SOCIEDAD ESPAÑOLA DE INVESTIGACIONES ÓSEAS Y METABOLISMO MINERAL - SEIOMM -

OSTEOPOROSIS POSTMENOPÁUSICA. Guía de Práctica Clínica. Versión resumida.

*Grupo de Trabajo de la SEIOMM**

Introducción

El aumento progresivo de la incidencia de osteoporosis, paralela al envejecimiento demográfico en España, su morbilidad y mortalidad, así como su importante impacto sanitario y económico, ha llevado a la SEIOMM a desarrollar una *Guía de Práctica Clínica sobre Osteoporosis Postmenopáusica* como un primer paso, dirigido al grupo poblacional más afectado. La SEIOMM ha constituido un Grupo de Trabajo para elaborar dicha guía siguiendo la metodología de la Medicina Basada en la Evidencia (MBE) es decir, en pruebas.

La presente Guía de Práctica Clínica pretende ofrecer un marco indicativo sobre el cual se puedan desarrollar, por los grupos de profesionales interesados, protocolos de actuación adaptados a cada ámbito asistencial. Quiere ello decir que se deben valorar sus recomendaciones como derivadas de la revisión de las pruebas científicas, pero que las decisiones clínicas deberán integrar, además, la experiencia de los profesionales, el escenario asistencial en que se apliquen, así como los valores y preferencias de las pacientes. Pueden haber, por tanto, decisiones clínicas diferentes a las aquí recomendadas, que constituyan también pautas de actuación perfectamente válidas.

1. Antecedentes

La osteoporosis es la enfermedad metabólica ósea más prevalente. Afecta a un 35% de mujeres españolas mayores de 50 años, porcentaje que se eleva a un 52% en las mayores de 70 años. Una de cada 5 mujeres de más de 50 años tiene al menos una fractura vertebral debida a la osteoporosis, que se asocia a deterioro de la calidad de vida y a riesgo aumentado de otras fracturas. La incidencia anual de fractura de fémur en mujeres de edad superior a 50 años es de 3 por 1000. La incidencia de fractura de antebrazo distal es de casi el doble. En la actualidad, el riesgo de padecer una fractura de fémur en lo que le resta de vida es, para una mujer española de 50 años, de entre un 12 y un 16%. La presencia de fracturas, especialmente la de fémur, produce un aumento de la mortalidad con relación a las pacientes sin fracturas.

2. Metodología

Durante dos años se ha elaborado el contenido de la Guía en las siguientes etapas: 1) Reunión de un grupo de expertos en osteoporosis para plantear las preguntas relevantes; 2) Creación de un equipo de revisión sistemática formado por un experto en MBE y dos becarios, encargados de la búsqueda, revisión estandarizada, análisis crítico y tabulación de los artículos relevantes; 3) Reuniones de expertos clínicos para organizar las evidencias jerarquizadas en recomendaciones clínicas; 4) Redacción de un borrador de la Guía; 5) Debate

público del mismo en un foro abierto a todos los miembros de la SEIOMM y otros especialistas.

En el proceso de debate han intervenido, además de los médicos de diferentes especialidades, representantes de Agencias de Evaluación, representantes del Ministerio de Sanidad y Consumo y de la Agencia Española del Medicamento. Además han intervenido, en representación de los pacientes y de la sociedad civil, representantes de la Federación Española de Derecho Farmacéutico, Asociación Nacional de Informadores de la Salud y de la entidad que agrupa a los pacientes de osteoporosis, la Fundación Hispana de Osteoporosis y Enfermedades Metabólicas Óseas. Todos ellos han realizado las aportaciones al documento que han considerado oportunas. Por último, la guía ha sido revisada y avalada por la Confederación Estatal de Pacientes Española.

La Guía ha sido revisada por un experto en economía de la salud que ha realizado las consideraciones farmaco-económicas. El Grupo de Trabajo ha aceptado la revisión sistemática realizada en la principal Guía de Práctica Clínica (GPC) basada en la metodología MBE que se ha publicado, la del Real Colegio de Médicos Británico, hasta diciembre de 1995. Se ha revisado sistemáticamente, por el equipo de revisión, la base de datos MEDLINE desde 1 de enero de 1996 hasta 1 de enero de 2000, así como la Cochrane Library, Best Evidence y los artículos recomendados por el Grupo de Trabajo. Se ha realizado una búsqueda complementaria, con estrategia similar, por parte de todo el Grupo de trabajo desde 1 de enero de 2000 hasta 15 de mayo de 2001. Se han aceptado artículos considerados relevantes publicados en los meses posteriores hasta el cierre del debate público sobre el borrador.

Las evidencias se han clasificado, de acuerdo a las recomendaciones del Centro de Medicina Basada en la Evidencia de Oxford, en nivel 1 a 5, otorgando sub-niveles a y b a los tres primeros (Tabla 1). Las recomendaciones se han clasificado en cuatro grados de evidencia:

Grado A: basado en revisiones sistemáticas de ensayos clínicos aleatorizados (ECA) o, al menos, un ECA bien diseñado. Estudios de cohortes prospectivos para factores pronósticos.

Grado B: estudios sistemáticos de cohortes, de casos y controles, ECA de baja calidad.

Grado C: series de casos, estudios de cohortes de baja calidad.

Grado D: opinión de expertos sin criterios de valoración explícitos.

La estrategia se detalla explícitamente en la versión a texto completo de la presente Guía.

3. Definición de osteoporosis

Por consenso, la osteoporosis se define como una enfermedad esquelética caracterizada por una resistencia ósea disminuida que predispone a una persona a un riesgo aumentado de fractura. La resistencia ósea refleja fundamentalmente la integración de densidad y calidad óseas. La densidad ósea viene expresada como gramos de mineral por área o volumen, y en un individuo determinado viene determinada por el pico de masa ósea y por la cantidad de pérdida ósea. La calidad ósea se refiere a la arquitectura, recambio, acúmulo de lesiones (es decir, microfracturas) y mineralización. La fractura ocurre cuando una fuerza inductora de rotura, como un traumatismo, se aplica sobre un hueso osteoporótico. Por lo tanto, la osteoporosis es un factor significativo de riesgo de fractura, si bien se debe distinguir entre factores de riesgo que afectan al metabolismo óseo y factores de riesgo de

fractura. Se ha establecido una definición diagnóstica basada en la densitometría que se detalla más adelante.

4. Factores de riesgo

Se ha demostrado que numerosos factores se asocian a riesgo elevado de fractura vertebral o de fémur (Tabla 2). En general son extraóseos (relacionados con riesgo de caídas o traumatismo) y óseos (relacionados con la resistencia ósea). Hay evidencia consistente de la asociación entre descenso de la densidad mineral ósea (DMO) y riesgo de fractura. Se están estudiando activamente factores genéticos asociados a riesgo de fractura y hay varios polimorfismos genéticos asociados de forma moderada a valores disminuidos de DMO. El sobrepeso es un factor protector de padecer osteoporosis y del riesgo de fracturas.

También se asocia con osteoporosis y riesgo de fractura un gran número de enfermedades. Entre estas, bien por su alta prevalencia, o por el alto riesgo de osteoporosis asociada, tienen especial relevancia en la mujer postmenopáusica el hiperparatiroidismo primario y el tratamiento con corticoides.

5. Evaluación diagnóstica

Todo caso de osteoporosis debe ser sometido a anamnesis, exploración física y analítica básica que excluya otra patología subyacente. El diagnóstico de osteoporosis se establece con la realización de una densitometría ósea. El método utilizado más ampliamente es la absorciometría radiológica de doble energía (DXA), validado como predictor del riesgo de fractura. Por convención, la DXA se acepta como patrón oro. Las zonas de medición más habituales son la columna lumbar y el cuello de fémur. La Organización Mundial de la Salud (OMS) ha establecido una definición densitométrica de osteoporosis, considerando su existencia cuando el paciente presenta un valor de DMO en índice T, en columna lumbar o en cuello de fémur, inferior a – 2.5 desviaciones estándar. Asimismo ha establecido otras categorías de diagnóstico que se exponen en la tabla 3.

El valor de DMO lumbar por DXA (Hologic), en mujeres españolas, que representa el pico de masa ósea (referencia para el índice T) es 1.040 ± 0.104 g/cm^2 (media $\pm$ DS). Este valor de DMO en cuello femoral por DXA (Hologic), es 0.840 ± 0.109 g/cm^2. Los valores equivalentes en equipos de otros fabricantes se pueden calcular mediante fórmulas de conversión.

Otras técnicas de medición de la densidad ósea, como ultrasonidos, tomografía axial computarizada o radiología digitalizada han obtenido valores predictivos similares de riesgo de fractura si bien su uso está más limitado o por razones técnicas, por peor reproducibilidad o por menor experiencia clínica. En general la predicción de riesgo de fractura de determinada región esquelética mejora al medirla directamente. Por cada desviación estándar de descenso de la densidad ósea, por diferentes técnicas, el riesgo relativo asociado de fractura oscila entre 1,3 y 3,9 (nivel de evidencia 2b). Los marcadores bioquímicos de remodelado óseo, especialmente los de resorción, en pacientes ancianos, se asocian a incremento de riesgo relativo de fractura, para diversos marcadores, de entre 1,39 y 2,3 (nivel de evidencia 2b).

Dado el coeficiente de variabilidad de las exploraciones DXA en columna lumbar y en cuello de fémur, parece razonable realizar las mediciones cada dos años. En la Tabla 4 se resumen las indicaciones de este Grupo de Trabajo para la realización de una densitometría ósea en mujeres postmenopáusicas.

6. Cribado de osteoporosis.

La estrategia más recomendable es la búsqueda selectiva de casos. Con ella, se pueden detectar casos en los que el médico puede aplicar los diferentes algoritmos de intervención. La confirmación diagnóstica se establecerá por la presencia de fracturas o, en su ausencia, por técnicas densitométricas. No se recomienda el cribado poblacional por no estar demostrada su relación coste-efectividad positiva.

7. Intervenciones no farmacológicas.

Como medidas poblacionales, son aplicables los consejos generales de promoción de la salud. Tanto en población general como en sujetos de riesgo, mujeres postmenopáusicas en este caso, es aconsejable un aumento de la actividad física, el cese del hábito tabáquico y el aumento en la ingestión de calcio, a pesar de que no se ha evaluado su efecto sobre la reducción de fracturas. Las diferentes intervenciones, y su grado de recomendación, se resumen en la Tabla 5.

Los programas de intervención combinada sobre varios factores de riesgo de caída en ancianos han demostrado eficacia, por lo que disminuyen el factor aleatorio fundamental de fractura (Grado de recomendación A).

8. Intervenciones farmacológicas.

Las mujeres cercanas a la menopausia, con factores de riesgo y valores densitométricos en el intervalo definido anteriormente como osteopenia, en ausencia de fractura, son susceptibles de recibir un tratamiento preventivo.

Para la prevención de la pérdida de masa ósea, los estrógenos, el etidronato, el alendronato y el raloxifeno han demostrado ser eficaces (Grado de recomendación A). Para la prevención primaria de fracturas vertebrales hay datos de eficacia para raloxifeno (Grado A) y estrógenos (Grado B-C). Para prevención primaria de fractura de fémur tan sólo hay datos para estrógenos (Grado A). Sin embargo, se trata de mujeres sin enfermedad clínica y con riesgo bajo de fractura. Dados los potenciales efectos secundarios y el elevado número necesario de pacientes a tratar para evitar un evento, su utilización se debe restringir a casos muy concretos, excepto que el tratamiento se justifique por otros factores diferentes al de la prevención de osteoporosis.

Los fármacos para el tratamiento de la osteoporosis han demostrado eficacia tan sólo en ensayos clínicos con tratamientos prolongados, en general de al menos dos a tres años. El médico y la paciente deben ser conscientes de la dudosa o nula utilidad de pautas inferiores a dicho período. Se debe asegurar la adherencia al tratamiento mediante el establecimiento de una buena relación médico-paciente y una explicación detallada del tratamiento a seguir.

La eficacia de los diferentes fármacos no es comparable entre sí. Dado que no existen ensayos aleatorizados que comparen frente a frente diversas alternativas, datos provenientes de ensayos distintos no son comparables por las diferencias de población estudiada, diseño, intervención y mediciones. Por tanto no se pueden jerarquizar los fármacos en función de la magnitud de su efecto y las decisiones sobre el uso de uno de ellos se deben basar en los datos de eficacia, el objetivo terapéutico deseado, la tolerabilidad, los efectos asociados positivos o negativos, la comodidad y pauta de administración y la opinión informada de la paciente.

8.1. Calcio y Vitamina D.

El calcio es un requerimiento nutricional básico del hueso. En mujeres postmenopáusicas se recomienda la ingesta de al menos 1500 mg/día para conseguir un balance metabólico equilibrado. Administrado como suplementos al de la dieta ordinaria de la paciente, hasta alcanzar esta cifra, es una medida recomendable y la mayoría de EAC sobre los diferentes fármacos administran conjuntamente al menos 500 mg de calcio al día.

En mujeres postmenopáusicas con ingesta deficiente, los suplementos farmacológicos disminuyen la pérdida ósea y el riesgo de fractura vertebral (Nivel de evidencia 1b). Dosis de 1000 mg al día muestran un descenso muy escaso, aunque significativo, del riesgo de fractura de fémur (Nivel de evidencia 2a).

El calcitriol y el alfacalcidiol disminuyen la pérdida ósea y la incidencia de fractura vertebral (Nivel de evidencia 2a) aunque no se ha demostrado su eficacia en la postmenopausia reciente (Nivel de evidencia 1b). La vitamina D asociada a calcio disminuye la incidencia de fractura de fémur y no-vertebral en población anciana asilada con niveles insuficientes de vitamina D (Nivel de evidencia 2a). Los análogos de la vitamina D incrementan el riesgo de hipercalcemia (Nivel de evidencia 2a).

8.2. Terapia hormonal sustitutiva

La terapia hormonal sustitutiva reemplaza la deprivación hormonal por el cese de actividad ovárica.

Hay datos de eficacia sobre DMO provenientes de EAC, si bien los ensayos dirigidos a reducir el riesgo de fractura, y específicamente la fractura vertebral, son escasos y la mayoría de la información sobre este aspecto procede de estudios observacionales o de un EAC con limitaciones metodológicas (Nivel de evidencia 2a y 2b respectivamente). Cuando se inicia el tratamiento antes de los 60 años de edad tiene eficacia en la reducción de fracturas no vertebrales (Nivel de evidencia 1a).

El tratamiento induce un ligero pero significativo incremento del riesgo de detección de cáncer de mama, más patente en tratamientos prolongados, (Nivel de evidencia 2a) y de enfermedad tromboembólica (Nivel de evidencia 1b).

8.3. Raloxifeno

El raloxifeno es un modulador selectivo del receptor estrogénico (SERM). Tiene efectos positivos sobre la masa ósea lumbar y femoral así como sobre el riesgo de fractura vertebral (Nivel de evidencia 1b). No ha demostrado eficacia en la prevención de fracturas no vertebrales (Nivel de evidencia 1b).

El raloxifeno incrementa el riesgo de tromboembolismo venoso de forma similar a los estrógenos. Disminuye el riesgo de cáncer de mama con receptor estrogénico positivo en población de bajo riesgo, como son mujeres osteoporóticas, y tiene efectos positivos sobre algunos marcadores subrogados de riesgo cardiovascular (Nivel de evidencia 1b para todos los datos).

Análisis de subgrupos no predeterminados (*post hoc*) han mostrado eficacia antifracturaria precoz (Nivel de evidencia 2b).

8.4. Tibolona

La Tibolona actúa de forma similar a los estrógenos de administración oral sobre el tejido óseo.

Es eficaz para prevenir la pérdida ósea (Nivel de evidencia 2b). No existen datos de eficacia sobre fracturas.

Es eficaz en el control de los sofocos (Nivel de evidencia 1b) por lo que puede ser una alternativa para mujeres en que las pérdidas menstruales cíclicas con THS son mal toleradas.

8.5. Bisfosfonatos.

8.5.1. Etidronato.

El etidronato es un bisfosfonato no aminado que se administra por vía oral, en ciclos quincenales cada tres meses.

Tiene efecto positivo sobre la DMO lumbar y de fémur. Disminuye el riesgo de fractura vertebral sin mostrar eficacia sobre fractura no vertebral (Nivel de evidencia 1a).

8.5.2. Alendronato.

El alendronato en un aminobisfosfonato que se administra por vía oral.

Tiene efecto positivo sobre la DMO lumbar y femoral. Disminuye el riesgo de fractura vertebral, no vertebral y de fémur (Nivel de evidencia 1a). La administración de una dosis única semanal tiene eficacia análoga a la dosis diaria sobre la DMO (Nivel de evidencia 1b) y puede mejorar la adherencia al tratamiento.

Los efectos secundarios más habituales, aunque poco frecuentes, son gastrointestinales y se deben seguir estrictamente las normas de administración para evitar lesiones esofágicas potencialmente importantes. Su baja absorción intestinal hace relevante su administración en ayunas.

Análisis de subgrupos no predeterminados (*post hoc)* han mostrado eficacia antifracturaria precoz (Nivel de evidencia 2b).

8.5.3. Risedronato.

El risedronato es un aminobisfosfonato que se administra por vía oral.

Tiene efecto positivo sobre la DMO lumbar y femoral. Disminuye el riesgo de fractura vertebral y no vertebral en mujeres con osteoporosis establecida (Nivel de evidencia 1b). Ha demostrado reducción de riesgo de fractura de fémur en un EAC diseñado "ad hoc" para dicho resultado de interés (Nivel de evidencia 1b).

Estudios endoscópicos demuestran una baja toxicidad sobre la mucosa digestiva (Nivel de evidencia 2b). Su baja absorción intestinal hace relevante su administración separada de la ingesta, a varias horas del día.

Análisis de subgrupos no predeterminados (*post hoc*) han mostrado eficacia antifracturaria precoz (Nivel de evidencia 2b).

8.5.4. Otros bisfosfonatos.

Otros bisfosfonatos están en fase de desarrollo preclínico.

Existen estudios, de validez variable, que demuestran un efecto positivo sobre DMO de Ibandronato, Clodronato, Pamidronato y Zoledronato.

No hay datos publicados sobre reducción de fracturas.

El tiludronato no demostró eficacia sobre DMO ni sobre fracturas en un EAC (Nivel de evidencia 1b).

8.6. Otros agentes inhibidores de la resorción.

8.6.1. Calcitonina.

La Calcitonina es una hormona que inhibe reversiblemente la actividad osteoclástica.

Tiene un débil efecto positivo sobre la DMO lumbar y femoral. (Nivel de evidencia 1b). Administrada por vía transnasal es eficaz en la reducción de fracturas vertebrales (Nivel de evidencia 2b), en un efecto no dependiente de dosis. Los datos sobre la reducción de fracturas no vertebrales proceden de estudios no aleatorizados (Nivel de evidencia 3b).

La calcitonina tiene efecto analgésico moderado demostrado en EACs de calidad variable (Nivel de evidencia 3).

8.6.2. Flavonoides.

Los flavonoides son agentes antiresortivos con efecto positivo controvertido sobre la masa ósea. No hay datos de eficacia sobre fracturas.

8.7. Agentes promotores de la formación.

8.7.1. Parathormona.

La hormona paratiroidea administrada intermitentemente tiene efectos positivos sobre la DMO.

El fragmento 1-34 de la hormona (recombinante) ha demostrado eficacia sobre la DMO y disminución de la incidencia de fractura vertebral y no vertebral administrada en inyección subcutánea diaria (Nivel de evidencia 1b).

La hipercalcemia transitoria leve es el efecto adverso más significativo (Nivel de evidencia 1b).

8.7.2. Flúor.

Las sales de flúor tienen un efecto promotor de la formación ósea trabecular.

Tienen eficacia en inducir incremento de los valores de DMO. Sin embargo no reducen el riesgo de fractura vertebral y aumentan, a los cuatro años de uso, el de fractura no vertebral a dosis altas. Las dosis bajas (20 mg) pueden reducir la fractura vertebral tras cuatro años de tratamiento.

Producen efectos secundarios gastrointestinales fundamentalmente.

La administración asociada de vitamina D anula el beneficio del flúor. Cuando se usa asociado a THS mejora su efecto sobre fractura vertebral (Nivel de evidencia 1a para todos los datos).

8.7.3. Esteroides anabolizantes.

Los esteroides anabolizantes tienen eficacia sobre la DMO (Nivel de evidencia 2b). No hay datos de eficacia sobre fracturas y su uso está limitado por sus efectos secundarios, principalmente relacionados con su acción androgénica.

8.8. Combinaciones de fármacos.

Diversos EAC han analizado la eficacia de combinaciones de fármacos sobre la DMO, demostrando, en general, un efecto aditivo. No hay datos que demuestren que las combinaciones mejoran la eficacia antifracturaria de los fármacos individuales. Por ello, hasta que no existan más pruebas, la posibilidad de sumar efectos secundarios así como el aumento de coste del tratamiento desaconsejan el uso de las combinaciones de fármacos.

Una excepción general a esta regla, ya mencionada, sería la adición de calcio y, en determinadas poblaciones de riesgo, vitamina D, a los diversos fármacos.

8.9. Consistencia de las recomendaciones

En función de los niveles de evidencia, los diferentes fármacos presentan los grados de recomendación, para cada una de las fracturas especificadas, que se resumen en la tabla 6. Todos ellos tienen eficacia sobre la DMO, con un Grado de recomendación A. Se debe resaltar que los datos de falta de eficacia para determinada fractura(s) se derivan de EAC diseñados para objetivos primarios distintos, generalmente fractura vertebral.

9. Consideraciones sobre el coste-efectividad del tratamiento

La relación entre el coste del tratamiento y sus beneficios en salud debe considerarse siempre a la hora de hacer recomendaciones. Esto es especialmente importante en tratamientos preventivos o crónicos donde la evaluación del coste del tratamiento, el coste de los efectos adversos o de la no-adherencia, tienen un impacto claro en los resultados esperados en condiciones de práctica clínica habitual a la hora de evitar eventos futuros Se ha realizado diversos análisis coste-efectividad basados en modelos de proyección futura de los costes incurridos en pacientes con fractura osteoporótica, que demuestran que el tratamiento es coste efectivo tanto en la fractura femoral como vertebral. Sin embargo, los resultados de estos estudios deben por el momento interpretarse con cautela debido a las suposiciones que se incluyen en los mismos. El único estudio basado en los métodos de meta-análisis usados por la Colaboración Cochrane realizado en Canadá indica que el alendronato y la calcitonina tienen una relación coste-efectividad similar y que son más coste-efectivos que etidronato en la prevención secundaria de fractura vertebral, femoral y de antebrazo si bien su validez viene fuertemente limitada por la diferente eficacia demostrada por dichos fármacos. No existen estudios coste-efectividad comparando con otros tratamientos ni en otros contextos nacionales.

10. Algoritmos de decisión clínica

Se han desarrollado los siguientes algoritmos sobre problemas clínicos en los que se realizan recomendaciones explícitas:

1) Paciente con fractura vertebral;
2) Paciente con osteoporosis, sin fracturas;
3) Paciente con fractura no vertebral.

A las pacientes que consultan sobre riesgo de osteoporosis/agrupación de factores de riesgo se les debe realizar una densitometría y, caso de tener osteoporosis, aplicar el algoritmo 2. A las pacientes ancianas frágiles, sin fracturas, se les debe aplicar un programa combinado de prevención de caídas y en caso de diagnosticar osteoporosis por densitometría, las traslada al algoritmo 3 (fractura no vertebral).

En todos los casos debe asegurarse una ingesta adecuada de calcio (incluyendo suplementos si fuera necesario), y administrarse vitamina D en las mujeres con riesgo de deficiencia (ancianas, baja exposición solar, dietas inadecuadas).

En los algoritmos desarrollados los tratamientos se ordenan en función de ser primera o segunda opción (en una ocasión, tercera). En los fármacos se hace

mención del grupo farmacológico y del principio o principios activos, citándolos por orden alfabético, sin que ello indique orden de preferencia.

11. Contraindicaciones de los principales fármacos aprobados

Las contraindicaciones establecidas por las autoridades reguladoras que se exponen en las fichas técnicas de los diferentes fármacos recomendados en esta guía se resumen en el anexo.

Estrógenos orales
Embarazo. Neoplasia mamaria o estrogeno-dependiente, metrorragias no diagnosticadas, hepatopatías graves, enfermedad tromboembólica recurrente. Contraindicaciones relativas: Enfermedad fibroquística mamaria, miomas uterinos, endometriosis e historia familiar de cáncer mamario.

Estrógenos transdérmicos
Carcinoma de mama o endometrio; endometriosis; sangrado vaginal de origen desconocido; lesión hepática grave; tromboflebitis activa o procesos tromboembólicos; hipersensibilidad a los estrógenos o a los componentes del preparado farmacológico. Embarazo y lactancia.

Progestágenos (medroxiprogesterona)
Tromboflebitis y fenómenos tromboembólicos, hepatopatías graves, metrorragias y menorragias no diagnosticadas, aborto retenido y en casos de sensibilidad conocida a acetato de medroxiprogesterona.

Raloxifeno
No se debe administrar a mujeres que pudieran quedar embarazadas o que no hubieran presentado la menopausia. Antecedentes pasados o actuales de episodios tromboembólicos venosos, incluyendo trombosis venosa profunda, embolia pulmonar y trombosis venosa de la retina. Hipersensibilidad al raloxifeno u otros ingredientes del comprimido. Alteración hepática, incluyendo colestasis. Alteración renal severa. Sangrado uterino inexplicado. Raloxifeno no se debe utilizar en pacientes con signos y síntomas de cáncer de endometrio porque no se ha estudiado convenientemente su seguridad en este grupo de pacientes.

Tibolona
Embarazo o lactancia. Tumores hormonodependientes conocidos o sospechados. Trastornos cardiovasculares o cerebrovasculares, como tromboflebitis, procesos tromboembólicos o historial previo de tales trastornos. Sangrado vaginal de etiología desconocida. Trastornos hepáticos graves.

Etidronato
Intolerancia conocida a etidronato. Osteomalacia. Insuficiencia renal grave.

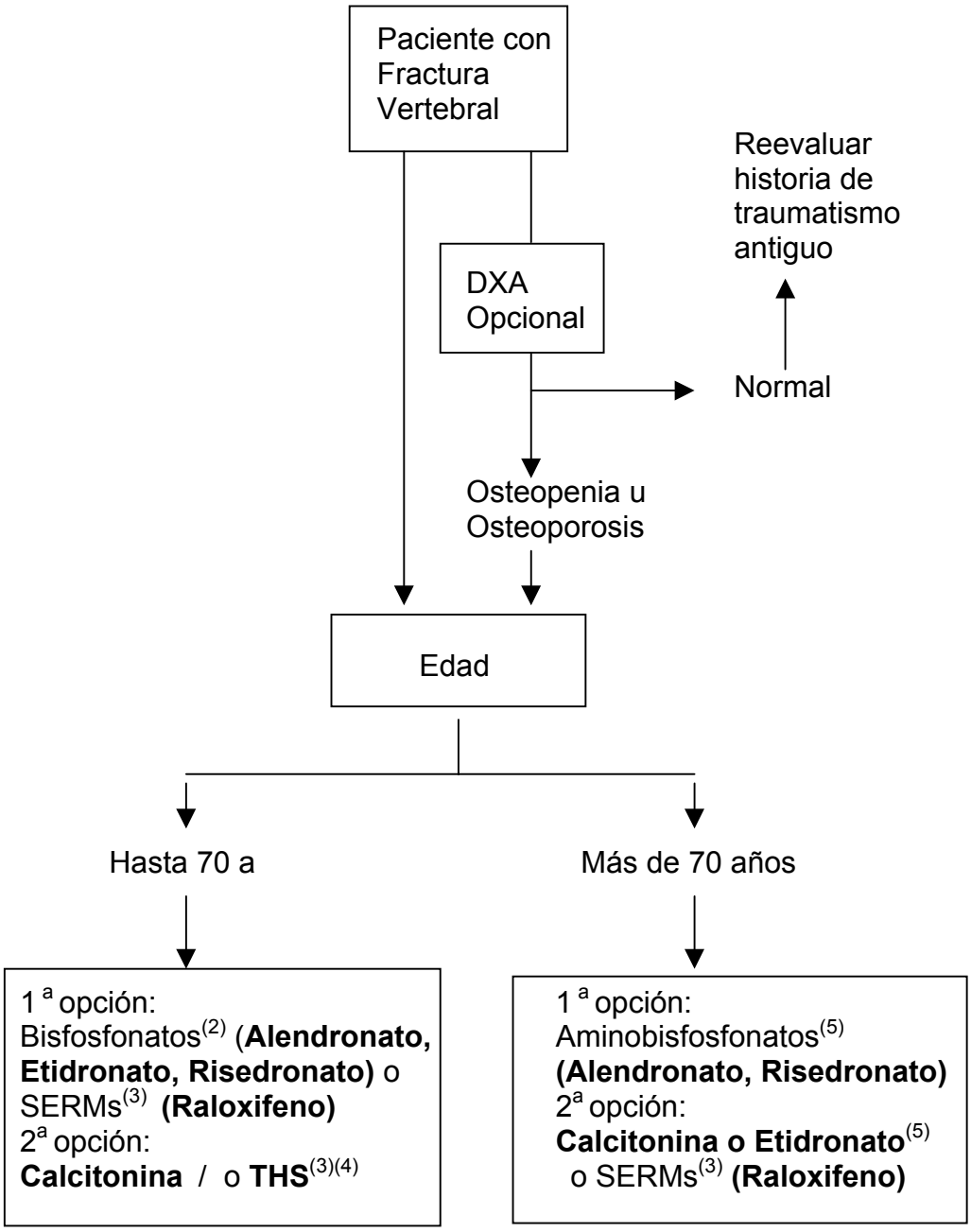
Alendronato
Anormalidades esofágicas que retrasan el vaciamiento esofágico, como las estenosis o la acalasia. Imposibilidad de permanecer en posición sentada erguida o en bipedestación durante al menos 30 minutos. Hipersensibilidad cualquier componente del producto. Hipocalcemia. En pacientes con aclaramiento de creatinina <35ml/min.

Risedronato
Hipersensibilidad conocida a risedronato sódico o a cualquiera de sus excipientes. Hipocalcemia. Embarazo y lactancia. Insuficiencia renal grave (aclaramiento de creatinina <30ml/min).

Calcio + vitamina D
Hipersensibilidad a algunos de los componentes. Hipercalcemia. Hipercalciuria. Insuficiencia renal grave.

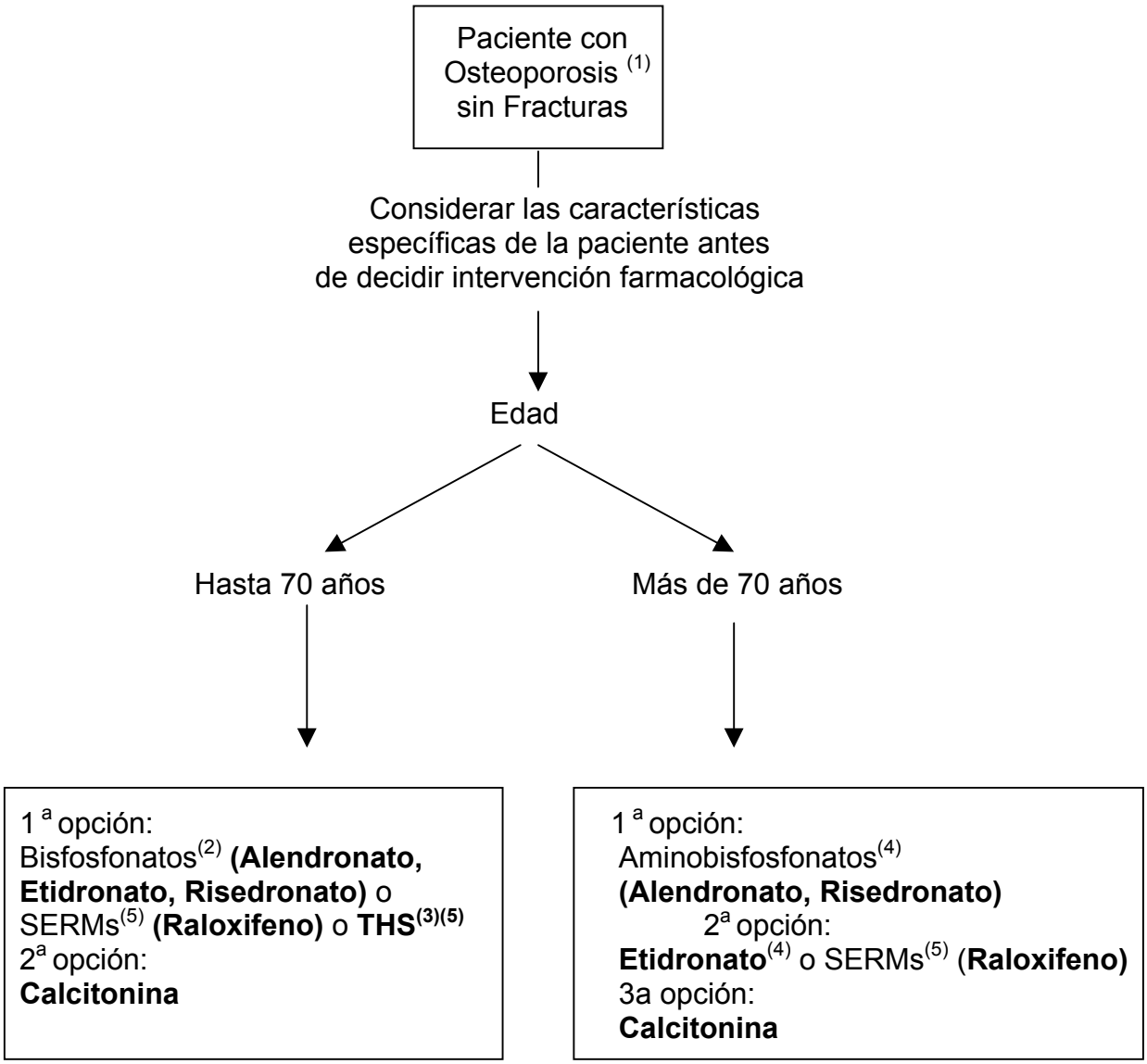
Calcitonina
Hipersensibilidad a la calcitonina o a cualquiera de los componentes del preparado. Embarazo y lactancia. Congestión / rinitis en administración nasal.

Algoritmo 1. Paciente con fractura vertebral[1]



[1] Se entiende fractura que ha acontecido de forma espontánea o tras un traumatismo mínimo en un paciente en que se ha descartado de forma razonable la existencia de enfermedades distintas de la osteoporosis.
(2)Si se valora un riesgo muy elevado de fractura de fémur, los aminobisfosfonatos pueden ser de primera elección. Valorar historia de enfermedad péptica gástrica o esofágica.
(3)Contraindicados en riesgo de enfermedad tromboembólica venosa.
(4)En postmenopáusicas recientes y/o con síntomas climatéricos, THS puede ser de primera elección. Contraindicados en historia o riesgo de cáncer de mama
(5)Valorar historia de enfermedad péptica gástrica o esofágica.

Algoritmo 2: Paciente con osteoporosis sin fracturas



* Estas pacientes tienen un riesgo bajo de fractura, lo que comporta un número elevado de pacientes a tratar para evitar una fractura. Se deben, por tanto, considerar cuidadosamente los costes, aceptabilidad y potenciales efectos secundarios frente a las reducidas disminuciones de riesgo absoluto que se obtienen.

(1) Se entiende diagnosticada por DXA. A partir de los 65 años es preferible la medición en cadera.

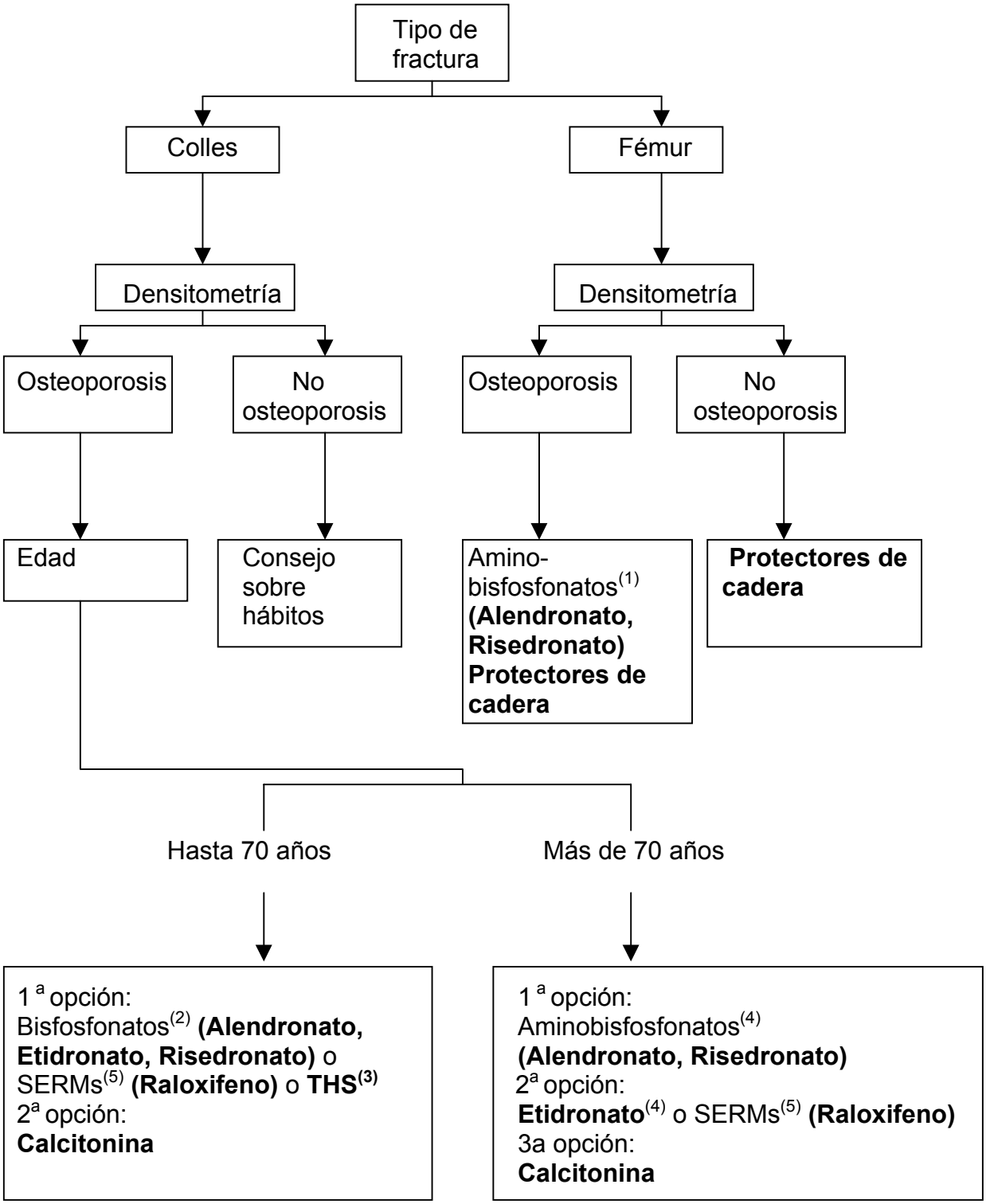
(2)Si se valora un riesgo muy elevado de fractura de fémur, los aminobisfosfonatos pueden ser de primera elección.

(3) En postmenopáusicas recientes y/o con síntomas climatéricos, THS puede ser de primera elección. Contraindicada en historia o riesgo de cáncer de mama.

(4) Valorar historia de enfermedad péptica gástrica o esofágica

(5) Contraindicados en riesgo de enfermedad tromboembólica venosa

Algoritmo 3. Paciente con fractura no vertebral (Colles o fémur)



En ancianas se debe valorar si sus condiciones individuales permiten un tratamiento farmacológico.

(1) Valorar historia de enfermedad péptica gástrica o esofágica. Contraindicados en pacientes encamados obligados a permanecer en decúbito

(2), (3), (4) y (5). Ver Algoritmo 2.

Glosario terminológico y de siglas.

Best Evidence: Publicación secundaria que recoge resúmenes estructurados con comentarios de publicaciones primarias seleccionadas por cumplir criterios de rigor metodológico.
CMO: contenido mineral óseo (*BMC, bone mineral content*)
DXA: absorciometría radiológica de doble energía. Sinónimos: DXA, densitometría ósea radiológica.
DMO: densidad mineral ósea (*BMD, bone mineral density*)
Densitometría ósea: cualquier método de medición del contenido mineral del hueso.
EAC: Ensayo clínico con asignación aleatoria.
Fractura de fémur: fractura no patológica, cervical o trocantérea, que asienta en el tercio proximal del fémur. Sinónimo: fractura de cadera.
Fractura osteoporótica: la producida por traumatismo mínimo en hueso desmineralizado no patológico (neoplasia, lesión localizada). Se acepta en cualquier hueso, excepto macizo facial y cráneo.
Fractura vertebral: hundimiento total o parcial, no patológico, del cuerpo vertebral. Sinónimo: deformidad vertebral.
GPC: Guía de Práctica Clínica
Indice T (*t- score*): valor densitométrico que representa el número de desviaciones estándar que se aparta el sujeto respecto al promedio de los valores de un grupo poblacional de adultos jóvenes del mismo sexo.
Librería Cochrane: Recurso electrónico formado por la Colaboración Cochrane, internacional, sin ánimo de lucro y que realiza revisiones sistemáticas, elabora protocolos y mantiene un registro de ensayos clínicos.
MBE: Medicina basada en la evidencia (*EBM, Evidence-Based Medicine*). Sinónimo: Medicina basada en pruebas.
MEDLINE: Base de datos bibliográficos de la National Library of Medicine
NNT: Número necesario a tratar o Número necesario de pacientes a tratar
OMS: Organización Mundial de la Salud.
RR: Riesgo relativo
SERM: Regulador selectivo del receptor estrogénico (*Selective Estrogen Receptor Modulator*)
THS: Tratamiento hormonal sustitutivo. Se restringe al uso de hormonas ováricas.

Grupo de trabajo de la SEIOMM

Las recomendaciones recogidas en esta GPC reflejan la opinión colectiva del Grupo de Trabajo, basada en la evidencia científica recogida, analizada y tabulada por el grupo "ad hoc". El nivel de evidencia que sustenta cada recomendación está explícitamente recogido en la versión amplia de la presente Guía.

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Tabla 1. Niveles de Evidencia de acuerdo a las recomendaciones del Centro de Medicina Basada en la Evidencia de Oxford*

Grado de Recomendación	Nivel de Evidencia	Tratamiento /Etiología	Pronóstico	Diagnóstico
A	1a	RS (con homogeneidad) de EAC	RS (con homogeneidad) de estudios de cohortes prospectivos GPC validadas.	RS (con homogeneidad) de estudios diagnósticos de nivel 1 o GPC validadas.
	1b	EAC con IC estrechos	Cohortes con seguimiento ≥ 80 %	Comparación independiente y ciega de un espectro apropiado de pacientes.
B	2a	RS (con homogeneidad) de cohortes	RS (con homogeneidad) de estudios de cohortes retrospectivos	RS (con homogeneidad) de estudios diagnósticos de nivel ≥ 2
	2b	Estudios de cohortes o EAC de baja calidad (tamaño muestral pequeño...)	Estudios de cohortes retrospectivos o GPC no validadas.	Ausencia de: - Comparación objetiva; - Espectro limitado de pacientes o pacientes no consecutivos. GPC no validadas.
	3a	RS (con homogeneidad) de estudios de casos y controles		
	3b	Estudio de casos y controles		No-realización de la prueba de referencia a todos los sujetos, respetando la independencia, la ceguera y el apropiado espectro de pacientes
C	4	Series de casos	Series de casos	
D	5	Opinión de expertos	Opinión de expertos"	Opinión de expertos

RS = revisión sistemática. EAC= Ensayo Clínico con asignación aleatoria. GPC = Guía de Práctica clínica

*Levels of Evidence and Grades of Recommendations (Revised on 18th November 1999) del Evidence-Based Medicine Centre (Oxford). http://www.cebm.ox.uk

Tabla 2: Factores de riesgo de osteoporosis/fractura

Factores	Riesgo asociado	Riesgo relativo (IC del 95%)	Nivel de evidencia
Factores de riesgo óseo			
≥ 2 fracturas vertebrales previas	Fractura vertebral	11,8 (5,1-22,6)	1b
Descenso DMO* *por cada -⊿ DE*	Fractura de fémur Fractura vertebral	3,8 a 5,8 (2,2-9,5)§ 1,6 (1,3-1,9)	1b
1 ó 2 fracturas vertebrales previas	Fractura vertebral	3,6 (2,5-5,2)	1b
Historia materna fractura fémur	Fractura de fémur	1,8 (1,2-2,7)	1b
Sedentarismo	Fractura de fémur	1,7 (1,2-2,4)	1b
Cualquier fractura a edad > 50 años	Fractura de fémur	1,5 (1,1-2,0)	1b
Edad (cada 5 años)	Fractura de fémur	1,4 (1,2-1,6)	1b
Estatura (a los 25 a., por cada 6 cm)	Fractura de fémur	1,3 (1,1-1,5)	1b
Consumo elevado de proteínas	Fractura de fémur o Fractura de antebrazo	1,22 (1,04-1,43)	1b
Hábito de fumar	Fractura de fémur	1,17 hasta 2,08 (1,05-2,54) según edad	2a
Fractura previa de antebrazo	Fractura de antebrazo	2,58 (1,84-3,72)	2b
Marcadores de remodelado	Fractura de fémur	1,39-2,3	2b
Nivel indetectable estradiol y SHBG	Fractura de fémur Fractura vertebral	6,9 (1,5-32)¥ 7,9 (2,2-28)¥	3b
Factores de riesgo de caída			
Uso prolongado de benzodiacepinas	Fractura de fémur	1,6 (1,1-2,4)	1b
Incapacidad para levantarse de una silla	Fractura de fémur	1,7 (1,1-2,7)	1b
Frecuencia cardíaca > 80 lpm	Fractura de fémur	1,7 (1,1-2,0)	1b
Factores protectores			
Consumo de alcohol, 5 a 7 dosis/semana**	Fractura vertebral	0,65 (0,53-0,99)	2b
Ejercicio físico moderado	Fractura fémur	0,64 (0,47-0,88)	2ª
Ejercicio físico intenso	Fractura fémur	0,64 (0,45-0,89)	2ª

Numerosos factores pueden afectar simultáneamente el metabolismo óseo y el riesgo de caída. *Diversas estimaciones; § varía en diferentes áreas medidas; ¥ ajustado por peso; ** en edad superior a 50 años

Tabla 3: Definición densitométrica de osteoporosis (OMS)

Valor de DMO* en índice T	Categoría diagnóstica
Por encima de -1	Normal
Entre -1 y -2,5	Osteopenia
Inferior a -2,5	Osteoporosis
Inferior a -2,5 y con fracturas por fragilidad	Osteoporosis establecida ("grave")

* Los valores se refieren como índice (*score*) T (ver glosario), que representa el número de desviaciones estándar que se aparta el sujeto respecto a la media de los valores de un grupo poblacional de adultos jóvenes del mismo sexo.

Tabla 4. Indicaciones de densitometría ósea diagnóstica en mujeres postmenopáusicas

Anomalías radiológicas vertebrales sugerentes de desmineralización
Fractura previa por fragilidad (vertebral, femoral, Colles)
Tratamientos prolongados con glucocorticoides
Insuficiencia ovárica prolongada
Historia de trastorno nutricional grave
Hiperparatiroidismo primario
Paciente que consulta por riesgo de osteoporosis/agrupación de factores de riesgo

Tabla 5. Intervenciones preventivas no farmacológicas y grado de recomendación

Intervención	DMO	Fractura vertebral	Fractura De fémur
Ejercicio físico*	A	B o C	B
Suplementos de calcio (± vitamina D)	A	B o C	B o C*
Calcio dietético	B o C	B o C	B o C
Cese de fumar	B o C	B o C	B o C
Reducción del consumo de alcohol	D	D	B o C
Protectores de cadera	-	-	A

* Una revisión sistemática sugiere esta eficacia mientras varias revisiones sistemáticas sostienen que no existen suficiente datos para afirmarla.

Tabla 6: Grado de recomendación para los diferentes fármacos en la reducción de riesgo de fractura:

Fármaco	Fractura		
	Fracturas vertebrales	Fracturas no vertebrales	Fracturas de fémur
Calcio	A	B o C	B o C
Vitamina D	C	C	C
Calcio + Vitamina D	-	A*	A*
THS	B	A	A¶
Raloxifeno	A	NE	NE
Tibolona	-	-	-
Etidronato	A	NE	NE
Alendronato	A	A	A
Risedronato	A	A	A
Calcitonina	B	NE	NE
Flavonoides	-	-	-
Parathormona	A	A	A¶
Anabolizantes	-	-	-

NE: no-eficacia demostrada en EAC, no diseñados específicamente para el tipo de fractura; * eficaz en población asilar con déficit, asociada a calcio; ¶ eficacia para fractura no vertebral, que incluye fémur. Los EACs se han realizado prácticamente en su totalidad añadiendo calcio y, en un gran número, vitamina D.

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SPANISH BONE AND MINERAL SOCIETY
- SEIOMM -

POSTMENOPAUSAL OSTEOPOROSIS. Clinical Practice Guidelines. Summary. *SEIOMM* working group*

Introduction

The increasing rise in the incidence of osteoporosis, together with the ageing of the Spanish population, its morbidity and mortality, as well as its relevant health and economic impact, have all led SEIOMM to carry out the *Clinical Practice Guidelines on Postmenopausal Osteoporosis*. This is seen as a first step in relation to the segment of the population that is most affected by this disease. SEIOMM has formed a working group in order to develop the mentioned guide according to the methodology established by the Evidence-Based Medicine (EBM).

These Clinical Practice Guidelines aim at offering an orientating framework as a starting point for the groups of professionals who are interested in developing protocols in order to act in every assistance ambit. This means, these recommendations must be taken into account as derived from the review of scientific evidence. However, the clinical decisions will also need to incorporate professional experience and the assistance scenario where they will be implemented, as well as the patients' values and preferences. Thus, there is room for different clinical decisions, from those here recommended, that may constitute absolutely valid patterns for action.

1. Background

Osteoporosis is the most prevalent metabolic disease. It affects a 35% of the Spanish women who are over 50. This percentage rises to 52% in those who are over 70. One of every five women who are over 50 has already suffered al least one vertebral fracture due to osteoporosis associated to deterioration of the quality of life and an increased risk of suffering further fractures. The annual incidence of the femoral fracture in women who are over 50 is 3 per 1000. The distal forearm fracture is nearly twice as frequent. Today, a Spanish 50-year-old woman's probability of suffering a femoral fracture at some point of her life is somewhat between 12% and 16%. And fractures (particularly the femur ones) lead to an increase of the mortality in relation with patients without fractures.

2. Methodology

The contents of the Guide have been developed for two years and according to the following phases: 1) Meetings of a group of experts in osteoporosis in order to set the relevant questions; 2) Creation of a team for systematic revision, formed by an expert in EBM that would coordinate two physicians in charge of the search, standardized revision, critical analysis and tabulation of the relevant articles; 3) Meetings of clinical experts in order to organize the hierarchized evidence into clinical recommendations;

4) Writing a first draft of the Guide; 5) Open debate for the members of the SEIOMM and other professionals to take part.

In this debate process, apart from physicians from several fields, other experts have taken part: representatives from the Agencies of Assessment, from the Ministry of Health and from the Spanish Agency for Medicines, as well as, representing patients and civil society, representatives from the *Federación Española de Derecho Farmacéutico* (Spanish Federation of Pharmaceutical Law), the *Asociación Nacional de Informadores de la Salud* (National Association of Scientific Journalists) and from the organization formed by osteoporosis patients, the *Fundación Hispana de Osteoporosis y Enfermedades Metabólicas Óseas* (Hispanic Foundation of Osteoporosis and Metabolic Bone Diseases). All of them have contributed their comments to the document. An expert in economy in the Health sector, who has also included the considerations related to drug and economy, has reviewed this guide. The working group has accepted the systematic revision carried out in the main Clinical Practice Guidelines (GPC), based on the EBM methodology that has been published, that of the British Royal College of Physicians, up to December 1995. The revision team has systematically reviewed the MEDLINE database from January 1st, 1996 to January 1st, 2000, as well as The Cochrane Library, Best Evidence and the articles recommended by the working group. A complementary search with a similar strategy was carried out by the whole working group from January 1st, 2000 to May 15th, 2001. Articles considered of relevance published in the following months until the end of the open debate of the draft have been accepted.

Evidence has been classified according to the recommendations of the Center of Evidence-Based Medicine de Oxford, into levels 1 to 5. The first three levels have also been given sub-levels “a” and “b” (Table 1). Recommendations have been classified into four grades of evidence:
Grade A: based on systematic revisions of aleatorized clinical assays (ECA), or, at least, a well-designed ECA. Studies of prospective cohorts for prognostic factors.
Grade B: systematic studies of cohorts, cases and controls, low-quality ECA.
Grade C: series of cases, poor cohort studies.
Grade D: opinion of experts without explicit assessment criteria.
The strategy is detailed in the full version of this Guide.

3. Definition of osteoporosis

It is consensual for osteoporosis to be defined as a skeleton disease characterized by a decreased bone-resistance that makes it likely for somebody to have an increased risk of being exposed to an increased risk of fracture.
Bone-resistance fundamentally reflects the integration of density and bone-quality. Bone density is expressed in grams of mineral per area or volume. In an individual, the peak bone determines bone density mass and by the amount of bone loss. Bone quality relates to architecture, replacement, accumulation of lesions (i.e., microfractures) and mineralization. Fracture takes place when a force that induces breaking, such as a traumatism, is applied onto an osteoporotic bone. This is the reason why osteoporosis is a significant factor of fracture risk. However, it is necessary to make a distinction between risk factors related to bone metabolism and other risk factors of fracture. A diagnostic definition based on densitometry has been given and is included in this Guide.

4. Risk Factors

It has been proved that many factors are associated with a high risk of vertebral or femoral fracture (Table 2). They are usually extra-osseous (i.e. related to fall risk or traumatisms) and osseous (related to bone-resistance). There is consistent evidence of the association between decrease in the bone mineral density (BMD) and fracture risk. Genetic factors (associated with fracture risk) are being actively studied. And there are some genetic polymorphisms moderately associated with diminished values of BMD. Overweight is a protecting factor from suffering osteoporosis and other fracture risks.

A large number of other diseases are also associated with osteoporosis and fracture risk. Among them, primary hyperparathyroidism and treatment with corticoids is especially relevant in postmenopausal women, due to their high prevalence or to the high risk of osteoporosis associated.

5. Diagnostic evaluation

Every case of osteoporosis must be subjected to anamnesis, physical exploration and basic blood-analysis so that any other subjacent pathology can be ruled out. Diagnose of osteoporosis is established by means of a bone densitometry. The most widely use method is the Dual-energy X-ray Absorptiometry (DXA), which has been validated as a predictor of fracture risk. DXA is accepted as the "gold standard". The most usual measurement areas are the lumbar spine and the femoral neck. The World Health Organization (WHO) has established a definition of osteoporosis based on densitometric values. The WHO establishes that there exists osteoporosis when the patient presents a BMD value in T-score, in the lumbar spine or in the femoral neck, lower than - 2.5 standard deviations. This organisation has also established other diagnostic categories that appear in Table 3.

The value of lumbar BMD by DXA (Hologic), in Spanish women, representing the peak bone mass (reference for the T-score) is 1.040 ± 0.104 g/cm^2 (mean $\pm$ DS). This BMD value in the femoral neck by DXA (Hologic), is 0.840 ± 0.109 g/cm^2. Equivalent values in other equipment can be calculated by means of conversion formulae.

Other techniques for the measurement of bone density, such as ultrasounds, computed tomographic scan or digitalized x-ray have obtained similar predictive values of fracture risk. However, they are not so widely used, either for technical reasons, because of a worse reproducibility, or due to a poorer clinical experience. In general terms, the prediction of the fracture risk in a certain skeletal region is enhanced when directly measured. For each standard deviation in the decrease of bone density, measured through different techniques, relative risk associated to fracture varies between 1.3 and 3.9 (level of evidence 2b). In the elderly, biochemical markers for bone remodeling, especially the resorption ones, are associated to an increase in the relative fracture risk of between 1,39 and 2,3 (level of evidence 2b).

Given the variability coefficient of the DXA explorations in the lumbar spine and the femoral neck, it seems only reasonable to take measurements every two years. In Table 4, there is a summary of the indications from this working group regarding bone densitometry in postmenopausal women.

6. Osteoporosis screening.

The most recommendable strategy is the selective search of cases. Thus, it is possible to detect cases on which the physician may apply the different intervention algorithms. Diagnostic confirmation will be established by presence of fractures or, if

there exists none, by means of densitometric techniques. Population-based screening is not recommended because its positive cost-effectiveness relation has not been proved yet.

7. Non-pharmacological interventions.

Here, general advice on health promotion applies. It is recommendable, both for the general public and risk-subjects (postmenopausal women, here), to increase physical activity, to stop smoking and to increase the calcium intake, even if the effect of these measures in decreasing fractures has not been evaluated. Different interventions and their grade of recommendation are summarized in Table 5.

Combined-intervention programs acting on several factors of fall risk in the elderly have proved their efficacy. Thus, they reduce the fundamental aleatory factor of fracture (Grade of recommendation A).

8. Pharmacological interventions.

Women who are close to menopause, with risk factors and densitometric values within the interval previously defined as osteopenia, with no fractures, are susceptible of receiving preventive treatment.

In the prevention of bone loss, estrogens, etidronate, alendronate and raloxifene have proved their efficacy (Grade of recommendation A). In the prevention of vertebral fractures, there exists data on the efficacy of raloxifene (Grade A) and estrogens (Grade B-C). In the prevention of femoral fracture, there only exists data on estrogens (Grade A). However, they are for women without clinical disease and with a low fracture risk. Given the potential side effects and the high necessary number of patients to be treated in order to avoid an event, their use must be restricted to specific cases unless the treatment is justified by other factors that differ from the prevention of osteoporosis.

Drugs for the treatment of osteoporosis have only proved their efficacy in clinical assays by means of extended treatments of at least between two and three years. The physician and the patient must be aware of the uncertain or invalid usefulness of any pattern that applies for a shorter period. Adherence to the treatment must be ensured by means of a good relationship physician-patient and a detailed explanation about the treatment.

It is not possible to compare the efficacy of the different drugs, since there are no aleatorized assays that compare each alternative. We only have data coming from different assays. And we cannot use these for comparisons, since the population studied in each of them is different, too. As it is the design of the study, the intervention and the measurements. This is why it is not possible to hierarchize these drugs according to the magnitude of their effect. Thus, any decision about the use of one of them must be based on data about their efficacy, the desired therapeutic objective, tolerability, associated effects whether positive or negative, patient's comfort, and administration pattern, and, finally, the patient's informed opinion.

8.1. Calcium and Vitamin D.

Calcium is a basic nutritional requirement for the bone. For postmenopausal women, a minimum intake of 1,500 mg per day is recommended in order to achieve a metabolic balance. Administered as a supplement to the patient's usual diet, up to

the mentioned dose, it is a recommendable measure, and most CAAs on different drugs recommend a joint administration of a minimum of 500 mg calcium per day.
In postmenopausal women that have a deficient intake, pharmacological supplements decrease bone loss and the risk of vertebral fracture (Level of evidence 1b). Doses of 1,000 mg per day show a scarce, though significant, decrease of the risk of femoral fracture (Level of evidence 2a).
Calcitriol and alphacalcidiol decrease bone loss and the incidence of vertebral fracture (Level of evidence 2a). However, their efficacy in recent postmenopause (Level of evidence 1b) has not been proved. Vitamin D associated with calcium decreases the incidence of femur and non-vertebral fracture in institutionalized elderly with insufficient levels of vitamin D (Level of evidence 2a). Analogues to vitamin D increase the risk of hypercalcaemia (Level of evidence 2a).

8.2. Hormone replacement therapy

Hormone replacement therapy substitutes hormone deprivation due to cessation of ovarian activity.
There exists data about its efficacy on BMD coming from CAAs. However, there are few assays with the aim of decreasing the risk of fracture (and, more specifically, the vertebral fracture, and most information on this aspect comes from observational studies or from a methodologically limited CAAs (Level of evidences 2a and 2b). If the treatment starts before the patient is 60 years old, it is efficacious in decreasing non-vertebral fractures (Level of evidence 1a).
This treatment induces a slight, though significant, increase in the risk of detection of breast cancer that is more patent in extended treatments, (Level of evidence 2a) and thromboembolic disease (Level of evidence 1b).

8.3. Raloxifene

Raloxifene is a selective estrogen receptive modulator (SERM). It has positive effects on lumbar and femoral bone mass and on the risk of non-vertebral fracture (Level of evidence 1b). Its efficacy in the prevention of non-vertebral fractures has not been proved (Level of evidence 1b).
Raloxifene increases the risk of venous thromboembolism in a similar way of that of the estrogens. It decreases the risk of breast cancer together with positive estrogen receptor in low-risk population, such as osteoporotic women, and has positive effects on some subrogated markers of cardiovascular risk (Level of evidence 1b for all data).
Analysis of non-predetermined subgroups (*post hoc*) have demonstrated early anti-fracture efficacy (Level of evidence 2b).

8.4. Tibolone

Tibolone acts similarly to oral-administration estrogens on the bone tissue.
It is efficacious in order to prevent bone loss (Level of evidence 2b). There exists no data about its efficacy on fractures.
It is efficacious in order to control hot flashes (Level of evidence 1b), so they can be an alternative for women that do not tolerate well cyclic menstrual bleeding with HRT.

8.5. Bisphosphonates.

8.5.1. Etidronate.

Etidronate is a non-amino bisphosphonate that is orally administered, in fortnightly cycles, every three months.
It has a positive effect on the lumbar and femoral BMD. It decreases the risk of vertebral fracture, but its efficacy on non-vertebral fracture has not been proved (Level of evidence 1a).

8.5.2. Alendronate.

Alendronate is an oral-administration aminobisphosphonate.
It has a positive effect on the lumbar and femoral BMD. It decreases the risk of vertebral, non-vertebral and femoral fracture (Level of evidence 1a). The administration of a single weekly dose has an analogue efficacy on the BMD to that of the daily dose (Level of evidence 1b) and may enhance adherence to the treatment.
The most usual side effects, although not frequent, are gastrointestinal. The administration pattern must be strictly followed in order to avoid potentially important esophageal lesions. Administration when fasting is important due to its low intestinal absorption.
Analysis of non-predetermined subgroups (*post hoc*) have demonstrated early anti-fracture efficacy (Level of evidence 2b).

8.5.3. Risedronate.

Risedronate is an oral-administration aminobisphosphonate.
It has a positive effect on the lumbar and femoral BMD. It decreases the risk of vertebral and non-vertebral fracture in women suffering established osteoporosis (Level of evidence 1b). It has proved to decrease the risk of femoral fracture in a CAA designed *ad hoc* for this result of interest (Level of evidence 1b).
Endoscopic studies demonstrate a low toxicity on the digestive mucosa (Level of evidence 2b). It should be administered separately from intake, at different times of day, due to its low intestinal absorption.
Analysis of non-predetermined subgroups (*post hoc*) have demonstrated early anti-fracture efficacy (Level of evidence 2b).

8.5.4. Other bisphosphonates.

There are other bisphosphonates that are currently being pre-clinically developed.
There exist studies, of varying validity, that prove a positive effect on BMD of the Ibandronate, Clodronate, Pamidronate and Zoledronate.
There are no data published on their potential for fracture-decrease.
Tiludronate has no proved efficacy either on BMD or in a CAA (Level of evidence 1b).

8.6. Other resorption-inhibiting agents.

8.6.1. Calcitonin.

Calcitonin is a hormone that inhibits osteoclastic activity reversibly.
It has a weak positive effect on lumbar and femoral BMD (Level of evidence 1b). If administered transnasally, it is efficacious in decreasing vertebral fractures (Level of evidence 2b) and its effect is not dose-dependent. Data about the decrease in non-vertebral fractures come from non-aleatorized studies (Level of evidence 3b).

Calcitonin has a moderate analgesic effect demonstrated in CAAs of varying accuracy (Level of evidence 3).

8.6.2. Flavonoids.

Flavonoids are antiresorptive agents that have a controversial positive effect on bone mass. There exists no data about its efficacy on fractures.

8.7. Formation-promoting agents.

8.7.1. Parathormone.

The parathyroid hormone has positive effects on BMD when administered intermittently.
Fragment 1-34 in the hormone (recombining) has proved its efficacy on BMD and it decreases the incidence of vertebral and non-vertebral fracture when administered in a daily subcutaneous injection (Level of evidence 1b).
The most significant adverse effect is the transitory slight hypercalcaemia (Level of evidence 1b).

8.7.2. Fluoride.

Fluoride salts have a promoting effect in the trabecular bone formation. They are efficacious in inducing an increase in the values of BMD. However, they do not decrease the risk of vertebral fracture and increase, after a four-year treatment, the risk of non-vertebral fracture with high doses. Low doses (20 mg) may decrease vertebral fracture after a four-year treatment.
Their side effects are mainly gastrointestinal.
Its administration associated with vitamin D invalidates the benefits of fluoride. When associated to HRT, it enhances its effect on vertebral fracture (Level of evidence 1a for all data).

8.7.3. Anabolic steroids.

Anabolic steroids are efficacious on BMD (Level of evidence 2b). There are no data about their efficacy on fractures and their use is limited due to their side effects, related, mainly, to their androgenic action.

8.8. Combinations of drugs.

Several CAAs have analyzed the efficacy of combinations of drugs on the BMD and have proved an additive effect, in general terms. There are no data to prove that combinations enhance the anti-fracture efficacy of each drug on its own. This is why, until more proves are available, the possibility of adding side effects and the increase in the cost of the treatment make it difficult to recommend the use of combinations of drugs.
A general, already-mentioned, exception to this rule would be the addition of calcium, and, in certain segments of population in risk, vitamin D, to different drugs.

8.9. Consistence of the recommendations

Depending on their levels of evidence, drugs present Grades of Recommendation for each of the specified fractures, as summarized in Table 6. All of them are efficacious on BMD, with a Grade of Recommendation A. It is important to stress that data about lack of efficacy for certain fracture(s) come from CAAs devised for different primary objectives (mainly vertebral fracture).

9. Considerations on the cost-effectiveness of the treatment

The relation between the cost of the treatment and its benefits must be always taken into account when making a recommendation. This is particularly important when it comes to preventive or chronic treatments where assessment of the cost of the treatment, the cost of the adverse effects or of the non-adherence, have a clear impact on the results expected in clinical practice conditions, which is the usual thing when it comes to avoiding future events. Different cost-effectiveness analysis based on models of future costs incurred in patients with osteoporotic fracture prove that the treatment is cost-effective both in femoral and vertebral fracture. However, the results from these studies must be interpreted with caution due to certain supposals they include. The only study based on the meta-analysis methods used by The Cochrane Collaboration has been carried out in Canada and indicates that alendronate and calcitonin have a similar cost-effectiveness relation and are more cost-effective than etidronate for the secondary prevention of vertebral, femoral and forearm fracture. However, their validity is strongly limited by the different efficacy shown by those drugs. There are no cost-effectiveness studies that compare different treatments or these treatments in other countries.

10. Algorithms for clinical decisions

The following algorithms about clinical problems have been developed. They include explicit recommendations:

4) Patient with vertebral fracture;
5) Patient with osteoporosis, without fractures;
6) Patient with non-vertebral fracture.

It is necessary to examine by means of a densitometry any patient attending due to risk of osteoporosis/accumulation of risk factors. And, if they suffer from osteoporosis, algorithm 2 must be applied. To old fragile patients, without fractures, a combined program for the prevention of falls must be applied, and, in case of diagnosing osteoporosis by means of a densitometry, they must be moved to algorithm 3 (non-vertebral fracture).

An adequate calcium intake (including supplements, if needed) is necessary in every case and it is also important to administer vitamin D to women in risk of deficiency (elderly women, women with a low exposure to sun or with unsuitable diets).

In the algorithms developed, treatments are listed according to the fact that they are the first or the second option (once, the third). In the drugs, the pharmacological group is mentioned, as well as the active constituent(s). They are alphabetically listed in order to avoid a misinterpretation about preference.

11. Counter-indications of the main drugs approved

The counter-indications that the relevant authorities have established and that appear in the technical information of the different drugs recommended in this Guide are summarized in the Annex.

Oral estrogens

Pregnancy. Breast or estrogen-dependent neoplasia, non-diagnosed endometrial bleeding, severe hepatopathy, recurrent thromboembolic disease. Relative counter-indications: Breast fibrocystic disease, uterus myoma, endometriosis and family history of breast cancer.

Transdermic estrogens
Breast or endometrial carcinoma; endometriosis; vaginal bleeding of unknown origin; severe hepatic lesion; active thrombophlebitis or thromboembolic processes; hypersensitivity to estrogens or to the components of the pharmacological product. Pregnancy and breast-feeding.

Progestagens (medroxiprogesterone)
Thrombophlebitis and thromboembolic phenomena, severe hepatopathies, endometrial bleeding and in cases of known sensitivity to medroxiprogesterone acetate.

Raloxifene
It should not be administered to women that could become pregnant or that have not reached menopause. History of venous thromboembolic episodes, including severe venous thrombosis, pulmonary embolism and venous retina thrombosis. Hypersensitivity to raloxifene or to other components of the tablet. Hepatic disorder, including cholestase. Severe renal disorder. Unexplained uterus bleeding. Raloxifene should not be used in patients with signs and symptoms of endometrial cancer, since its safety has not been conveniently studied for this group of patients.

Tibolone
Pregnancy or breast-feeding. Known or suspected hormone-dependent tumors. Cardiovascular or cerebrovascular disorders, such as thrombophlebitis, thromboembolic processes or previous history of such disorders. Vaginal bleeding of unknown etiology. Severe hepatic disorders.

Etidronate
Known intolerance to etidronate. Osteomalacia. Severe renal insufficiency.

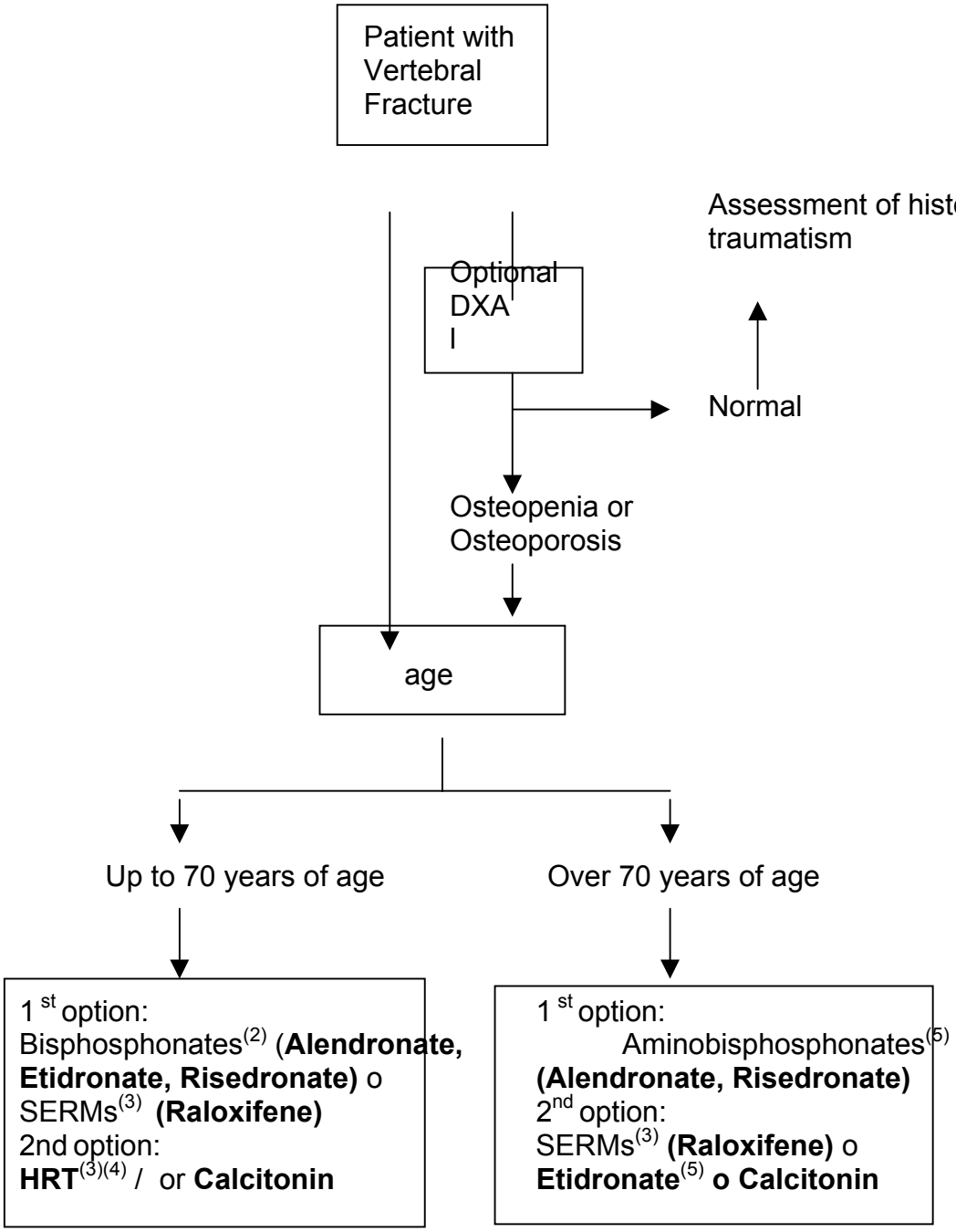
Alendronate
Esophageal abnormalities that retard the process of emptying the esophagus, such as estenosis or the achalasia. Inability to sit erect or to stand for at least 30 minutes. Hypersensitivity to any component of the product. Hypocalcaemia. In patients with creatinin thinning-down <35ml/min.

Risedronate
Known hypersensitivity to risedronate sodium or to any of its excipients. Hypocalcaemia. Pregnancy and breast-feeding. Severe renal insufficiency (creatinin thinning-down <30ml/min).

Calcium + vitamin D
Hypersensitivity to any of the components. Hypercalcaemia. Hypercalciuria. Severe renal insufficiency.

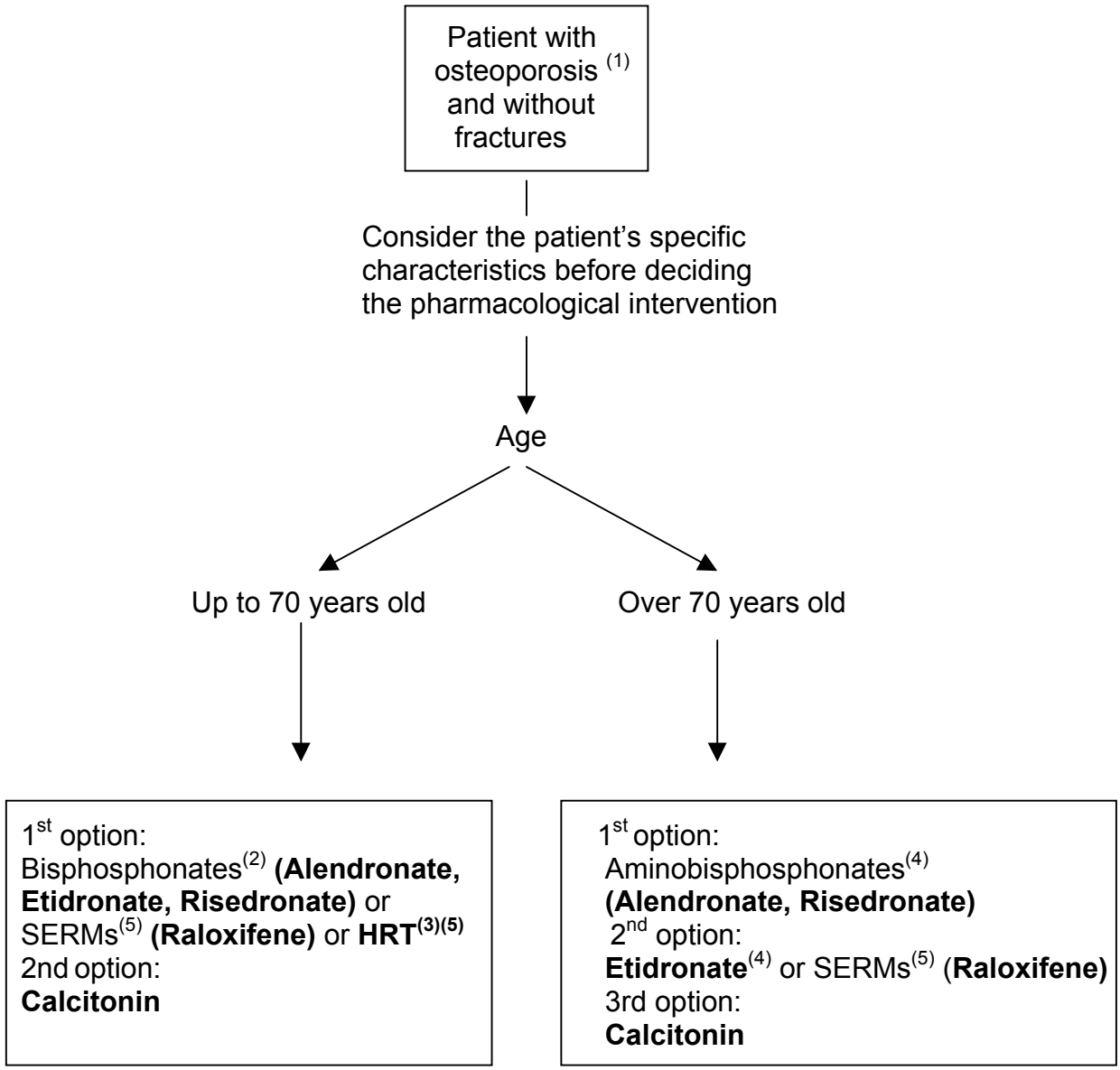
Calcitonin
Hypersensitivity to calcitonin or to any of the components of the product. Pregnancy and breast-feeding. Congestion / rinitis in nasal administration.

Algorithm 1. Patient with vertebral[1] fracture



[1] A fracture that has taken place spontaneously or after a minimal traumatism, when the existence of any diseases different from osteoporosis has been reasonably ruled out.
(2) If a very high risk of femoral fracture is assessed, aminobisphosphonates may be the first option. Assess history of esophageal or peptic gastric disease.
(3) Counter-indicated in case of risk of venous thromboembolic disease.
(4)In recently postmenopausal women and/or with climacteric symptoms, HRT may be the first option. Counter-indicated in case of history or risk of breast cancer.
(5)Assess history of esophageal or peptic gastric disease.

Algorithm 2: Patient with osteoporosis and without fractures



* These patients have a low risk of fracture, which implies a large number of patients to be treated in order to avoid a fracture. It is necessary, thus, to carefully consider the costs, acceptance and potential side effects, given the limited decreases in absolute risk that can be obtained.

(1) Diagnosed by means of DXA. In patients over 65 years of age, hip measurement is preferable.

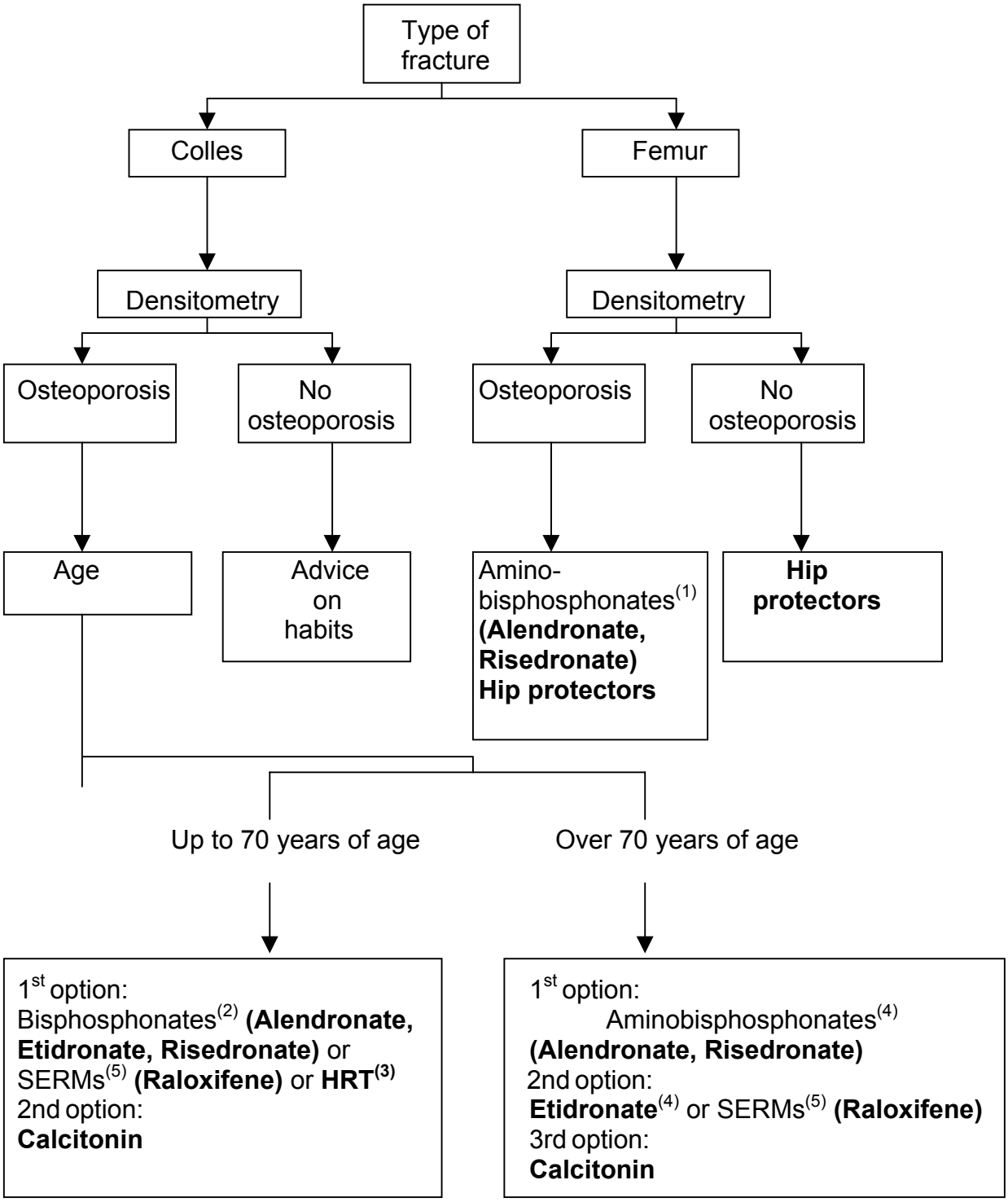
(2)If a very high risk of femoral fracture is assessed, aminobisphosphonates may be the first option.

(3) In recently postmenopausal women and/or with climacteric symptoms, HRT may be the first option. Counter-indicated in case of history or risk of breast cancer.

(4) Assess history of peptic or esophageal gastric disease.

(5) Counter-indicated in case of risk of venous thromboembolic disease.

Algorithm 3. Patient with non-vertebral fracture (Colles or femur)



In the elderly, it is necessary to assess whether their individual condition allow for a pharmacological treatment.
(1)Assess history of peptic o esophageal gastric disease. Counter-indicated in patients who are forced to stay in in bed.
(2), (3), (4) y (5). See Algorithm 2.

Glossary (terms and abbreviations).
Best Evidence: Secondary publication that gathers structured, commented summaries from publications that have been selected due to their methodological accuracy.
BMC: bone mineral content.
DXA: Dual-energy x-ray absorptiometry. Synonyms: DXA, x-ray bone densitometry.
BMD: bone mineral density.
Bone Densitometry: any method that measures of bone mineral content.
CAA: Clinical Aleatory-assignment Assay.
Femoral fracture: non-pathological trochantereal or cervical fracture that locates itself in the proximal area of the femur. Synonym: hip fracture.
Osteoporotic fracture: produced by a minimal traumatism in non-pathological demineralized bone (neoplasia, local lesion). It is accepted in any bone, with the exceptions of those in the face and the skull.
Vertebral fracture: total or partial, non-pathological, sinking of the vertebral body. Synonym: vertebral deformity.
CPG: Clinical Practice Guide
T-score: densitometric value that represents the number of standard deviations that the subject stands apart in relation to the average of the values of a population-group formed by young adults of the same sex.
Cochrane Library: Electronic resource offered by The Cochrane Collaboration. It is international, non-profit making and offers systematic revisions, carries out protocols and keeps a register of clinical assays.
EBM: Evidence-Based Medicine.
MEDLINE: Bibliographic database of the National Library of Medicine
NNT: Necessary number for treatment or Number of patients that is necessary to treat
WHO: World Health Organization.
RR: Relative Risk.
SERM: Selective Estrogen Receptor Modulator.
HRT: Hormone Replacement Therapy. It is restricted to the usage of ovarian hormones.

Working group de la SEIOMM
All recommendations gathered in these CPGs reflect the collective opinion of the working group. This opinion is based on the scientific evidence gathered, analyzed and tabulated by the group *ad hoc*. The level of evidence that supports each of the recommendation is explicitly gathered in the full version of this Guide.

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Table 1. Level of evidences according to the recommendations of the Centre of Evidence-Based Medicine in Oxford*

Grade of Recommendation	Level of evidence	Treatment / Etiology	Prognosis	Diagnose
A	1a	SR (with homogeneity) of CAAs	RS (with homogeneity) of studies of prospective cohorts. Validated CPG.	RS (with homogeneity) of diagnostic studies of level 1 from validated CPG.
	1b	CAAs with narrow CI	Cohorts with a follow-up ≥ 80 %	Independent and blind comparison of a suitable spectrum of patients.
B	2a	RS (with homogeneity) of cohorts	RS (with homogeneity) of studies of retrospective cohorts	RS (with homogeneity) of diagnostic studies of level ≥ 2
	2b	Studies of cohorts or poor CAAs (small sample size...)	Studies with retrospective cohorts or non-validated CPG	Lack of: - Objective comparison; - Limited spectrum of patients or non-consecutive patients. Non-validated CPG
	3a	RS (with homogeneity) of studies of cases and controls		
	3b	Study of cases and controls		No reference test applied to all subjects, respecting independence, blindness and the suitable spectrum of patients
C	4	Series of cases	Series of cases	
D	5	Opinion of experts	Opinion of experts	Opinion of experts

SR = systematic revision. CAA = Clinic Aleatory-assignment Assay.
CPG = Clinical Practice Guide
*Levels of Evidence and Grades of Recommendations (Revised on 18th November 1999) from the Evidence-Based Medicine Centre (Oxford). http://www.cebm.ox.uk

Table 2: Risk factors for osteoporosis/fracture

Factors	Associated risk	Relative risk (CI del 95%)	Level of evidence
Bone risk factors			
≥ 2 previous vertebral fractures	Vertebral fracture	11.8 (5.1-22.6)	1b
Reduction BMD* *per each -⊿ DE*	Femoral fracture Vertebral fracture	3.8 to 5.8 (2.2-9.5)§ 1.6 (1.3-1.9)	1b
1 or 2 previous vertebral fractures	Vertebral fracture	3.6 (2.5-5.2)	1b
Mother history of femoral fracture	Femoral fracture	1.8 (1.2-2.7)	1b
Sedentary life-style	Femoral fracture	1.7 (1.2-2.4)	1b
Any fracture before 50 years of age	Femoral fracture	1.5 (1.1-2.0)	1b
Age (every 5 years)	Femoral fracture	1.4 (1.2-1.6)	1b
Height (at 25, per each 6 cm)	Femoral fracture	1.3 (1.1-1.5)	1b
High protein consumption	Femoral fracture or forearm fracture	1.22 (1.04-1.43)	1b
Smoking habit	Femoral fracture	1.17 to 2.08 (1.05-2.54) depending on age	2a
Previous forearm fracture	Forearm fracture	2.58 (1.84-3.72)	2b
Remodeling markers	Femoral fracture	1.39-2.3	2b
Undetectable level of estradiol and SHBG	Femoral fracture Vertebral fracture	6.9 (1.5-32)¥ 7.9 (2.2-28)¥	3b
Fall risk factors			
Extended use of benzodiazepines	Femoral fracture	1.6 (1.1-2.4)	1b
Inability to rise from a chair	Femoral fracture	1.7 (1.1-2.7)	1b
Cardiac frequency > 80 lpm	Femoral fracture	1.7 (1.1-2.0)	1b
Protecting factors			
Alcohol consumption, 5 to 7 doses/week**	Vertebral fracture	0.65 (0.53-0.99)	2b
Moderate exercise	Femoral fracture	0.64 (0.47-0.88)	2a
Intense exercise	Femoral fracture	0.64 (0.45-0.89)	2

Many factors can simultaneously affect bone metabolism and fall risk. *Different estimates; § varies in different areas measured; ¥ adjusted per weight; ** over 50 years of age

Table 3: Densitometric definition of osteoporosis (WHO)

BMD* value in T-score	Diagnose category
Over –1	Normal
Between -1 and –2.5	Osteopenia
Under –2.5	Osteoporosis
Under –2.5 and with fractures due to fragility	Established osteoporosis ("severe")

* Values appear as T-score (see glossary). This represents the number of standard deviations that the subject stands apart in relation to the mean of the values of a population group of young adults of the same sex.

Table 4. Indications of Diagnostic Bone Densitometry in postmenopausal women

Vertebral x-ray abnormalities that suggest demineralization
Previous (vertebral, femoral, Colles) fracture due to fragility
Extended treatments with glucocorticoids
Extended ovarian insufficiency
History of severe nutritional disorder
Primary hyperparathyroidism
Patient that goes to see a doctor due to risk of osteoporosis/accumulation of risk factors

Table 5. Preventive non-pharmacological interventions and grade of recommendation

Intervention	BMD	Vertebral fracture	Femoral fracture
Exercise*	A	B or C	B
Calcium supplements (± vitamin D)	A	B or C	B or C*
Diet calcium	B or C	B or C	B or C
Smoking cessation	B or C	B or C	B or C
Decrease in alcohol consumption	D	D	B or C
Hip protectors	-	-	A

* One systematic revision suggests this efficacy, while some other systematic revisions state that there does not exist enough data to confirm it.

Table 6: Grade of recommendation for the different drugs in decrease of fracture risk:

Drug	Fracture		
	Vertebral fractures	Non-vertebral fractures	Femoral fractures
Calcium	A	B or C	B or C
Vitamin D	C	C	C
Calcium + Vitamin D	-	A*	A*
HRT	B	A	A¶
Raloxifene	A	NE	NE
Tibolone	-	-	-
Etidronate	A	NE	NE
Alendronate	A	A	A
Risedronate	A	A	A
Calcitonin	B	NE	NE
Flavonoids	-	-	-
Parathormone	A	A	A¶
Anabolic steroids	-	-	-

NE: non-efficacy demonstrated in CAAs that were not specifically devised for that type of fracture; * efficacious in institutionalized population with a deficit, associated with calcium; ¶ efficacy for non-vertebral fracture, including femur. These CAAs have nearly all been developed by adding calcium, and, in many cases, vitamin D.

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