







EVALUATION OF POST-SURGICAL MANAGEMENT OF FRAGILITY FRACTURES

AVALIAÇÃO DA CONDUTA PÓS CIRÚRGICA NAS FRATURAS POR FRAGILIDADE ÓSSEA

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ABSTRACT

Objective: To evaluate the conduct of Brazilian orthopedists regarding preventive treatment after fragility fracture surgery. **Methods:** A questionnaire was applied to Brazilian orthopedists. Statistical analyses were performed using the SPSS 16.0 program. **Results:** 257 participants were analyzed. Most participants, 90.7% (n = 233), reported that they cared for patients with fractures and 62.3% (n = 160) treated them. The most indicated treatments were vitamin D (22.6%; n = 134) and calcium supplementation (21.4%; n = 127). According to the experience of the physicians – experienced (n = 184) and residents (n = 73) – fragility fractures were more common in the routine of residents (98.6%; n = 72) than experienced physicians (87.5%; n = 161), p = 0.0115. While treatment conduction was more reported by experienced physicians (63.6%; n = 117) than residents (58.9%; n = 43), p = 0.004. More experienced orthopedists (21.4%; n = 97) indicated treatment with bisphosphates than residents (14.2%; n = 20), p = 0.0266. **Conclusion:** Although most professionals prescribe treatment after fragility fracture surgery, about 40% of professionals still do not treat it, with differences in relation to experience. In this sense, we reinforce the importance of secondary prevention in the management of fragility fractures. **Level of Evidence II, Prospective comparative study.**

Keywords: Femoral Fractures. Osteoporosis. Orthopedics. Vitamin D.

RESUMO

Objetivo: Avaliar a conduta adotada por ortopedistas brasileiros em relação ao tratamento adjuvante após a cirurgia de fraturas de fragilidade. **Métodos:** Foi aplicado um questionário aos ortopedistas brasileiros. A estatística foi realizada no programa SPSS 16.0. **Resultados:** Foram analisados 257 participantes. A maioria dos participantes 90,7% (n = 233) relataram atender os pacientes com fraturas e 62,3% (n = 160) relataram tratar. Os tratamentos mais indicados foram a suplementação de vitamina D (22,6%; n = 134) e de cálcio (21,4%; n = 127). De acordo com a comparação médicos experientes (n = 184) versus médicos residentes (n = 73), a rotina de fraturas de fragilidade foi mais observada por médicos residentes (98,6%; n = 72) que por médicos experientes (87,5%; n = 161), p = 0,0115. Enquanto a conduta de tratamento foi mais relatada por médicos experientes (63,6%; n = 117) versus médicos residentes (58,9%; n = 43), p = 0,004. A maior proporção de médicos experientes (21,4%; n = 97) indicaram o tratamento com bifosfatos versus médicos residentes (14,2%; n = 20), p = 0,0266. **Conclusão:** Apesar da maioria dos profissionais prescreverem um tratamento após a cirurgia de fraturas de fragilidade, cerca de 40% dos profissionais ainda não tratam, sendo observadas diferenças em relação à experiência. Neste contexto, reforçamos a importância da prevenção secundária na conduta de fraturas de fragilidade. **Nível de Evidência II, Estudo prospectivo comparativo.**

Descritores: Fraturas do Fêmur. Osteoporose. Ortopedia. Vitamina D.

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INTRODUCTION

Osteoporosis is a multifactorial disease that usually affects individuals over the age of 50 and it is the main cause of fragility fractures. Osteoporosis epidemiology is significant because it affects more than 200 million older adults worldwide; fracture of the hip being the most frequent. In the United States more than 53 million people have osteoporosis or are in the risk group for the development of this disease.^{1,2}

The prevalence of all types of fragility fracture in Brazil is high, ranging from 11% to 23.8%. According to national studies, osteoporosis and fragility fractures are considered a public health problem, since the prevalence of fragility fractures is high; they are associated with patient mortality, physical disability and recurrent fractures.³ The existence of a previous history of fragility fracture is an important risk indicator for future fractures. These individuals present a much higher risk of having another fracture in the future,^{4,5} and the risk is

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The study was conducted at Universidade Federal de São Paulo, Paulista School of Medicine, Department of Orthopedics and Traumatology. Correspondence: João Carlos Pedro Filho. Rua Napoleão de Barros, 715, 1º andar, São Paulo, SP, Brazil, 04024002. joaocarlosedpedrofilho@gmail.com

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even higher during the first year after the fracture.⁴ Thus, patients with previous fractures are an obvious opportunity for preventive interventions.

Practical and low-cost methods for screening at risk populations can quantify the problem and allow the planning of early interventions, which may prevent or delay the occurrence of primary and recurrent fragility fractures.⁶ Primary prevention depends mainly on the health professional, because patients' perception of fracture risks is considered low.⁷ Thus, orthopedists have the opportunity to prevent new injuries.

Although fragility fractures have epidemiological relevance in orthopedics and geriatrics, there is no standardized and uniform clinical approach for their treatment. In this sense, the aim of this study was to evaluate the conduct of Brazilian orthopedists in relation to treatment after fragility fractures surgery.

MATERIALS AND METHODS

Study

This is a prospective, cross-sectional and observational study, conducted at the Department of Orthopedics and Traumatology of the *Hospital São Paulo da Universidade Federal de São Paulo*


– *UNIFESP (EPM)*, São Paulo, Brazil. It was performed from June to August 2020. The study was submitted and approved by the Research Ethics Committee of UNIFESP/EPM (1195761900005505). The questionnaires were applied via the Google Forms platform.

Inclusion and exclusion criteria

Inclusion factors were Brazilian orthopedists and residents in orthopedics and traumatology, men or women that agreed to answer the questionnaire and signed the free and informed consent form. As requested by the ethics committee, the form was sent to participants via Google Forms. The exclusion criteria were participants of other nationalities, non-participating physicians and incomplete questionnaires.

QUESTIONNAIRE APPLICATION

During the study period, a letter inviting individuals to answer an exclusively digital questionnaire was sent to the Regional Societies of Orthopedics and Medical Residency Services of this specialty. Individuals were invited to answer a questionnaire with six questions, which addressed independent and dependent variables (Figure 1), about the conduct of Brazilian orthopedists in relation to preventive treatment after fragility fracture surgery.



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Evaluation of post-surgical conduct of fragility fractures

The goal of this questionnaire is to evaluate the approach and treatment of osteoporosis/osteopenia in fragility fracture patients.

- 1) In what Brazilian state do you practice medicine? _____

- 2) You are:
 Resident in Orthopedics and Traumatology (skip to question 4)
 Orthopedist

- 3) Do you have a specialty?
 No
 Yes. Which one?

- 4) Are proximal humerus, distal radio and/or proximal femur fractures part of your work routine?
 Yes
 No (end of the questionnaire)"

- 5) In these patients with boné fragility, does your conduct involve osteoporosis/osteopenia treatment?
 Yes
 No (end of the questionnaire)
 I refer the patient to a specialist. Which one? _____(end of the questionnaire)

- 6) What options do you recommend for treatment? Choose between the options bellow.
 Calcium supplementation
 Vitamin D supplementation
 Bisphosphonates
 Hormonal therapy"
 Muscle strengthening exercise
 Others: _____

Figure 1. Supplementary material.

Statistical analysis

To obtain a sample with statistical power, sample calculation was performed considering a 95% confidence level and 5% sampling error; the sample number of 243 participants was obtained. Descriptive analysis was expressed as frequency and proportion. To test homogeneity between proportions, the chi-square test or Fisher's exact test were used. The results were analyzed with the SPSS 16.0 software (Chicago, USA) and GraphPad Prism 5.0 (Software Inc., USA), considering a 5% significance level ($p < 0.05$) as statistically significant.

RESULTS

Sample characterization

The study population consisted of 257 interviewed participants. Most of the participants were from the Southeast region (60.7%; $n = 156$) and had already finished residency (Experienced physicians: 71.6%; $n = 184$). Among the subspecialties, half of the professionals (50.6%) had no specialty (20.2%; $n = 52$). Among the reported subspecialties, the most common were knee (14.4%; $n = 37$), orthopedic trauma (11.7%; $n = 30$) and hip (8.2%, $n = 21$) (Table 1).

Table 1. Description of the sample of Brazilian orthopedists.

Variable	N	%
Region		
Midwest	12	4.7%
Northeast	30	11.7%
North	13	5.1%
Southeast	156	60.7%
South	46	17.9%
Professionals		
Experienced physician	184	71.6%
Resident physician	73	28.4%
Subspecialty		
None	52	20.2%
Undefined	78	30.4%
Surgery (spine)	6	2.3%
Surgery (hand)	8	3.1%
Orthopedic trauma	30	11.7%
Shoulder/elbow	9	3.5%
Hip	21	8.2%
Knee	37	14.4%
Foot/ankle	11	4.3%
Sports Orthopedics	2	0.8%
Bone tumor	3	1.2%

Legend: 257 orthopedists were interviewed.

Regarding the routine and treatment of fragility fractures, more than 90% ($n = 233$) of the interviewed professionals routinely deal with proximal humerus, distal radio and/or proximal femur fractures. Among the approaches adopted in patients with bone fragility, the majority (62.3%, $n = 160$) of the responders reported using the treatment of osteoporosis/osteopenia, while approximately 28% reported not applying any treatment nor referring the patient to a specialist (Table 2).

Table 2. The routine and conduction of fragility fracture treatment of Brazilian orthopedists.

Variable	N	%
Routine with fractures		
Yes	233	90.7%
No	24	9.3%
Conducts treatment		
Yes	160	62.3%
No	42	16.3%
Refers to specialist	30	11.7%
Undefined	25	9.7%
Referred Specialist		
Undefined/ does not refer	228	88.7%
Endocrinologist	2	0.8%
Orthomolecular/Osteometabolic	7	2.7%
Geriatric Specialist	5	1.9%
Obstetrician and Gynecologists	3	1.2%
Other	12	4.7%

257 orthopedists were interviewed. *Fractures of the proximal humerus, distal radius and/or proximal femur were considered routine fragility fractures.

Treatments used by the interviewed orthopedists

The professionals mainly used treatment with vitamin D supplementation (22.6%; $n = 134$), followed by calcium supplementation (21.4%; $n = 127$) and bisphosphonates (19.7%; $n = 117$). The most unusual treatment was hormone therapy (1.7%; $n = 10$) (Table 3).

Table 3. Treatments used by the interviewed Brazilian orthopedists.

Treatment	N	%
Vitamin D Supplementation	134	22.6%
Calcium Supplementation	127	21.4%
Bisphosphonates	117	19.7%
Muscle strengthening exercise	100	16.8%
Undefined	93	15.7%
Other	13	2.2%
Hormone therapy	10	1.7%

We interviewed 257 orthopedists.

Fragility fracture treatment according to orthopedist's experience

When separating the interviewees according to their professional experience – experienced physicians ($n = 184$, 71.6%) and resident physicians ($n = 73$, 28.4%) – no statistically significant difference was found between Southeast and Other regions ($p > 0.05$). In relation to subspecialties, this association was statistically significant and, as expected, most experienced physicians (67.9%) had some defined subspecialty and almost all resident physicians (97.3%) declared no subspecialty (Table 4).

Table 4. Description of the sample according to experience.

Variable	Experienced Physician (n=184)		Resident Physician (n=73)		p
	N	%	N	%	
Region					
Southeast	107	58.2%	49	67.1%	0.2355
Others	77	41.8%	24	32.9%	
Subspecialty					
None	52	28.3%	0	0.0%	<0.0001*
Undefined	7	3.8%	71	97.3%	
Surgery	14	7.6%	0	0.0%	
Orthopedic trauma	30	16.3%	0	0.0%	
Shoulder/elbow	9	4.9%	0	0.0%	
Hip	19	10.3%	2	2.7%	
Knee	37	20.1%	0	0.0%	
Foot/ankle	11	6.0%	0	0.0%	
Sports Orthopedics	2	1.1%	0	0.0%	
Bone tumor	3	1.6%	0	0.0%	

257 orthopedists were interviewed. *Chi-square association test was performed considering as subspecialty groups: "Undefined," "None" and "Some," the latter being the sum of all defined subspecialties.

Regarding the routine and treatment of fragility fractures, we observed that even though most professionals reported that they attend to fragility fractures cases in their routine, this was more frequent in resident physicians' reports (n = 72, 98.6%) (p = 0.01). However, experienced physicians conducted treatment more often (63.6%; n = 117) than residents (58.9%; n = 43) – p = 0.004. No significant differences were observed regarding referral to other specialists (p > 0.05) (Table 5).

Table 5. Brazilian orthopedists' routine and treatment conduct of fragility fractures.

Variable	Experienced Physician (n = 184)		Resident Physician (n = 73)		p
	N	%	N	%	
Fragility fracture in the routine					
Yes	161	87.5%	72	98.6%	0.0115
No	23	12.5%	1	1.4%	
Conducts treatment					
Yes	117	63.6%	43	58.9%	0.004 ^b
No	20	10.9%	22	30.1%	
Refers to specialist	23	12.5%	7	9.6%	0.2314 ^c
Undefined	24	13.0%	1	1.4%	
Referred Specialist					
Undefined/does not refer to specialist	160	87.0%	68	93.2%	
Endocrinologist	1	0.5%	1	1.4%	
Orthomolecular/ Osteometabolic	7	3.8%	0	0.0%	
Geriatric Specialist	3	1.6%	2	2.7%	
Obstetrician and Gynecologists	3	1.6%	0	0.0%	
Other	10	5.4%	2	2.7%	

257 orthopedists were interviewed. *Chi-square association test was performed considering as conduct groups: "Yes," "No" and "Refers to specialist"; the undefined cases were disregarded in the Chi-square Association Test, considering the following groups: "Undefined/does not refer to specialist" and "Some," the latter being the sum of all defined specialties.

Among the treatment options chosen by the professionals, we found a significant difference regarding the fragility fracture treatment with bisphosphonates according to the experience. More experienced physicians reported using this type of treatment more often than residents (21.4% versus 14.2%, p < 0.05) (Table 6).

Table 6. Fragility fracture treatment, according to the experience of Brazilian orthopedists.

Treatment	Physician Experienced		Resident Physician		p
	n	%	n	%	
Bisphosphonates	97	21.4%	20	14.2%	0.0266*
Vitamin D Supplementation	98	21.6%	36	25.5%	0.8389
Calcium Supplementation	95	21.0%	32	22.7%	0.5879
Muscle strengthening exercise	81	17.9%	19	13.5%	0.0911
Undefined	64	14.1%	29	20.6%	0.7099
Other	11	2.4%	2	1.4%	0.5256
Hormone therapy	7	1.5%	3	2.1%	NS

257 orthopedists were interviewed. *Chi-square association test was performed considering as conduct groups: "Yes," "No."

DISCUSSION

Fragility fractures are associated with morbidity, reduced life expectancy, pain, functional disability, decreased self-esteem, reduced quality of life and increased risk of recurrent fractures. Fragility fractures have epidemiological relevance in orthopedics, mainly in the older adults group of the population.⁸ However, there is still no standardized and uniform clinical approach for the management and treatment of fragility fractures, which shows the importance of this study on the conduct of Brazilian physicians regarding preventive treatment after fracture surgery.

This study analyzed the clinical conduct and treatment management of 257 orthopedists. More than 90% (n = 233) of the interviewed professionals routinely deal with proximal humerus, distal radio and/or proximal femur fragility fractures. Most orthopedists reported treating fragility fractures with medications used for osteoporosis and not referring patients to other specialists.

The frequency of fractures observed in this study, according to the affected anatomical region, is consistent with the epidemiology: other studies have also reported higher frequency of fragility fractures in the proximal humerus, radio and femur.^{2,9,10} In Brazil, femoral fractures stand out due to their impact on the health of older adults, mortality and morbidity rates. Studies report that patients with femoral fracture have a 15 to 20% reduction in life expectancy, with mortality rates ranging between 15 and 50% in the first year after the fracture.^{9,10}

Regardless of the initial fracture location, the history of a previous fracture confers a higher risk of subsequent fractures, which justifies preventive treatment. Systematic reviews on the prevention of secondary fractures demonstrate that the treatment of primary fractures reduces relative and absolute risk of new fractures.^{11,12} Regarding the conduct of the responders, we can observe that the main type of treatment was vitamin D supplementation, followed by Calcium and Bisphosphonate supplementation.

Vitamin D is a factor associated with the genesis of bone deterioration. A study involving fragility fractures reported high rates of vitamin D deficiency in patients with peripheral fractures and vertebral fractures.¹³ Despite the clear connection between low-energy fractures and vitamin D deficiency, the literature is not in complete agreement with the preventive effect of this treatment. According

to Chapuy et al.,¹³ the administration of tricalcium phosphate associated with cholecalciferol in women (mean age of 84 years) for 18 months decreased the rate of hip fractures in 29% and non-vertebral fractures in 24%, with preventive effect during 3 years of treatment. However, other studies have shown that vitamin D administration is unlikely to avoid fragility fractures. When administered with calcium supplements, it reduces the risk of hip fractures, especially in institutionalized patients.^{14,15}

In order to identify whether the conduct of the professionals differed according to experience, the responders were stratified among experienced physicians (n = 184, 71.6%) and resident physicians (n = 73, 28.4%). Among the treatment options chosen by the professionals, we noticed a significant difference in the treatment of fragility fractures with bisphosphonates, according to their experience. More experienced physicians reported using this type of treatment more often than residents (21.4% versus 14.2%, p < 0.05) (Table 6). Several treatment options with bisphosphonates are available, the most widely used of the bisphosphonate group are alendronate, risedronate and etidronate, which can be used as initial treatments.^{11,16}

The conduct of experienced orthopedists is consistent with meta-analysis studies that evaluated the treatment with alendronate and etidronate to reduce the occurrence of fragility fractures, presenting evidence classified as "gold" and "silver" level, respectively.^{11,16} Regarding the administration of alendronate, we observed a reduction in relative (RR) and absolute (RA) risk of vertebral fractures (45% RR, 6% RA), non-vertebral (23% RR, 2% RA), hip (53% RR; 1% RA) and wrist (50% RR; 2% RA).¹¹

Despite the efficacy of already established drugs, such as bisphosphonates, side effects and loss of potency due to recurrent use of the same drug may limit the long-term use of a single drug. Therefore, treatment continuation and patient follow-up are essential. In addition, sequential and combinatorial use of current medications can provide an alternative approach, which motivates the continued update of fragility fracture treatments.¹⁷

Resident physicians have vitamin D supplementation as their preferred therapeutic treatment. This calcium and/or vitamin D based treatment may be indicated in cases of deficiency of these substances, or in patients with a high risk of fractures and/or undergoing osteoporosis treatment. In patients with postmenopausal osteoporosis, it is necessary to dose the amount of 25 hydroxyvitamin D before starting drug treatment. However, the use of calcium and vitamin D does not seem to be effective in fracture prevention.

Hormone therapy was the less used treatment, regardless of the experience of the prescribing physician. In the review study, Levin et al.¹⁸ suggests that low-dose transdermal hormone therapy has important characteristics such as cost, safety and efficacy for primary prevention and treatment of osteoporosis and fragility fractures, especially for menopausal women. Thus, hormone therapy could be applied in menopausal women to reduce risks of osteoporosis fractures.

In this study, 62.3% (n = 163) of the responders conduct the treatment of fragility fractures, which corroborates data from the literature. However, we can observe that approximately 40% of the responders do not treat fragility fractures, which reflects a worrying situation. Iolascon et al.¹⁹ emphasize that patients who have already suffered a fragility fracture are generally not adequately investigated and are almost never treated with osteoporosis medications.¹⁹

Many referral services for the prevention of recurrence fractures are increasing in the world due to good results. Naranjo et al.²⁰ propose the establishment of a framework of good practices and performance indicators to implement and monitor the coordination of fracture services and primary care in clinical practice, demonstrating the need for treatment of secondary fractures.

The occurrence of previous fractures and risk factors for osteoporosis are already indicative of the need for specialized follow-up and appropriate treatment. In this sense, we reinforce the need for preventive treatment of primary and secondary fragility fractures.

CONCLUSION

Although most professionals have reported that they prescribe preventive treatment after fragility fracture surgeries, about 40% of professionals still do not treat this condition. In addition, we observed a difference in the indicated treatment according to the experience of the physician. Despite the non-standardization of clinical management of fragility fractures in Brazil, we reinforce the importance of primary and secondary fractures prevention, which is supported by the literature and can have a positive impact on patient mobility and mortality.

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REFERENCES

1. Curtis EM, Moon RJ, Harvey NC, Cooper C. The impact of fragility fracture and approaches to osteoporosis risk assessment worldwide. *Bone*. 2017;104:29-38.
2. The National Institutes of Health. Osteoporosis overview. Maryland: The National Institutes of Health, 2018.
3. Pinheiro MM, Eis SR. Epidemiology of osteoporotic fractures in Brazil: what we have and what we need. *Arq Bras Endocrinol Metab*. 2010;54(2):164-70.
4. Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, et al. Fracture risk following an osteoporotic fracture. *Osteoporos Int*. 2004;15(3):175-9.
5. Stolnicki B, Oliveira LG. For the first fracture to be the last. *Rev Bras Ortop*. 2016;51(2):121-6.
6. Dang DY, Zetumer S, Zhang AL. Recurrent Fragility Fractures: A Cross-sectional Analysis. *J Am Acad Orthop Surg*. 2019;27(2):e85-e91.
7. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-22.
8. Caitriona C, Mark MG, Elaine H, Claire G, Michelle F, Persson UMC, et al. Management of hospitalised osteoporotic vertebral fractures. *Arch Osteoporos*. 2020;15(1):14.
9. Haentjens P, Magaziner J, Colón-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, et al. Meta-analysis: Excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010;152(6):380-90.
10. Soares DS, de Mello LM, da Silva AS, Martinez EZ, Nunes AA. Fraturas de fêmur em idosos no Brasil: Análise espaço-temporal de 2008 a 2012. *Cad Saude Publica*. 2014;30(12):2669-78.
11. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD001155.
12. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(1):CD004523.
13. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and Calcium to Prevent Hip Fractures in Elderly Women. *N Engl J Med*. 1992;327(23):1637-42.

14. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: Randomised double blind controlled trial. *BMJ*. 2003;326(7387):469.
15. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: A meta-analysis of randomized controlled trials. *Arch Intern Med*. 2009;169(6):551-61.
16. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, et al. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;2008(1):CD003376.
17. Li H, Xiao Z, Quarles LD, Li W. Osteoporosis: Mechanism, Molecular Target and Current Situation in Drug Development. *Curr Med Chem*. 2020;27:73-93.
18. Levin VA, Jiang X, Kagan R. Estrogen therapy for osteoporosis in the modern era. *Osteoporos Int*. 2018;29(5):1049-55.
19. Iolascon G, Moretti A, Toro G, Gimigliano F, Liguori S, Paoletta M. Pharmacological therapy of osteoporosis: What's new? *Clin Interv Aging*. 2020;15:485-91.
20. Naranjo A, Ojeda S, Giner M, Balcells-Oliver M, Canals L, Cancio JM, et al. Best Practice Framework of Fracture Liaison Services in Spain and their coordination with Primary Care. *Archives of osteoporosis*. 2020;15(63):1-7.