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Chronic pain in hemodialysis patients: Role of bone mineral metabolism

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Abstract *Background:* Pain is one of the most common complaints in clinical practice because it is a symptom for a myriad of physical and mental problems. The high prevalence of pain in the chronic kidney disease (CKD) population is particularly concerning because pain has been shown to adversely affect quality of life. The aim of this study was to evaluate the prevalence and possible causes of chronic pain in patients with end stage renal disease on long-term hemodialysis (HD).
Methods: We prospectively enrolled 100 patients who were undergoing maintenance HD for at least 6 months or more. Pain was evaluated using the Brief Pain Inventory (BPI). Data collected on each participant included age, gender, body mass index (BMI), time on dialysis and biochemical findings.
Results: The average age was 42.06 years ranged from 22 to 58 years; the average duration on dialysis was 4.97 years. 52 patients were males and 48 were females. Although 52% of patients experienced chronic pain, only 25% described the pain as severe, 28% described pain as moderate while 52% of patients described as mild. Musculoskeletal pain was the most frequent form of chronic pain reported by patients who were on HD (54%). Malnutrition and high CRP were highly statistically associated with chronic pain ($p < 0.001$). High statistical significant correlation was found between lower calcium, lower 25(OH) D3 levels, higher parathyroid hormone (PTH) levels and experienced chronic pain ($p < 0.001$).
Conclusion: Chronic pain is highly experienced in long-term hemodialysis patients. Malnutrition, high CRP and disturbed bone mineral metabolism are highly correlated with the incident of this pain.

1. Introduction

Pain is a frequent complaint of hemodialysis (HD) patients.[1,2] The information regarding its origins, frequency, and management is relatively scarce. Most published data come indirectly

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from studies focusing on health-related quality of life.[1,2] The reported frequency of pain varies widely in these patients. Murtagh et al.,[3] in a review of symptoms in ESRD, reported that the mean prevalence of pain is of 47%, with a range of 8–82%. The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with an actual or potential harm to the body".[4] In most patients, severity of pain ranges from moderate to severe.[5] Important sources of pain are musculoskeletal disorders, peripheral neuropathy and critical limb ischemia. Moreover renal replacement therapy with hemodialysis or peritoneal dialysis is associated with additional pain manifestations.[6,7] Three quarters of ESRD patients suffer unnecessarily from inadequately or untreated pain.[1,5] In the Dialysis Outcomes and Practice Patterns Study (DOPPS), 74% of subjects reported a moderate to severe pain without analgesic prescription.[8] These hurdles are due to several factors: The caregivers are frequently unaware of this problem and have concerns about adverse effects of the analgesic therapy, and the patients fear the side effects of medication, the extra burden of daily tablets and the potential risk of addiction in the case of opiate medication.[9] Although well-accepted guidelines are available for the management of cancer-related pain, no such recommendations exist for pain associated with HD.[10] One review[11] suggested using the same step-wise approach declared by the World Health Organization to treat cancer pain; however, the treatment of HD patients is complicated by the need to adjust frequently the dosage of analgesic drugs and by increased risk for adverse effects.[12,13] because of the high prevalence and adverse effects of this complaint, and we designed this study aiming to evaluate its incidence and characters of distribution in our hemodialysis community and trying to find out the major determinants of this very common complaint.

2. Patients and methods

This prospective cross-sectional study was carried out in the internal medicine department and renal unit, Zagazig university hospital, Egypt. One hundred eligible patients who had been undergoing maintenance HD for at least 6 months were recruited for this study. They were followed for one year (from December 2013 to December 2014). Informed written consent was taken from all participants and then they were randomly selected and interviewed during dialysis sessions. They were divided according to the presence or absence of chronic pain into two groups: **Group 1**: it included 48 patients. They were 25 males and 23 females, with age range from 22 to 50 years (mean ± SD: 42.12 ± 10.32 years). They were treated with a regular HD for ⩾6 months and they did not experience chronic pain. **Group 2:** it included 52 patients. They were 28 males and 24 females, with an age range from 21 to 58 years, (mean ± SD: 42.06 ± 10.26 years). They were treated with a regular HD for ⩾6 months and they were complaining from different types of chronic pain.

Inclusion criteria: All patients who were free from diabetes mellitus (DM), connective tissue diseases, heart failure, liver diseases or evident acute infection and were not receiving medications that may modify pain or the immune response like non-steroidal anti-inflammatory medications or corticosteroids were included in the study.

Exclusion criteria: Patients with central venous catheters and Arteriovenous fistula (AVF) that were prone to limb ischemic pain were excluded from the study. Also, patients with recurrent pain due to needling, headaches and muscle cramps during the HD procedure were excluded as these conditions may be perceived as a chronic pain and so can affect the results of our study. Our patients were free of cancer for the last 2 years prior to the study.

They were treated thrice weekly HD sessions for 4 h duration using volumetric machines and high-flux polysulphone membrane (Haidylena Medical SAE, Cairo, Egypt). The dialysate flow was 500 mL/min and the blood flow rate ranged from 270 to 350 mL/min. We used standard bicarbonate dialysate (38 mEq/l) with normal calcium bath of 1.25 mmo/l.

Demographic and clinical data were collected for all patients. Demographic data included complete history taking, age, gender, body mass index (BMI), nutritional status, time on dialysis and the type of blood access. Clinical data included the following: complete blood count (CBC), serum calcium, phosphorus, uric acid, intact parathyroid hormone (iPTH by immunoradiometric assay (N-TACT PTH SP IRMA; DiaSorin), 25-hydroxyvitamin D3 [25(OH)D3] by Elisa, serum albumin, alanine transaminase (ALT), aspartate transaminase (AST), and C-reactive protein (CRP). Also, we determined serum low-density lipoprotein (LDL), serum high-density lipoprotein (HDL) and triglyceride (TG), and single pool Kt/V using Daugirdas formula.[14]

A Hitachi747 Clinical Analyzer was used to determine the serum levels of albumin, glucose, iron, calcium, and phosphorus. A Hitachi 917 was used for C-reactive protein, and Advia 120 (Bayer, Leverkusen, Germany) was used to determine hemoglobin levels. Serum total cholesterol (TC), triglycerides (TGs), HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C), were measured calorimetrically using commercially available kits on the fully auto analyzer of Clinical Biochemistry Laboratory

2.1. Pain assessment (brief pain inventory score)

All patients were interviewed during their HD session evaluated for the presence of pain by using the Brief Pain Inventory (BPI)[15] which is an instrument for evaluating pain that assesses the intensity and characteristics of pain and determines the impact of pain on important aspects of a patient's life. The BPI uses a 10-point scale to evaluate the intensity of pain whereby 0 = "no pain" and 10 = severe pain.[15] On the basis of the BPI scale, pain was classified as mild (1–4 points), moderate (5–6 points), or severe (7–10 points).[17] Chronic pain was defined as pain of >3 months duration.[17]

2.2. Dialysis malnutrition score

Assessment of the nutritional status uses Modified Subjective Global Assessment – Dialysis Malnutrition Score which consists of seven features: weight change, dietary intake, GI symptoms, functional capacity, comorbidity, subcutaneous fat and signs of muscle wasting. Each component has a score from 1 (normal) to 5 (very severe). Thus the malnutrition score (sum of all seven components) is a number between 7 (normal) and 35 (severely malnourished). Lower score denotes tendency toward a normal nutritional status. A higher score is considered to be an indicator of the presence of malnutrition elements i.e. protein energy malnutrition.[16]

Table 1 Demographic characteristics and laboratory values of studied HD groups.

Variable	Group I Pain free (n = 48)	Group II Complaining from pain (n = 52)	t	P
Age (year) X ± SD	42.12 ± 10.32	42.06 ± 10.26	0. 02	NS
Gender (%)				
Male	25	28	0.59	NS
Female	23	24		
BMI (kg/m^2) X ± SD	19.95 ± 1.84	19.35 ± 1.49	1.79	NS
Duration (years) X ± SD	5.11 ± 2.16	4.97 ± 1.82	0.34	NS
CRP (mg/dl) X ± SD	3.37 ± 1.40	8.13 ± 2.75	10.89	< 0.001
Hb (Gm/dl) X ± SD	10.60 ± 0.79	10.58 ± 0.76	0.11	NS
Uric acid (mg/dl) X ± SD	5.73 ± 1.32	5.96 ± 1.33	0.86	NS
Kt/V X ± SD	1.33 ± 0.22	1.41 ± 0.27	0.56	NS
Na + 2 (mEq/l) X ± SD	137.6 ± 7.23	138.4 ± 6.73	0.57	NS
K + (mEq/l) X ± SD	4.61 ± 0.57	4.79 ± 0.52	4.41	NS
SGA X ± SD	8.84 ± 2.24	18.22 ± 8.48	7.55	< 0.001
Albumin (g/dl) X ± SD	3.61 ± 0.64	3.51 ± 0.68	0.02	NS
ALT Mg/dl X ± SD	30 ± 7.88	31.3 ± 6.98	4.41	NS
AST Mg/dl X ± SD	29 ± 6.98	30.9 ± 6.97	4.13	NS
LDL Mg/dl X ± SD	108.3 ± 13.15	116 ± 14.35	2.79	< 0.05
HDL mg/dL X ± SD	45 ± 2.97	36.78 ± 4.25	11.21	< 0.001
TG mg/dL X ± SD	195.9 ± 24.55	262.9 ± 45.18	9.21	< 0.001

BMI: body mass index, CRP: C-reactive protein, Hb: hemoglobin, Cr: Creatinine, Na: Sodium, K: potassium, SGA: modified subjective global assessment, ALT: alanine transaminase, AST: aspartate transaminase, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride.

2.3. Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures were coded, entered and analyzed using Microsoft Excel software. Data were then imported into the statistical package for the social sciences (SPSS version 20.0) software for analysis. Continuous variables are presented as mean ± SD or median and range. The Chi-square test was used for qualitative data (frequency and proportion), independent t-test was used to compare 2 groups and one-way ANOVA test was used to compare more than 2 groups. Statistical significance was set at 5% ($P < 0.05$).

3. Results

Table 1 summarizes the basic demographic characteristics and laboratory values of the studied groups. On analysis of the demographic data, it was found that there was no significant difference between both groups regarding age, gender, BMI, duration of dialysis and dialysis adequacy (Kt/v) $p > 0.05$. However, on Analysis of the laboratory parameters it was revealed that there was no significant difference found between the two groups regarding hemoglobin, uric acid, serum sodium and potassium ($p > 0.05$). CRP was significantly higher in pain group than in non-pain group ($p < 0.001$). Regarding the nutritional status of both groups, although there was no significant difference between both groups regarding serum albumin ($p > 0.05$), Malnutrition was highly significant higher in group 2 (pain group) in comparison with the other group using our modified subjective global assessment score (SGA) ($p < 0.001$). Liver enzymes (ALT and AST) did not show any significant changes in both groups of patients ($p > 0.05$). Dyslipidemia in the form of high LDL, low HDL and high triglycerides was significantly higher in group 2 (pain group) than the other free group (group 1) ($p < 0.05$, < 0.001 and < 0.001 respectively).

Regarding bone mineral study in both groups, parathyroid hormone was statistically significantly higher in patients with pain in comparison with other patients without pain

Table 2 Bone minerals in both groups.

Variable	Group I Pain free (n = 48)	Group II Complaining from pain (n = 52)	t	P
Ca (mg/dl) X ± SD	9.99 ± .34	7.77 ± .45	−9.73	<0.001
Ph (mg/dl) X ± SD	5.41 ± .65	5.42 ± .63	.11	NS
PTH (pg/ml) X ± SD	219 ± 68	775 ± 270	14.09	<0.001
OHD3 (nmol/L) X ± SD	73.34 ± 23.18	40.3 ± 13.48	−6.03	<0.001

NS: non-significant $p > 0.05$, Ca: Calcium, Ph: phosphorus, PTH: parathyroid hormones, OHD3: 25-hydroxyvitamin D3.

($p < 0.001$). Serum calcium level was significantly lower in patients with pain in comparison with those without pain $p < 0.001$. Also, serum: 25-hydroxyvitamin D3 was highly significantly lower in patients with pain in comparison with patients without pain ($p < 0.001$). However, no significant difference was found between both groups regarding serum phosphorus level $p > 0.05$. See Table 2.

Regarding grades of pain in group 2, 52% of patients had mild pain (grade 2), 28% of patients had moderate pain (grade 3) and 20% of patients had severe pain (grade 4). 27 patients of the 52 patients (52%) who had pain reported musculoskeletal pain, 12 patients reported headache (23%), 7 patients reported peripheral neuropathic pain (13.5%), 3 patients reported abdominal pain (5.7%) and 3 other patients reported pain of different sources (5.7%). Moreover, 36 (69.2%) patients reported more than one type of pain.

Pain grade was significantly more pronounced in older age groups and in patients with more time on hemodialysis ($p < 0.001$). Moreover, it was less in patients with more BMI ($p < 0.001$). The grades of pain were significantly increased in patients with higher PTH and patients with low albumin level ($p < 0.001$). However, no significant difference was found between the pain grades in relation to hemoglobin (HB), calcium, phosphorus, 25-hydroxyvitamin D3(OHD3), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and uric acid ($p > 0.05$). See Table 3.

Table 3 Comparison of pain grades in relation to socio-demographic characteristics and clinical Parameters of group II complaining from pain.

Variable	Pain grades			F	P value
	Grade 2 (n = 26)	Grade 3 (n = 14)	Grade 4 (n = 12)		
Age (year) X ± SD	36.11 ± 8.59	45.42 ± 8.5	52.8 ± 3.93	17.9	0.001
BMI (kg/m^2) X ± SD	19.9 ± 1.1	19.42 ± 1.59	17.8 ± 1.22	9.78	0.001
Duration (years) X ± SD	4.0 ± 1.13	4.96 ± 1.56	7.5 ± 1.08	28.0	0.001
Hb (Gm/dl) X ± SD	10.82 ± 0.79	10.26 ± 0.708	10.42 ± 0.594	2.91	0.06
Ca (mg/dl) X ± SD	7.71 ± 0.45	7.77 ± 0.45	7.93 ± 0.47	0.76	0.47
Ph (mg/dl) X ± SD	5.40 ± 0.57	5.53 ± 0.78	5.33 ± 0.61	0.32	0.72
iPTH (pg/ml) X ± SD	744.23 ± 218.2	655.0 ± 234.5	1024 ± 305.14	7.24	0.001
OHD3 (nmol/L) X ± SD	42.88 ± 23.54	37.86 ± 30.55	37.5 ± 24.3	0.2	0.7
Albumin (g/dl) X ± SD	3.87 ± 0.38	3.39 ± 0.83	2.7 ± 0.25	16.94	0.001
ALT (mg/dl) X ± SD	35.76 ± 5.77	36.42 ± 8.41	37.5 ± 8.24	0.21	0.81
AST (mg/dl) X ± SD	30.38 ± 6.31	30.71 ± 7.55	32.5 ± 8.24	0.33	0.72
Uric acid (mg/dl) X ± SD	9.12 ± 1.64	6.46 ± 1.43	6.25 ± 1.39	2.45	0.09

NS: non-significant $p > 0.05$, Hb: hemoglobin, Ca: calcium, Ph: Phosphorus, iPTH: intact parathyroid hormones, OHD3: 25-hydroxyvitamin D3, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

4. Discussion

Patients with end-stage renal disease (ESRD) receiving maintenance dialysis suffer from a multitude of physical and emotional symptoms, exhibit a particularly high prevalence of pain, and experience substantial impairments in quality of life (QoL).[18] Moreover, as many as 50% of patients suffer from pain, which in longitudinal analysis has been associated with an increased risk of death.[19] Our study showed that pain is common in patients who are on long-term HD and 52% of our patients experienced chronic pain. This is in agreement with other reports in the literature. Davison SN in 2003[1] on his study on 205 Canadian HD patients reported that 50% of patients had chronic pain. In a systematic review of Murtagh et al.[3] they reported that weighted mean prevalence of pain was 47% but with a range from 8% to 82%. This wide range is probably due to differences in the definition of chronic pain and the method used to assess it, as well as differences in the perception of pain among the diverse population studied.

52% of our patients who had chronic pain reported mild pain (grade 2), 28% of patients had moderate pain (grade 3) and only 20% of patients had severe pain (grade 4). In the study done by Davison SN in 2003,[1] he reported that 55% of patients rated their pain as severe. In another study done by Eliezer et al.,[18] he reported that 49% of patients described their pain as mild, 31.4% as moderate, and 19.6% as severe. Differences in the perception of pain between our study and the others may be explained by the cultural and ethnic variations. Kimmel et al.,[20] described similar differences in HD patients in Taiwan while discussing the impact of spiritual beliefs, psychosocial factors, and ethnicity on QoL and HD.

No significant difference was found between age, sex, BMI and pain in hemodialysis patients. Also, highly statistical significant difference was found between C-reactive protein (CRP) and chronic pain in hemodialysis patients. This result is in accordance with the result of other studies.[18] CRP is an acute-phase reactant and it is a sensitive and independent marker of malnutrition, anemia, and amyloidosis which have possible roles in increasing perception of chronic pain in hemodialysis patients.[21]

In contrast to other studies,[22] no significant difference was found between Hemoglobin level and chronic pain in hemodialysis patients. However, similar result was found in the study done by Eliezeret al.[18] This is most probably because the hemoglobin level of most of our patients was within the recommended range due to better control of anemia.

In our study, high statistical significant difference was found between malnutrition and pain through using modified Subjective Global Assessment (SGA) – Dialysis malnutrition score. Vasantha et al.,[23] stated that malnutrition is widely prevalent among patients on hemodialysis. Malnutrition is a frequent complication which affects QoL and is associated with increased risk of mortality and morbidity in maintenance hemodialysis patients as it leads to osteoporosis, muscle weakness, atherosclerosis and elevation of low density of lipoprotein (LDL) cholesterol which cause chronic ischemic pain.

Also in this study, it was found that iPTH was highly statistically significant higher in pain group together with low calcium and low 25-hydroxyvitamin D3. This is in agreement with other reports who reported the same results but in diabetic patients.[24,25] Also, it is in accordance with other study done by Rengin et al.,[26] who reported that chronic pain is correlated with bone metabolism markers, namely intact parathyroid hormone, and may be used to assess the intensity of chronic bone pain in long-term HD patients. However, in the study done by Eliezeret al.,[18] they reported that the levels of intact parathyroid hormone, calcium, and calcitriol (but not 25-hydroxyvitamin D3) differed significantly between those who experienced chronic pain and those who did not.

Low calcium and vitamin D are associated with endothelial dysfunction.[27] Lower levels of calcium and 25-hydroxyvitamin D3 observed in our patients may play a role in the development of chronic ischemic pain in various organs by their impact on endothelial dysfunction. Analysis of data from the prospective Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) reported that disturbed mineral metabolism was associated with muscle pain and cramps in dialysis patient.[28] In our study, there was no statistical significant effect of phosphorus level on pain. This is in contradiction to another study done by Noordzijet al.,[28] who described a positive correlation between phosphorus levels and pain in hemodialysis patients. This difference in the result may come from the tight control of phosphorus in almost all of our patients, both with and without pain. Also, it can be explained by different estimates of pain and from the different study design, longitudinal versus case-control trials.

5. Conclusion

Our work points out the likelihood that disturbed mineral metabolism, especially calcium, PTH, and 25(OH) D3 has a strong association with chronic pain experienced by HD patients and causes psychological, physical, emotional and social problems. Further studies on more patients may be required to confirm this relationship for better diagnosis and management of chronic pain in HD patients.

5.1. Limitations

This study has some limitations; first, it was designed as a cross-sectional study but with almost equal sized groups and almost equal gender distribution so it can be misleading as a case control study. Also, it contributes to small numbers of participant and this may preclude drawing firm cause-and-effect conclusions from our data.

Second, we couldn't obtain information about the use of certain drugs that can affect parameters of bone mineral metabolism like using of phosphate binders (calcium carbonate or sevelamer hydrochloride), active vitamin D3 (Calcitriol) and calcimimetics (cinacalcet). Third, it was better to do Logistic Regression Analysis to Determine Factors Associated with chronic pain in long-term HD patients.

Conflict of interest

None.

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None.

References

1. Davison SN. Pain in hemodialysis patients: prevalence, cause, severity and management. *Am J Kidney Dis* 2003;**42**:1239–47.
2. Shayamsunder AK, Patel SS, Jain V, Peterson RA, et al. Sleepiness, sleeplessness, and pain in end-stage renal disease: distressing symptoms for patients. *Semin Dial* 2005;**18**:109–18.
3. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end stage renal disease: a systematic review. *Adv Chronic Kidney Dis* 2007;**14**:82–99.
4. Merskey H, Bogduk N. *Classification of Chronic Pain*. Seattle, WA: International Association for the Study of Pain Press; 1994, p. 210.
5. Barakzoy AS, Moss AH. Efficacy of the world health organization analgesic ladder to treat pain in end-stage renal disease. *J Am Soc Nephrol* 2006;**17**:3198–203.
6. Binik YM, Baker AG, Kalogeropoulos D, Devins GM, et al. Pain, control over treatment, and compliance in dialysis and transplant patients. *Kidney Int* 1982;**21**:840–8.
7. Milinkovic M, Zidverc-Trajkovic J, Sternic N, Trbojevic-Stankovic J, et al. Hemodialysis headache. *Clin Nephrol* 2009;**71**:158–63.
8. Bailie GR, Mason NA, Bragg-Gresham JL, Gillespie BW, et al. Analgesic prescription patterns among hemodialysis patients in the DOPPS: potential for underprescription. *Kidney Int* 2004;**65**:2419–25.
9. Weisbord SD, Fried LF, Mor MK, Resnick AL, et al. Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol* 2007;**2**:960–7.
10. Zech DF, Grond S, Lynch J, Hertel D, et al. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995;**63**:65–76.
11. Cohen LM, Moss AH, Weisbord SD, Germain MJ. Renal palliative care. *J Palliat Med* 2006;**9**:977–92.
12. Davison SN. Chronic pain in end-stage renal disease. *Adv Chronic Kidney Dis* 2005;**12**:326–34.
13. Auret KA, Toye C, Goucke R, Kristjanson LJ, Bruce D, Schug S. Development and testing of a modified version of the brief pain inventory for use in residential aged care facilities. *J Am Geriatr Soc* 2008;**56**(2):301–6.
14. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993;**4**:1205–13.
15. Larue F, Colleau SM, Brasseur L, Cleeland CS. Multicentre study of cancer pain and its treatment in France. *BMJ* 1995;**310**:1034–7.
16. Davison SN, Jhangri GS. The impact of chronic pain on depression, sleep, and the desire to withdraw from dialysis in hemodialysis patients. *J Pain Symptom Manage* 2005;**30**:465–73.
17. Janardhan V, Soundararajan P, Rani NV, Kannan G, et al. Prediction of malnutrition using modified subjective global assessment dialysis malnutrition score in patients on hemodialysis. *Indian J Pharm Sci* 2011;**73**(1):38–45.
18. Eliezer G, Haggiag I, Os P, Bernheim J. Incidence of chronic pain in hemodialysis patients and its association to calcium, parathyroid hormone and vitamin D. *Clin J Am Soc Nephrol* 2009;**4**(8):1374–80.
19. Hedayati SS, Bosworth HB, Briley LP, et al. Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression. *Kidney Int* 2008;**74**:930–6.
20. Kimmel PL, Emont SL, Newmann JM, et al. ESRD patient quality of life: symptoms, spiritual beliefs, psychosocial factors, and ethnicity. *Am J Kidney Dis* 2003;**42**:713–21.
21. Panichi V, Migliori M, De Pietro S, Metelli MR, et al. Plasma C-reactive protein in hemodialysis patients: a cross-sectional, longitudinal clinical survey. *Blood Purif* 2000;**18**(1):30–6.
22. Plantinga LC, Fink NE, Jaar BG, Huang IC, Wu AW, Meyer KB, et al. Relation between level or change of hemoglobin and generic and disease-specific quality of life measures in hemodialysis. *Qual Life Res* 2007;**16**:755–65.
23. Vasantha P, Soundararajan N, Vanitha R, et al. *Indian J Pharm Sci* 2011;**73**(1):38–45.
24. Martinez I, Saracho R, Moina I, et al. Is there a lesser hyperparathyroidism in diabetic Patients with chronic renal failure? *Nephrol Dial Transplant* 1998;**13**(3):9–11.
25. Pittas AG, Lau J, Hu FB, et al. The role of vitamin D and calcium in type 2 diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2007;**92**:2017–29.
26. Rengin E, Baris A, Esra M. Bone pain assessment and relationship with parathyroid hormone and health-related quality of life in hemodialysis. *Renal Fail* 2013;**35**(5):667–72.
27. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;**117**:503–11.
28. Noordzij M, Boeschoten EW, Bos WJ, et al. NECOSAD Study Group: disturbed mineral metabolism is associated with muscle and skin complaints in a prospective cohort of dialysis patients. *Nephrol Dial Transplant* 2007;**22**:2944–9.