causes stress that leads to acute and chronic psychological health risks such as low life satisfaction and increase depression.[25]

Study pointed that large scale interventions are needed at the organizational level to lessen the work family conflict among professionals. Large scale interventions at workplace such as developing relational support culture, supportive schedule arrangements and wide-ranging workplace wellness initiatives such as fitness and meditation trainings may help to reduce stress and may provide pathway to increase wellbeing.[12]

Findings indicated that religious coping strategies can be effective to enhance mental well-being because many factors of religiosity such as prayer viewed as a form of meditation which has the calming effect.[26]

Similar findings of the regression analysis and ANN analysis in the present research also boost the perception that ANN can be a best alternative of the regression models because it gives clearer picture of prediction/relationship.

Study should be considered within the light of some limitations. Religiosity scale was used that measured single dimension of religiosity. Multidimensional measure should be used for broader concept of religiosity. Multi method approach should be used for data collection.

It provides important practical knowledge, that religiosity can be very helpful for boosting the mental well-being so this concept can be used as the home treatment to increase mental wellbeing. Psychologists might work on the religiosity and make therapies that must evolve religious aspect for dealing with mental well-being. It also contributed to medical literature by covering the topic relevant to medical professionals. Present research has implications for human resource managers to plan such strategies that least cause work family strain among employees. It emphasized towards considering the role of artificial intelligence methods (e.g artificial neural network) for exploring behavioral data in psychology.

Conclusion

Bidirectional work family conflict as W-FC and F-WC both negatively correlated with mental wellbeing among medical professionals. Present study provided empirical evidence that religiosity can positively predict mental well-being. Current study identified the need to plan the effective strategies by the organizations that minimize work family conflict among medical professionals and help them to achieve work-life balance and to raise their mental wellbeing.

REFERENCES

1. Mihelic KK, Tekavcic M. Work-Family Conflict: A Review of Antecedents and Outcomes. IJMIS 2013;18(1):15–26. doi: https://doi.org/ 10.19030/ijmis.v18i1.8335
2. Greenhaus JH, Beutell NJ. Sources of conflict between work and family roles. Acad Manage Rev 1985;10(1):76-88.
3. Barling J, Kelloway EK, Frone MR, editors. Handbook of work stress. Thousand Oaks: SAGE Publications; 2005. doi: http://dx.doi.org/ 10.4135/9781412975995
4. World Health Organization. Promotion of mental well-being: pursuit of happiness. [Internet]. 2013[cited 2016 April 29]. Available from: https://apps.who.int/iris/handle/10665/205709
5. Iddagoda YA, Opatha HHDNP. Religiosity Towards a Conceptualization and An Operationalization. Sri L J HR Manag 2017;7(1):59-69. doi: http://doi.org/ 10.4038/sljhrm.v7i1.5637
6. Zhou S, Da S, Guo H, Zhang X. Work-family conflict, and mental health among female employees A sequential mediation model via negative affect and perceived stress. Front Psychol 2018;9:544. doi: https://doi.org/ 10.3389/fpsyg.2018.00544
7. Kinnunen U, Mauno S, Geurts S, Dikkers J. Work-family culture in organizations: Theoretical and empirical approaches. Work and family: An international research perspective. 2005 Mar 23:87-120.
8. Achour M, Nor MR, Yusoff MY. Work–family demands and subjective well-being among female academicians the role of Muslim Religiosity. Rev Relig Res 2015;57(3):419-33. doi: https://doi.org/10.3389/fpsyg.2019.01525
9. Alaedein-Zawawi J. Religious commitment and

psychological well-being Forgiveness as a mediator. Eur Sci J 2015;11(5).117–41.
10. Abdel-Khalek AM, Tekke M. The association between religiosity, well-being, and mental health among college students from Malaysia. Revista Mexicana de Psicología. 2019;36(1):5-16.
11. Frone MR, Russell M, Cooper ML. Relation of work-family conflict to health outcomes A four-year longitudinal study of employed parents. J Occup Organ Psychol 1997;70(4):325–35. doi: https://doi.org/10.1111/j.2044-8325.1997. tb00652.x
12. Kossek EE, Hammer LB, Kelly EL, Moen P. Designing work, family & health organizational change initiatives. Organ Dyn 2014;43(1):53–63. doi: 10.1016/j.orgdyn.2013.10.007
13. Pandey J, Singh M. Positive Religious Coping as a Mechanism for Enhancing Job Satisfaction and Reducing Work-family Conflict a Moderated Mediation Analysis. J Manag Spiritual Relig 2019;16(3):314–338. doi: 10.1080/14766086.2019.1596829
14. Irfan M, Saeed S, Awan NR, Gul M, Aslam M, Naeem F. Psychological Healing in Pakistan: From Sufism to Culturally Adapted Cognitive Behaviour Therapy. J Contemp Psychother 2017;47(2):119–24. doi: https://doi.org/10.1007/s10879-016-9354-3
15. Ferri P, Guadi M, Marcheselli L, Balduzzi S, Magnani D, Di Lorenzo R. The impact of shift work on the psychological and physical health of nurses in a general hospital: a comparison between rotating night shifts and day shifts. Risk management and healthcare policy. 2016;9:203.
16. Carlson DS, Kacmar KM, Williams LJ. Construction and Initial Validation of a Multidimensional Measure of Work-Family Conflict. J Vocat Behav 2000;56(2):249–76. doi: http://dx.doi.org/10.1006/jvbe.1999.1713
17. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The Warwick-Edinburgh mental well-being scale (WEMWBS) development and UK validation. Health Qual Life Outcomes 2007;5(1):63. doi: 10.1186/1477-7525-5-63.
18. Worthington Jr EL, Wade NG, Hight TL, Ripley JS, McCullough ME, Berry JW, et al. The Religious Commitment Inventory—10 Development refinement and validation of a brief scale for research and counseling. J Couns Psychol 2003;50(1):84-96. doi: 10.5539/ijbm. v15n6p118.
19. Tayarani A, Baratian A, Bagher Naghibi Sistani M, Saberi MR, Tehranizadeh Z. Artificial neural networks analysis used to evaluate the molecular interactions between selected drugs and human cyclooxygenase2 receptor. Iranian journal of basic medical sciences. 2013;16(11):1196-1202.
20. Stangierski J, Weiss D, Kaczmarek A. Multiple regression models and Artificial Neural Network (ANN) as prediction tools of changes in overall quality during the storage of spreadable processed Gouda cheese. European Food Research and Technology. 2019 Nov;245(11):2539-47.
21. Guerrero L, Miguel A. Modelling building construction speed by using linear regression analysis artificial neural networks and n-dimensional finite elements. PhD Thesis. Universidad de Alicante; 2016.
22. Maier HR, Jain A, Dandy GC, Sudheer KP. Methods used for the development of neural networks for the prediction of water resource variables in river systems Current status and future directions. Environ Modell Software 2010;25(8):891–909. doi: 10.1016/j.envsoft.2010.02.003
23. Zhang G, Eddy Patuwo B, Hu M. Forecasting with artificial neural networks the state of the art. Int J Forecast 1998;14(1):35–62. doi: 10.1016/S0169-2070(97)00044-7
24. International Business Machines Corporation. IBM SPSS Neural Networks 22. [Internet]. New York: Armonk;[cited 2012 April 16]. Available from http://www.sussex.ac.uk/its/pdfs/SPSS_Neural_Network_22.pdf
25. Poms LW, Fleming LC, Jacobsen KH. Work–Family Conflict, Stress, and Physical and Mental Health: A Model for Understanding Barriers to and Opportunities for Women's Well-Being at Home and in the Workplace. World Med Health Policy 2016;8(4):444–57. doi: https://doi.org/10.1002/wmh3.211
26. Ismail Z. Soha DP. Religiosity and Psychological Well-Being. International Journal of Business and Social Science. 2012 [cited 2020 Sep 1]; 3(11):20-28. Available from: https://ijbssnet.com/journal/index/1294

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Utility of iRat as a Tool to Identify Low Academic Performers in 1st Year MBBS with High Scores in Pre-Medical Examination

Sana Malik, Atteaya Zaman, Saima Saleem, Saima Mumtaz Khatak, Anbreen Aziz, Madiha Imran

ABSTRACT

Objective: To identify low performers by utilizing individual readiness assurance test (i-RAT) scores in first year MBBS students using Team-based learning (TBL) strategy.

Study Design: Cross sectional observational study

Place and Duration of Study: Study was conducted in Federal Medical College Islamabad from 10th January to 31st March 2022.

Materials and Methods: TBL were introduced in 1st year MBBS. Six TBL activities were practiced by Anatomy Department during the 12-week respiratory and CVS course program. Premedical examination scores, first week individual readiness assurance scores and average i-RAT scores of 6 weeks were gathered. Mean and standard deviation were calculated. Difference in the first week i-RAT scores of three groups based on their premedical examination scores i.e., upper percentile group (A), middle percentile group (B) and lower percentile group (C). Each group comprised of 37 students, was calculated using One Way ANOVA Method. Pearson correlation coefficient (r) was used to access strength and direction of linear association between premedical examination scores and i-RAT scores. The data was analyzed in the statistical package for social sciences (SPSS) version 21 for analysis.

Results: High scorers in premedical examination (Group A) showed lowest scores in first week iRAT (i-RAT 1) and Average i-RAT when compared with group B and C with significant p value < 0.05. Significant increase was seen in progressive i-RAT scores in all 3 groups. Negative linear association (r= -0.2) was found between premedical examination scores and i-RAT 1 scores. A strong positive linear association with r= 0.54 was found between first i-RAT and average i-RAT scores.

Conclusion: High achievers in premedical examinations struggled the most in 1st year of medicine.

Key Words: *Individual Reassurance Test , MBBS, Premedical Scores, Team Based Learning.*

Introduction

Study of medicine is a challenging and tortuous course. It is declared as one of the lengthiest and stressful academic programs.[1] Once entering MBBS, students require knowledge and skill to gain marks that will be sufficient for them to become good doctors in future. Students are selected on merit in 1st year MBBS but at the end of year show poor performance irrespective of their premedical exceptional scores. Admission to medical college is extremely competitive. Medical studies are associated with chronic and high stress, and evidence has shown that such stress is linked to worse performance, intentions to quit, and elevated depression.[2] Literature has given the evidence that previous academic performance is used as a predictor for future performance in studies of selected students in a medical college though relation of antecedent scores with future performance in medical school years need to be explored.[3]

Studies have shown that pretest identifies low performers that might need extra support in learning and once the students at risk are identified educational intervention can help support such students.[4] For this purpose to identify low performers in 1st academic year of medicine with high premedical scores i-RAT is used in this study while conducting TBL exercises.

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TBL is one of the popular and effective strategy used in different educational systems.[5] Many medical collages have been using this strategy as primary mode of learning in undergraduate medical setup.[6] The benefits of TBL have been documented in literature many times stating that learning among students increases by active engagement in teamwork and practical skill.[7] Medical curriculum can be strengthened by implementing this instructional approach format, in earlier phases of the first year program where the focus is on basic science, leading to clinical importance as students move towards clinical years.[8]

Team based learning exercise for implementation is divided into three phases; preparatory phase; where students study before they come to class, readiness assurance test; where students take both individual and team assurance test to assess their understanding of pre-class material and application phases, where students apply learnt knowledge. In last phase students work as a team to share and improve learning.[9,10]

Individual readiness assurance test (i-RAT) helps to assess understanding of desired topic from pre class study directions and individual preparation. Team readiness assurance test (t-RAT) gives student an opportunity to get immediate feedback on assessment and team learning. The activity center around students being engaged in groups to solve problem related to topic of concern.[11]

i-RAT scores can be used to identify struggling students.[12] Single TBL exercise exposure of first year students of medicine were helpful in identifying top performers and struggling ones.[13] Individual readiness assurance test has significant value as literature suggests that it helps to pin down students that might not perform well in academic years of MBBS. TBL programs result in improvement in results of final examination of students interpreting that academically underperforming students are more assisted by team bases learning methodology.[7]

Research has been conducted previously to determine factors like personality, IQ, peer and family pressure contributing to be responsible for low performance in students of 1st year medical college.[14] Less evidence is available how to identify these low performers especially those with high premedical examination scores.

TBL activities help in tracking down students at peril to show low academic results. Such students require early interventions to strengthen their performance and educational experience. TBL methodology can be used as a tool for early screening out of students that might perform below par in first year of MBBS irrespective of being high marks achievers in premedical examination. The purpose of carrying out this research project was to utilize an active learning strategy to identify low performers in medical school by utilizing iRAT scores in first year CVS and Respiratory Anatomy Module.

Materials and Methods

It was a cross sectional observational study with the duration of 12 weeks. Study was conducted for students of 1st year MBBS (Session 2021) of Federal Medical College Islamabad. Whole class of One hundred and eleven students participated using nonprobability convenient sampling technique. Written consent was collected by all students before start of study.

After ethical approval of FMTI ethical review board (15th November 2021 letter number ECPIMS/02/16).Whole class was included with their consent. The Team based learning activity was introduced in 1st academic session in CVS and Respiratory modules of 6-week duration each. Six TBL activities were practiced by anatomy department during the course program which covered most of the taught anatomy content of the course. Each TBL activity was conducted as a large group discussion engaging whole class at the beginning of week 2,4,6 ,8, 10 and 12. Data was collected for 3 groups of students based on their premedical examination scores i.e., upper percentile group (A), middle percentile group (B) and lower percentile group (C). Each group comprised of 37 students. Following scores were gathered.

1. Premedical examination scores
2. Individual readiness assurance scores
3. Average i-RAT scores of 6 weeks

The premedical scores were obtained from college administration listed on basis of merit, i-RAT scores were maintained for each bi- weekly activity and documented on excel sheet and average i-RAT was calculated at the end of 12 week by calculating average of i-RAT scores obtained in six TBL activities. Validity and reliability of the test was ensured as per

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institutional policy. Mean and standard division of first week iRAT scores and average iRAT scores in 6 TBL activities were calculated for the 3 groups as mentioned in methodology. Difference in the first week i-RAT scores of three groups was calculated using One Way ANOVA Method. Pearson correlation coefficient (r) was used to access strength and direction of linear association between premedical examination scores and i-RAT scores. The data was analyzed in the statistical package for social sciences (SPSS) version 21 for analysis.

Result

Group A showed lowest scores in first week i-RAT (i-RAT 1) and Average i-RAT when compared with group B and C with significant p value< 0.05 indicating that the high achievers in premedical examinations struggled the most in 1st year of medical studies as briefed in table I.

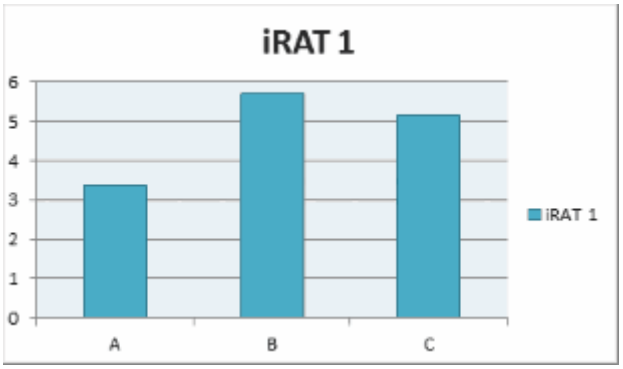

Figure 1: Comparison between i-RAT 1 and Premedical Examination Scores

Table I: Intergroup Comparison of p Values of i-RAT 1 and Average i-RAT

PARAMETER	GROUP A VS B	GROUP A VS C	GROUP B VS C
i-RAT 1 SCORES	0.00**	0.03*	0.37
AVERAGE i-RAT	0.02*	0.05	0.90

Significant increase is seen in progressive iRAT scores in all 3 groups, with maximum improvement seen in fifth and sixth week and minimum improvement is seen in upper percentile group when compared with the group B and C .

Negative linear association (r= -0.2) was found between premedical examination scores and i-RAT 1 scores of whole class with significant p value < 0.05, while very minimal negative association (r= -0.15) was found between premedical examination scores and average i-RAT with non-significant p value by using *bivariate Pearson Correlation. Negative association help fulfill the objective of identifying low* performers in medical school by utilizing i-RAT scores. A strong positive linear association with Pearson coefficient r= 0.54 and significant p value of 0.01 was found between first i-RAT scores and average i-RAT scores showing persistent improvement.

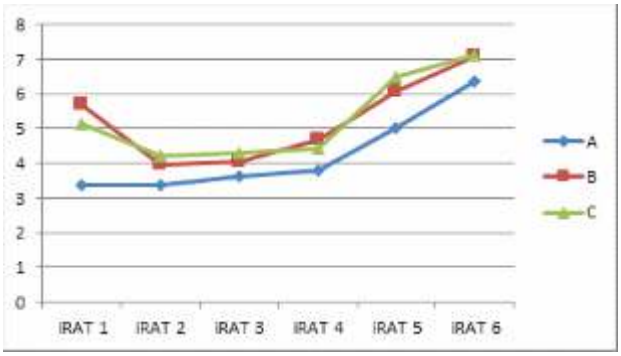

Figure 2: Progressive i-RAT Scores in 6 Weeks TBL Activities

Discussion

In early phase of the TBL activity i-RAT assesses students independent learning ability to learning materials shared before class[15]. We found that consistent improvement in weekly i-RAT in students performing in middle and lower percentile as compared to upper percentile students. Studies have documented that premedical scores are high predictors of good academic performance but contradictory evidence is also available in literature that shows no correlation between entrance test examination scores and academic performance.[16] In this study we gathered scores of premedical examination and i-RAT, we identified that the upper percentile students with highest scores in premedical examinations struggled the most in their first year of medical studies as indicated by their low i-RAT scores in first week of team based learning activity.

Negative association between premedical examination scores and first week i-RAT proved that high scorers lack in performing their best on entering medical college. Literature is also in favor of our finding where the MDCAT scores are not a determinant of good performance in initial preclinical years.[17]

Low scores in first week activity showed that high scorers struggled in their 1st year of medical collages. This factor is documented as one of the tool to

identify students who might be at risk to suffer in initial academic years.[18]

Individual readiness assurance test is utilized to identify these high scorers early in their academic years to give them early support to sustain their good performance in preceding clinical years. Positive association between first week i-RAT and average i-RAT is in favor of the fact that the identified students maintain their performance and this factor can be taken as a tool to predict their future performance. To identify students who might struggle in first academic year of MBBS is only beginning to preview and stream line approaches in terms of management, policymaking, teaching and counseling, to reduce failure, encourage and foster ways for students to success in beginning years of medical studies.[19]

Conclusion

We concluded using i-RAT that students with high scores in premedical examination don't perform well in medical colleges.

REFERENCES

1. Wang L, Lin C, Han C, Huang Y, Hsiao P, Chen L. Undergraduate nursing student academic resilience during medical surgical clinical practicum: A constructivist analysis of Taiwanese experience. Journal of Professional Nursing. 2021;37(3):521-8. https://doi.org/10.1016/j.profnurs.2021.02.004.
2. Bergmann C, Muth T, Loerbroks A. Medical students' perceptions of stress due to academic studies and its interrelationships with other domains of life: a qualitative study. Medical education online. 2019;24(1):1603526. https://doi.org/10.1080/10872981.2019.1603526.
3. Schneid SD, Kelly CJ, Brandl K. Relationships between preadmission variables and academic outcomes for postbaccalaureate students in medical school. Advances in Health Sciences Education. 2022;27(4):1033-48.) https://doi.org/10.1007/s10459-022-10129-3.
4. Aronson BD, Eddy E, Long B, Welch OK, Grundey J, Hinson JL. Identifying Low Pharmaceutical Calculation Performers Using an Algebra-Based Pretest. American Journal of Pharmaceutical Education. 2022;86(1). DOI: https://doi.org/10.5688/ajpe8473.
5. Parmelee D. Team-based learning. An Introduction to Medical Teaching: The Foundations of Curriculum Design, Delivery, and Assessment: Springer; 2022. p. 77-84. DOI: 10.1007/978-3-030-85524-6_6.
6. ELSHAMA SS. HOW TO APPLY TEAM-BASED LEARNING IN MEDICAL EDUCATION? Quantum Journal of Medical and Health Sciences. 2021;1(2):15-22. https://qjmhs.com/index.php/qjmhs/article/view/15.
7. James M, Baptista AMT, Barnabas D, Sadza A, Smith S, Usmani O, et al. Collaborative case-based learning with programmatic team-based assessment: a novel methodology for developing advanced skills in early-years medical students. BMC medical education. 2022;22(1):81. https://doi.org/10.1186/s12909-022-03111-5.
8. Burgess A, Matar E, Roberts C, Haq I, Wynter L, Singer J, et al. Scaffolding medical student knowledge and skills: team-based learning (TBL) and case-based learning (CBL). BMC medical education. 2021;21(1):1-14.https://doi.org/10.1186/s12909-021-02638-3.
9. Burgess A, Matar E. Team-based learning (TBL): theory, planning, practice, and implementation. Clinical Education for the Health Professions: Theory and Practice. 2020;20:1-29. https://doi.org/10.1007/978-981-13.
10. Gullo C, Ha TC, Cook S. Twelve tips for facilitating team-based learning. Medical Teacher. 2015;37(9):819-24. https://doi.org/10.3109/0142159X.2014.1001729.
11. Hopper MK. Alphabet Soup of Active Learning: Comparison of PBL, CBL, and TBL. HAPS Educator. 2018;22(2):144-9. doi: 10.21692/haps.2018.019.
12. Carrasco GA, Behling KC, Lopez OJ. First year medical student performance on weekly team-based learning exercises in an infectious diseases course: insights from top performers and struggling students. BMC medical education. 2019;19(1):1-5. https://doi.org/10.1186/s12909-019-1608-9.
13. Carrasco GA, Behling KC, Gentile M, Fischer BD, Ferraro TN. Effectiveness of a Team-Based Learning exercise in the learning outcomes of a medical pharmacology course: insight from struggling students. Naunyn-Schmiedeberg's Archives of Pharmacology. 2021:1-8. https://doi.org/10/1007/s 00210-021-02093-3.
14. Chakrabarti S, Anand VV. FACTORS CONTRIBUTING for DECREASED ACADEMIC PERFORMANCE AMONG FIRST YEAR MEDICAL STUDENTS. European Journal of Molecular & Clinical Medicine. 2020;7(9):164-79. ISSN 2515-8260.
15. Lin JW. The impact of team-based learning on students with different self-regulated learning abilities. Journal of Computer Assisted Learning. 2019;35(6):758-68. https://doi.org/10.1111/jcal.12382.
16. Rocha BAdSR, Toledo A. Predictive Factors of Graduation Delay in a Medical Program: a Retrospective Cohort Study in Brazil, 2010-2016. Revista brasileira de educação médica. 2020;44. https://doi.org/10.1590/1981-5271v44.1-20190205.ING.
17. Wu W, Garcia K, Chandrahas S, Siddiqui A, Baronia R, Ibrahim Y. Predictors of Performance on USMLE Step 1. The Southwest Respiratory and Critical Care Chronicles. 2021;9(39):63-72. https://doi.org/10.12746/swrccc.v9i39.813.
18. Christensen J, Harrison JL, Hollindale J, Wood K. Implementing team-based learning (TBL) in accounting courses. Accounting Education. 2019;28(2):195-219. https://doi.org/10.1080/09639284.2018.1535986.
19. Ahmady S, Khajeali N, Sharifi F, Mirmoghtadaei ZS. Factors related to academic failure in preclinical medical education: A systematic review. Journal of Advances in Medical Education & Professionalism. 2019;7(2):74. https://doi.org/10.30476%2FJAMP.2019.44711.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Spiritual Intelligence, Self-Management Skills, Depression and Anxiety in Patients with Tuberculosis

Sidra Saleem[1], Saima Majeed[2]

ABSTRACT

Objective: The present study aimed to examine the relationship between spiritual intelligence, self-management skills, depression, and anxiety in patients with tuberculosis.

Study Design: Correlational survey research design was used.

Place and Duration of the Study: This study was conducted in Pakistan and data was collected from Government TB Hospital Sargodha, from year December 1, 2019, to September 2020.

Materials and Methods: Participants comprised Tuberculosis patients (*N*= 113) both in and outpatients of Government TB, Hospital Sargodha. Four self-report measures including Spiritual Intelligence Self-Report Inventory,[1] The Self-Control and Self-Management Skills Scale,[2] Hamilton Depression Rating Scale,[3] and Hamilton Anxiety Rating Scale[4] were used for data collection. Both descriptive and inferential statistics were employed for the analyses of data.

Results: The results of Pearson product-moment correlation revealed that spiritual intelligence has a significant positive correlation with self-management skills ($r = .42$, $p < .001$) and a significant negative relationship with depression ($r = -.25$, $p < .01$) and anxiety ($r = -.27$, $p < .01$); self-management has a momentous negative relationship with depression ($r = -.59$, $p < .001$) and anxiety ($r = -.38$, $p < .001$). Depression has a significant positive association with anxiety ($r = .73$, $p < .001$). Hierarchical Regression analysis showed that self-management clarified 14 % variance in anxiety with $F(1, 111) = 18.51$, $p < .001$; and self-management clarified 35 % variance in depression with $F(1, 111) = 60.21$, $p < .001$.

Conclusion: The outcomes of the present study revealed that there is an important negative association between spiritual intelligence, depression, and anxiety. It was also revealed that there is a substantial positive relationship between spiritual intelligence and self-management skills in the present population of patients with tuberculosis.

Key Words: *Anxiety, Depression, Spiritual Intelligence, Self-Management Skills.*

Introduction

Tuberculosis is a chronic transferable illness.[5] In the individuals that are affected with TB there is a greater tendency to have psychological problems such as mood, addiction, depression, and anxiety disorders. The World Health Survey which was directed at 48 LMICs, concluded that there is a greater comorbidity between depression and TB.[6] The Individuals that are affected with psychological disorders such as depression are at greater risk to face the negative outcome of TB as compared to those who don't have depressive symptoms.[7] A lot of research that used psychological measures for checking mental health found that by taking the treatment of TB there will be a lower risk of developing psychological disorders. It was observed that treating TB at the very initial stage of the disease will increase the probability of developing good mental health.[8]

TB patients face a lot of mental and physical distress that results in poor outcomes of the disease.[9] The studies showed that there is a strange occurrence of depression and anxiety in patients with Tuberculosis in comparison to the general population which is about 3 to 17 percent and 7 to 82.3 percent correspondingly.[10] The occurrence of anxiety and depression comprehends an adverse impact on an

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individual self-care, value of life, and health care cost, etc.[11]A study used the global mental health assessment tool primary care version (GMHAT/PC) and stated that TB patients ached from psychological disorders for example stress, anxiety, depression, hypochondriasis and obsessive-compulsive disorder (OCD).[12] Although it has been stated that there is an association between psychological disorders and chronic illness pain but most of the research on this association has been done only in the Western populace. There is very less amount of knowledge about their relationship in the non-Western states.[13] In Pakistan very little research has been done on these variables in this combination of variables and with this population. The research on these variables in Pakistan has been done from a different perspective, research was done to discover the factors that are related to anxiety and depression.[14] A study was done to dig out the occurrence of depressive disorder in chronic illness patients.[15] The rationale for conducting a study on the association between Spiritual Intelligence (SI), self-management skills, depression, and anxiety in patients with Tuberculosis (TB) lies in the potential benefits it can provide to TB patients. TB is a chronic infectious disease that not only affects physical health but also has a significant impact on mental well-being. Depression and anxiety are common comorbidities among TB patients, further exacerbating their overall health and quality of life. Conducting a study on the association between SI, self-management skills, depression, and anxiety in TB patients can provide valuable insights into the interplay of these variables and their impact on the mental health outcomes of individuals with TB. The findings of this study can inform the development of targeted interventions, comprehensive care models, and support strategies that address the unique needs of TB patients, leading to improved treatment adherence, better mental health outcomes, and enhanced overall well-being.

Materials and Methods

A correlational survey research design was followed and employed a self-reported survey method for data collection. The sample of the present study consisted of tuberculosis patients (*N*= 113). Data were collected from the patients of tuberculosis from Government TB, Hospital Sargodha only. Data consisted of both males (*n*= 61) and females (*n*= 52). The individuals with Tuberculosis who were admitted to the hospital as well as those who came into the outpatient department were included. The individuals in the first and second stages of Tuberculosis were also included in the study. The patients who were having another physical disease along with Tuberculosis were not included in the study. As well as the individuals who were diagnosed with psychological disorders were not included in the study. After approval of the Board of Studies (BOS) of Riphah Institute of Clinical and Professional Psychology, Riphah International University, Lahore Campus, Pakistan (RICPP19/02K20/0238, 19 February 2020) present study was carried out. All ethical standards of APA were followed during the study. The enclosure and barring ethics were acknowledged by the researcher during the study. All the participants were ensured that their privacy will be maintained throughout the study and that the data collected from them will be used only for the study. The participants were provided with the free hand to leave the research at any time if they want without any penalty. All the participants were informed about the purpose of the study. An informed consent and approval form was taken from the participants before getting the data from participants. The participants were asked to fill out the demographic sheet and the four scales that were being used in the study. On average it took 20 to 25 minutes to fill all these scales. The data was normally distributed so parametric tests were chosen for the analyses. Pearson product-moment correlational analysis was used for the assessment of the relationship between variables as all the variables were continuous in nature. Hierarchical regression analysis was employed for prediction. All the collected data were analyzed by using SPSS version 21.

Results

The analysis of Pearson Product Moment Correlation indicated that Spiritual Intelligence has a positive association with self-management skills and a negative relationship with depression and anxiety. Hierarchical Regression Analysis revealed that spiritual intelligence and self-management skills negatively predicted depression and anxiety. Table 1 showed the frequency and percentage of the

participants in the study. Table 2 revealed the Psychometric Properties such as reliability, standard deviation, mean, Skewness and kurtosis, etc. of the variables under study. Table 3 revealed that spiritual intelligence has a positive and noteworthy association with self-management skills (r = .42, p < .001) and a noteworthy negative relationship with depression (r = -.25, p < .01) and anxiety (r = -.27, p < .01). The findings also indicate that self-management has a significant negative relationship with depression (r = -.59, p < .001) and anxiety (r = -.38, p < .001). Depression has a noteworthy positive relationship with anxiety (r = .73, p < .001). Table 4 showed that self-management clarified a 14 % variance in anxiety with *F* (1, 111) = 18.51, *p* < .001. Table 5 showed that self-management clarified 35 % variance in depression with *F* (1, 111) = 60.21, *p* < .001.

Discussion

The objectives of this research were to examine the relationship between spiritual intelligence, self-management skills, depression, and anxiety.

Table I: Demographic Data of Participants (N = 113)

Demographic variables	F	%
Gender		
Men	61	54
Women	52	46
Age		
Adulthood	46	40.7
Late adolescence	67	59.3
Marital Status		
Married	82	72.6
Unmarried	18	15.9
Separated	4	3.5
Widow	9	8
Stage of Tuberculosis		
1st stage	101	89.4
2nd stage	12	10.6
Type of treatment		
At home with medication	102	90.3
Admitted in hospital	11	9.7
Smoking		
Smoker	18	15.9
Non-smoker	75	66.4
Quit smoking due to illness	20	17.7

Table II: Psychometric Properties of the Study Variable (N= 113)

Range									
Variables	**Items**	***N***	***M***	***SD***	***A***	**Potential**	**Actual**	**Skewness**	**Kurtosis**
Spiritual Intelligence	24	113	36.78	11.38	.93	0-96	0-77	-.42	.19
Self-management skills	16	113	35.00	25.67	.65	0-80	0-68	.21	-1.22
Depression	17	113	22.27	14.58	.92	0-68	2-37	-.13	-.89
Anxiety	14	113	30.29	13.84	.88	0-56	1-56	1.32	1.59

Table III: Pearson Correlation between Spiritual Intelligence, Self-Management Skills, Depression and Anxiety (N= 113)

Variables	1	2	3	4
Spiritual Intelligence	--	.42***	-.25**	-.27**
Self-management skills	--	--	-.59***	-.38***
Depression	--	--	--	.73***
Anxiety	--	--	--	--

Table IV: Hierarchical Regression Results for Anxiety (N= 113)

Variables	B	95% CI		SE. B	B	R^2	ΔR^2
		LL	UL				
Step 1						.14	.14***
Constant	47.24***	39.04	55.44	4.14			
Self-management	-.48***	-.71	-.26	.11	-.38***		
Step 2						.16	.02
Constant	47.55***	39.38	55.74	4.13			
Self-management	-.41***	-.65	-.17	.12	-.32**		
Spiritual intelligence	-.08	-.19	.03	.06	-.14		

Note. ***p< .001; CI = confidence interval

Different hypotheses were made based on previous literature. After data collection and data analysis, significant results were obtained, and all hypotheses were accepted. Preliminary analysis also shows all assumptions of data normality and reliability of all scales were adequate to carry out inferential statistics. The results of Pearson product-moment correlation revealed that spiritual intelligence has a significant positive correlation with self-management skills (r = .42, p < .001) and a significant negative relationship with depression (r = -.25, p < .01) and anxiety (r = -.27, p < .01); self-management

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Table V: Hierarchical Regression Results for Depression (N= 113)

Variables	*B*	*95% CI*		*SE.B*	*B*	R^2	ΔR^2
		LL	*UL*				
Step 1						.35	.35***
Constant	47.50***	40.73	54.27	3.41			
Self-management	-.72***	-.90	-.54	.09	-.60***		
Step 2						.35	.01
Constant	47.52***	40.70	54.32	3.44			
Self-management	-.71***	-.92	-.52	.10	-.59**		
Spiritual intelligence	-.003	-.09	.08	.05	-.01		

Note. ***p< .001; CI = confidence interval

has a momentous negative relationship with depression (r = -.59, p < .001) and anxiety (r = -.38, p < .001). Depression has a significant positive association with anxiety (r = .73, p < .001). Research not only in Pakistan but around the world supported the present study results. for example, research was done to check the connection between spiritual intelligence, burnout, and mental health. It was an applied and descriptive correlational study. Standardized questionnaires of spiritual intelligence and mental health-related issues were used to collect the data. The Pearson Product Moment correlation analysis was applied to check the hypothesis. The results indicated a positive connection between spiritual intelligence and mental health and a negative and significant association was found between depression and spiritual intelligence.[16] Another research was conducted in Lahore, Pakistan to check out the association between stress and religious spiritual well-being, depression, and anxiety among the students at the university. It was a descriptive and analytical study. The sample of this study comprised 138 university students. By using the random sampling technique data was collected. For the analysis of results ANOVA, Independent sample t-test, regression, and Pearson Product moment correlation analysis were used. The outcomes of the study indicated that Religious spiritual well-being was negatively related to stress, anxiety, and depression.[17]

Likewise, research was done to check the association between spiritual status and the level of anxiety in patients who were suffering from Pulmonary Tuberculosis. This research was an investigative observational study in which a cross-sectional method was used. Spirituality was taken as the independent variable whereas anxiety was taken as the dependent variable. The sample of the study consisted of 55 patients with pulmonary tuberculosis. The sample was approached by using a simple random sampling technique. The findings of the research indicated that most of the patients have a normal level of anxiety, but they have a high level of spiritual outcomes. Thus, the consequences of the study indicated that an increased level of spiritual experience helps reduce anxiety.[18] The results of a study indicated that the practice of spiritual intelligence reduced stress, grief, and depression in youths. So, by the outcomes of this research, it could be determined that low levels of spiritual intelligence are related to stress and emotional overburden.[19]

The findings of the present research showed after Hierarchical Regression analysis that self-management clarified 14 % variance in anxiety and self-management clarified 35 % variance in depression. Self-management skills are negative predictors of depression and anxiety. Researchers conducted experimental research and results indicated that in the experimental group, the spiritual intelligence intervention decreased depression, anxiety, phobia, interpersonal sensitivity, aggression, and paranoid ideation in comparison to the control group. Thus, the outcomes of the research indicated that the training of spiritual intelligence is capable to reduce psychosomatic adversities and to increase the level of psychological health among students at higher secondary school.[20]

Furthermore, another research finding showed a positive and noteworthy association between spiritual intelligence and general health. So, on the results of this study, it was concluded that by improving the level of spiritual intelligence the general health of the nursing students will be good. It was also concluded that the promotion of spiritual intelligence increases the mental health along with physical health of the students of nursing.[21]

Similarly, other research findings were the same as the present study results. Researchers investigated the connection between spiritual intelligence and emotional well-being in teachers at primary schools. The research design of descriptive correlation was used in the research. By using the general health

questionnaire (GHQ) and spiritual intelligence self-report inventory 24 (SISRI-24) the data was collected. The regression and Pearson coefficient correlation analysis were used for analyzing the outcomes of the study. The outcomes of the research determined that the increased level of spiritual intelligence will lead to good mental health in teachers.[22]

A study was done to find out the influence of spirituality in the self-management of long-lasting illnesses in white and older Africans. This was a qualitative study, and the data was collected by using in-depth interviews with 88 people who were 65 years or older than 65 years. To conclude the outcomes of the research thematic content analysis was used. The outcomes of the present research indicated that there were cultural alterations in the usage of spirituality in the self-management of long-lasting illnesses. Results also showed that instead of these racial alterations spirituality was also an essential part of an individual's health and was significantly and positively related to self-management skills and the well-being of chronically ill patients[23].

Above mentioned literature shows that a plethora of research both national and international supported the present study results.

Conclusion

The outcomes of the present study revealed that spiritual intelligence has an inverse relationship with depression and anxiety. It was also revealed that there is a substantial positive relationship between spiritual intelligence and self-management skills in the present population of patients with tuberculosis. High levels of spiritual intelligence in patients show fewer symptoms of depression and anxiety among them. The self-management skills of the patients were also influenced by their level of spiritual intelligence and showed a positive relationship.

Implications

This study will help individuals to understand how their spiritual intelligence influences their general, mental, and physical health. This study will help individuals to realize that by developing a greater level of spiritual intelligence they can cope with their diseases easily and quickly. So, this study will give awareness to them that they could use interventions for developing spiritual intelligence to cope with their illness effectively. This study will help psychologists and other healthcare providers to develop spiritual intelligence among patients to enable them to cope with their illnesses effectively. This study will also provide awareness to the people how their lower level of spiritual intelligence will lead them toward developing mental illnesses such as depression and anxiety. And to also make them that how the level of spiritual intelligence will affect their self-management skills.

REFERENCES

1. King DB. Personal meaning production is a component of spiritual intelligence. Int J Exist Psychol Psychother. 2010;3(1) Corpus ID: 142905437
2. Mezo PG. The self-control and self-management scale (SCMS): Development of an adaptive self-regulatory coping skills instrument. J Psychopathol Behav Assess. 2009;31(2):83-93https://doi.org/10.1007/s10862-008-9104-2
3. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23(1):56. DOI: 10.1136/jnnp.23.1.56
4. Hamilton MA. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32(1):50-5. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x
5. Division of Tuberculosis Elimination. Centre for Disease Control and Prevention. Available from: https://www.cdc.gov/tb/topic/basics/glossary.htm
6. Papakostas GI, Shelton RC, Kinrys G, Henry ME, Bakow BR, Lipkin SH, et al. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. Mol Psychiatry. 2013;18(3):332-9. DOI: 10.1038/mp.2011.166
7. Ahmad N, Javaid A, Syed Sulaiman SA, Basit A, Afridi AK, Jaber AA, et al. Effects of multidrug-resistant tuberculosis treatment on patients' health-related quality of life: results from a follow-up study. PLoS One. 2016;11(7) https://doi.org/10.1371/journal.pone.0159560
8. Babikako HM, Neuhauser D, Katamba A, Mupere E. Feasibility, reliability, and validity of health-related quality of life questionnaire among adult pulmonary tuberculosis patients in urban Uganda: a cross-sectional study. Health Qual Life Outcomes. 2010;8(1):1-8 DOI: 10.1186/1477-7525-8-93
9. Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR. Perceptions of tuberculosis patients about their physical, mental, and social well-being: a field report from South India. Soc Sci Med. 2005;60(8):1845-53 DOI: 10.1016/j.socscimed.2004.08.024
10. Morrison SD, Banushi VH, Sarnquist C, Gashi VH, Osterberg L, Maldonado Y, et al. Levels of self-reported depression and anxiety among HIV-positive patients in Albania: a cross-sectional study. Croat Med J. 2011;52(5):622-8 doi: 10.3325/cmj.2011.52.622
11. Horn, E.K., van Benthem, T.B., Hakkaart-van Roijen, L. *et al.* Cost-effectiveness of collaborative care for chronically ill

patients with comorbid depressive disorder in the general hospital setting, a randomised controlled trial. *BMC Health Serv Res* 7, 28 (2007). https://doi.org/10.1186/1472-6963-7-28
12. Peltzer, K., Naidoo, P., Matseke, G. *et al.* Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. *BMC Psychiatry* 12, 89 (2012). https://doi.org/10.1186/1471-244X-12-89
13. Barker C, Pistrang N, Elliott R. Research methods in clinical psychology: An introduction for students and practitioners. Chichester, UK: John Wiley & Sons; 2015.
14. Husain N, Chaudhry IB, Afridi MA, Tomenson B, Creed F. Life stress and depression in a tribal area of Pakistan. Br J Psychiatry. 2007;190(1):36-41 DOI: 10.1192/bjp.bp.106.022913
15. Motiani B, Haidri FR, Rizvi N. Frequency of depression in Chronic Obstructive Pulmonary Disease (COPD) patients. Pak J Med Sci. 2011;27(5) https://pjms.com.pk/index.php/pjms/article/view/1397
16. Bhaware GM, Quazi SZ, Muneshwar SM. Assessment of Mental Status of MDR Patients in Wardha District Using Global Mental Health Assessment Tool-Primary Care Version. J Academia Ind Res. 2014;3(6):274 https://www.academia.edu/9450537/Assessment_of_Mental_Status_of_MDR_Patients_in_Wardha_District_Using_Global_Mental_Health_Assessment_Tool_Primary_Care_Version
17. Tabarsa N, Jalaei HR. The relationship between spiritual intelligence with mental health and job burnout (Case study: Rural cooperative organization of Golestan province). Dutch J Finance Manag. 2017;1(2):46 DOI:10.29333/DJFM/5822
18. Taheri-Kharameh Z, Abdi M, Omidi Koopaei R, Alizadeh M, Vahidabi V, Mirhoseini H. The relationship between religious-spiritual well-being and stress, anxiety, and depression in university students. Health Spirituality Med Ethics. 2016;3(1):30-5 http://ijn.iums.ac.ir/article-1-2358-en.html
19. Widyastuti M, Hastuti P, Kirana SA, Farendita NH. The Correlation of Spiritual Status and Anxiety Level in Patients with Pulmonary Tuberculosis. J Ners. 2020;15(2):67-71 https://doi.org/10.20473/jn.v15i1Sp.18946
20. Ebrahimi M, Jalilabadi Z, Chenagh KG, Amini F, Arkian F. Effectiveness of training of spiritual intelligence components on depression, anxiety, and stress of adolescents. J Med Life. 2015;8(Spec Iss 4):87 PMID: 28316712; PMCID: PMC5319280.
21. Charkhabi M, Mortazavi A, Alimohammadi S, Hayati D. The effect of spiritual intelligence training on the indicators of mental health in Iranian students: An experimental study. Procedia Soc Behav Sci. 2014;159:355-8. doi:10.1016/j.sbspro.2014.12.387
22. Heravi-Karimooi M, Rejeh N, Sharif Nia H. The relationship between nursing students' spiritual intelligence and their general health in Tehran. Iran J Med Educ. 2014;14(1):1-4 http://ijme.mui.ac.ir/article-1-2810-en.html
23. Harvey IS, Silverman M. The role of spirituality in the self-management of chronic illness among older African and Whites. J Cross Cult Gerontol. 2007 Jun;22(2):205-20. doi: 10.1007/s10823-007-

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

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The manuscript should be typed in MS Word. Each manuscript should include a title page (containing email address, cell numbers, institution, and postal address of the corresponding author), abstract, key words, text, acknowledgements (if any), references, tables (each table, complete with title and footnotes) and legends for illustrations and photographs. Each component should begin on a new page. Sub-headings should not be used in any section of the script except in the abstract.

TEXT ORGANIZATION

All manuscripts except Short Communication and Letter to the Editor should be divided into the following sections.

ABSTRACT

Abstracts of original article should be in structured with following sub-headings:

- Objective
- Study Design
- Place & Duration of Study
- Materials & Methods
- Results
- Conclusion

Four elements should be addressed: "why did you start?", "what did you do?", "what did you find?" and "what does it mean? “.” Why did you start?" is addressed in the objective. "What did you do?" constitutes the methodology and could include design, setting, patients or other participants, interventions, and outcome measures. "What did you find?" is the 'results', and "what does it mean?" would constitute the conclusions. Please label each section clearly with the appropriate sub-headings. Structured abstract for an original article, should not be more than 250 words. At least 3 key words should be written at the end of the abstract. Review articles, case reports and others require a short, unstructured abstract. Commentaries do not require an abstract.

INTRODUCTION

Write this section with references as per following instructions:

1. Give background information about the subject matter and the issues your study intends to address. Only strictly pertinent references should be cited, and the subject should not be extensively reviewed.
2. Describe what is known (in the literature) and what is not clear about the subject with reference to relevant literature thus identifying the literature gap.
3. You write the rationale (justification) of your study.
4. Finally, you mention the objective of your study

MATERIALS AND METHODS

Methodology is written in past tense.

Follow this sequence **without headings:**

- Study design
- Place and Duration of Study
- Sample size
- Sampling technique
- Mention about permission of the ethical review board and other ethical issues addressed.
- Inclusion and Exclusion Criteria
- Data collection procedure-
- Type of data: parametric or nonparametric
- Data analysis: including Statistical Software used, and statistical test applied for the

calculation of p value and to determine the statistical significance. Exact p-values and 95% confidence interval (CI) limits must be mentioned instead of only stating greater or less than level of significance. All percentages must be accompanied with actual numbers.

RESULTS

These should be presented in logical sequence in the text, tables, and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized. No opinion should be given in this portion of the text.

DISCUSSION

This section should include the author's comments on the results. Write in present tense, active voice except for results, which are written in past tense. It should be written in following sequence:

- First, very briefly summarize, Interpret and discuss main results and don't merely repeat the results.
- Discuss key studies relevant to your study.
- Compare your work with other's work.
- Describe limitations of your study.
- Suggest future work if necessary.

CONCLUSION

Conclusion should be provided under a separate heading. It should be in congruence with the objective. No recommendations are needed under this heading.

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References must be written in Roman Number and in the Vancouver Style only. References should be numbered in the order in which they are superscripted in the text. At the end of the article, the full list of references should give the names and initials of all authors (unless there are more than six when only the first six should be given followed by et al). The author's names are followed by the title of the article; title of the journal abbreviated according to the style of the Index Medicus (see "List of Journals Indexed", printed yearly in the January issue of Index Medicus); year, volume, and page number, e.g., Hall, RR. The healing of tissues by C02 laser. Br J. Surg: 1970; 58:222-225. References to books should give the names of editors, place of publication, publisher, and year. The author must verify the references against the original documents before the article. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication.

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Tables and illustrations should be merged within the text of the paper, maximum number of tables and illustrations should not exceed four, and legends to illustrations should be typed on the same sheet. Tables should be simple and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 ½" x 11' paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scattergrams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be made with MS Excel and be sent as a separate Excel file even if merged in the manuscript. For scanned photographs the highest resolution should be used.

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- Cover Letter

- JIIMC Checklist
- JIIMC Conflict of Interest Performa
- JIIMC CopyRight and Undertaking Agreement
- IRC Certificate
- Bank draft as initial processing fee (Original bank draft send in JIIMC office)

Template of these files is available in the download section.

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