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Original Scientific Paper

FRAX IN HAEMODIALYSIS PATIENTS: PRELIMINARY RESULTS

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SUMMARY – The incidence of bone fractures is several times higher in haemodialysis (HD) patients than in the general population. FRAX is a fracture risk evaluation tool and shows a 10-year probability of bone fracture. The aim of this study was to evaluate the FRAX score in haemodialysis patients.

The study included 214 HD patients (81 female). We used the following calculation tool: https://www.sheffield.ac.uk/FRAX/?lang=cr. Increased risk for major fracture (MF) was defined as FRAX > 20% and for hip fracture (HF) > 3%.

If renal osteodystrophy (ROD) is defined as primary osteoporosis, the average FRAX value for MF is 7.4 ± 6.4% and for HF 3.5 ± 4.1%, and as secondary osteoporosis, the average FRAX value for MF is 10.3 ± 8.4 %, for HF 5.4 ± 5.9%. 13.6% of patients or 49.1% had an increased risk for MF or HF if ROD was defined as secondary osteoporosis. If it was defined as primary osteoporosis, the results were 7.1% for MF or 39.2% for HF. In women, FRAX values were significantly higher for both HF and MF.

According to our preliminary results, a large number of patients have an increased FRAX score risk, especially if we define ROD as secondary osteoporosis. The FRAX score is higher in women.

Key words: *FRAX, haemodialysis, bone fracture*

Introduction

Renal osteodystrophy (ROD) is a common complication of chronic kidney disease (CKD). Bone fractures are very often a consequence of ROD. Therefore identifying individuals at risk is an unmet need. [1,2]

FRAX is a known tool for assessing the risk of bone fractures in patients with primary osteoporosis. Several studies have shown that the FRAX tool may also help assess the risk of bone fractures in patients with CKD. [3,4]

We present preliminary results of FRAX results in haemodialysis patients. The goal of our study was to evaluate the FRAX score in a cohort of haemodialysis patients and to evaluate the difference between female and male patients. Also, we wanted to see if there is any difference if we define ROD as primary or secondary osteoporosis.

Patients and methods

We conducted an observation as a cross-sectional multicentre study. Our cohort consisted of 218 haemodialysis patients (81 female), all of them aged 20 years and older. After the approval of the local ethics committee, all patients signed informed consent. Ten-year probability of a major fracture, i.e. spine, forearm,

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hip, or shoulder (MF) and hip fracture (HF), were calculated using the Croatian version of the FRAX calculator without bone densitometry. (https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=cr). First, we have defined renal osteodystrophy as primary osteoporosis, and after that, as secondary osteoporosis, i.e. ROD as a disorder strongly associated with osteoporosis. Increased risk for MF was defined as FRAX > 20% and for HF > 3%.

Descriptive statistics were used for baseline demographic information. Most of the variables did not follow the normal distribution, and therefore the statistics were non-parametric. Numerical results were presented as means with standard deviations, median values and ranges, and categorical variables as count (percent).

Results

The baseline characteristic of our cohort is described in Table 1. Altogether, 81 female and 137 male haemodialysis patients from three dialysis centres were included.

If ROD is defined as primary osteoporosis, the average FRAX value for MF is 7.4 ± 6.4% and for HF 3.5 ± 4.1%, and as secondary osteoporosis, the average FRAX value for MF is 10.3 ± 8.4%, for HF 5.4 ± 5.9%. 13.6% of patients or 49.1% had an increased risk for MF or HF if ROD was defined as secondary osteoporosis. If defined as primary osteoporosis, the increased risk of fracture was in 7.1% of patients for MF and 39.2% for HF.

If we define ROD as secondary osteoporosis, there is a statistically significant higher risk for MF and HF. (Table 2.)

In females, FRAX values were significantly higher for both HF and MF. (Table 3) The result for HF was 8.5 ± 7.6% for MF and 15.9 ± 10.4% as secondary osteoporosis, and 4.8 ± 5.2 for HF, and 10.3 ± 8.2% for MF, as primary osteoporosis. (p<0.001 to male population). Over 6 months, we recorded fractures in two patients.

Both had a FRAX>20% for MF and >3% for HF.

Discussion

Renal osteodystrophy is a part of a more severe entity, chronic kidney disease mineral and bone disorder (CKD-MBD).[1] Vascular and soft tissue calcification, left ventricular hypertrophy, cardiovascular disease, bone disease, and bone fractures are the clinical manifestation of CKD-MBD.[5] A lot of data shows that in CKD patients, the prevalence of bone fractures is much higher than in the general population. Based on experimental and clinical data, there is no doubt that bone strength is impaired in CKD patients. Both parts of bone strength, i.e., bone quality determined by bone turnover, bone microarchitecture, bone microdamage, bone collagen properties and bone quantity, trabecular, and cortical bone density, are impaired in CKD.[6,7] It is clear why the incidence and prevalence of bone frac-

Table 1. Baseline characteristics of 218 patients included in the study

		Mean	SD	Number	%
Age (years) Haemodialysis vintage (years)		67.3 7.4	14.3 5.3		
Body weight (kg)		74.4	17.7		
Body height (cm)		169	11		
BMI (kg/m2)		26.08	5.53		
FRAX, MF, (SO)		10.3	8.4		
FRAX, HF, (SO)		5.4	5.9		
FRAX, MF, (PO)		7.4	6.4		
FRAX, HF (PO)		3.5	4.1		
MF, (SO)	NO			185	86.4%
	YES			29	13.6%
MF, (PO)	NO			197	92.9%
	YES			15	7.1%
HF, (SO)	NO			109	50.9%
	YES			105	49.1%
HF, (PO)	NO			129	60.8%
	YES			83	39.2%

PO, primary osteoporosis, SO secondary osteoporosis, MF major fractures, HF hip fractures.

Table. 2. Change in FRAX score according to whether the secondary osteoporosis parameter was included

	SO	PO	P
MF	10.3 ± 8.4	7.4 ± 6.4	<0.001
HF	5.4 ± 5.9	3.5 ± 4.1	<0.001

MF, major fractures, HF hip fractures primary osteoporosis, SO secondary osteoporosis
P – Wilcoxon paired test

Table 3. Differences in parameters by gender (a comparison made by Mann-Whitney test)

		Gender								
		Female				Male				
		Mean	SD	Number	N %	Mean	SD	Number	N %	P*
Age (years)		69.1	14.5			66.2	14.2			0.056
Haemodialysis vintage (years)		7.8	5.5			7.1	4.2			0.92
Body weight (kg)		67.5	16.4			78.6	17.1			<0.001
Body height (cm)		160	9			174	9			<0.001
BMI (kg/m2)		26.46	6.38			25.86	4.96			0.951
FRAX, MF, (SO)		15.9	10.4			6.8	4.2			<0.001
FRAX, HF, (SO)		8.5	7.6			3.5	3.4			<0.001
FRAX, MF, (PO)		10.3	8.2			5.7	4.2			<0.001
FRAX, HF, (PO)		4.8	5.2			2.6	2.9			0.009
MF (SO)	NO			53	65.4%			132	99.2%	<0.001
	YES			28	34.6%			1	0.8%	
MF (PO)	NO			70	86.4%			127	96.9%	0.202
	YES			11	13.6%			4	3.1%	
HF (SO)	NO			27	33.3%			82	61.7%	<0.001
	YES			54	66.7%			51	38.3%	
HF (PO)	NO			38	46.9%			91	69.5%	0.001
	YES			43	53.1%			40	30.5%	

*Mann-Whitney test, PO, primary osteoporosis, SO secondary osteoporosis, MF major fractures, HF hip fractures.

tures in CKD is high.[8] The incidence of bone fractures is increased from the early stages of CKD to the end stage, i.e., dialysis. In a retrospective analysis of 9041 incident dialysis patients, Iseri K. et al. identified the crude incidence rate of major fractures 17/1000 and after dialysis initiation 24/1000 patient-years.[9] In the study of Matias PJ et al., an incidence rate of 31/1000 persons-years was observed in 341 prevalent haemodialysis patients.[10] In Croatian surveys, in 31 out of 767 prevalent haemodialysis patients, a total of 36 bone fractures were observed.[2] Therefore, it is imperative to predict bone fractures in these high-risk patients. Bone mineral densitometry (BMD) is the gold standard in diagnosing osteoporosis and predicting bone fractures in the general population. In ROD, all components of bone strength are impaired, not only bone density.[7,8] There are some studies that show that BMD could be useful for fracture risk prediction in CKD, even more in predicting mortality. But some questions remain unanswered. At this moment, we do not know what is the best method for bone densitometry and at which part to measure density. It is known that in severe hyperparathyroidism, cortical bone loss is more expressed. [11,12,13] Bone biopsy is the gold standard in the evaluation of the ROD. With bone biopsies, measurements of the turnover, mineralization, and volume, markers of bone quality, are made. There are three types based on the above measurements: high or low turnover, and mixed. Fracture rates among these types are not consistent.[14]

FRAX is a well-known computer-based tool to evaluate fracture risk. FRAX assesses the 10-year probability of fractures. The output of FRAX is the 10-year probability of the major osteoporotic fractures: hip, spine, humerus, or forearm, and the 10-year probability of hip fracture. Risk is calculated from age, body mass index, history of previous fractures, smoking, alcohol consumption, glucocorticoid use, and causes of secondary osteoporosis. Femoral neck densitometry can be optionally input in the calculation.[15] There are controversial results of fracture risk prediction by FRAX in ROD.[16] Recently Whitlock RH and co-authors, among more than 10099 patients, between them 2154 with CKD stage 3 (eGFR 30-60 ml/min/1.73m2)

and 540 CKD stage 4-5 (eGFR <30ml/min/1.73m2) find a stringer relationship between FRAX and major fractures in patients with CKD than in those with preserved kidney function.[4] Previously Jamal SA et al. found, among 353 subjects, that FRAX was able to discriminate fracture status.[17] Very recently, two Polish groups have shown a value of FRAX in predicting bone fractures in haemodialysis patients. In one centre, Brunelova L and co-authors described that apart from other factors, a high FRAX score for major fractures was associated with low-trauma fractures.[18] Two studies by Przedlacki J and his group have shown that FRAX enables good assessment of major fracture in haemodialysis patients and that the FRAX prognostic threshold for identifying an increased risk of major bone fractures in haemodialysis patients is >5%. [19,20]

In the end, there is a very interesting study by Hayashi T et al. In the prospective study in 252 haemodialysis patients, they find that among Japanese haemodialysis patients, the FRAX levels were useful for predicting death.[21]

In our study, we have investigated the FRAX score in prevalent dialysis patients. First, we want to explore two options, i.e., to calculate the risk fractures score for ROD as primary osteoporosis or to use other options for secondary osteoporosis. However, CKD is not on the list of secondary osteoporosis in the FRAX computer program. In our group of patients, the FRAX score is higher for hip fractures and major fractures if we accept ROD as secondary osteoporosis. Also, the risk score was higher in the female group of patients.

Based on our first, very preliminary results, we think that the FRAX score could be used in haemodialysis patients. At least a high score should encourage us to improve mineral and bone disorder therapy in haemodialysis patients. It is a simple method without cost and takes just a bit of time. We will continue to follow up with our patients to see the correlation between FRAX score and the prevalence of fragility fractures in the future.

Literature

1. Pavlović D, Katičić D, Gulin T, Josipović J, Orlić L. Chronic kidney disease mineral bone disorder. Period biol 2015; 117: 81-85.
2. Šimunović I, Pavlović D, Kudumija B, Mihaljević D, Lovčić V, Jakić M. Bone fragility fractures in hemodialysis patients: Croatian surveys. Coll Antropol 2015; 39: 71– 74
3. Kanis JA, Harvey NC, Johansson H, Oden A, Leslie DW, McCloskey EW. FRAX update. J Clin Densitometry 2017; 20:360-367. doi: 10.1016/j.jocd.2017.06.022.
4. Whitlock RH, Leslie WD, Shaw J, Rigatto C, Thorlacius L, Komenda P et al. The fracture risk assessment tool (FRAX) predicts fracture risk in patients with chronic kidney disease. Kidney Int 2019; 95:447-454. doi: 10.1016/j.kint.2018.09.022.
5. Allen MR, Swallow EA, Metzger CE. Kidney disease and bone: changing the way we look at skeletal health. Curr Osteop Report 2020;18:242-246. doi.org/10.1007/s11914-020-00580-9
6. Nikolić V, Pavlović D. Bone: biomechanic and endocrine function. Period biol 2015; 117:1-4.
7. Parfitt AM. A structural approach to renal bone disease. J Bone Miner Res 1998; 13:1213-1220. doi.org/10.1359/jbmr.1998.13.8.1213
8. Cohen-Solal M, Funck-Brentano T, Urena Torres P. Bone fragility in patients with chronic kidney disease. Endocrine Connections 2020;9: R93-R101. doi.org/10.2215/CJN.00720116
9. Iseri K, Carrero JJ; Evans M, Fellander-Tsao L, Berg HE, Runesson B et al. Incidence of fractures before and after dialysis initiation. J Bone Miner Res. 2020 Jul 27. doi: 10.1002/jbmr.4141. Online ahead of print.
10. Matias JP, Laranjinha I, Azevedo A et al. Bone fracture risk in prevalent hemodialysis patients, J Bone Min Metab 2020; 38:205-212. doi: 10.1007/s00774-019-01041-9.
11. Orlic L, Crncevic Z, Pavlovic D, Zaputovic L. Bone mineral densitometry in patients on hemodialysis: difference between genders and what to measure. Ren Fail. 2010; 32:300-8. doi: 10.3109/08860221003611661.
12. Orlic L, Mikolasevic I, Crncevic-Orlic Z, Jakopcic I, Josipovic J, Pavlovic D. Forearm bone mass predicts mortality in chronic hemodialysis patients. J Bone Miner Metab. 2017;35:396-404. doi: 10.1007/s00774-016-0766-7.
13. Bover J, Urena-Torres P, Torregrosa JV, Rodriguez-Garcia M, Castro-Alonso C, Gorriz JL et al. Osteoporosis, bone mineral density and CKD-MBD complex: diagnostic consideration. Nefrologia 2018;38:476–490. doi.org/10.1016/j.nefroe.2018.10.005
14. Ott SM. Bone Histomorphometry in renal osteodystrophy. Semin Nephrol 2009; 29:122-132 doi.org/10.1016/j.semnephrol.2009.01.005
15. Kanis JA, Johansson H, Harvey NC, McCloskey. A brief history of FRAX. Arch Osteoporosis 2019; 13:118-145. https://doi.org/10.1007/s11657-018-0510-0
16. Pimentel A, Urena-Torres P, Zillikenes MC et al. Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European calcified Tissue Society and the European Renal association of Nephrology Dialysis and Transplantation. Kidney Int 2017; 92:1343-1355. doi: 10.1016/j.kint.2017.07.021.
17. Jamal SE, WEST SL, Nickolas TL. The clinicaly utility of FRAX to discriminate fracture status in men and women with chronic kidney disease. Osteoporosis Int 2014;25:71-76. doi: 10.1007/s00198-013-2524-1.

18. Brunerova L, Lažanska L, Kasalicky P, Verešova J, Potočkova J, Fialova A et al. Predictors of bone fractures in a single-centre cohort of hemodialysis patients: a 2-year follow-up study. Inter Urol Nephrol 2018;50:1721-1728. doi.org/10.1007/s11255-018-1958-y

19. Przedlacki J, Buczyńska-Chyl J, Koźmiński P, Niemczyk E, Wojtaszek E, Gieglis E et al. FRAX prognostic and intervention thresholds in the management of major bone fractures in hemodialysis patients: a two-year prospective multicenter cohort study Bone. 2020 Apr;133:115188. doi: 10.1016/j.bone.2019.115188. Epub 2019 Dec 13.

20. Przedlacki J, Buczynska-Chyl J, Kozminski P, Niemczyk E, Wojtaszek E, Gieglis E et al. The utility of Frax in predicting bone fractures in patients with chronic kidney disease on hemodialysis: a two-year prospective multicentre cohort study. Osteoporosis Int 2018; 29:1105-1115. doi: 10.1007/s00198-018-4406-z.

21. Hayashi T., Joki,N., Tanaka Y.,Iwasaki M, Kubo S, Asakawa T et al. The FRAX as a predictor of mortality in Japanese incident hemodialysis patients: an observational, follow-up study. J Bone Miner Metab 2015;33:674–683. doi.org/10.1007/s00774-014-0631-5

Sažetak

FRAX U BOLESNIKA NA HEMODJALIZI - PRELIMINARNI REZULTATI

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Učestalost prijeloma kosti nekoliko je puta veća u bolesnika na dijalizi (HD) nego u ostaloj populaciji. FRAX je alat za evaluaciju rizika prijeloma i prikazuje 10-godišnju vjerojatnost prijeloma kosti. Cilj rada je evaluacija vrijednosti FRAX u bolesnika na hemodijalizi.

U ispitivanje je uključeno 214 HD bolesnika (81 žena). Rabili smo alat za izračun: https://www.sheffield.ac.uk/FRAX/?lang=cr. Povišeni rizik za velike prijelome (VP) definiran je kao FRAX > 20 %, a za prijelom kuka (PK) > 3 %.

Ako renalnu osteodistrofiju (ROD) definiramo kao primarnu osteoporozu, prosječna FRAX vrijednost za VP je 7,4±6,4 % a za PK 3,5± 4,1 %, a kao sekundarnu osteoporozu prosječna FRAX vrijednost za VP je 10,3±8,4 %, za PK 5,4± 5,9 %, 13,6 % bolesnika odnosno 49,1 % imalo je povišeni rizik za VP odnosno PK ako je ROD definiran kao sekundarna, a kao primarna osteoporoza 7,1 % za VP odnosno 39,2 % za PK. U žena FRAX vrijednosti su bile značajno više za PK i VP, 8,5±7,6 % odnosno 15.9 ± 10,4 %, kao sekundarna, te 4,8 ± 5,2, i 10,3±8,2 % kao primarna osteoporoza.

Prema preliminarnim rezultatima veliki broj bolesnika ima povišene vrijednosti FRAX-a, posebno ako ROD definiramo kao sekundarnu osteoporou. Vrijednosti FRAXA-a su više u žena.

Ključne riječi: *FRAX, hemodijaliza, prijelom kosti*