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Research Article

Exploring Beta-2 Microglobulin-Related Amyloidosis in Pediatric End Stage Renal Disease Patients on Regular Hemodialysis

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Abstract

This study aimed at exploration of dialysis-related amyloidosis (DRA) as a medical problem in end stage renal disease patients (ESRD) on regular hemodialysis (HD), as well as estimation of s. beta-2 microglobulin (B_2M) changes in those patients. It comprised 55 patients with ESRD on regular HD therapy, 36 males and 19 females, with a mean age of 11.45 ± 3.22 years. They were compared to 20 healthy subjects. The patients were subjected to clinical evaluation, biochemical investigations included serum B_2M, serum creatinine, creatinine clearance and blood urea nitrogen. S. B_2M estimation was repeated after changing the dialyzer membrane from unsubstituted cellulose to synthetic polysulfone in 10 patients. Radiographic examination for cervical and lumbar vertebrae and big joints, M-mode and 2-dimensional echocardiography were done. Pathologic examination for DRA was performed in subcutaneous fat biopsy from 25out of the 55 studied patients. There was a significant higher concentration of s. B_2M in patients 10280 ± 647 ng/ml compared to the control group 1570 ± 710 ng/ml $p < 0.001$. A significantly better clearance was achieved by using the synthetic polysulfone membrane dialyzer (14181 ± 378 dropped to 3590 ± 590 ng/ml) $p < 0.001$. Radiographic and echocardiographic findings correlated positively with s. B_2M. Four of the biopsied patients (16%) had positive amyloid deposits. Their median duration of dialysis was 33 months and all of them had clinical manifestations of carpal tunnel syndrome (CTS) and bilobed interatrial septal thickening in the echocardiography. To conclude, the ESRD patients receiving regular HD are vulnerable to DRA. S. B_2M as a potential precursor for DRA is significantly elevated in those patients. Better clearance of B_2M can be achieved by using synthetic polysulfone dialyzers.

Keywords: *Beta-2 Microglobulin; Amyloidosis; Renal Disease; Hemodialysis*

Introduction

Replacement dialytic therapy has resulted in a large population of survivors with ESRD. Despite the fact that dialysis has prolonged the life expectancy, many morbidity factors are still remaining as major problems [1].

Dialysis related amyloidosis (DRA) represents a major complication of adult uremic patients treated by all forms of renal replacement therapy especially chronic HD. This syndrome comprises carpal tunnel syndrome, destructive osteoarthropathy and cystic bone lesions [2].

The DRA is a unique type of systemic amyloidosis in which beta-2 microglobulin (B_2M) represents the major constituent protein in the amyloid fibrils [3]. The magnitude of the problem in the pediatric age group is still unrevealed.

Aim of the Study

The aim of the study was to investigate this problem in the pediatric ESRD patients under regular HD and to study the changes in serum B_2M as a potential precursor of DRA.

Subjects and Methods

The study was carried out in the Pediatric Dialysis Unit, Children's Hospital, Ain Shams University. It comprised 55 patients with ESRD on regular HD for more than 6 months. They were 19 females and 36 males, their mean age was 11.45 ± 3.22 years. The mean duration of HD was 21.56 ± 10.04 months. They were compared to 20 healthy subjects as a control group, 9 males and 11 females with a mean age of 8.4 ± 3.65 years. The studied group was subjected to the following:

a- Careful history taking focusing on the clinical symptomatology of DRA including those of carpal tunnel syndrome (CTS) specifically.

b- Clinical examination to explore the clinical relevance of the history data mainly the CTS manifestations (tinel's sign, Phalen's sign and median nerve sensory loss).

c- Investigations:

   a. Laboratory: Serum B_2M assay by enzyme immunoassay (COBAS CORE, Switzerland). The sample was taken at the end of the HD session. A second sample was taken from 10 patients who were subjected to hemodialyzer membrane change from unsubstituted cellulose to synthetic polysulfone to study the B_2M clearance of both types. The timing of the second sample was chosen to be after one month of change to give adequate time to test the chronic balanced effect of the new dialyzer membrane. The criteria for selection of these 10 patients were: the older age, the longer dialysis duration, the higher B_2M levels and the presence of clinical criteria suggestive of DRA.

   b. Imaging procedures:

      i. Conventional radiology to detect the common but non-specific bone abnormalities for DRA.

      ii. Echocardiography to detect the common as well as specific cardiac pathology like granular sparkling and thickened interatrial septal wall.

   c. Histopathologic examination: An abdominal subcutaneous fat biopsy was obtained from 25 out of 55 studied subjects as a conclusive evidence of DRA. The inclusion criteria for biopsy were the same as for the dialyzer membrane change but with selection of bigger number.

The tissue specimen was stained by the congo red dye and visualized under the polarized light.

The EPI info version 5 computer program was used for database construction and statistical analysis.

Results

Of the 55 studied patients 4 (7.2%) had clinical manifestations of CTS in the same arm harboring the arterio-venous fistula. The other nonspecific cardiovascular and orthopedic manifestations were present in 23.6 and 25.5% of the patients respectively. The mean serum B_2M level was significantly higher in the studied group (10280 ± 647 ng/mL) compared to the control group (1570 ± 710 ng/mL) ($p < 0.001$) (Figure 1).

A significant reduction in the mean s. B_2M was observed after changing the type of dialyzer membrane in 10 patients from unsubstituted cellulose to synthetic polysulfone from (14810 ± 378 to 3590 ± 590 ng/mL) ($p < 0.001$) (Figure 2).

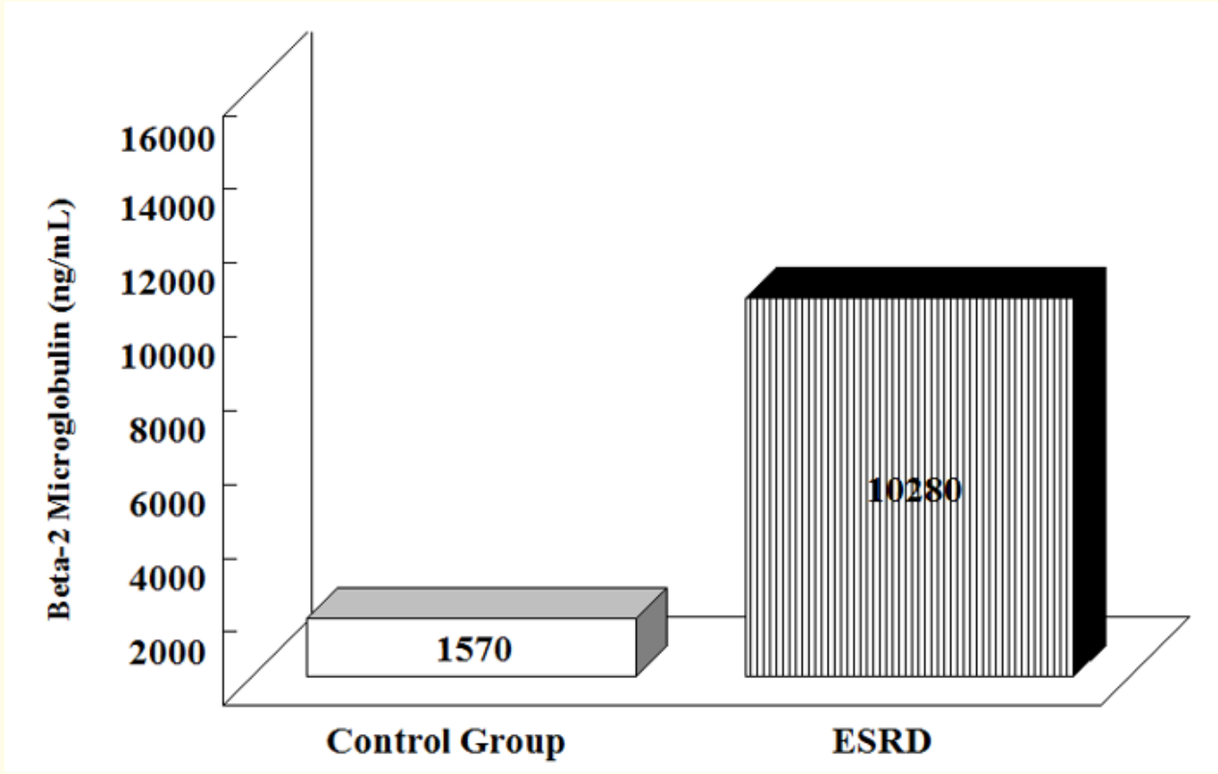

Figure 1: *Comparison between mean serum B2M in the control group and children with ESRD on regular HD*

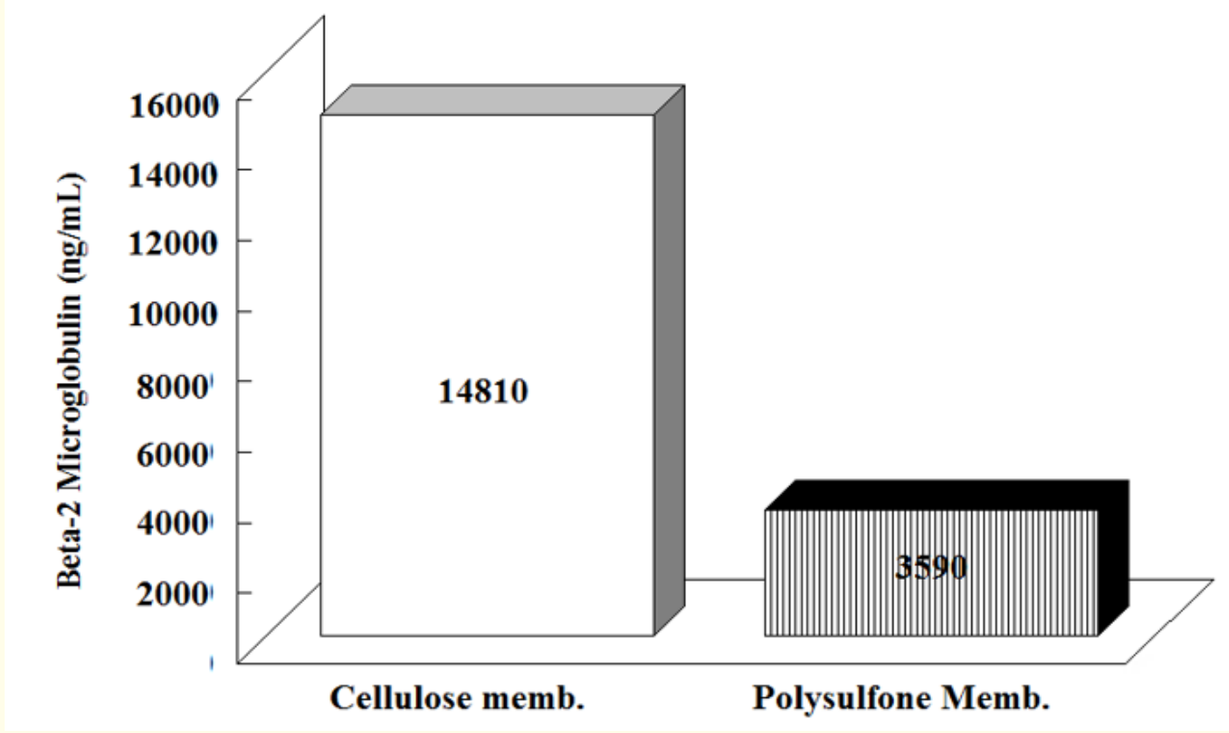

Figure 2: *The effect of dialyzer membranes on clearance of B2M.*

No significant correlation could be elicited between s. B_2M and duration of dialysis ($r = 0.16$, $p > 0.05$) or the number of dialysis hours per week ($r = 0.24$, $p > 0.05$). Furthermore, no significant correlation was detected between s. B_2M and the biochemical parameters which included, s. calcium, phosphorus, sodium, potassium, creatinine, urea and creatinine clearance. The mean serum B_2M was 15480 ± 558 ng/ml in patients with pathologic radiographic finding which included cystic changes, erosions, osteopenia, fractures, deformities and spondyloarthropathies. This level was significantly higher compared to the mean s. B_2M of patients without radiographic finding 8830 ± 599 (z value 2.95, $p < 0.01$).

Also the patients who had abnormal echocardiographic findings (including symmetrical ventricular thickening, interatrial septal wall hypertrophy, granular sparkling, pericardial effusion, valvular thickening and valvular regurge) had mean s. B_2M of 17130 ± 285 ng/ml. When compared to mean s. B_2M of patients free of these findings 9120 ± 620 ng/ml, it was significantly higher (z value 3.00, $p < 0.01$).

DRA radiographic and echocardiographic (Figure 3) findings were positively correlated with s. B_2M level ($p < 0.01$ in both).

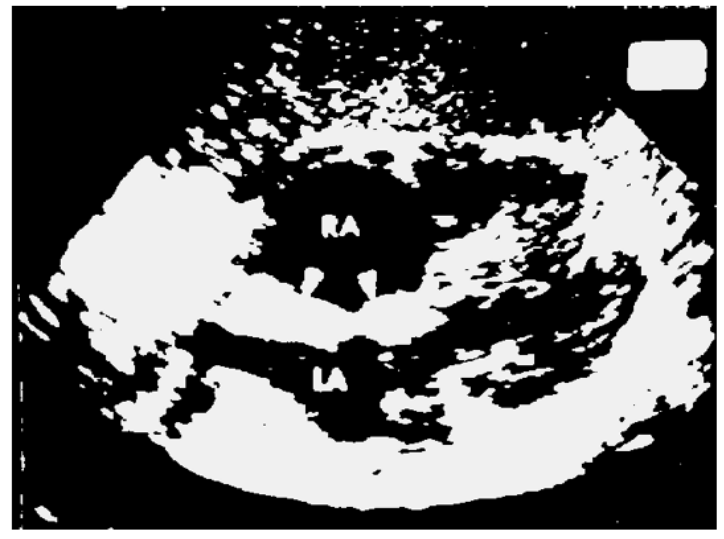

Figure 3: *2D-Echocardiography showing hypertrophied interatrial septum with the characteristic bilobed configuration.*

The amyloid deposits were demonstrated in 4 out of 25 biopsied patients (16%). The mean s. B_2M in the amyloid positive cases was 16000 ± 294 ng/dL compared to 9830 ± 647 ng/dL in those free of amyloid deposits. All of them had clinical CTS and characteristic bilobed appearance of interatrial thickening in echocardiography. Their median duration of HD therapy was 33 months.

Discussion

In the present study serum B_2M was significantly higher in ESRD patients on regular HD in comparison to the control group. Gejyo., *et al.* [4] suggested that the protracted increase in s. B_2M level is either related to retention and lack of filtration or to enhanced synthesis rate in uremic patients. More than 95% of all free B_2M is filtered by the normal glomerulus and subsequently almost completely reabsorbed and catabolized by the cells of the proximal convolutes tubules. So, retention and lack of B_2M catabolism in ESRD patients leads to serum level elevation [5]. Stein., *et al.* [6] reported s. B_2M elevation of more than 20 times the normal in patients with CRF.

The change of the dialyzer membrane type from unsubstituted cellulose to the synthetic polysulfone resulted in significant improvement in the B_2M clearance in the studied patients. This may be explained by the higher flux of the synthetic membrane that allows better clearance of the high molecular weight substances [3]. Moreover, Floege., *et al.* [7] reported s. B_2M level elevation in patients dialyzed using cellulose membrane dialyzer.

The amyloid deposits were present in 4 patients out of 25 (16%). Gregory., *et al.* [5] reported a prevalence of 5% in ESRD patients dialyzed for 5 years. The higher prevalence in our study may be explained by the difference in the sample size being smaller in ours.

Recent clinical studies showed that elevated s. B_2M level, long dialysis duration and advanced age are the three major risk factors for DRA [8]. However, protracted increase of s. B_2M level is not the only prerequisite for amyloid fibrils formation [9]. Nevertheless, the modification of the native intact B_2M into different forms is the accepted current concept on the pathogenesis of DRA [10].

All of the amyloid positive biopsied patients were presented clinically by manifestations of CTS. CTS is the most prominent manifestation of DRA [11]. Moreover, the same patients had common echocardiographic finding which is the thickening of the interatrial septum sparing the foramen ovale giving the peculiar bilobed appearance. Campistol., *et al.* [12] stated that echocardiogram is considered suggestive of amyloidosis if an atrial septal thickening is there.

Conclusion

To conclude, DRA is unexpectedly prevalent among the ESRD pediatric population undergoing regular HD. Clinical manifestations of CTS and the characteristic bilobed appearance of the interatrial thickening are the most sensitive clinical indicators of DRA. Moreover, s. B_2M as a potential precursor of DRA is significantly elevated in those patients. A better clearance of this material was accomplished by using the synthetic polysulfone dialyzer membrane instead of the unsubstituted cellulose membrane dialyzers.

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