

Frequency of destructive spondyloarthropathy among patients on regular hemodialysis

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Objective Musculoskeletal complications occur in patients suffering from chronic kidney diseases. The cause of destructive spondyloarthropathy (DSA) among those patients is not well known. This study aims to study the frequency of DSA among hemodialysis patients.

Patients and methods The study was conducted on 75 patients known to be end-stage renal disease patients: they were divided into three groups: chronic kidney disease on regular hemodialysis for more than or equal to 5 years group ($n=25$), patients on regular hemodialysis for less than 5 years group ($n=25$), and end-stage renal disease prior to hemodialysis as a control group ($n=25$). All of them were subjected to: full medical history, clinical examination, and plain radiographs of the whole spine in two views. Serum beta 2-microglobulin ($\beta 2$ -M) levels were determined.

Results A comparison of $\beta 2$ -M serum levels in three groups showed a highly significant difference being highest in group I and lowest in group III ($P<0.001$). There was high statistically significant increase in the frequency of DSA in group I compared with group II and in group II compared with group III ($P<0.001$). As regards the affected site among positive cases, DSA was observed to affect the cervical region in 82.35% more than the lumbar in 11.76%, and rarely to involve both cervical and lumbar in the same patient in 5.88%, DSA was observed to affect men (58.8%) more than the women (41.2%). Comparison of age, duration of dialysis, and intact

parathyroid hormone levels between positive and negative DSA cases revealed that DSA is significantly more prevalent in older age patients ($P<0.05$), and those with long dialysis duration ($P<0.001$), and those having higher intact parathyroid hormone levels ($P<0.001$).

Conclusion DSA is the most serious spinal complication in patients on long-term hemodialysis. Serum $\beta 2$ -M is elevated in patients receiving long-term hemodialysis (>5 years) and is positively correlated with destructive changes (DSA).

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Introduction

Musculoskeletal complications occur in patients suffering chronic kidney diseases. Kuntz and colleagues described a syndrome of destructive spondyloarthropathy (DSA) without microbial infection. It is characterized by mild pain and stiffness, accompanied with destruction of the spine. Also, this DSA is associated with juxta-articular cystic bone defects and median nerve entrapment. The cause of this syndrome is not known. Many causes have been suggested, including hyperparathyroidism, amyloidosis, and hydroxyapatite microcrystal precipitation [1].

Beta 2-microglobulin ($\beta 2$ -M) forms the light chain of class I major histocompatibility complex proteins and so it is present on the surface of all nucleated cells [2]. In healthy individuals, most of the $\beta 2$ -M is excreted by glomerular filtration followed by proximal tubular reabsorption and catabolism, while among patients with end-stage renal disease, due to marked reduction of estimated glomerular filtration rate, the plasma levels of $\beta 2$ -M are elevated and tissue precipitation occurs [3]. DSA has been suggested to

be one of the osteoarticular manifestations of dialysis-related amyloidosis (DRA) [4].

It is well known that dialysis treatment is considered as an inflammatory stimulus that leads to cytokine generation and complement stimulation; elevated levels of cytokines might play a role in DRA. The released cytokines induce the formation and release of $\beta 2$ -M by the macrophages and increase $\beta 2$ -M expression. These inflammatory amyloid deposits may lead to destructive lesions of bones and joints in DRA patients [5]. Hyperparathyroidism is usually also present and play a role in the pathogenesis of DSA. The control of hyperparathyroidism including subtotal parathyroidectomy helps to slow progression of DSA. Intervertebral disks, facet joints, and ligamentum flavum are the most susceptible sites for $\beta 2$ -M

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accumulation in the vertebral column. This can lead to DSA [6].

Previous reports have suggested that lesions are predominantly observed in highly mobile areas, such as C5–C7 and L3–L5 indicating that the collagen that has been injured by mechanical stress has liability for β 2-M deposition. So, a prior disorder of spine alignment enhances the development of DSA in hemodialysis patients [7].

This study aims to detect the frequency of DSA among hemodialysis patients and its correlation to regular hemodialysis duration and β 2-M serum level.

Patients and methods

This cross-sectional case-control study was conducted on 75 male and female patients with end-stage renal disease categorized according to kidney disease outcomes quality initiative [8] they were matched as regard age and sex (38 women and 37 men) and their age ranged from 20 to 87 years. Patients consented to conduct the study. They were divided into three groups according to the duration of dialysis (groups I, II, and III) and all were selected from the Nephrology Unit of Al Zahraa University Hospital to participate in the study in the period from February 2016 till January 2017; group I involved 25 patients of chronic kidney disease on regular hemodialysis for more than or equal to 5 years; group II involved 25 patients on regular hemodialysis for less than 5 years; group III involved 25 patients with ESDR prior to hemodialysis as a control group. Patients with evidence of malignancy, pregnancy, and ongoing infection or rheumatic diseases were excluded from the study. All procedures performed in the study were in accordance with the ethical standards of the Faculty of Medicine, Al Zahraa University Research committee and the 1964 Helsinki Declaration and its later amendments or ethical standards.

All patients were subjected to: full medical history taking with special emphasis on age, duration of dialysis, history of low back pain, or peripheral joint affection. Full clinical examination: including thorough rheumatologic examination as regards examination of the spine and peripheral joints and examination of other systems. Laboratory investigations including: complete blood count, erythrocyte sedimentation rate first hour, C-reactive protein, blood urea, serum creatinine, albumin, uric acid, serum calcium, and phosphorus, β 2-M, intact parathyroid hormone (iPTH). Three milliliters of venous blood samples

was taken from each patient participating in the study and was left to clot. Serum was separated by centrifugation at 3000g for 10 min and the separated serum was stored at -20°C for determination of calcium, phosphorous, uric acid, iPTH, and β 2-M. Determination of calcium, phosphorous, and uric acid were carried out on Dimension RxL Max analyzer (Siemens Healthcare GmbH, Erlangen, Germany by colorimetric techniques). Determination of serum iPTH was performed using an Immulite 2000 analyzer by solid-phase two-site chemiluminescent enzyme-labeled immunometric assay (Siemens AG, Erlangen, Germany) [9]. β 2-M was determined using an ELISA kit supplied from Orgentec Digostika (Orgentec Digionostika GmbH, Carl-Zeiss-Straße, Mainz, Germany) [10]. The estimated glomerular filtration rate was calculated using Cockcroft-Gault equation [11]. Plain radiographs of the whole spine (anteroposterior and lateral views). All cases with DSA were classified into three stages according to Maruo's criteria [12] as follows: stage 1, vertebral erosion; stage 2, intervertebral disk space narrowing without osteophyte; and stage 3, destruction of the vertebra and instability of the spine.

Statistical analysis

Data were analyzed using Statistical Program for the Social Sciences (SPSS, IBM Corp, NY, USA), version 20.0. Quantitative data were expressed as mean \pm SD. Qualitative data were expressed as frequency and percentage. Independent samples *t* test of significance was used when comparing between two means. One-way analysis of variance (ANOVA) was used when comparing between more than two means. χ^2 test of significance was used in order to compare proportions between two qualitative parameters. Pearson's correlation coefficient (*r*) test was used for correlating data. A *P* value less than 0.05 was considered significant and less than 0.01 was considered as highly significant. Receiver operating characteristic analysis was used to find out the overall predictivity of parameter and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.

Results

No significant difference was observed among groups regarding age and sex. Demographic data of the study participants is illustrated in Table 1.

There are no significant difference between three groups as regard calcium and phosphorus levels (Table 2).

Table 1 Demographic data of the study participants

Demographic data	Group I (N=25)	Group II (N=25)	Group III (N=25)	Test	P value
Age (years)					
Mean±SD	52.76±12.81	53.96±11.94	50.00±19.85	F=0.441	0.645 (NS)
Range	23–70	25–72	21–87		
Sex					
Female	13 (52)	10 (40)	15 (60)	$\chi^2=2.027$	0.360 (NS)
Male	12 (48)	15 (60)	10 (40)		

F, analysis of variance test. χ^2 , χ^2 test.

Table 2 Comparison of calcium and phosphorus levels among three groups of the study

Laboratory data	Group I (N=25)	Group II (N=25)	Group III (N=25)	ANOVA	P value
Ca (mg/dl)					
Mean±SD	8.64±1.01	8.92±0.54	8.54±1.15	1.094	0.341 (NS)
Range	6.1–10.7	7.9–10.1	6.3–11		
Ph (mg/dl)					
Mean±SD	5.30±1.94	4.42±1.40	4.37±1.14	2.925	0.060 (NS)
Range	2.2–11	2.5–8.3	2.5–7		

ANOVA, analysis of variance; Ca, calcium; Ph, phosphorus.

Table 3 Comparison of beta 2-microglobulin levels among three groups of the study

Beta 2-microglobulin ($\mu\text{g/ml}$)	Group I	Group II	Group III	ANOVA	P value
Mean±SD	56.57±12.01	32.47±5.88	1.56±0.87	317.242	<0.001 (HS)
Range	43–84.3	25–51.3	0.6–3		
P1		<0.001 (HS)	<0.001 (HS)		
P2			<0.001 (HS)		

ANOVA, analysis of variance; HS, highly significant. P1, difference between group I and group III, also group I and group II are significant. P2, difference between group II and group III.

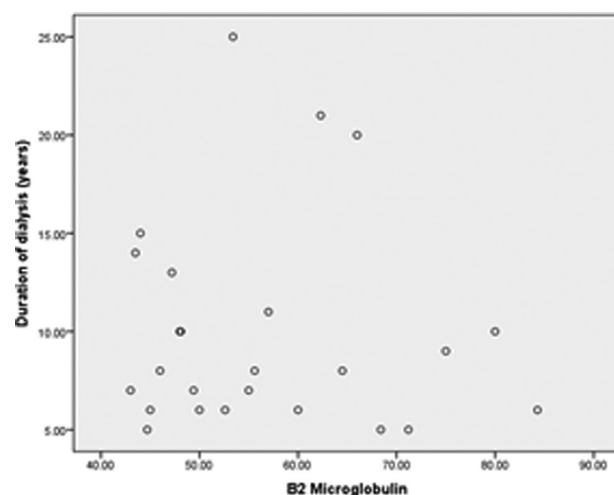
Comparison of β_2 -M levels in the three groups of the study showed a highly significant difference being the highest in group I and the lowest in group III ($P<0.001$) (Table 3, Fig. 1).

Comparison of iPTH levels in the three groups of the study showed a significant difference, the difference being highest in group I and lowest in group III ($P=0.039$) (Table 4).

Comparison of serum uric acid levels in the three groups of the study showed significant difference, the difference being the highest in group I and the lowest in group III (Table 5).

There was high statistically significant increase in the frequency of DSA in group I compared with group II and in group II compared with group III based on the radiographic finding, P value less than 0.001 (Table 6, Fig. 2).

After confirmation of DSA diagnosis of patients ($n=17$) among the three groups of the study, redistribution of all the study participants into two groups was done

Figure 1

Positive correlation between beta 2-microglobulin level and duration of dialysis.

according to DSA diagnosis group DSA positive ($n=17$), and group DSA negative ($n=58$).

As regards the affected site among positive cases, based on clinical and radiological data DSA was observed to

Table 4 Comparison of intact parathyroid hormone levels among the three groups of the study

Laboratory data	Group I (N=25)	Group II (N=25)	Group III (N=25)	ANOVA	P value
iPTH (pmol/l)					
Mean±SD	462.68±216.17 ^{ab}	417.05±203.95 ^c	362.10±179.49	4.291	0.039 (S)
Range	49–2534	135.8–1117	100–1117.6		

ANOVA, analysis of variance; iPTH, intact parathyroid hormone; S, significant. ^aDifference between group I and group III. ^bDifference between group I and group II. ^cDifference between group II and group III.

Table 5 Comparison of serum uric acid levels (mg/dl) among the three groups of the study

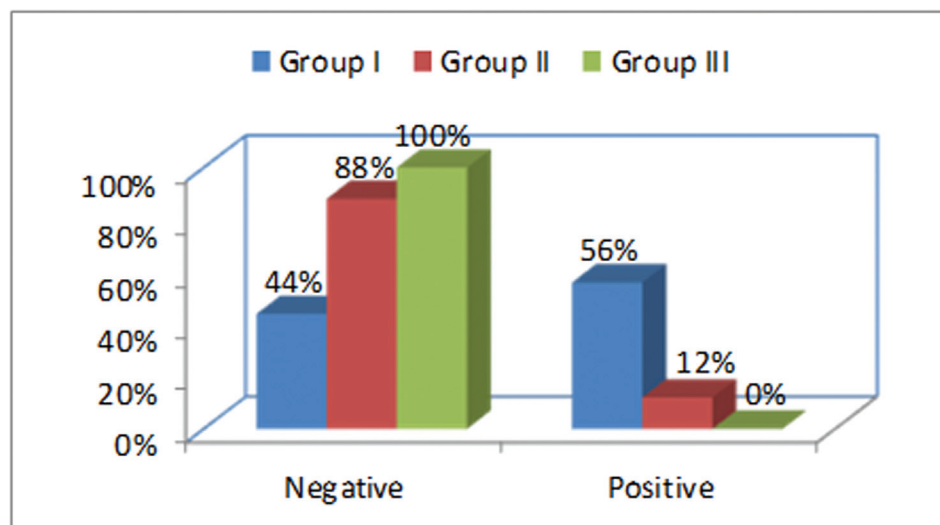
Serum uric acid (mg/dl)	Group I (N=25)	Group II (N=25)	Group III (N=25)	ANOVA	P value
Mean±SD	8.01±1.51	6.83±1.30	5.46±2.77	11.877	<0.001 (HS)
Range	5–11	5–9.8	2.5–8		
P1		0.012 (S)	<0.001 (HS)		
P2			0.029 (S)		

ANOVA, analysis of variance; HS, highly significant; S, significant. P1, difference between group I and group II, also group I and group III. P2, difference between group II and group III.

Table 6 Frequency of destructive spondyloarthropathy in each group based on radiographic findings

Radiography	Group I (N=25)	Group II (N=25)	Group III (N=25)	χ^2 test	P value
Negative	11 (44)	22 (88)	25 (100)	24.797	<0.001 (HS)
Positive	14 (56) ^{a,b}	3 (12) ^c	0 (0)		

HS, highly significant. ^aDifference between group I and group III. ^bDifference between group I and group II. ^cDifference between group II and group III.

Figure 2

Comparison of frequency of DSA based on radiographic findings among three groups of the study. DSA, destructive spondyloarthropathy.

affect the cervical region in 82.35% more than the lumbar in 11.76%, and rarely to involve both cervical and lumbar in the same patient (5.88%) (Fig. 3).

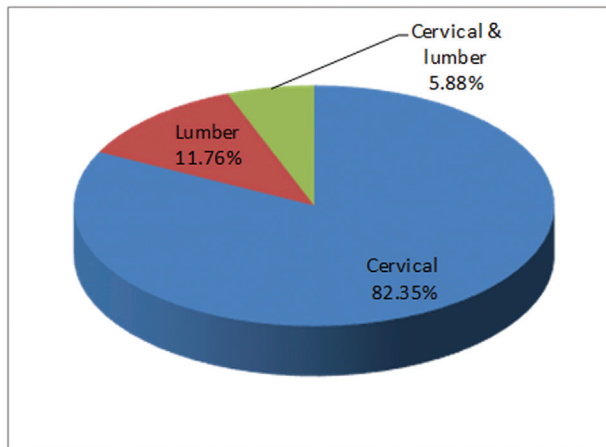
Demographic, clinical, and radiological data of DSA positive cases are illustrated in Table 7.

Comparison of age, duration of dialysis, and iPTH levels between positive and negative DSA cases among all patients showed that DSA is significantly more

prevalent in older age patients ($P<0.05$), and those with long dialysis duration ($P<0.001$), and those having higher β_2 -M and iPTH levels ($P<0.001$), while comparison of calcium, phosphorus, and uric acid levels between positive and negative DSA cases showed nonsignificant difference (Table 8, Figs 4 and 5).

The output data of receiver operating characteristics curve was used to define the best cutoff value of β_2 -M (Table 9).

Figure 3



Distribution of DSA positive cases according to the site of lesion. DSA, destructive spondyloarthropathy.

Table 7 Characteristics of patients with destructive spondyloarthropathy

Patient characteristics	Total (N=17)
Demographic data	
Sex	
Male	10 (58.8)
Female	7 (41.2)
Age (years)	59.95±7.19
Duration of hemodialysis	8.71±1.83
Symptoms	
Asymptomatic	9 (52.9)
Pain	7 (41.2)
Neurological deficit	1 (5.9)
Radiographic finding	
Stage I	3 (17.6)
Stage II	13 (76.5)
Stage III	1 (5.9)

Discussion

Musculoskeletal complications occur in patients suffering from chronic kidney diseases. The cause of DSA is not well known. It is the most serious spinal complication of DRA in patients on long-term hemodialysis [4]. Comparison of the three groups of this study showed significant difference in serum levels of β 2-M, the difference being highest in group I as compared with group II and group III ($P<0.001$) (Table 3). This finding was in agreement with Scarpioni *et al.* [3] who reported that β 2-M amyloidosis affects patients maintained on long-term hemodialysis for more than 5 years. This study also showed that there was significant increase of serum uric acid the increase being highest in group I as compared with group II and group III ($P<0.001$) (Table 5). This result was in accordance with Nemati and colleagues who found a significant positive

correlation between dialysis duration and serum level of uric acid. He attributed this positive correlation to higher adequacy of dialysis improving the nutritional state [13]. Statistical analysis of the current study showed that there was high statistically significant increase in the frequency of DSA in group I compared with group II and in group II compared with group III based on clinical and radiological findings, P value less than 0.001. This was in agreement with Maruyama *et al.* [7] who reported that the duration of hemodialysis was a risk factor for the development of DSA. Also, this study has shown that sex distribution among DSA positive cases was observed to affect men (58.8%) more than women (41.2%) (Fig. 4). These findings were in line with the study carried out by Maruo *et al.* [14] who found that, DSA was seen in 21 men and 15 women. Also, the study carried out by Hayami *et al.* [4] found that male patients on hemodialysis with DSA were more than women (61 vs. 39%). Aging is found to be one of the most important risk factors of DSA; in this study DSA development was associated with increased patients' age. The mean±SD among positive cases was 55.41±12.49 versus 51.31±15.84 years among negative cases ($P<0.05$) (Table 8). These findings were matched with the study carried out by Nagamachi and colleagues who stated that patient's age at the initiation of hemodialysis positively correlated to progression of destructive changes. Older patients with long duration of hemodialysis had more destructive changes. If the cause of DSA is suggested to be deposition of β 2-M in the disk, ligament, and vertebrae, it is not enough to explain the mechanism of DSA development. If β 2-M deposition is the only cause of DSA, destructive changes should occur in young patients [15]. Also, this was agreed with the study carried out by Tsvetkova *et al.* [16] who said that; the destructive changes were related to the age of the patient's on long-term hemodialysis. In the present study, cervical spine was the most common site of DSA: 82.35% of diagnosed DSA cases were cervical (Fig. 3). This could be explained by the study carried out by Nagamachi and colleagues who stated that DSA developed mostly in the lower cervical spine where the range of motion was extreme [15]. In this study, 52.9% of diagnosed DSA cases were asymptomatic and 41.2% were associated with mild or moderate neck or back pain, while only 5.9% were associated with neurological deficit (Table 7). This was in agreement with the study carried out by Daphne and colleagues who reported that mild to moderate back or neck pain and stiffness were the most common clinical manifestation, although the patients with DSA were largely asymptomatic. Radiculopathy, myelopathy, and spinal cord affection that may mandate surgical decompression and fixation have been reported [17]. Also, these results

Table 8 Comparison between positive and negative destructive spondyloarthropathy cases among all patients as regards age, duration of dialysis, and laboratory data

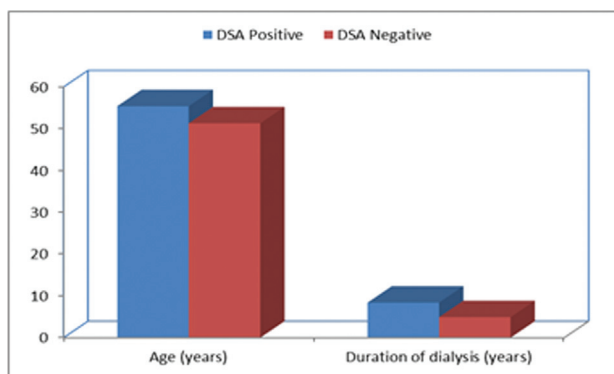
Parameters	DSA		$t/\chi^2\#$	P value
	Positive (N=17)	Negative (N=58)		
Age (years)	55.41±12.49	51.31±15.84	2.715	0.033*
Duration of dialysis (years)	8.41±5.20	4.92±2.68	5.981	<0.001**
Ca (mg/dl)	8.46±0.96	8.77±0.93	1.376	0.245
Ph (mg/dl)	4.84±2.23	4.65±1.34	0.186	0.668
iPTH (pmol/l)	488.5±321.5	292.1±194.2	6.761	<0.001**
Uric acid (mg/dl)	6.57±2.10	6.56±2.10	0.000	0.986
Beta 2-microglobulin	37.75±5.94	23.25±4.82	10.336	<0.001**

Ca, calcium; DSA, destructive spondyloarthropathy; iPTH, intact parathyroid hormone; Ph, phosphorus. *Significant. **Nonsignificant. #X2.

Table 9 Diagnostic performance of beta 2-microglobulin in discrimination of groups

Group	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
I vs. II	>40	100	96	96.2	100	98.2
I vs. III	>30	100	100	100	100	100
II vs. III	>30	100	100	100	100	100

NPV, negative predictive value; PPV, positive predictive value.

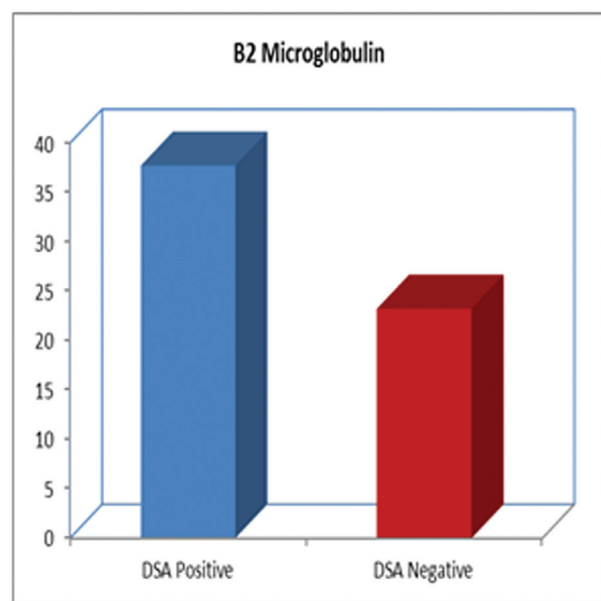
Figure 4

Comparison between positive and negative DSA cases as regards age and duration of dialysis. DSA, destructive spondyloarthropathy.

came in accordance with Moe *et al.* [18] who reported that chronic kidney disease, and mineral and bone-related disorders often were asymptomatic, and symptoms appear late. The current study showed significant positive correlation between DSA and β 2-M level P value less than 0.001 (Table 8). This was matched with Maruo *et al.* [14] who stated that β 2-M amyloidosis is a significant factor for DSA development. Amyloid precipitation occur at the facet joints, intervertebral disk, and at the ligamentum flavum.

Conclusion

DSA is the most serious spinal complication in patients on long-term hemodialysis. Serum β 2-M is elevated in patients receiving long-term hemodialysis (>5 years on dialysis) and is positively correlated with destructive changes.

Figure 5

Comparison between positive and negative DSA cases according to beta 2-microglobulin levels. DSA, destructive spondyloarthropathy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Kuntz D, Naveau B, Bardin T, Dkueke T, Treves K, Dryll A. A new syndrome: destructive spondylarthropathy in hemodialyzed patients. *Arthritis Rheum* 1984; **27**:369–375.
- Lu P, Chen J, He L, Ren J, Chen H, Rao L, *et al.* Generating hypoinnogenic human embryonic stem cells by the disruption of beta 2-microglobulin. *Stem Cell Rev* 2013; **9**:806–813.

- 3 Scarpioni R, Ricardi M, Albertazzi V. Secondary amyloidosis in auto-inflammatory diseases and the role of inflammation in renal damage. *World J Nephrol* 2016; **5**:66–75.
- 4 Hayami N, Hoshino J, Suwabe T, Sumida K, Mise K, Hamanoue S, *et al*. Destructive spondyloarthropathy in patients on long-term peritoneal dialysis or hemodialysis. *Ther Apher Dial* 2015; **19**:393–398.
- 5 Zumrutdal A. Role of β 2-microglobulin in uremic patients may be greater than originally suspected. *World J Nephrol* 2015; **4**:98–104.
- 6 Tsai TT, Kaliya-Perumal AK, Jenq CC, Niu CC, Ho NY, Lee TY, Lai PL. The unresolved problem of beta-2 microglobulin amyloid deposits in the intervertebral discs of long-term dialysis patients. *J Orthop Surg Res* 2017; **12**:194.
- 7 Maruyama K, Matsuyama Y, Yanase M, Sakai Y, Katayama Y, Imagama S, *et al*. The relationship between the type of destructive spondyloarthropathy and its 10 years ago cervical spine alignment. *Eur Spine J* 2009; **18**:900–904.
- 8 KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013; **3** (Suppl):1–150.
- 9 Almqvist M, Bondeson AG, Bondeson L, Malm J, Manjer J. Serum levels of vitamin D, PTH and calcium and breast cancer risk-a prospective nested case-control study. *Int J Cancer* 2010; **127**:2159–2168.
- 10 Argyropoulos CP, Chen SS, Ng YH, Roumelioti ME, Shaffi K, Singh PP, Tzamaloukas AH. Rediscovering Beta-2 microglobulin as a biomarker across the spectrum of kidney diseases. *Front Med (Lausanne)* 2017; **4**:73.
- 11 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**:31–41.
- 12 Maruo S, Taniguchi M, Otsuka S. The pathogenesis and treatment for DSA on long-term hemodialysed patients. *Sekitsui Sekizui J* 1997; **10**:1065–1070.
- 13 Nemat E, Khosravi A, Einollahi B, Meshkati M, Taghipour M, Abbaszadeh S. The relationship between dialysis adequacy and serum uric acid in dialysis patients; a cross-sectional multi-center study in Iranian hemodialysis centers. *J Renal Inj Prev* 2016; **6**:142–147.
- 14 Maruo K, Moriyama T, Tachibana T, Inoue S, Arizumi F, Kusuyama K, Yoshiya S. Prognosis and adjacent segment disease after lumbar spinal fusion surgery for destructive spondyloarthropathy in long-term hemodialysis patients. *J Orthop Sci* 2017; **22**:248–253.
- 15 Nagamachi A, Takahashi M, Mima N, Adachi K, Inoue K, Jha SC, *et al*. Radiographic changes of cervical destructive spondyloarthropathy in long-term hemodialysis patients: a 9-year longitudinal observational study. *J Med Investig* 2017; **64**:68–73.
- 16 Tsvetkova SB, Blagov B, Batalov A. Amyloid arthropathy in haemodialysis patients – radiological findings. *J IMAB* 2006; **69**:1945–1953.
- 17 Daphne JT, Stavroula JT, Donald R. Imaging in the dialysis patient: imaging in dialysis spondyloarthropathy. *Dialysis* 2008; **15**:290–296.
- 18 Moe S, Drüeke T, Cunningha J, Goodman W, Martin K, Olgaard K, *et al*. Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; **69**:1945–1953.