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Significance of Beta 2-Microglobulin to predict the development of HIV/AIDS

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Abstract

Background: Beta 2-Microglobulin (β2M) is a component of the Class I major histocompatibility molecule which is present on the surface of almost all nucleated host cells. An increase in β2M serum levels has been associated with AIDS development and death and higher concentrations are found in patients with early progression to AIDS.

Objective: The aim of this study was to find out the significance and correlation between β2M and CD4+ T lymphocyte count in HIV/AIDS progression.

Materials and Methods: One hundred forty HIV seropositive patients were enrolled over a period of one year. Blood sample was collected in K2 EDTA vial to carry out CD4+ T lymphocyte count and in plain vial for Beta 2-Microglobulin. Pearson correlation was used to calculate the relationship between β2M and CD4+ T lymphocyte count.

Results: A significant negative correlation was observed between CD4+ T lymphocyte count and β2M with spearman correlation (r= -0.632) The mean value of β2M is simultaneously increased in serum as their CD4+ T lymphocyte counts declined in HIV infected patients..

Conclusion: β2M is a sensitive surrogate marker for predicting the extent and severity of HIV infection.

Keywords: beta 2-microglobulin, cd4+ t lymphocyte counts, surrogate markers

1. Introduction

Several immunological and serological variables have become established in recent studies as valuable markers to identify Human Immunodeficiency Virus (HIV) positive individuals at higher risk for rapid disease progression. Beta 2-Microglobulin (β2M) has been useful to define the stage of HIV infection, to predict clinical outcome (progression to Acquired Immunodeficiency Syndrome (AIDS) or death) and even to support therapeutic decisions, such as when to start antiretroviral treatment and to monitor the response to this [1, 2, 3].

Beta 2-Microglobulin (β2M) is a component of the Class I major histocompatibility (MHC class I) molecule which is present on the surface of almost all nucleated host cells [4] Free β2M is found in body fluids under physiological conditions because of its shedding from surface or intracellular release. Viral replication interferes with normal cellular protein synthesis and functions and ultimately death of infected cells. The process may contribute to increased turnover of membrane β2M. Its concentration in serum increases during immune activation and lymphoid cell destruction. An increase in β2M serum levels has been associated with AIDS development and death, [5] and higher concentrations are found in patients with early progression to AIDS [6] During asymptomatic HIV infection, raised concentration of β2M are associated with a six fold increased risk of disease progression [7] It is positively correlated with viral load and negatively correlated with $CD4^+$ T lymphocytes count [8, 9]

Our study have indicated the importance of markers of immune deficits ($CD4^+$ T lymphocytes count decrease) and immune stimulation (increased levels of Beta 2-microglobulin). In this study, we evaluate the clinical utility of β2M concentrations in serum as early indicators of HIV infection. This marker is byproducts of immune activation and cellular activity and has proven predictive value in HIV positive patients.

2. Material and Methods

This study was carried out in Department of Microbiology, Sawai Man Singh Medical College, Jaipur from August 2014 to July 2015. The study protocol was approved by the Ethics Committee of SMS Hospital. We enrolled 140 antiretroviral therapy (ART) naive HIV sero-positive patients who visited Integrated Counseling and Testing Centre (ICTC) in SMS Medical College. The HIV status of patients was confirmed at ICTC by three tests with different antigen or principle as per NACO guidelines [10] After obtaining informed consent from the patients, the socio-demographic details, clinical sign and symptoms, occupation, education and history of risk behavior were filled on a standard proforma. HIV positive patients above 18 years of age and ART naive were included in the present study.

Five milliliter of blood was collected with standard precaution in K2 EDTA vacutainer for $CD4^+$ T lymphocytes counts and in plain vial for Beta 2-Microglobulin. $CD4^+$ T lymphocytes count was determined by single platform BD FACS Calibur ™ (Becton, Dickinson and Company, San Jose, United States of America) as per manufacturer instructions.

Beta 2 microglobulin was measured by Enzyme Linked Immunosorbent Assay (Immuno-Biological Laboratories, Inc. IBL-America and Calbiotech, CA U.S.A respectively) as per manufacturer instructions.

3. Statistical analysis

Statistical analyses were done using computer software (SPSS Trial version 20 and primer). The qualitative data were expressed in proportion and percentages and the quantitative

data expressed as mean and standard deviations. Pearson correlation was used to calculate the relationship between β2M and $CD4^+$ T lymphocyte count. Significance levels for tests were determined as 95% (P< 0.05).

4. Results

A total of 140 HIV positive ART naive patients were included in this study, among which 94(67.14%) were males and 46(32.86%) were females. The mean age was 37.66 ± 8.99 years ranging from 19-65 years. The mean $CD4^+$ T lymphocyte count and β2M were 254.85±150.91 cells/µl and 2.75±1.38 µg/ml respectively. Out of 140 HIV positive patients, 68(48.57%), had $CD4^+$ T lymphocyte count less than 200 cells/µl, 36 (25.71%) had $CD4^+$ T lymphocyte count between 200-350 cells/µl, 33(23.57%) had $CD4^+$ T lymphocyte count between 350-500 cells/µl and 03(2.14%) patients had $CD4^+$ T lymphocyte count greater than 500 cells/µl. A significant negative correlation was observed between $CD4^+$ T lymphocyte count and β2M. Lower $CD4^+$ T lymphocyte count is significantly associated with high concentration of β2M. Association of $CD4^+$ T lymphocyte count with β2M is summarized in Table 1. Comparison of the mean value of $CD4^+$ T lymphocyte count and β2M at baseline and after 6 months of follow up are depicted in Table 2.

Table 1: Association of CD4+ T lymphocyte count with Beta 2 microglobulin

$CD4^+$ T lymphocyte count (Cells/µl)	Beta -2 microglobulin				
	More than 2 µg/ml		Less than or equal to 2 µg/ml		Total
	No	%	No	%	
< 200	65	52.00	03	20.00	68
200- 350	33	26.40	03	20.00	36
351-500	26	20.80	07	46.66	33
>500	01	0.80	02	13.33	03
Total	125	100.00	15	100.00	140

Table 2: Comparison of $CD4^+$ T cell count and β2M at baseline and after 6 months

	At Baseline		After 6 months	
$CD4^+$ T cell count range (Cells/ µl)	$CD4^+$ T cell count mean ±SD (Cells/µl)	β2M Mean ±SD (µg/ml)	$CD4^+$ T cell count mean ±SD (Cells/µl)	β2M Mean ±SD (µg/ml)
< 200	139 ±46.254	3.88 ± 1.239	165 ±55.0422	3.52 ±1.226
200- 350	286 ±44.546	3.26 ±0.732	380 ±59.246	3.15 ±0.724
351-500	407 ±41.188	3.08 ±0.849	386 ±39.094	3.11 ±0.889
>500	821 ±338.475	2.03 ±1.193	-	-

5. Discussion

Reduced $CD4^+$ T lymphocyte count and increased serum β2M levels, which reflect immunological activation and dysregulation are important markers of HIV disease progression. β2M is economical markers to RNA viral load and $CD4^+$ T lymphocyte count in resource limited settings. The predictive value of β2M is equal to $CD4^+$ T lymphocyte count and it is significant joint predictors in addition to $CD4^+$ T lymphocyte count. The upper limit of reference range of serum β2M is 2.0µg/ml in healthy individual.

In this study we found a significant negative correlation between $CD4^+$ T lymphocyte counts and β2M with spearman correlation (r= -0.632); that is consistent with other studies reported from India [5, 11, 12, 13, 14]. There are studies from abroad conducted by Kramer A et al [15], Maria M Chan *et al* [16], A.R. Lifson *et a*l [17], Radkowski M *et al* [18], Dunne J *et al*, [19] who also reported high degree of negative correlation between $CD4^+$ T lymphocyte counts and β2M. Bhalla et al [20] and Zolla-Pozner *et al* [21] also observed elevated β2M levels in patients with AIDS or AIDS Related Complex (ARC). In contrast to these studies, Ortigao-de-Sampaio MB *et al* [22] from Brazil reported that Beta 2 microglobulin does not correlate well with $CD4^+$ T lymphocyte counts or clinical findings.

We also found that the mean value of β2M is simultaneously increased in serum as their $CD4^+$ T lymphocyte counts declined in HIV infected patients (Table 3). Our results are in accordance with the study conducted by Dunne J *et al* [19] who suggest that these markers, particularly β2M, is a useful indicators of the inflammatory process associated with opportunistic infection at later stages of disease where other laboratory markers may be atypical.

Viral replication interferes with normal cellular protein syntheses and functions and ultimately death of infected cells. The process may contribute to increased turnover of membrane β2M.

In this study we compare the mean value of $CD4^+$ T lymphocyte count and β2M at first time diagnosis of HIV infection i.e. baseline and after the 6 months of follow up. We found that in Group I those who have $CD4^+$ T lymphocyte count < 200 Cells/µl had mean value of $CD4^+$ T lymphocyte count and β2M are 139 ±46.254 and 3.88 ± 1.239 respectively while after the 6 months of follow up of the value has changed to 165 ±55.0422 and 3.52 ±1.226 respectively which indicates that as their $CD4^+$ T lymphocyte counts increased the mean value of β2M is simultaneously decreased in serum. Similarly in Group II those who have $CD4^+$ T lymphocyte count 200-350 Cells/µl the mean value of $CD4^+$ T lymphocyte count and β2M have been changed from baseline 286 ±44.546 and 3.26 ±0.732 respectively to after 6 months of follow up 380 ±59.246 and 3.15 ±0.724 respectively which predicts the clinical outcome the negative correlation between $CD4^+$ T lymphocyte count and β2M.

In group III those who have $CD4^+$ T lymphocyte count 351-500 cells/µl didn't initiate ART as CD4 count of ≤ 350 cells/ µl as cutoff for initiating of ART. In this group the mean $CD4^+$ T lymphocyte count was decreased and β2M were increased after the 6 months follow up because their immunity gets decreasing slowly.

In group IV those who have $CD4^+$ T lymphocyte count > 500 cells/µl was only 3 patients. Among that only one patient has turned up after the 6 months follow up and we didn't observe any significant difference in their $CD4^+$ T lymphocyte count and β2M.

Our results are in accordance with the study conducted by various authors [12, 18,20,21] who suggest that β2M is a useful indicators of the inflammatory process associated with opportunistic infection at later stages of disease where other laboratory markers may be atypical.

For clinical monitoring, the $CD4^+$ T lymphocyte count has been remarkably consistent and useful tool for defining stage of disease and as the indication for when to initiate treatment. The serum β2M assay is reproducible [23] and inexpensive; it is estimated to cost half of the $CD4^+$ T lymphocyte count and a fifth of the viral load assay. It requires only minimal laboratory infrastructure to perform by ELISA method therefore β2M can add significant independent prognostic information. Integrating $CD4^+$ T lymphocytes count and β2M identifies patients with a greater than 10 fold increased risk of progression [19].

Our results provide a rationale for its further study and potential application in defining populations at greatest need for antiretroviral therapy, either as a supplement or possibly alone, in areas of the world where measurement of $CD4^+$ T lymphocyte count and viral load are not readily available.

Viral replication interferes with normal cellular protein syntheses and functions and ultimately death of infected cells. The process may contribute to increased turnover of membrane β2M. In other words, the decline in β2M concentration is indicative of an improving immune status, whereas increases in β2M concentration depicted disease progression.

6. Conclusion

B2M is a sensitive surrogate marker for predicting the extent and severity of HIV infection. Measurement of β2M is feasible using only a few microlitre of serum and inexpensive for patient monitoring in a resource limited settings.

7. References

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