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Osteoporosis and polypharmacy

Due to the worldwide demographic changes, the number of osteoporotic fractures continues to increase and adequate management is needed [1]. In addition to the severe health-related consequences for individual patients, the socioeconomic costs are substantial. For Germany, the annual cost is close to 3 billion euro [2]. Especially in geriatric patients, osteoporotic fractures are strongly related to falls. A fragility fracture caused by a fall is often the first symptom of underlying osteoporosis. One of three elderly aged over 65 years experiences one fall per year, while in those above 80 years, it is already one out of two. One out of ten falls requires hospital treatment and one out of 100 falls leads to a hip fracture [3].

Currently elderly patients aged >75 years take eight different drugs on average. For each decade, one can find one more drug and up to ten medications in the age group >80 years. In addition, the patients enlarge their prescribed medication with three to four over-the-counter (OTC) drugs. Nine out of 10 patients take at least one OTC drug, while 1 patient out of 10 takes ≥5 OTC drugs. This practice is particularly common in elderly women with a higher level of education. Two thirds of these drugs are analgesics.

Due to the high prevalence of osteoporosis and polypharmacy in geriatric patients, one could actually expect that osteoporosis treatment is very common and well established. In contrast, the treatment rate of patients with osteoporosis is an example of pharmacological undertreatment. Despite the impact of osteoporotic fractures and the number of different treatment options available, only 11% of the patients in Germany receive a specific anti-osteoporotic drug treatment according to the guidelines [4]. Even after the patient sustained an osteoporotic fracture, the treatment rate remains low. At least 42.7% of hip fracture patients had sustained an osteoporotic fracture years before [5]. In the United States, only 2% of hip fracture patients receive a specific osteoporosis treatment after their hospitalization [6]. Contrary to expectations osteoporosis treatment is also rare in patients under extensive medication [7, 8]. Kuijpers et al. [7] demonstrated the phenomenon of the linear correlation of polypharmacy and undertreatment. Physicians often consider polypharmacy as a reason not to start osteoporosis treatment, because they are afraid of aggravating the problem and the risk of drug interactions. On the other hand, the association of multimedication and low compliance rates is beyond controversy [9]. In particular, patient adherence with oral medication is still low in anti-osteoporotic drug treatment and it is known to be under 50% after 1 year.

The present paper discusses the question whether preexisting polypharmacy could be a reasonable argument against osteoporosis treatment or, to the contrary, in favor of treatment. First, we discuss the risk of interactions of osteoporosis drugs (oral and parenteral bisphosphonates, raloxifene, strontium ranelate, teriparatide, denosumab) with other medications, then we give an overview of common medications in elderly patients and their impact on bone metabolism and fracture risk.

Drug interactions

The absorption of all oral bisphosphonate derivatives may be impaired by concomitant oral intake of antacids. The probable primary mechanism of this interaction is binding of the bisphosphonate derivative to polyvalent cations in the form of a nonabsorbable (or very poorly absorbable) chelate. The most common polyvalent cations are calcium and magnesium. Beside oral supplements, nutrition may also decrease the absorption of bisphosphonate, especially milk products or mineral water. These interactions can reduce the absorption rate by 85%.

The concomitant intake of raloxifene and warfarin may shorten the prothrombin time. Due to concerns that hypercalcemia produced by teriparatide could predispose cardiac glycoside-receiving patients to enhanced (toxic) cardiac effects, teriparatide product labeling recommends caution when using teriparatide in patients receiving digoxin or other cardiac glycosides.

According to the US Food and Drug Administration (FDA) over the last decade approximately 4% of all newly approved medications had a critical or dangerous risk of drug interactions. However, drugs for osteoporosis treatment definitely do not belong to this group.

Except for denosumab, impaired renal function with a creatinine clearance

Abstract · Zusammenfassung

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Abstract

Osteoporosis is very common in elderly patients. Despite the severe health-related consequences for individual patients and the socioeconomic costs caused by osteoporotic fractures, treatment rates are still low. Due to drug interactions and patient compliance, polypharmacy is often mentioned as a reason for undertreatment. Several drugs have a direct or indirect effect on bone metabolism. The present paper discusses the risk of interactions of anti-osteoporotic drugs (oral and parenteral bisphosphonates, raloxifene, strontium ranelate, teriparatide, and denosumab) with other common medications in elderly patients and their impact on bone metabolism and fracture risk. In summary, the number and risk of drug interactions of all common anti-osteoporotic drugs are small and clinically rather irrelevant. However, patients with a polypharmacy are at a higher risk of fractures and should receive osteoporosis treatment, if indicated.

Keywords

Osteoporosis · Polypharmacy · Fracture risk · Elderly · Drug interactions

Osteoporose und Polypharmazie

Zusammenfassung

Osteoporose hat eine hohe Prävalenz bei älteren Patienten. Trotz der enormen individuellen Folgen für die Betroffenen und die hohen sozioökonomischen Kosten osteoporotischer Frakturen sind die Therapieraten weiterhin sehr gering. Als Begründung wird immer wieder die Polypharmazie genannt, insbesondere im Hinblick auf mögliche Medikamenteninteraktionen sowie die Compliance. Zahlreiche Medikamente haben einen direkten oder indirekten Einfluss auf den Knochenmetabolismus. Im vorliegenden Review wird die Bedeutung möglicher Interaktionen diskutiert sowie das Frakturrisiko im Rahmen einer Polypharmazie dargestellt. Einerseits zeigt sich, dass das Interaktionspotenzial der zugelassenen Osteoporosemedikamente gering ist. Andererseits haben Patienten mit einer Polypharmazie ein erhöhtes Frakturrisiko und sollten eine Osteoporosetherapie erhalten, wenn diese indiziert ist.

Schlüsselwörter

Osteoporose · Polypharmazie · Frakturrisiko · Ältere · Medikamenteninteraktionen

<35 ml/min is a contraindication for a specific treatment. As a consequence all drugs that may lead to a decrease of renal function should be prescribed with caution.

Drugs with a potential effect on bone metabolism and fracture risk

Glucocorticoids

The negative effects of an existing glucocorticoid therapy on bone metabolism are well known. However, the number of patients with long-term glucocorticoid therapy receiving adequate osteoporosis treatment is still low [10]. Glucocorticoids have an inhibitory effect on osteoblasts. They inhibit the production of IGF 1 and testosterone, increase the apoptosis of osteoblasts and osteocytes and raise the secretion of parathyroid hormone. As a result one can find a dual deterioration of bone metabolism, on the one hand, impairment of bone formation and, on the other hand, an enhancement of bone resorption.

Reid et al. [11] showed that the intake of 20 mg of prednisolone daily for 1 year reduced bone density of the lumbar spine by 21%. Glucocorticoid treatment leads to a clear increase of fracture risk depending on the dose rate and length of treatment [12].

Loop diuretics

Loop diuretics, e.g., furosemide, raise the loss of calcium by blocking the reabsorption in the loop of Henle. In a controlled study, Reijnmark et al. [13] compared the effect on bone metabolism of the loop diuretic bumetanide versus placebo in 87 healthy postmenopausal women. Bumetanide raised the excretion of calcium by 17% and serum parathyroid hormone level by 9%, whereas bone density on the hip decreased by 2% and totally by 1.4% [13]. Already in 1991, Heinrich et al. [14] demonstrated that the risk of hip fracture was 3.9-fold higher in patients treated with furosemide compared to a control group. A recent study with an observation time of 4.4 years confirmed the negative effect on bone metabolism with regard to a significant decrease of bone density, however, with no effect on fracture risk [15].

Antidepressants and serotonin reuptake inhibitors

Tricyclic antidepressant agents (TCA) as well as serotonin reuptake inhibitors (SSRIs) are known to increase fracture risk. TCA may raise the risk by adverse cerebral drug reactions like dizziness, sedation and confusion but also due to hypotension. SSRIs seem to have a direct effect on bone metabolism by the 5-HTT receptor [16]. Long-term therapy with SSRIs leads to a loss of bone density and may have negative effects on the microarchitecture of the bone [17]. The 5-HTT receptor can be found in osteoblasts as well as in osteoclasts and may play an important role in bone metabolism [16].

Richards et al. [18] showed that daily intake of SSRIs results in a significant increase of fracture risk (HR 2.1, 95% CI 1.3–3.4). Bone mineral density (BMD) of the hip decreased significantly, in the spine only by trend. Moreover SSRIs raised the risk of falls. All effects were dose dependent. In the same context, the results of Verdel et al. [16] are of interest. They showed that antidepressant therapy caused a significant increase of osteoporotic fractures but not of other fractures.

SSRIs have been associated with lower BMD and increased rates of bone loss, as well as increased rates of fracture after accounting for falls. The significance of these studies is limited by confounding because depression is potentially associated with both the outcome of interest (BMD and fracture) and the exposure (SSRIs) [19].

Vitamin K antagonists and heparin

The additional supplementation of vitamin K to vitamin D and calcium reduces the fracture risk in postmenopausal women by 25% [20]. As a consequence it seems to be reasonable that vitamin K antagonists may impair bone metabolism. Vitamin K antagonists inhibit the γ-carboxylation of osteocalcin. As a result osteocalcin is not able to bind calcium. Vitamin K already plays a role in the treatment of osteoporosis and there is evidence in the literature that antagonists of vitamin K have negative effects on bone metabolism. Patients treated with warfarin have a lower bone density than control patients [21]. Long-term treatment results in a higher risk for vertebral fractures. In-hospital male patients with atrial fibrillation treated for >1 year had a significant increase in osteoporotic fractures (OR 1.63, 95% CI 1.26–2.10) [22].

The knowledge about the effects of heparin on bone metabolism results from trials in pregnant females. In most indications heparin is only used over a short period and consequently the effect on the bone can be expected as weak and not significant, whereas long-term heparin use leads to a significant decrease of bone density up to 10% [23]. In a further study on 184 pregnant women receiving heparin, 2% sustained a vertebral fracture [24]. The effect of low molecular heparin seems to be weaker than that of heparin [25].

Thyroid hormones

Triiodothyronine receptors are located at the nucleus of osteoblasts and osteoclasts. There is some evidence that thyroid hormones are directly involved in the calcium metabolism, either by a direct activation of osteoclasts or by osteoblasts, which can increase the bone resorption by stimulating osteoclasts [26]. Finally, these pathways lead to an increase in bone resorption.

Whether treatment with thyroid hormones can increase the fracture risk is still unclear. In one trial with an observation period of 5 years, women aged >65 years with lowered TSH-serum levels had a higher fracture rate compared to a group with normal TSH-serum levels (2.5% vs. 0.9%). However the difference was not significant [27]. A further study did not confirm these results. Nevertheless a meta-analysis of longitudinal studies showed a significant reduction of bone density in postmenopausal women [28].

Proton pump inhibitors

Proton pump inhibitors (PPIs) inhibit the production and gastric secretion of hydrochloric acid, which is believed to be an important mediator of calcium absorption in the small intestine. Obviously there is difference between the calcium absorption from supplements and nutrition. Omeprazole decreases the absorption of calcium carbonate in fasting postmenopausal women [29], whereas in healthy people omeprazole did not affect calcium absorption from different foods (milk, cheese) [30]. One explanation may be that nutrition itself induces a sufficient secretion of hydrochloric acid.

Different studies emphasized an increased fracture risk in patients under long-term therapy with PPIs [31, 32]. Most studies showed a higher risk of hip fractures, although a recent study could not confirm these results. However, the authors described a higher risk of vertebral and peripheral fractures [33].

Even if the relationship between osteoporotic fractures and the use of PPIs is plausible, causal proof is still missing. Furthermore, in vitro studies showed that omeprazole is able to inhibit the proton pump of osteoclasts, which results in a decrease of bone resorption [34].

Thiazolidinedione

Thiazolidinedione (TZDs) are agonists of the peroxisome proliferator-activated receptor gamma (PPARγ) nuclear transcription factor. This receptor can also be found in bone, where it affects the differentiation of mesenchymal stem cells to osteoblasts [35]. The administration of rosiglitazone induced a significant decrease of bone density in animal experiments as well as in a trial in postmenopausal women [36].

In the Analysis from a Diabetes Outcome Progression Trial (ADOPT), a comparison of different oral antidiabetics (rosiglitazone, metformin, glibenclamide) over 4–6 years, the analysis of adverse drug events revealed a significant increase of the fracture rate in women [37]. Similar results were shown for pioglitazone [38]. A large case–control study from Great Britain showed a 2.5-fold higher fracture risk in the group of patients treated with a TZD as compared to a control group [39]. The increase in the fracture risk linked to rosiglitazone and pioglitazone is dose dependent but not related to gender.

Chemotherapeutics

The causes leading to osteoporosis during or after cancer therapy are multifold. One reason could be the blockage of the estrogen synthesis by aromatase inhibitors, while another may be the induction of hypogonadism as a consequence of chemotherapy or radiation. Moreover, it should be mentioned that many chemotherapeutic drugs have a direct negative effect on bone metabolism. In the context of polypharmacy and elderly patients, the most important agents effecting bone metabolism are aromatase inhibitors.

In a subgroup of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial, the authors demonstrated the effect of anastrozole and tamoxifen on bone metabolism compared to a control group over 1 year. Anastrozole led to a significant increase in bone resorption and bone formation markers, whereas tamoxifen decreased bone turnover due to the antagonistic effect to estrogens [40]. After 2 years of treatment, anastrozole induced a significant decrease of bone density in the spine and hip [40]. After 5 years of treatment with anastrozole, an association with a higher rate of osteoporotic fractures could be shown, especially the risk of vertebral fractures increased significantly [41].

Antiepileptic agents

Phenytoine, primidone, phenobarbital, and carbamazepine have a significant effect on vitamin D metabolism. The most relevant point is the increased reduction of vitamin D metabolites due to induction of the cytochrome P450 systems [42]. Patients with a long-term antiepileptic treat-

Tab. 1 Impact of nine medication classes on falls in elderly persons. (Adapted from [52])

Medication classes	Odds ratio
Antihypertensive agents	1.26 (1.08–1.46)
Diuretics	1.03 (0.84–1.26)
β-Blockers	1.14 (0.97–1.33)
Sedatives/hypnotics	1.31 (1.14–1.50)
Neuroleptics/antipsychotics	1.71 (1.44–2.04)
Antidepressants	1.72 (1.40–2.11)
Benzodiazepines	1.60 (1.46–1.75)
Narcotics	0.89 (0.5–1.58)
NSAIDs	1.65 (0.98–2.77)

ment have a 2- to 3-fold higher fracture risk compared to control patients. One out of two of these patients develop osteopathy [42]. The effect of newer antiepileptic drugs, e.g., lamotrigine, gabapentin, and levetiracetam, on bone metabolism is still unknown.

Cholestyramine

This drug inhibits the intestinal reuptake of bile acid and as a result reduces the intestinal absorption of vitamin D. Long-term treatment may induce severe osteomalacia [42].

NSAIDs and analgesics

A recent study showed a significant increase of the fracture rate in patients treated with NSAIDs. The pathogenesis of this effect is still rather unclear, because no effect on bone density could be demonstrated. Furthermore, there was also a trend towards more fractures in patients treated with opioids or paracetamol, but without any significance [43].

Statins

Several experimental trials in bone cells and in animal models clearly showed that the inhibition of the HMG-CoA reductase induces a significant increase of bone density by activating BMP-2. Several statins, e.g., simvastatin and mevastatin, are able to activate BMP-2. Due to this mechanism, statins should have a positive effect on bone density, but according to current literature there is not enough evidence that statins are able to reduce the fracture risk [44]. Previous studies allow the interpretation that the positive effects on bone metabolism are too weak to significantly decrease the fracture risk [45].

Thiazides

Thiazide diuretics reduce the urinary calcium excretion. In epidemiological studies a treatment with these drugs leads to a 30% decrease of fractures. A causal association is still missing. However a controlled trial in healthy elderly people showed a small increase in bone density [46].

β-Blockers

The sympathetic neuronal system seems to be an important modulator of bone metabolism. In animal models, an inactivation causes an inhibition of osteoclastic bone resorption and an increase of osteoblastic bone formation [47, 48]. The use of β-blockers resulted in increased bone density and lower fracture risk in one large case control study [49].

Risk of falls

The number of prescribed drugs is the most important risk factor for adverse drug events [50]. A fall before hospital admission may indicate a severe adverse drug reaction [51]. Besides negative metabolic effects, many drugs increase fracture risk by increasing the risk of falls. The effect of nine common drug classes on the risk of falls is shown in **Tab. 1** [52].

Conclusion

Several drugs may have a negative effect on bone metabolism. Consequently, these drugs decrease bone density and may lead to an increased fracture risk. Furthermore, many drugs raise the risk of falls. However, there are only few drugs with a positive effect on bones.

The number and the risk of drug interactions of all common anti-osteoporotic drugs are small and clinically rather irrelevant. The problem of lower drug adherence in patients with multimedication can be avoided by administering newer parenteral osteoporosis drugs. In summary, it should be emphasized that preexisting polypharmacy can never justify the omission of osteoporotic treatment if indicated. On the contrary, it can be expected that patients with polypharmacy are at a higher risk of fractures and, therefore, this group of patients should absolutely be treated, if indicated.

Practical conclusions

- **Many patients with a preexisting multimedication, nevertheless, require osteoporosis treatment.**
- **Several drugs have a negative effect on bone metabolism.**
- **Falls are known to be a common adverse drug event, especially in cases of polypharmacy.**
- **Patients with multimedication are a special risk group for osteoporotic fractures.**
- **The number and the risk of drug interactions of all usual anti-osteoporotic drugs are small and clinically rather irrelevant.**
- **A preexisting polypharmacy can never justify the omission of osteoporosis treatment, if it is clinically indicated.**
- **In case of polypharmacy, the medication has to undergo a critical evaluation, on the one hand, to check the indication of each drug, on the other to reduce the risk of fractures.**

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References

1. Leung F, Blauth M, Bavonratanavech S (2010) Surgery for fracture—streamlining the process. Osteoporos Int 21(Suppl 4):519–552
2. Bartl R (2008) Osteoporose – Prävention – Diagnostik – Therapie. Georg Thieme, Stuttgart-New York, pp 1–2
3. Becker C, Gebhard F, Muche R et al (1999) Epidemiologie der Stürze Älterer. Z Orthop 137:482–485

4. Häussler B, Gothe H, Göl D et al (2007) Epidemiology, treatment and costs of osteoporosis in Germany-the BoneEVA Study. Osteoporos Int 18:77–84
5. Kammerlander C, Gosch M, Kammerlander-Knauer U et al (2011) Long-term functional outcome in geriatric hip fracture patients. Arch Orthop Trauma Surg 131:1435–1444
6. Jennings LA, Auerbach AD, Maselli J et al (2010) Missed opportunities for osteoporosis treatment in patients hospitalized for hip fracture. J Am Geriatr Soc 58:650–657
7. Kuijpers MA, Marum RJ van, Egberts AC et al (2008) Relationship between polypharmacy and underprescribing. Br J Clin Pharmacol 65:130–133
8. Gosch M, Roth T, Kammerlander C et al (2011) Treatment of osteoporosis in postmenopausal hip fracture patients after geriatric rehabilitation: changes over the last decade. Z Gerontol Geriatr 44:381–386
9. Solomon DH, Brookhart MA, Tsao P et al (2011) Predictors of very low adherence with medications for osteoporosis: towards development of a clinical prediction rule. Osteoporos Int 22:1737–1743
10. Kirigaya D, Nakayama T, Ishizaki T et al (2011) Management and treatment of osteoporosis in patients receiving long-term glucocorticoid treatment: current status of adeherence to clinical guidelines and related factors. Intern Med 50:2793–2800
11. Reid IR, Heap SW (1990) Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. Arch Intern Med 150:2545–2548
12. Van Staa TP, Leufkens HG, Cooper C (2002) The epidemiology of cortisteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13:777–787
13. Rejnmark L, Vestergaard P, Heickendorff L et al (2006) Loop diuretics increase bone turnover and decrease BMD in osteopenic postmenopausal women: results from a randomized controlled study with bumetanide. J Bone Miner Res 21:163–170
14. Heidrich FE, Stergachis A, Gross KM (1991) Diuretic drug use and the risk for hip fracture. Ann Intern Med 115:1–6
15. Lim LS, Fink HA, Blackwell T et al (2009) Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. J Am Geriatr Soc 57:855–862
16. Verdel BM, Souverein PC, Egberts TC et al (2010) Use of antidepressant drugs and risk of osteoporotic and non-osteoporotic fractures. Bone 47:604–609
17. Haney EM, Chan BK, Diem SJ et al (2007) Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. Arch Intern Med 167:1246–1251
18. Richards JB, Papaioannou A, Adachi JD et al (2007) Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med 167:188–194
19. Haney EM, Warden SJ, Bliziotes MM (2010) Effects of selective serotonin reuptake inhibitors on bone health in adults: time for recommendations about screening, prevention and management? Bone 46:13–17
20. Gajic-Veljanoski O, Bayoumi AM, Tomlinson G et al (2012) Vitamin K supplementation for the primary prevention of osteoporotic fractures: is it cost-effective and is future research warranted? Osteoporos Int (Epub ahead of print)
21. Philip WJ, Martin JC, Richardson JM et al (1995) Decreased axial and peripheral bone density in patients taking long-term warfarin. QJM 88:635–640
22. Gage BF, Birman-Deych E, Radford MJ et al (2006) Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med 166:241–246
23. Barbour LA, Kick SD, Steiner JF et al (1994) A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol 170:862–869
24. Dahlman TC (1993) Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 168:1265–1270
25. Pettilä V, Leinonen P, Markkola A et al (2002) Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost 87:182–186
26. Ross FP (2006) M-CSF, c-Fms, and signaling in osteoclasts and their precursors. Ann N Y Acad Sci 1068:110–116
27. Leese GP, Jung RT, Guthrie C et al (1992) Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH. Clin Endocrinol (Oxf) 37:500–503
28. Faber J, Galløe AM (1994) Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol 130:350–356
29. O'Connell MB, Madden DM, Murray AM et al (2005) Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med 118:778–781
30. Serfaty-Lacrosniere C, Wood RJ, Voytko D et al (1995) Hypochlorhydria from short-term omeprazole treatment does not inhibit intestinal absorption of calcium, phosphorus, magnesium or zinc from food in humans. J Am Coll Nutr 14:364–368
31. Yang YX, Lewis JD, Epstein S, Metz DC (2006) Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 296:2947–2953
32. Laine L (2009) Proton pump inhibitors and bone fractures? Am J Gastroenterol 104(Suppl 2):21–26
33. Gray SL, LaCroix AZ, Larson J et al (2010). Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. Arch Intern Med 170:765–771
34. Zaidi M (1990) Modularity of osteoclast behaviour and "mode-specific" inhibition of osteoclast function. Biosci Rep 10:547–556
35. Heikkinen S, Auwerx J, Argmann CA (2007) PPARgamma in human and mouse physiology. Biochim Biophys Acta 1771:999–1013
36. Grey A (2008) Skeletal consequences of thiazolidinedione therapy. Osteoporos Int 19:129–137
37. Kahn SE, Zinman B, Lachin JM et al (2008) Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care 31:845–851
38. Motola D, Piccinni C, Biagi C et al (2012) Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones: a disproportionality analysis of the US FDA adverse event reporting system database. Drug Saf 35:315–323
39. Meier C, Kraenzlin ME, Bodmer M et al (2008) Use of thiazolidinediones and fracture risk. Arch Intern Med 168:820–825
40. Eastell R, Hannon RA, Cuzick J et al (2006) Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). J Bone Miner Res 21:1215–1223
41. Howell A (2005) Adjuvant aromatase inhibitors for breast cancer. Lancet 366:431–433
42. Bartl R, Bartl C, Gradinger R (2009) Drug-induced osteopathies. Drugs, pathogenesis, forms, diagnosis, prevention and therapy. Orthopade 38:1245–1260
43. Vestergaard P, Hermann P, Jensen JE et al (2012) Effects of paracetamol, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, and opioids on bone mineral density and risk of fracture: results of the Danish Osteoporosis Prevention Study (DOPS). Osteoporos Int 23:1255–1265
44. Gosch M (2003) Are statins of value in therapy of osteoporosis? Wien Med Wochenschr 153:255–257
45. LaCroix AZ, Cauley JA, Pettinger M et al (2003) Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. Ann Intern Med 139:97–104
46. LaCroix AZ, Ott SM, Ichikawa L et al (2000) Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 133:516–526
47. Graham S, Hammond-Jones D, Gamie Z et al (2008) The effect of beta-blockers on bone metabolism as potential drugs under investigation for osteoporosis and fracture healing. Expert Opin Investig Drugs 17:1281–1299
48. Togari A, Arai M, Kondo A (2005) The role of the sympathetic nervous system in controlling bone metabolism. Expert Opin Ther Targets 9:931–940
49. Pasco JA, Henry MJ, Sanders KM et al (2004) Beta-adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. J Bone Miner Res 19:19–24
50. Laroche ML, Charmes JP, Nouaille Y et al (2007) Is inappropriate medication use a major cause of adverse drug reactions in the elderly? Br J Clin Pharmacol 63:177–186
51. Mannesse CK, Derkx FH, Ridder MA de et al (2000) Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing 29:35–39
52. Woolcott JC, Richardson KJ, Wiens MO et al (2009) Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 169:1952–1960. (Review. Erratum in: Arch Intern Med 2010 170:477)