

Is there any relationship of serum Growth Differentiation Factor 15 and Iron Profile with Age?

Awais Amjad, Aiman Farogh Anjum

ABSTRACT

Objective: To compare growth differentiation Factor-15(GDF-15), iron and ferritin levels in younger and elderly patients suffering from end stage renal disease on hemodialysis and to determine is there any age-related change in these markers?

Methodology: This cross-sectional comparative study was conducted in the Nephrology Department of Sheikh Zayed Hospital Lahore from January 2018 to December 2018 after getting approval from Institutional Review Board of National Health Research Complex (NHRC) with vide no. F39/NHRC/Admin/IRB/372 Written consent was taken from patients. Group A has < 60 years, while group B was with patients of ≥ 60 years of age. Serum GDF-15, serum iron and ferritin of hemodialysis patients were determined by ELISA. Statistical analysis was done by SPSS 22.0. P value ≤ 0.05 is taken statistically significant.

Results: The total number of patients was 140. Group A has 86 patients (40 male and 46 female). Group B had 54 patients (36 male and 17 female). Group A and Group B participants had serum median (IQR) GDF-15 levels 684(120-1604) and 2650(369-3625) pg/ml respectively, (P value 0.001).

Conclusion: GDF-15 levels were significantly elevated in patients ≥ 60 years of age and ferritin levels were similar in all age groups.

KEYWORDS: Age, Ferritin Growth differentiation factor 15, Inflammation, Iron

INTRODUCTION

Growth Differentiation Factor -15 (GDF-15) is a new marker of the growth super family.¹ The physiological role of GDF-15 is unclear and still under research. It is described in iron metabolism in literature. In healthy people normal GDF-15 levels are 460 – 920 pg/ ml. Intracellular iron deficiency due to any reason leads to increased secretion of GDF-15 by cells.² Its secretion is also induced by stress, hypoxia and inflammation. GDF-15 is expressed by most of the tissues of body such as brain, intestines, lungs and circulatory

system. It seems that it is a physiological compensatory response of these tissues after cellular injury, increased GDF-15 levels may have a protective effect on these tissues.³

GDF-15 is a well-recognized biomarker for a number of chronic diseases such as cardiovascular disease.⁴ Its levels are elevated in neurological patients suffering from mitochondrial diseases.⁵ Some studies reported high levels in diabetes also.⁶ Its levels are raised in cognitive decline disease also.⁷ Many cancers such as lung, ovarian & colon cancer have reported elevated levels up to 5000 pg/dl. Rheumatoid arthritis were also found to have elevated levels of GDF-15 depending upon severity of disease.⁸ GDF-15 protein is increased in chronic inflammation.⁹

The relationship between aging & Growth differentiation factor protein is very interesting and ongoing. We conducted this study to find out any relation of serum GDF-15 levels to age of patients

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on hemodialysis. Aging is associated with progressive deterioration of human physiology and increase in organ pathology. The immune system of the human body weakens with age. Aging is associated with chronic low- grade inflammation. So GDF-15 levels should increase with age. It is mentioned that Growth Differentiation Factor is a anti-aging protein that can reverses age-related hypertrophy in cells. There is reversal of age-related dysfunction in skeletal muscle cells of mouse by GDF protein.¹⁰ A recent study done showed that GDF-15 also has anti-aging actions on mice and human cells.¹¹

METHODOLOGY

This cross-sectional comparative study was conducted in Nephrology Department of Sheikh Zayed Hospital Lahore from January 2018 to December 2018 after getting approval from Institutional Review Board of National Health Research Complex (NHRC), vide no F39/NHRC/ Admin/IRB/372. Sample size of 140 was calculated by using 95% confidence level, 90% power, U1-U2 (5218 – 5026), $\sigma^2=12200$ and $Z=1.96$ by formula: $n = 2 \sigma^2 (Z_{1-\alpha/2} + Z_{1-\beta})^2 / (U1-U2)$. Where Z = normal distribution of values, α level of significance, β = power of test, σ^2 = variance and U1- U2 is mean difference of IGF of two groups. The inclusion criteria was male and female adult patients undergoing hemodialysis with age more than 18 years. Patients who fulfilled inclusion criteria were selected by purposive sampling technique. Subjects were stratified into two groups based on age. Group A had an age < 60 years and group B had age \geq to 60 years. The exclusion criteria included acute active inflammation, thrombosis, acute heart failure, absolute and functional iron deficiency. All these conditions also raise serum GDF-15 levels. Venous blood samples were collected after taking informed consent from included patients. Centrifugation was used to separate serum from blood. Serum was frozen at -20C. Growth differentiation factor 15 was measured by ELISA (R & D systems, Minneapolis, USA

CAT no DGD 150) at National health Research Centre. Serum ferritin, serum iron were measured at biochemistry laboratory of Sheikh Zayed Hospital.

The data was analyzed using IBM-SPSS (Statistical Package for Social Sciences) version 22. Quantitative variables such as GDF15, time duration on hemodialysis of patients, iron, ferritin, TIBC, hemoglobin was reported as median with inter-quartile range. Categorical variables like gender are presented as frequencies and percentages. Shapiro Wilk test was used to check the normality of data. Non-parametric Mann Whitney U test was used to compare the difference in quantitative variables as data had non-normal distribution. Chi square(X^2) test was applied to compare gender distribution among the both groups Statistical significance was set at p value \leq to 0.05.

RESULTS

Total number of patients was 140. Group A (Age <60) had 86 patients (40 male &46 female) Group B (\geq 60 years) had 54 patients (37 male &17 female). Gender distribution of the both groups are presented in figure1 a & b. In group A 46(53.5%) were females and only 40 (46.5%) were male (figure1a). In comparison to group A, majority 37 (68.5%) of total group B population was comprised of male patients and females were only 17(31.5%).

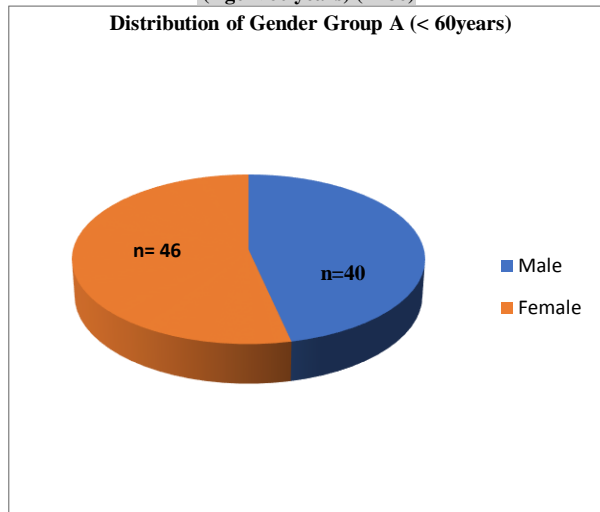
Table 1: Comparison of Age & Biochemical Characteristics of Study Population.

	Group A / Age <60 n= 86 median (IQR)	Group B age\geq60 n=54 median (IQR)	P Value
Median age	33(18-58)	65 (60-70)	<0.001
GDF-15(pg/ml)	684 (120 – 1604)	2650 (369 - 3625)	<0.001
Ferritin (ng/ml)	371 (342 - 526)	390 (258 - 599)	0.51
Time duration on hemodialysis of patients in yrs	4 (1 – 6)	3 (1- 6)	0.892
Serum Iron(ug/dl)	42 (35.3- 48.5)	40.0 (35.0 – 46.0)	0.236

P value \leq 0.05 was significant

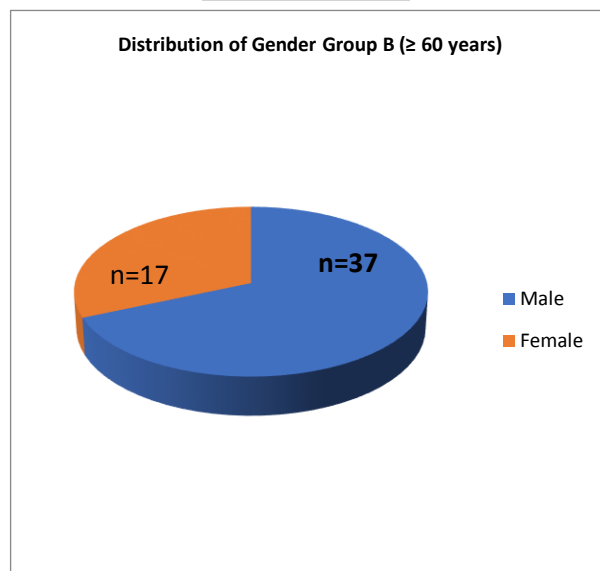
Chi square (X^2) test showed significant difference in gender distribution among the both groups with p value 0.260.

Figure 1a: Distribution of Gender among Group A
(Age < 60 years) (n=86)



There was significant difference in GDF-15 between groups. Group B had significantly higher serum GDF15 levels than Group A. Serum median GDF-15 levels in patients in group B with age ≥ 60 were 2650 (369 - 3625) pg/ml whereas median GDF-15 levels in group A patients with age < 60 were 684 (120 - 1604) pg/ml. (p value < 0.05). There was no significant difference in median time duration on hemodialysis, serum ferritin; serum iron between group A and B as p value were > 0.05

Figure 1 b: Distribution of Gender among Group B
(age ≥ 60 years) (n=54)



DISCUSSION

Aging is a cellular stress response to molecular damage. Damaged tissues secrete GDF-15 via stress and inflammatory responses and pathways. GDF15 has also been reported to be a senescence-associated secretory phenotype (SASP) protein, indicating its role in cellular senescence. Serum GDF-15, similar to telomere length of chromosome, can predict life span of an individual. It is emerging as a biomarker for aging process in chronic diseases and thus a target for drug interventions aimed to promote healthy aging. Increased GDF-15 levels predicted mortality in patients with chronic diseases by influencing several cellular processes such as apoptosis, mitochondrial dysfunction and endoplasmic reticulum stress. However the specific mechanisms underlying its involvement in aging is unclear and areas of further research.¹²

In our study elderly hemodialysis patients had significantly higher GDF-15 levels than younger ones. In this our study patients aged ≥ 60 years had serum GDF-15 levels of 2650 (369 - 3625) pg/ml whereas patients aged < 60 had GDF-15 levels of 684 (120 - 1604) pg/ml. P value = 0.001.

Our study showed no significant difference between ferritin levels and serum iron levels in hemodialysis patients with age more than 60 and less than 60.

Doerstling et al demonstrated that GDF-15 strongly linked with age and its levels increased as age increased. Doerstling study did not study iron and ferritin levels.¹³ A study done by Tavenier et al in Denmark showed that GDF-15 is a stress related protein and aging increases its plasma levels. Elevated GDF15 levels were associated with aging.¹⁴ Pence BD reported that GDF-15 is highly expressed during aging.¹⁵ A study done by Mattia et al showed GDF-15 is significantly associated with age. Their sample size was 180 patients and was divided into three groups (16-18), (30-32) & over 70 years.¹⁶ Mattia et al study also showed no difference between serum iron and serum ferritin in various age groups.

There are many possible mechanisms that may explain increased GDF-15 in older people. Firstly iron deficiency in older people may induce GDF-15 secretion by erythroid precursor cells.¹⁷ Secondly increased inflammatory stress in elderly population may cause increased GDF-15 secretion.¹⁸

Risk stratification and prediction of prognosis of hemodialysis patients are very challenging, serum GDF-15 can be a useful clinical tool to guide clinical management of patients.¹⁹

Limitations: Our study was a single Centre study. Serum GDF-15 was measured just one time for each patient and its trend, variations during longitudinal observational period remains unknown. Other systemic conditions or infections might have affected serum GDF-15 levels. This study lacked a healthy control group and thus could not compare GDF15 levels between healthy people and patients with end stage renal disease.

CONCLUSION

We conclude that elderly hemodialysis patients had significantly higher GDF-15 levels than younger ones. Serum GDF-15 is related to the age of hemodialysis patients. Iron and ferritin levels were similar in all ages groups.

Recommendations: This is a pioneer study in Pakistan to find a link between serums GDF-15 with age of hemodialysis patients. Therapeutic strategy for those hemodialysis patients with elevated serum GDF-15 remains a concern for future. More studies of GDF-15 will be required in normal people with no kidney disease. Studies are required to explore the pathophysiological of increased mortality in hemodialysis patients with high GDF-15 levels.

Conflict of Interest: None to declare.

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