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STUDY OF SERUM FERRITIN IN SARS COVID-2 POSITIVE DIABETES MELLITUS PATIENTS.

Dr.Ch.KALAVATHI[1], Dr. V.LAKSHMI NARSAMMA[2], Dr.KESUBATHULA .VENKATESWARLU[3], Dr.U.SREELAKSHMI [4]

Affiliations:

1. Professor and head, Department of Biochemistry, Government Medical College, Nandyal, AP

2. Professor and head Department of Biochemistry, Government Medical College, Kadapa, AP

3. Associate professor, Department of Biochemistry, Government Medical College, Nandyal, AP

4. Assistant professor, Department of Biochemistry, Government Medical College, Nandyal, AP

Corresponding Author-DR.U.SREELAKSHMI

Assistant professor, Department of biochemistry, Government medical college, Nandyal

Email:-usreelakshmi2@gmail.com

Phone:-8500532082

Abstract:

Introduction: COVID-19 is a global pandemic caused by [severe acute respiratory syndrome-corona virus] SARS-CoV-2 which belongs to genera beta corona virus. In the pathogenesis of the present pandemic many inflammatory markers are being rised and are causing cellular damage.

Objectives of present study includes [1] study serum ferritin levels in type 2 diabetes mellitus patients who are confirmed as covid positive cases by RT-PCR technique and[2] To compare serum ferritin in covid cases without any co-morbidities.

Methods: - Present study is a case control study done at department of Biochemistry at state covid clinical laboratory, Government general hospital, Kurnool, Andhra Pradesh for about 4 months from April2020 to July 2020. It includes 50 covid positive cases who are known diabetic and 50 were controls who are also tested covid positive but without any co morbidities**.**

Results:-Data is entered in excel spreadsheet and statistically analyzed using spss software. Mean with serum Ferritin in cases is 573.13±94.79, P value-<0.0001 and controls are 268.50±40.48, P value-<0.0001.

Conclusion:- A statistical significant results shows that high serum ferritin levels in covid positive diabetes mellitus cases is attributed to cellular damage caused by hyperglycemia and in turn serum ferritin causing hyperinsulinemia and hyperglycemia

Key words:-COVID-19, SARS-COV-2, RT-PCR, Serum ferritin, hyperglycemia.

1. INTRODUCTION

The global pandemic covid-19 is caused by SARS COV-2 belonging to betacoronavirus genus. Coronaviruses are known to cause disease in humans and animals. Among these, four (human coronaviruses 229E, NL63, OC43 and HKU1) typically infect only the upper respiratory tract and cause relatively minor symptoms. However, there are three coronaviruses (severe acute respiratory syndrome coronavirus (SARS- CoV), Middle East respiratory syndrome coronavirus

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(MERS- CoV) and SARS- CoV-2) that can replicate in the lower respiratory tract and cause pneumonia, which can be fatal. Like the other respiratory coronaviruses, SARS- CoV-2 is transmitted primarily via respiratory droplets. On infection, the median incubation period is approximately 4–5 days before symptom onset with 97.5% of symptomatic patients developing symptoms within 11.5 days[1]

The pathophysiology of SARS- CoV-2 infection closely resembles that of SARS- CoV infection, with aggressive inflammatory responses. Disease severity in patients is not only because of the viral infection but also the host response. The pattern of increasing severity with age and co morbidities is also broadly consistent with the epidemiology of SARS- CoV and MERS- CoV.

There is unrestrained inflammatory cellular infiltration causing damage in the lung through excessive secretion of proteases and reactive oxygen species, in addition to the direct damage resulting from the virus. In addition to local damage, cytokine storm also has ripple effects across the body .Older people (those aged over 60 years) and people with co- morbidities are more likely to develop such a dysfunctional immune response that causes pathology and also fails to successfully eradicate the pathogen. [2]

Acute phase reactants like CRP, FERRITIN, begins to rise in the serum of covid-19 patients. Ferritin is storage form of iron in the cells and serum ferritin levels are widely measured as indicators of iron status. Human ferritin is some 12-nm diameter overall, with a 2nm thick protein shell and a hollow internal 8-nm diameter cavity capable of holding up to 4500 iron atoms.[3] Since intracellular ferritin is a means of storing iron safely, and indeed its synthesis is increased in response to oxidative stress one should not expect serum ferritin to be related to biomarkers reflecting hydroxyl radical formation via the Fenton reaction that is catalyzed by unliganded iron.

Serum ferritin exists, despite the fact that ferritin is not synthesized in the serum. Serum ferritin lacks most of the iron it contained when intracellular. The intracellular ferritin must have ‘dumped’ its unliganded iron somewhere, where it can participate in Haber-Weiss and Fenton reactions, creating hydroxyl radicals and consequent further cellular damage. . The serum ferritin protein is itself considered benign yet the level of serum ferritin correlates with numerous inflammatory and degenerative disease.

Serum ferritin and glycemic levels are well correlated in various studies. Diabetes mellitus itself is the result of oxidative stress. Oxidative stress plays an important role in the pathogenesis of the complications seen in T2DM. Superoxide and hydrogen peroxide appear to be the primary generated species. These reactive oxygen species play a role in the generation of additional and more reactive oxidants, including the highly reactive hydroxyl radical in which iron salts play a catalytic role in a reaction. This reaction is referred to as the metal catalyzed Haber-Weiss reaction.

The role of iron in the pathogenesis of diabetes is suggested by an increased incidence of type 2 diabetes in diverse causes of iron overload and reversal or improvement in diabetes (glycemic

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control) with a reduction in iron load achieved using either phlebotomy or iron chelation therapy . The importance of protein glycation is well known in the pathogenesis of diabetic vascular complications. Transition metals also play a role in protein glycation induced by hyperglycemia. It has been shown that glycated proteins have a substantial affinity for the transition metals, and the bound metal retains red ox activity and participates in catalytic oxidation. Ferritin has been referred as a marker for insulin resistance possibly due to iron deposition in the liver leading to hepatic insulin resistance and increased hepatic glucose production.[4]

AIMS & OBJECTIVES :-

1] To study serum ferritin levels in type 2 diabetes mellitus patients who are confirmed as covid positive cases by RT-PCR technique.

2] To compare serum ferritin levels in covid cases with and without any co-morbidities

MATERIALS AND METHODS

- STUDY AREA: Department of biochemistry at state covid hospital-24hrs clinical laboratory, GGH , kurnool, Andhra Pradesh.
- STUDY PERIOD: 4 months (April 2020 to July 2020)
- STUDY DESIGN: Prospective case control study.
- SAMPLE SIZE: 50 cases and 50 controls within age group of 35-60years.

❑ INCLUSION CRITERIA: 100 covid positive cases confirmed by either RT-PCR or through chest CT, of which 50 cases are having type 2 diabetes mellitus as co morbidity and remaining 50 patients without any co morbidities.

❑ EXCLUSION CRITERIA:

1. Type 1 diabetes mellitus
2. Patients with repeated blood transfusions
3. Patients on iron supplementation
4. Patients with history of hypertension, coronary artery disease, stroke.
5. Patients with chronic inflammatory conditions
6. Pregnant women

SAMPLE COLLECTION AND METHODOLOGY

1] 5 ml of blood was collected under aseptic precautions from selected subjects on overnight fasting of 8- 12 hours for fasting blood glucose.

2] 2 hours postprandial blood samples were collected for estimation of postprandial blood glucose, CRP, and serum ferritin.

3] Blood glucose estimation was done by Glucose oxidase - peroxidase method

4] Serum ferritin was estimated by Latex particle immuno turbidometric method using fully automated analyzer

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RESULTS

- The data is entered in excel spreadsheet and statistically analyzed using spss software. 21.
- Student't' test has been used to find the significance of serum ferritin levels between cases/controls**.**

Parameters(Mean±SD)	Cases	controls	P value
FBS (mg/dl)	**143.96±19.33**	**89.16±9.41**	**<0.0001**
Serum ferritin (ng/ml)	**579.13±64.79**	**268.50±20.48**	**<0.0001**
CRP(mg/dl)	**105.01±56.04**	**34.27±32.72**	**<0.0001**

DISCUSSION

Covid -19 positive cases especially with co morbidities are at worst prognosis. Under normal physiological conditions approximately 90% of body glucose is metabolized by glycolytic pathway and remaining 10% glucose is metabolized by Hexose-monophosphate shunt pathway. From glycolysis and Krebs's cycle ATP, NADH and $FADH_2$ are generated due to oxidative Phosphorylation and substrate level Phosphorylation.[5]

Similarly in hyperglycemia more of glucose undergo metabolism and more of NADH is produced depleting the NAD^+ reserves.

NADH is an electron carrier, donates its electrons at complex- I of electron transport chain. During oxidation of NADH at complex-I, proton pumping occurs. More NADH produced in hyperglycemia causes electron pressure over mitochondria. But mitochondria works up to its capacity and electrons leaking occurs at complex-I and they partially reduce oxygen to superoxides.

Superoxide is the precursor of reactive oxygen species [ROS]. More superoxides are produce in diabetes and increase the ROS [Reactive oxygen species] which leads to the development of oxidative stress.

Oxidative stress promotes branching off pathways to glucose metabolism. There are five such pathways:[6]

1) Polyol pathway
2) Hexosamine pathway
3) Protein kinase-C activation pathway
4) Advanced glycation end products[AGEs]
5) Glyceraldehydes autoxidation pathway.

Chronic hyperglycemia in diabetics causing oxidative damage of tissues resulting in liberation of free iron into blood stream. Ferrous iron liberated is a potent pro oxidant causing

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inhibition of insulin internalisation and action, resulting in hyperinsulinemia and insulin resistance.

SARS-COV-2 infection in alveolar cells and dendritic cells causes the release of inflammatory signals which act upon dendritic cells, macrophages and monocytes.interleukin-1, interleukin-10, tumor necrotic factor alpha. Interleukins acts over tissues and endothelial cells of blood vessels. Interleukins over liver causes increased CRP, Ferritin, hepcidin, and fibrinogen and decreased Albumin. Thus macrophages and cytokines are involved in production of serum ferritin in covid Cases.Hyperferritinemia which in turn promotes production of pro-inflammatory (IL-β) and anti-Inflammatory cytokines (IL-10).

CONCLUSION

High serum ferritin levels in covid patients are attributed to host defence mechanism and High ferritin levels in diabetes patients is due to hyperglycaemia and insulin resistance .So in diabetes mellitus cases with covid positivity are at more vulnerable when compared to cases without co morbidities. Hence treatment modalities need to be changed in treating covid positive diabetes patients in order to reduce morbidity and mortality.

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