Φαρμακευτικά αίτια σκελετικής ευθραυστότητας

Θεμιστοκλής Ι.Τεμεκονίδης

Ρευματολόγος-Καβάλα

Σύγκρουση συμφερόντων:καμμία.

Περίγραμμα ομιλίας

- Αναστολείς αρωματάσης
- Αναστολείς της αντλίας πρωτονίων
- SSRI’s
- Κορτικοστεροειδή
- Οστεοπόρωση από φάρμακα

Osteoporos Int. 2019 Jan;30(1):187-200. doi: 10.1007/s00198-018-4758-4. Epub 2018 Nov 9.

Hormone therapy and osteoporosis in breast cancer survivors: assessment of risk and adherence to screening recommendations.

Hamood R[1], Hamood H[2,3], Merhasin I[4], Keinan-Boker L[1,5].

Author information

Abstract

The long-term impact of hormone therapy for breast cancer on risk of osteoporosis and the extent to which bone screening recommendations are implemented in daily practice remain unknown. We found that the aromatase inhibitor-induced risk of osteoporosis did not continue in the off-treatment follow-up. Adherence to screening recommendations was suboptimal.

INTRODUCTION: A case-cohort study was undertaken to better understand the impact of hormone therapy on breast cancer patients' risk of osteoporosis, and to estimate the extent to which current bone mineral density screening recommendations are implemented in real-life daily practice.

METHODS: This study is based on 1692 female breast cancer survivors recruited from "Leumit" healthcare fund, who were diagnosed with primary nonmetastatic invasive breast cancer between 2002 and 2012. A 20% random subcohort was sampled at baseline, and all osteoporosis cases were identified. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) were estimated by weighted Cox proportional hazards models.

RESULTS: Of 1692 breast cancer survivors, 312 developed osteoporosis during a median follow-up of 5 years. The crude cumulative incidence of osteoporosis accounting for death as a competing risk was 25.7% (95% CI, 21.9-29.5%). In multivariable analyses, osteoporosis was positively associated with the aromatase inhibitor (AI) sequential treatment after tamoxifen (HR, 3.14; 95% CI, 1.44-6.88; P = .004) but was more pronounced with AI use as upfront monotherapy (HR, 5.53; 95% CI, 1.46-20.88; P = .012). This effect did not continue in the off-treatment follow-up. In subgroup analysis by menopausal status, tamoxifen did not seem to confer a protective effect on bone health in postmenopausal patients. Adherence to screening recommendations in AI-treated postmenopausal women was suboptimal, particularly at baseline and after 48 months of continuous AI use.

CONCLUSIONS: The natural, age-related reduction in bone density is exacerbated by breast cancer active AI treatment. Future research should focus on investigating screening adherence-related barriers/facilitators and effective strategies to bring practice in line with agreed standards.

Life Sci. 2019 Feb 1;218:213-223. doi: 10.1016/j.lfs.2018.12.058. Epub 2018 Dec 31.

Proton pump inhibitors therapy and risk of bone diseases: An update meta-analysis.

Liu J[1], Li X[2], Fan L[3], Yang J[1], Wang J[1], Sun J[4], Wang Z[5].

Osteoporos Int. 2019 Jan;30(1):103-114. doi: 10.1007/s00198-018-4788-y. Epub 2018 Dec 12.

Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies.

Poly TN[1,2], Islam MM[1,2], Yang HC[2], Wu CC[1,2], Li YJ[3,4,5,6].

Rheumatol Int. 2018 Nov;38(11):1999-2014. doi: 10.1007/s00296-018-4142-x. Epub 2018 Aug 29.

Proton pump inhibitors' use and risk of hip fracture: a systematic review and meta-analysis.

Hussain S[1], Siddiqui AN[1], Habib A[2], Hussain MS[3], Najmi AK[4].

-32 μελέτες(13 ΗΠΑ,10 Ευρώπη,6 Κίνα,2 Ωκεανία),2.181.546 άτομα.

-Αύξηση του κινδύνου κατάγματος σε όλα τα σημεία

-Διαταραχή στην ανάπτυξη των οστών και της αποκατάστασης του κατάγματος

-Μεγάλη προσοχή στη συνταγογράφηση (ηλικιωμένοι,παιδιά!)

-Άγνωστη η σχέση μεταξύ BMD-PPI's

-Περαιτέρω έρευνα(βασική έρευνα,κλινικές μελέτες)

Association of Selective Serotonin Reuptake Inhibitors and Bone Mineral Density in Elderly Women

Smita Saraykar,[1] Vineeth John,[1] Bo Cao,[1] Matthew Hnatow,[2] Catherine G. Ambrose,[2] and Nahid Rianon,[3]*

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- Αλληλεπίδραση κατάθλιψης και οστεοπόρωσης.
- Δεν υπάρχει διαφορά στη BMD στον αυχένα του μηριαίου(χρήστες SSRI's και μη)
- Τάση μείωσης της BMD στην ΣΣ στους χρήστες των SSRI's, μόνον όταν έπαιρναν συγχρόνως και αγωγή για την οστεοπόρωση
- Περαιτέρω έρευνα και μελέτες…

Mol Med Rep. 2019 Feb 1. doi: 10.3892/mmr.2019.9924. [Epub ahead of print]

Fluoxetine induces direct inhibitory effects on mesenchymal stem cell-derived osteoprogenitor cells independent of serotonin concentration.

Koura SM[1], Salama M[1], El-Hussiny M[2], Khalil MEA[1], Lotfy A[3], Hassan SA[1], Gad Elhak SA[1], Sobh MA[4].

- Μεσεγχυματικά κύτταρα από ποντίκια –πηγή για οστεοπρογονικά κύτταρα(osteoprogenitors)
- Φαίνεται ότι η αυξανόμενη επίπτωση της οστικής απώλειας στους ασθενείς που παίρνουν φλουοξετίνη (Ladose) οφείλεται σε μηχανισμό απόπτωσης των οστεοπρογονικών κυττάρων (fluoxetine-induced apoptosis)

Οστεοπόρωση οφειλόμενη σε κορτικοστεροειδή.

Osteoporos Int. 2018 Sep;29(9):2121-2127. doi: 10.1007/s00198-018-4591-9. Epub 2018 Jun 11.

Abnormal microarchitecture and stiffness in postmenopausal women using chronic inhaled glucocorticoids.

Liu Y[1], Dimango E[2], Bucovsky M[3], Agarwal S[3], Nishiyama K[3], Guo XE[4], Shane E[3], Stein EM[5].

Author information

Abstract

Postmenopausal (PM) women using inhaled glucocorticoids (IGCs) had substantial abnormalities in volumetric BMD (vBMD), microarchitecture, and stiffness using high resolution peripheral computed tomography (HRpQCT) compared to age- and race-matched controls. Abnormalities were most severe at the radius. These preliminary results suggest that there may be major, heretofore unrecognized, skeletal deficits in PM women using IGCs.

INTRODUCTION: While oral glucocorticoids are well recognized to have destructive skeletal effects, less is known about the effects of IGCs. The detrimental skeletal effects of IGCs may be greatest in PM women, in whom they compound negative effects of estrogen loss and aging. The goal of this study was to evaluate microarchitecture and stiffness in PM women using chronic IGCs.

METHODS: This case-control study compared PM women using IGCs for ≥ 6 months (n = 20) and controls matched for age and race/ethnicity (n = 60). Skeletal parameters assessed included areal BMD (aBMD) by DXA, trabecular and cortical vBMD and microarchitecture by HRpQCT of the radius and tibia, and whole bone stiffness by finite element analysis.

RESULTS: By DXA, mean values in both groups were in the osteopenic range; hip aBMD was lower in IGC users ($P < 0.04$). By HRpQCT, IGC users had lower total, cortical, and trabecular vBMD at both radius and tibia (all $P < 0.05$). IGC users had lower cortical thickness, lower trabecular number, greater trabecular separation and heterogeneity at the radius (all $P < 0.03$), and greater heterogeneity at the tibia ($P < 0.04$). Whole bone stiffness was lower in IGC users at radius ($P < 0.03$) and tended to be lower at the tibia ($P = 0.09$).

CONCLUSIONS: PM women using IGCs had substantial abnormalities in vBMD, microarchitecture, and stiffness compared to controls. These abnormalities were most severe at the radius. These preliminary results suggest that there may be major, heretofore unrecognized, skeletal deficits in PM women using IGCs.

GIOP

- Ann Endocrinol . 3/2018 **Bone and glucocorticoids.**Briot K.
- Endocrine. 3/18 REVIEW **Glucocorticoid-induce osteoporosis.**Compston J.
- N Engl J Med. 12/2018 **Glucocorticoid-Induced Osteoporosis** Humphrey M.
- Osteoporos Int. 2/2019 Feb 25 **GIOP** Adami G , Saag KG
- J Rheumatol. 3/19 **Evaluation of the implementation of guidelines on the treatment of osteoporosis in patients with rheumatoid arthritis.** Gossec L, Dougados M.

Συμπεράσματα

- Η GIOP είναι η πιο συχνή αιτία 2οπαθούς οστεοπόρωσης
- Προηγούμενη έκθεση σε GCs αυξάνει τον κίνδυνο κατάγματος(**διάστημα χορήγησης** και **δόση**)
- Ελλειπή τα μέσα πρόβλεψης (FRAX,ΜΟΠ)
- Προληπτική αγωγή σε όλους τους ασθενείς που παίρνουν GCs!
- Νέες οδηγίες αντιμετώπισης αλλά..η GIOP είναι **υπο-διεγνωσμένη**

  και **υπο-θεραπευμένη** (6-8**%** DXA, 18/% ασβέστιο,12% βιτ D,13-28% θεραπεία!)

Συμπεράσματα

- Θεραπεία 1ης επιλογής:διφωσφονικά
- Zolendronic acid,teriparatide,denosumab,raloxifene(2η,3η,4η επιλογή)
- Αναστολείς σκληροστίνης;;;

Denosumab

- Ασθενείς μικρής ηλικίας που θα διακόψουν τα κορτικ/δή σύντομα.
- Πόσο καιρό θα το πάρουν, πώς θα γίνει η διακοπή και τι θα γίνει μετά;

Denosumab

- Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O (2017)
- Clinical features of 24 patients with rebound associated vertebral fractures after denosumab discontinuation: systematic review and additional cases

  J Bone Miner Res 32:1291– 1296.

Vertebral fractures cascade: potential causes and risk factors

H. Che[1] · V. Breuil[2] · B. Cortet[3] · J. Paccou[3] · T. Thomas[4] · L. Chapuis[5] · F. Debiais[6] · N. Mehsen-Cetre[7] · R.M. Javier[8] · S. Loiseau Peres[9] · C. Roux[10] · K. Briot[10]

Received: 28 May 2018 / Accepted: 29 November 2018

Abstract

Summary We performed a study to identify potential causes and risk factors of vertebral fracture cascade. Vertebral fracture cascade is a severe clinical event in patients with bone fragility. Only half of patients have an identified cause of secondary osteoporosis.

Introduction Vertebral fracture (VF) is the most common osteoporotic fracture, and a strong risk factor of subsequent VFs leading to VF cascade (VFC). We prompted a study to identify potential causes and risk factors of VFC.

Methods VFC observations were collected retrospectively between January 2016 and April 2017. VFC was defined as an occurrence of at least three VFs within 1 year.

Results We included in 10 centers a total of 113 patients with VFC (79.6% of women, median age 73, median number of VFs in the cascade, 5). We observed 40.5% and 30.9% of patients with previous major fractures and a previous VF, respectively, and 68.6% with densitometric osteoporosis; 18.9% of patients were currently receiving oral glucocorticoids and 37.1% in the past.

VFC was attributed by the physician to postmenopausal osteoporosis in 54% of patients. A secondary osteoporosis associated with the VFC was diagnosed in 52 patients: glucocorticoid-induced osteoporosis (25.7%), non-malignant hemopathies (6.2%), alcoholism (4.4%), use of aromatase inhibitors (3.6%), primary hyperparathyroidism (2.7%), hypercorticism (2.7%), anorexia nervosa (2.7%), and pregnancy and lactation-associated osteoporosis (1.8%). A total of 11.8% of cases were reported following a vertebroplasty procedure. A total of 31.5% patients previously received an anti-osteoporotic treatment. In six patients, VFC occurred early after discontinuation of an anti-osteoporotic treatment, in the year after the last dose effect was depleted: five after denosumab and one after odanacatib.

Conclusion The results of this retrospective study showed that only half of VFC occurred in patients with a secondary cause of osteoporosis. Prospective studies are needed to further explore the determinants of this severe complication of osteoporosis.

Bone. 2019 Mar;120:94-100. doi: 10.1016/j.bone.2018.08.019. Epub 2018 Aug 30.

Long term time trends in use of medications associated with risk of developing osteoporosis: Nationwide data for Denmark from 1999 to 2016.

Skjødt MK[1], Ostadahmadli Y[2], Abrahamsen B[3].

Author information

Abstract

PURPOSE: To evaluate the development in the use of medications associated with an increased risk of developing osteoporosis over the time period from 1999 to 2016.

METHODS: We extracted data on total sale, sales rate and usage rate for the medications of interest from www.medstat.dk, which is an online, open-source database reporting the monthly sale of both over-the-counter and prescription-based medications in Denmark. The dataset covers both the primary and secondary health sectors.

RESULTS: Most medications exhibited an increasing use from 1999 to 2016, though some had stable (e.g. glucocorticoids) or declining use. Notably, some medications showed widespread and increasing use, including proton pump inhibitors (PPI), selective serotonine reuptake inhibitors (SSRI) and venlafaxine. For PPI, sales rates increased by 461% from 1999 to 2016, with 9% of men and 11.4% of women filling at least one prescription in 2016. The use of SSRI and venlafaxine increased by 114% and 613%, respectively. This was more pronounced in women and for SSRI also in the elderly (80+ years). The sale of aromatase inhibitors was moderate (1-10 DDD per 1000 capita per day) in 2016, yet grew by 2400% from 1999, almost exclusively in women aged 80 years or older.

CONCLUSION: We found a trend of increasing use from 1999 to 2016 of most medications with a potential for causing osteoporosis, often most pronounced in fracture risk groups (postmenopausal women and/or in the elderly). This may play a clinically relevant role in both current and future causality of osteoporosis.

Expert Opinion on Drug Safety

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Drug-induced bone loss: a major safety concern in Europe

Khac-Dung N guyen, Bahador Bagheri & Haleh Bagheri

- Η απώλεια οστού από φάρμακα είναι η πιο συχνή αιτία καταγμάτων με αποτέλεσμα μεγάλη αύξηση στη θνησιμότητα.
- Κορτικοστεροειδή,αναστολείς αρωματάσης,GnRHαγωνιστές, medroxyprogesterone acetate,αντιεπιληπτικά,SSRI's,ηπαρίνες,αντιπηκτικά από το στόμα,διουρητικά της αγκύλης,αντιικά ,ppi's,χημειοθεραπευτικά,μορφίν και οπιοειδή,θυρεοειδική ορμόνη,αντιαρρυθμικά,λίθιο,σίδηρος.
- **Μικρότερη δόση και μικρότερο διάστημα θεραπείας!**
- Αύξηση της προσοχής και συνεχής επιμόρφωση.

Drugs suspected	Mechanism	Duration effect	Prevention by calcium and vitamin D supplementation	Prevention by Antiresorptives
Glucocorticoids ***	Decreased bone formation	About 3 months to 2 years, dose depending	Yes	Bisphosphonates
Antiepileptic drugs **	Uncertain (maybe stimulating bone turnover)	About 2 years	Yes	Unclear (bisphosphonates)
Thyroid hormone (used at suppressive dose) *	Increased bone resorption	About 2-5 years	Yes	Bisphosphonates but not calcitonin
Gonadotropin-releasing hormone agonists and other androgen deprivation therapy **	Hypogonadism	About from 6 months	Recommended but not enough	Bisphosphonates, denosumab, raloxifen or toremifen
Aromatase inhibitors **	Reduced oestrogen production. Increased bone resorption and decreased bone density	About 2-5 years	Yes	Bisphosphonates or denosumab
Medroxyprogesterone acetate (depot) **	Inhibited oestrogen production	Unclear	Yes	Not recommended
Selective serotonin reuptake inhibitors *	Inhibition of serotonin transporter	From 6 weeks to several years	Yes	Not recommended
(Unfractionated) heparins **	Decreased bone formation, increased resorption	About 6 months, dose depending	Yes	Not recommended

Drugs suspected	Mechanism	Duration effect	Prevention by calcium and vitamin D supplementation	Prevention by Antiresorptives
Oral anticoagulants *	Uncertain	Unclear (maybe several years)	No information but should recommended	No information
Loop diuretics *	Inhibited calcium reabsorption, increased resorption and bone turnover	Unclear (maybe several years)	No information but should recommended	No information
Calcineurin inhibitors *	Increased bone resorption	Unclear (maybe about 2 year)	Yes	Bisphosphonates
Anti-retroviral therapy **	Increased osteoclastogenesis and bone resorption	About 48 weeks	Yes	Alendronate, zolendronate
Methotrexate *	Increased osteoblastic activity and decreased bone resorption	Uncertain (short-term to several years)	Yes	Bisphosphonates
Proton pump inhibitors **	Decreased calcium absorption through a direct effect on osteoclast activity	About 1 -5 years	Recommended (with prudence in elderly patient)	Avoid

Ευχαριστώ πολύ!