Endocrinol Diabetes Nutr. 2017;64(S1):1–6

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

CONSENSUS DOCUMENT

Recommendations on the effect of antidiabetic drugs in bone☆

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KEYWORDS
Antidiabetic drugs;
Bone;
Osteoporosis;
Bone mineral density;
Fractures;
Bone metabolism;
Calciotropic hormones;
Bone markers

Abstract
Objective: To provide recommendations on the effect of antidiabetic drugs on bone fragility to help select the most adequate antidiabetic treatment, especially in diabetic patients with high risk of fracture.
Participants: Members of the Bone Metabolism Working Group of the Spanish Society of Endocrinology.
Methods: The GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation) was used to establish both the strength of recommendations and the quality of evidence. A systematic search was made in MEDLINE (Pubmed) using the following terms associated to the name of each antidiabetic drug: AND ''osteoporosis'', ''fractures'', ''bone mineral density'', ''bone markers'', ''calciotropic hormones''. Papers in English with publication date before 30 April 2016 were reviewed. Recommendations were jointly discussed by the Working Group.

☆ Please cite this article as: Rozas-Moreno P, Reyes-García R, Jódar-Gimeno E, Varsavsky M, Luque-Fernández I, Cortés-Berdonces M, et al. Recomendaciones sobre el efecto de los fármacos antidiabéticos en el hueso. Endocrinol Nutr. 2017;64:1–6.

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http://dx.doi.org/10.1016/j.endien.2016.11.002

Conclusions: The document summaries the data on the potential effects of antidiabetic drugs on bone metabolism and fracture risk.

PALABRAS CLAVE
Fármacos antidiabéticos;
Hueso;
Osteoporosis;
Densidad mineral ósea;
Fracturas;
Metabolismo óseo;
Hormonas calciotropas;
Marcadores óseos

Recomendaciones sobre el efecto de los fármacos antidiabéticos en el hueso

Resumen
Objetivo: Proporcionar recomendaciones sobre el efecto de las diferentes terapias antidiabéticas en la fragilidad ósea con el fin de ayudar a seleccionar el tratamiento antidiabético más adecuado, especialmente en pacientes diabéticos con elevado riesgo de fractura.
Participantes: Miembros del Grupo de trabajo de Osteoporosis y Metabolismo Mineral de la SEEN.
Métodos: Se empleó el sistema *Grading of Recommendations, Assessment, Development, and Evaluation* (GRADE) para establecer tanto la fuerza de las recomendaciones como el grado de evidencia. Se realizó una búsqueda sistemática en PubMed usando las siguientes palabras clave asociadas al nombre de cada tratamiento antidiabético: AND «osteoporosis», «fractures», «bone mineral density», «bone markers», «calciotropic hormones». Se revisaron artículos escritos en inglés con fecha de inclusioín hasta 30 de abril de 2016. Tras la formulación de las recomendaciones, estas se discutieron de forma conjunta por el Grupo de Trabajo.
Conclusiones: Este documento resume los datos acerca de los potenciales efectos de los diferentes tratamientos antidiabéticos sobre el metabolismo óseo y el riesgo de fractura.

Introduction

Patients with diabetes have an increased risk of fracture, and it is therefore important to understand the effect of antidiabetic drugs on bone. Recommendations were made based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to establish the strength of recommendations and the level of evidence. A distinction is made between strong recommendations, expressed as ''We recommend'' and number 1, and weak recommendations, expressed as ''We suggest'' and number 2. The quality of evidence is expressed using symbols: ØOOO indicates very low evidence; ØØOO low evidence; ØØØO moderate evidence; and ØØØØ high evidence.

Metformin

Recommendations

- We suggest use of metformin as first choice drug to treat T2DM in patients with osteoporosis (2ØØOO). Treatment with metformin causes a slightly increase in bone mineral density (BMD) (2ØØOO), and its effect on risk of fracture is neutral or beneficial (2ØØOO).

Evidence

Few studies are available on the effects of metformin in humans. Observational data show a protective effect on risk of fracture, with a hazard ratio (HR) of 0.7 (95% confidence interval [CI]: 95%: 0.6–0.96)[1] and an odds ratio (OR) of 0.8 (95% CI: 0.7–0.93).[2] In the A Diabetes Outcome Progression Trial (ADOPT), there were no beneficial effects of metformin on risk of fracture at 4 years of follow-up, although levels of formation and resorption markers decreased at 12 months of treatment start.[3,4] As regards the effect of metformin on BMD, the Borges et al. study[5] found a slight increase in BMD in the lumbar spine, total hip, and distal third of radius in patients treated with metformin for 80 weeks.

Glitazones

Recommendations

- We recommend that use of glitazones is avoided in women with diabetes and osteoporosis or with high fracture risk (1ØØØO). If used, we recommend that such use is considered as a major risk factor for osteoporosis when risk of osteoporotic fracture is assessed (1ØØØO).
- We recommend consideration that glitazones cause variable changes in remodeling markers (BRM) (1ØØØO) and decreases in lumbar, femoral and appendicular BMD (1ØØØO), and double the risk of osteoporotic fractures, especially in menopausal women (1ØØØO).

Evidence

Data about the effect of rosiglitazone on BMD are conflicting (reviewed in Lecka-Czernik[6]), and a recent meta-analysis of 18 trials did not show a consistent pattern in BRM changes.[7]

Glitazones decrease BMD in lumbar spine (difference −1.1%; 95% CI: −1.6 to −0.7), total hip (−1.0%; 95% CI: −1.4 to −0.6), and forearm (−0.9%; 95% CI: −1.6 to −0.3). Changes in BMD persist one year after treatment discontinuation.[7] As regards risk of fracture, observational studies have shown increases (pioglitazone: OR 2.59; 95% CI: 0.96–7.01, and rosiglitazone: OR 2.38; 95% CI: 1.39–4.09) related to age (greater in subjects from 65 years of age) and to longer treatment duration. The risk is higher in females and in subjects with prior fractures. An increased risk has also been reported in males (observational studies, reviewed in Lecka-Czernik[6]). By contrast, in a case-control study conducted in an Asian population, glitazones were associated to an increased risk of fracture, especially in women under 64 years of age (OR 1.74–2.58).[8] In the ADOPT study[3], rosiglitazone monotherapy was associated to a higher fracture rate (9.30% in 5 years) as compared to metformin (5.08%) and glibenclamide (3.47%) (RR 1.81 and 2.13 respectively). Pioglitazone also increases fracture risk in women (1.9 versus 1.1 fractures per 100 patient-years) (reviewed in Lecka-Czernik[6] and McCulloc[9]). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,[10] use of glitazones (74% rosiglitazone, 13% pioglitazone) increased the fracture rate in women only from one year of use (HR $\geq$2), and risk decreased from one year after drug discontinuation. A meta-analysis[11] of controlled studies (13,715 participants) and observational studies (31,679 participants) confirmed that glitazones double the risk of fracture, but only in females.

Sulfonylureas

Recommendations

- We suggest that treatment with sulfonylureas may increase risk of hip fracture in patients over 65 years of age and in subjects with documented hypoglycemia (2ØØOO), and also the incidence of falls in institutionalized patients (2ØØOO).

Evidence

A prospective, randomized study reported an increase in BMD related to use of sulfonylureas (SU), mediated by increased endogenous C-peptide and proinsulin levels.[12] On the other hand, a higher risk of hypoglycemia may increase falls and risk of fracture. In a case-control study, authors reported a lower risk of hip fracture in patients treated with SU.[2] In another case-control study with less cases, there was no association between treatment with SU and risk of fracture (OR 0.77; 95% CI: 0.44–1.37).[13] Analysis of the risk of vertebral fracture showed that treatment with SU was a protective factor in females but not in males.[13]

A systematic review conducted in 2013 concluded that no adequate evidence is available to state that a relationship exists between use of SU and risk of fracture.[14] However, in a subsequent observational study in patients with diabetes older than 65 years, use of SU was associated to greater risk of hip fracture (OR 1.46; 95% CI: 1.17–1.82) both in females and males. Risk of hip fracture is higher in patients with documented hypoglycemia (OR 2.42; 95% CI: 1.35–4.34).[15] In institutionalized patients, start of treatment with SU was not associated to greater risk of fracture, but was related to higher risk of fall (HR 1.13; 95% CI: 1.00–1.26).[16]

GLP-1 receptor agonists (GLP-1 RAs) and DPP-4 inhibitors

Recommendations

- We think that use of DPP-4 inhibitors does not modify risk of fracture (1ØØØO).
- We think that treatment with GLP-1 RAs (exenatide, liraglutide) does not affect BMD (1ØØOO) or risk of fracture (1ØØØO).

Evidence

In the study Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI), there were no differences in risk of fracture between saxagliptin and placebo.[17] These results were confirmed by a cohort study,[18] conducted from 2007 to 2012, which found no differences in risk of fracture between patients treated with DPP-4 inhibitors and controls (adjusted HR 0.89; 95% CI: 0.71–1.13). Treatment with DPP-4 inhibitors did not increase the risk as compared to other non-insulin antidiabetic therapies (HR 1.03; 95% CI: 0.92–1.15). However, as admitted by the authors, treatment duration may have been too short to determine the effect.[18] These results are in contrast with those of a meta-analysis of clinical trials[19] that showed a 40% decrease in fracture risk in users of DPP-4 inhibitors as compared to active treatment or placebo. Identification of fractures as adverse effects rather than as the primary objective, the low number of fractures seen, and use of different comparators may have influenced the results. In a population study[20] of patients with T2DM (mean age, 52 years), use of sitagliptin was not related to higher risk of fracture, while a greater risk was seen in patients treated with sulfonylureas or insulin.

In 66 patients with T2DM treated with metformin, treatment with exenatide (n = 33) or insulin glargine (n = 33) for 44 weeks did not affect BMD, BRMs, or calciotropic hormones.[21] A subanalysis of 61 patients from the LEAD 3 study,[22] there were no significant changes from baseline in the BMD of patients given liraglutide or glimepiride after 104 weeks of treatment.

Different meta-analyses[23,24] and cohort studies have confirmed that treatment with GLP-1 RAs does not affect fracture risk. In a cohort study,[25] a lower risk of fracture was not seen in patients treated with GLP-1 RAs as compared to those who had never received them (adjusted HR 0.97; 95% CI: 0.72–1.32). No relationship was also seen between risk of failure and cumulative dose. These findings were confirmed in another case-control study[26] where treatment with GLP-1 RAs was not associated to a decreased risk of fracture (OR 1.16; 95% CI: 0.83–1.63). No relationship was also seen between current treatment with GLP-1 RAs and risk of osteoporotic fracture (OR 0.78; 95% CI: 0.44–1.39).

In the meta-analysis by Su et al.,[24] treatment with liraglutide was associated to a decrease in the risk of incident fractures (Mantel-Haenszel OR 0.38; 95% CI: 0.17–0.87), while exenatide was associated to an increased risk of incident fractures (Mantel-Haenszel OR 2.09; 95% CI: 1.03–4.21). According to the authors, the greater homology of liraglutide with human GLP-1, as well as a longer half-life, could explain the different effects on risk of fracture. However, the low number of fractures reported and the short duration of the studies limit the strength of conclusions.

SGLT2 inhibitors

Recommendations

- We recommend consideration of the fact that use of canagliflozin is associated to increases in BRMs and to a slight decrease of BMD in total hip (1ØØOO).
- We suggest that treatment with empagliflozin may increase urinary bone resorption markers with no significant increase in number of fractures (2ØØOO).
- We suggest caution when dapagliflozin and canagliflozin are used in some groups of patients, because they may increase risk of fracture (2ØØOO).

Evidence

Use of canagliflozin and dapagliflozin has been related to a mild increase in phosphate, magnesium, and iPTH levels, with no significant changes in serum calcium levels and a slight decrease in 1,25-dihydroxyvitamin D levels.[27] In a randomized, double-blind study,[28] treatment with canagliflozin was associated to decreased serum estradiol levels, a significant increase in BRMs at 52 weeks of treatment, and a decrease in total hip BMD (−0.9% and −1.2% for canagliflozin 100 mg and 300 mg respectively). Changes seen in BRMs and BMD are partly explained by the weight loss seen. No significant changes were found in the bone resistance parameters tested.[28] Treatment with dapagliflozin has not been associated to significant changes in BRMs, 25-hydroxyvitamin A (25OHD) or BMD in the different regions analzed.[29] No significant changes have been reported in serum calcium, phosphorus, 25OHD, iPTH or alkaline phosphatase with empagliflozin, but the 25 mg dose did slightly but significantly increase urinary levels of amino-terminal collagen crosslinks (NTX).[30] As regards BMD, use of empagliflozin does not appear to be associated to clinically significant changes based on the results of a substudy of the comparative clinical trial with glimepiride.[30]

With regard to fractures, the risk may be increase in some patient subgroups, but limited data are available. Phase IIb/III studies with dapagliflozin have not shown a significant increase in fracture risk.[31] However, among patients with moderate kidney failure, 9.4% and 6% of those treated with dapagliflozin 10 mg and 5 mg respectively sustained a fracture during treatment at 104 weeks, while subjects given placebo sustained no fractures. After excluding fractures in not typically osteoporotic locations, 7% of patients on dapagliflozin 10 mg sustained fractures.[32] In a recent meta-analysis of nine clinical trials, use canagliflozina was related to an increased incidence of fractures, mainly in subjects participating in the Canagliflozin Cardiovascular Assessment Study (CANVAS) (4% canagliflozin vs 2.6% placebo), representing an older population with high cardiovascular risk.[33] Mean drug exposure was 85 weeks, and although the risk appears in the first weeks of treatment, it seems to continue over time. Finally, the results of the EMPA-REG OUTCOME study.[34] and the analysis of pooled data from different clinical trials do not appear to suggest a greater fracture rate with empagliflozin as compared to placebo.[35]

Insulin

Recommendations

- We suggest the insulin treatment is related to an increased risk of fractures in patients with hypoglycemia and an increased incidence of falls (2ØØOO).

Evidence

Several observational studies found a positive relation between insulin treatment and greater risk of fracture in both males and females with type 1 and 2 diabetes mellitus.[13–39] These data should be interpreted with caution because of the presence of prescription bias, the greater use of insulin in patients with kidney failure and more advanced diabetes, and the possible coexistence of microvascular complications. However, the relationship of insulin treatment with fracture risk continues after adjustment for different confounding factors, but it cannot be ruled out that it is due to a greater risk of fall because of hypoglycemia, rather than to an effect of insulin itself.[40] On the other hand, observational studies do not support the relation between insulin treatment and fractures,[41] and even show a non-significant trend to a lower number of fractures.[2]

Conclusion

Diabetes is associated to a greater risk of fracture, and the effects on bone should therefore be considered an additional factor to be taken into account when antidiabetic treatment is selected. This is particularly relevant in patients with T2DM, in which different treatment options are available. While little evidence is available in some cases, the effect on BMD and risk of fracture of the most recently developed antidiabetic therapies, such as pioglitazone, incretin therapies, and SGLT2 inhibitors, is better defined. Except for the glitazone family, it may be stated that all other antidiabetic drug classes are reasonably safe for bone. Consideration of fracture risk associated to antidiabetic treatments may be particularly relevant in patients with diabetes who also have other risk factors for osteoporosis and fracture such as postmenopausal state, advanced age, and presence of chronic macrovascular and microvascular complications.

Funding

No funding was received to conduct this study.

Conflicts of interest

The authors state that they have no conflicts of interest in relation to preparation of this article.

Note of authors

This article is the executive summary of the complete document, which may be consulted at the web site of the Spanish Society of Endocrinology and Nutrition.[42]

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