OSTEOPOROSIS POST-MENOPÁUSICA, UNA REVISIÓN EXHAUSTIVA DE SU MANEJO ACTUAL.

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POST-MENOPAUSAL OSTEOPOROSIS, A COMPREHENSIVE REVIEW OF CURRENT MANAGEMENT

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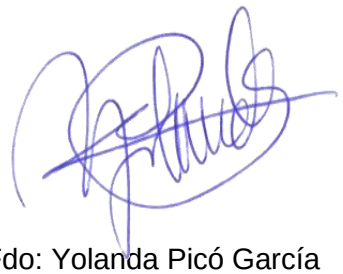
CERTIFICA QUE:

La licenciada, Soledad Herrero Rochina, ha estado trabajando bajo mi dirección durante más de 4 años en la elaboración de la tesis "OSTEOPOROSIS POST-MENOPÁUSICA, UNA REVISIÓN EXHAUSTIVA DE SU MANEJO ACTUAL" por lo que autoriza su presentación para optar al grado de Doctor por la Universitat de València.

Burjassot, 13 de Octubre de 2015



Fdo: Yolanda Picó García

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Post-menopausal osteoporotic women's treatments, what's new? How can we manage long-term treatments?

Can healthy life prevent us from post-menopausal osteoporosis? Myths and trues

LISTADO DE ABREVIATURAS

AE, Adverse Events, Eventos Adversos

AEMPS, Agencia Española del Medicamento y Productos Sanitarios

BILANZ , Comparison of the effect of an ongoing treatment with Alendronate or a drug holiday on the fracture risk in Osteoporotic patients with Bisphosphonate long term therapy, Estudio comparativo del efecto de la continuación con Alendronato o la realización de un descanso en el riesgo de fractura en pacientes osteoporóticos que ya están en tratamiento con Bifosfonatos durante largo plazo.

BMD, Bone Mass Density, Densidad Mineral Ósea

CI, Confidence Interval, Intervalo de Confianza

DE, Desviación Estándar

DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus alendronate; Estudio de eficacia para comparar el inicio de tratamiento con Denosumab versus Alendronato

DEFEND, DEnosumab FortifiEs boNe Density; Estudio para evaluar el incremento de densidad mineral ósea con Denosumab

DIVA-LTE, Dosing IntraVenous Administration Long Term Extension, Estudio de extensión a largo plazo de la dosificación intravenosa

DXA, Dual X-ray Absorciometry, Abosrciometría Dual de Rayos X

ELISA, enzyme-linked immunosorbent assay, ensayo por inmunoabsorción ligado a enzimas

EMA, European Medicine Agency, Agencia Europea del Medicamento

ESCEO, European Society for Clinical & Economic aspects of Osteoporosis and Osteoarthritis, Sociedad Europea de Aspectos Económicos y Clínicos relacionados con la Osteoporosis y la Osteoartritis

FDA, Food & Drugs Administration, Agencia Americana de Fármacos y Alimentos

FLEX, Fracture Intervention Trial Long-Term Extension, estudio de extensión en la intervención de fracturas a largo plazo

FRAX, Fracture Risk Algorithm, Algoritmo de Riesgo de Fractura

FREEDOM, Pivotal study for the Fracture REduction Evaluation of Denosumab in Osteoporosis; Estudio pivotal para evaluar la reducción de fractura producida por Denosumab para el tratamiento de la Osteoporosis

HORIZON PFT, Health Outcomes and Reduced Incidence with Zolendronic acid Once yearly Pivotal Fracture Trial, estudio de reducción de incidencia de fractura con Ácido Zolendrónico

HPLC, High-performance liquid chromatography, cromatografía líquida de alta eficacia

HR-pQ CT, TAC cuantitativo periférico de alta resolución

IOF, International Osteoporosis Foundation, Fundación Internacional de Osteoporosis

ISCD, International Society for Clinical Densitometry, Sociedad Internacional de Densitometría Clínica

MOBILE-LTE, Monthly Oral IBandronate in LadiEs Long Term Extension study, estudio de extensión en mujeres tratadas con Ibandronato oral mensualmente

NOF, National Osteoporosis Foundation, Fundación Nacional para la Osteoporosis

NOFSA, National Osteoporosis Foundation of South Africa, Fundación Nacional para la Osteoporosis en Sud África

ONJ, OsteoNecrosis of the Jaw, osteonecrosis mandibular

OPG, osteoprotegerina

PMO, Post-Menopausal Osteoporosis, Osteoporosis Post-Menopáusica

PMOW, Post-Menopausal Osteoporotic Women, Mujeres con Osteoporosis Post-Menopáusica

PMW, Post-Menopausal Women, Mujeres Post-Menopáusicas

PROOF, Prevent Recurrence of Osteoporotic Fractures Study; Estudio de prevención en la recurrencia de fracturas osteoporóticas.

PTH, Parathyroid Hormone, Hormona Paratiroidea

RANK, Receptor activador del factor nuclear-ĸB

RANK-L, ligando del receptor activador del factor nuclear-ĸB

SEIOMM, Sociedad Española de Investigación Ósea y del Metabolismo Mineral

SERM, Selective Estrogen Receptor Modulator, Moduladores Selectivos del Receptor de Estrógenos

TAC, Tomografía Axial Computerizada

UTE, Ultrashort-echo-time, resonancia magnética ultra rápida

VERT-MN, Vertebral Efficacy with Risedronate Therapy, estudio de eficacia vertebral con risendronato

WHO, World Health Organization, Organización Mundial de la Salud

OBJETIVOS

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La Osteoporosis es una enfermedad caracterizada por una baja densidad mineral y un deterioro de la micro-arquitectura ósea, lo que desencadena una fragilidad de la misma y una mayor probabilidad de tener una fractura. Se estima que unos 200 millones de personas la sufren actualmente, y que el 30-40% de las mujeres post-menopáusicas la padecen. Además, debido a que es una enfermedad en muchas ocasiones silente, un gran porcentaje de mujeres no están diagnosticadas.

El presente trabajo tiene como objetivo realizar una revisión sistemática y exhaustiva de la bibliografía publicada a nivel mundial sobre el diagnóstico y tratamiento de la osteoporosis post-menopaúsica, incluyendo medidas paliativas y así:

- Conocer cómo y cuándo se diagnostica la osteoporosis en las mujeres post-menopáusicas y las diferencias en función del país, y la efectividad de los distintos protocolos instaurados en cada país.

- Establecer la metodología que se utiliza en el diagnóstico de dicha enfermedad, como el análisis de factores de riesgo, determinación de parámetros de laboratorio o técnicas que se utilizan para la medición de la densidad mineral ósea, evaluando las ventajas y desventajas de cada una de ellas.

- Evaluar los tratamientos que pueden prescribirse para la osteoporosis post-menopáusica y revisar la problemática surgida con los tratamientos a largo plazo.

- Examinar los hallazgos más recientes y las últimas recomendaciones en relación al tratamiento de la osteoporosis, así como su instauración en la práctica clinica.

- Examinar la importancia de una vida sana con actividad física diaria así como la influencia de los suplementos nutricionales en la prevención de la osteoporosis. Para ello, se estudian los componentes naturales más utilizados en la prevención y/o como paliativos a la osteoporosis post-menopáusica y determinando las bases científicas que demuestran o no su efectividad.

INTRODUCCIÓN GENERAL

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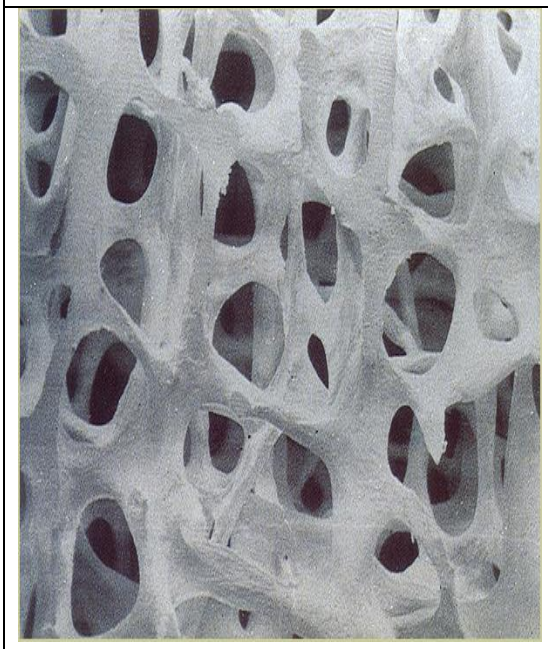
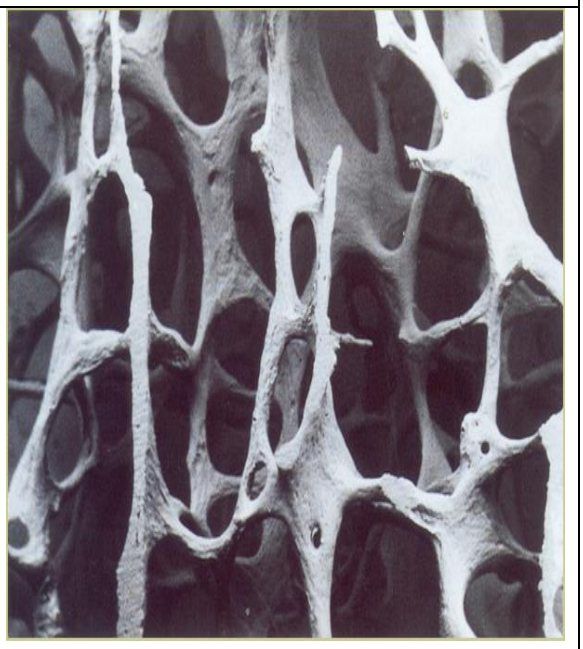
En 1994, la Organización Mundial de la Salud (WHO) definió la osteoporosis como aquella caracterizada por una baja masa ósea y un deterioro en la micro-arquitectura del tejido óseo, dando lugar a fragilidad ósea y a un incremento en el riesgo de fractura. [1]

Figura 1.

Arquitectura del hueso normal y osteoporótico. [1]

Hueso de persona sana	Hueso de persona osteoporótica
	

Entre la formación y la resorción ósea debe haber un equilibrio, hasta los 35 años aproximadamente la formación es superior a la resorción, alcanzándose entonces el pico máximo de masa ósea. Entre los 50 y 60 años, comienza a ganar terreno la resorción, acelerándose dicho desequilibrio en, el caso de las mujeres, en la menopausia, por la caída brusca de estrógenos y en el de los hombres si existe cáncer

de próstata, por la deprivación androgénica del tratamiento recibido. A partir de los 60 años se produce una pérdida rápida de masa ósea debida a la edad en ambos sexos.

EPIDEMIOLOGÍA DE LA ENFERMEDAD

La osteoporosis es una enfermedad que afecta a 200 millones de personas en el mundo, de hecho cada 3 segundos se produce una fractura como consecuencia de la osteoporosis [2]

El 20-25% de las mujeres mayores de 50 años tienen 1 ó más fracturas vertebrales [3], concretamente en Estados Unidos el 25% [4], en Australia el 20% [5], en Marruecos el 26% [6] en Europa Occidental un 19% y en el Norte de Europa un 26% [7]. En Sud-África no existen datos de fracturas, pero sí se sabe que la incidencia de la osteoporosis en mujeres blancas, asiáticas procedentes de India y de raza mixta es muy similar a la de países desarrollados [8] En Irán, 2 millones de personas están dentro del riesgo de fracturas según el Centro de Investigación en Endocrinología y Metabolismo (=Endocrinology and Metabolism Research Center (EMRC)). Sin embargo, en el resto de Oriente Medio no existen registros fiables de fracturas, en Arabia Saudí, la prevalencia de fracturas de cadera se considera inferior a la de otros países, sin embargo, en Kuwait la incidencia de las mismas se consideró superior a la de otros países asiáticos, pero comparable a la de Estados Unidos y Oeste de Europa. El Registro del Ministerio de Sanidad de Irán estima que anualmente se producen que aproximadamente 8000 fracturas de cadera [9].

Tabla 1:

Estimación del número total de fracturas osteoporóticas personas mayores de 50 años según las zonas del planeta. [1]

	Cadera	Columna	Húmero proximal	Antebrazo	% de todas las Fracturas Osteoporóticas
África	800	1200	600	1600	0,8
América	31100	21400	11100	24800	15,7
Sud-Este Asiático	22100	25300	12100	30600	17,4
Europa	62000	49000	25000	57400	34,8
Mediterráneo Oriental	3500	4300	2100	5300	2,9
Pacífico Occidental	43200	40500	19700	46400	28,6

La mortalidad asociada a la osteoporosis está directamente relacionada con la incidencia de fracturas, de aquí que un diagnóstico precoz y una buena prevención sean de vital importancia y en muchos casos, el cuidado que reciban las personas tras padecerlas, de hecho, por ejemplo, en el Líbano la probabilidad de fallecer tras una fractura de cadera tras el primer año es del 7%, pero se incrementa al 18% a los 5 años de haberla sufrido, estos porcentajes son inferiores a los de la población occidental, y la razón por la que se cree que ocurre es porque en el Líbano la familia asume la responsabilidad de cuidar de sus familiares en casa, sin embargo en muchas localizaciones occidentales, el cuidado lo realiza el equipo de Enfermería a domicilio, en muchos casos, escaso, especialmente por recortes presupuestarios en tiempos de crisis como el actual [9]. En general, hasta un 20% de las personas que sufren una fractura de cadera mueren durante el primer año y más del 50% nunca recuperan una

funcionalidad que les permita tener una vida independiente. La morbilidad y mortalidad de las fracturas vertebrales son muy similares a las descritas en las de cadera [8]

Pero la osteoporosis no sólo afecta a mujeres, los hombres también la padecen, de hecho se estima que 1 de cada 5, y 1 de cada 3 mujeres, tendrán una fractura relacionada con la osteoporosis a partir de los 50 años.

La incidencia de fracturas en la población aumenta paralela a la esperanza de vida de cada región [9], por ejemplo en Marruecos, en 1981 era de 59 años, en 2010 de 72 años y actualmente sigue incrementándose, con ello el número de fracturas, que en 2010 fueron diagnosticadas unas 3500 y se estima que para 2030 se duplique su cantidad [6] En Estados Unidos se estima que para dentro de 20 años, con el envejecimiento de la población, se duplique el número de mujeres post-menopáusicas y que con ello, se triplicará el número de fracturas osteoporóticas para 2040 [10]

Las fracturas más comunes ocurren en vertebras, fémur proximal, radio distal, y menormente en húmero, costillas y pelvis. [8]

El coste anual directo que supuso en 2010 la osteoporosis en Europa ascendió a 29 billones de euros en los cinco mayores países (Francia, Alemania, Italia, España e Inglaterra), sumando un total de 28,7 billones en los 27 países europeos.

En mujeres mayores de 45 años, las fracturas de cadera en Reino Unido, Europa y Estados Unidos, ocupan más camas de hospital que otras enfermedades comunes en la población femenina, como la diabetes, enfermedades cardiovasculares o cáncer de mama. [11]

Por esto, y cerca de convertirse en una de las enfermedades crónicas más relevantes del siglo XXI, la osteoporosis exige a los profesionales sanitarios mejoras sustanciales en la calidad asistencial a sus pacientes. Por ello, concienciar a la sociedad a través de medidas preventivas eficaces, fomentar la educación del paciente y su compromiso

con el control de la enfermedad, conocer las nuevas opciones terapéuticas y las intervenciones sanitarias más adecuadas, son los pilares para su tratamiento racional y eficaz.

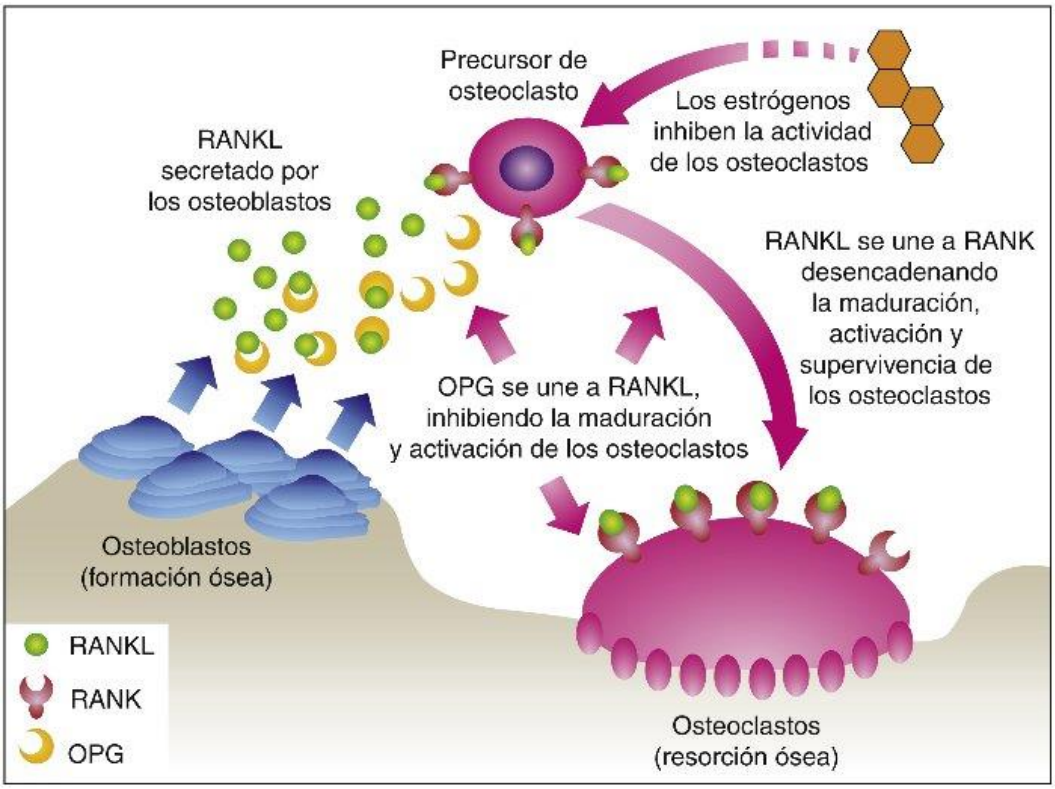
ETIOLOGÍA DE LA OSTEOPOROSIS:

El hueso está en constante remodelación, y en la misma están implicados los osteoblastos, o células formadoras de hueso y los osteoclastos, o células resortivas. Una desregularización en ambas puede producir osteopetrosis si se incrementa en exceso la formación u osteoporosis si es la destrucción la mayoritaria.

El número de osteoclastos activos viene determinado por el resultado neto de la diferenciación y fusión de los precursores, más la pérdida de osteoclastos por apoptosis. En muchos desórdenes, incluida la osteoporosis post-menopáusica, está incrementado el tamaño de osteoclastos activo, y con ello la resorción ósea y por lo tanto disminuida la formación.

Figura 2.

Unidad metabólica ósea [12]



Los osteoblastos producen la activación de señales como la Hormona del Crecimiento (GH), Interleukinas (IL-1, IL-6) y Hormona paratiroidea (PTH). Además estimulan la síntesis de Osteoprotegerina (OPG), la cual produce la inactivación del RANK

El factor estimulante de crecimiento de macrófagos (M-CSF) y el ligando del RANK (RANKL) son los principales mediadores del reclutamiento y diferenciación de osteoclastos.

Otras células implicadas en mantener el ambiente óseo son las células dendríticas con los linfocitos T y B. Concretamente las células T inhiben la diferenciación y acción de los osteoblastos, causando una apoptosis prematura de los mismos mediante activación y liberación de citoquinas como la IL-7

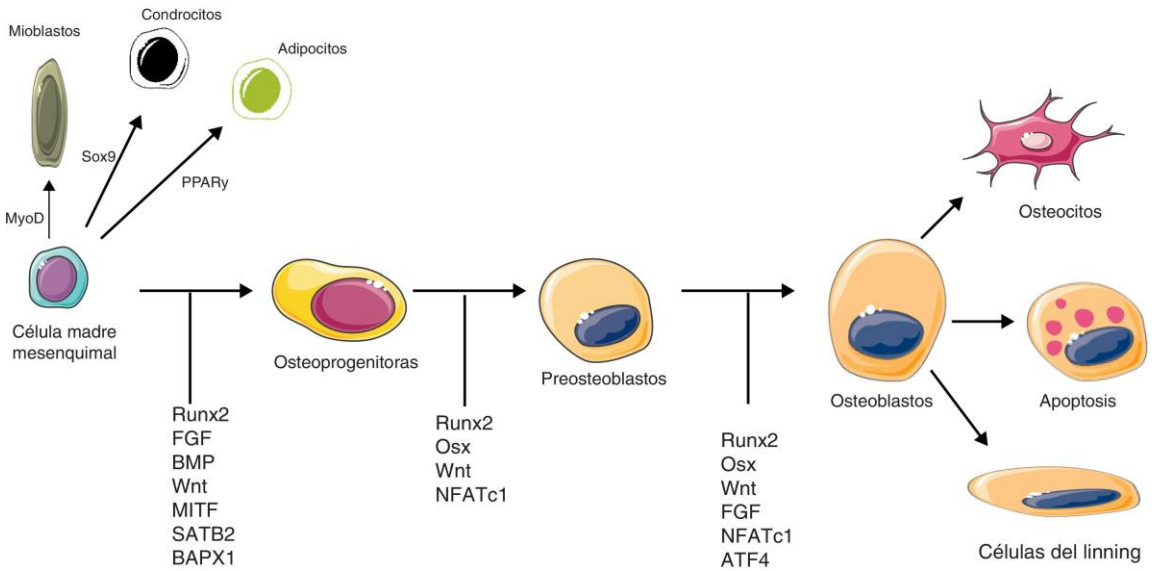
Los estrógenos afectan al remodelado óseo indirectamente mediante citokinas y factores de crecimiento locales

El déficit estrogénico (i) sensibiliza al hueso a la acción de la hormona paratiroidea, (ii) estimula la acción del RANKL e inhibe la OPG, produciéndose un mayor reclutamiento y actividad de osteoclastos (iii) los linfocitos T promueven el reclutamiento, diferenciación y supervivencia de osteoclastos vía IL-1, IL-6 y vía el factor de necrosis tumoral (TNF-alfa) (iiii) la unidad formadora de colonias de macrófagos se incrementan

Osteoblastos y osteoclastos provienen de diferentes linajes, los primeros derivan de las células madre mesenquimales y los osteoclastos de las células precursoras hematopoyéticas de monocitos-macrófagos [13]

Figura 3.

Diferenciación y nacimiento de osteoblastos [14]

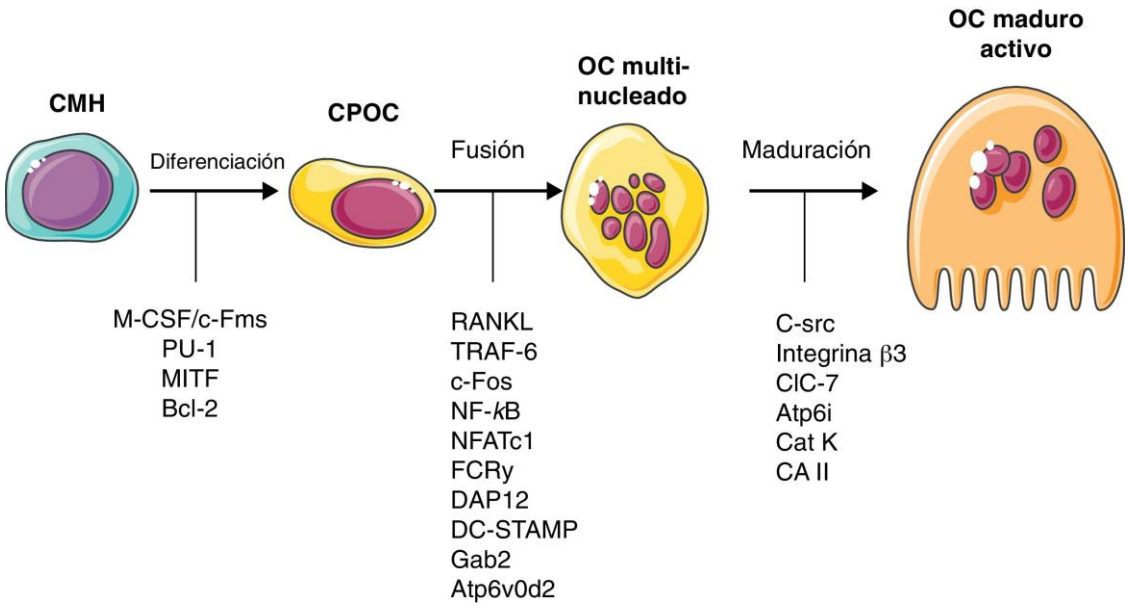


Runx2 es un marcador clave de osteoblastogénesis, aunque no es suficiente para que la célula progenitora se diferencie, también son necesarios FGF (factor de crecimiento

de fibroblastos), BMP (proteína morfogénica de hueso), MITF (factor de trasncripción asociado a la microftalmia), SATB2 (special AT-rich sequence-binding 2): Proteína de la matriz nuclear que estimula la osteoblastogénesis a través de Runx2), BAPX1 (bagpipe homeobox protein homologue 1): Factor de transcripción que estimula la osteoblastogénesis en esqueleto axial), Osx (osterix): Factor de transcripción principal que estimula la diferenciación osteoblástica, actuando en un nivel distal a Runx2), NFATc1 (factor nuclear activador de células T citoplasmáticas), ATF4 (factor de activación 4) y la vía Wnt (término proveniente de la unión del nombre del gen Wg (wingless) de la Drosophila y su homólogo Int (Integration 1) de los mamíferos. Es una familia de glucoproteínas que desencadenan cascadas de señal que intervienen en procesos clave del desarrollo embrionario y la regeneración tisular. La vía Wnt-_-catenina es la más conocida y desempeña un papel clave en el desarrollo y función osteoblástica.) [14]

Figura 4.

Diferenciación y nacimiento de osteoclastos [14]



Al igual que ocurre en la diferenciación osteoblástica, en la osteoclástica también intervienen diferentes moléculas para optimizar la cadena de maduración, entre ellas, el M-CSF (factor estimulante de colonias de macrófagos, implicado en los estadíos iniciales), el PU.1 (Factor de transcripción que regula la función de las células B), el MITF (factor de transcripción asociado a la microftalmia, que participa en estadíos iniciales), el Bcl-2 ((B-cell CLL/lymphoma 2): Molécula antiapoptótica por su acción inhibidora de la liberación de citocromo C mitocondrial, que promueve la diferenciación, activación y supervivencia de osteoclastos y osteoblastos), el RANK (receptor activador del factor nuclear B): Receptor de membrana de tipo I expresado en la superficie de los osteoclastos. Su ligando es RANKL) el TRAF6 (factor de necrosis tumoral asociado al factor 6, tiene una función crítica en la transducción de la señal intracelular de las IL-1R/TLR y TNFR), el c-Fos (Factor de transcripción implicado en la diferenciación osteoblástica), el NF-kB (factor nuclear), el NFATc1 (factor nuclear activador de células T), el FcRy ((receptores gamma para el Fc): Receptores que reconocen la porción Fc de la IgG y son importantes en la respuesta de los leucocitos a los inmunocomplejos, participando además en el desarrollo del linaje osteoclástico), el DAP12 ((DNAX-activating protein de 12 kDa): desempeña un papel esencial en la transducción de la señal RANK)), el DC-STAMP (célula dendrítica específica transmembrana que participa en la fusión osteoclástica), el Gab-2 (GRB2-associated binding protein 2): participa en la trasmisión intracelular de diversas señales en respuesta a estímulos procedentes de receptores de citocinas y factores de crecimiento), las Atp6v0d2 y Atp6i (Isoformas de la ATPasa vacuolar que forman parte de la bomba de protones permitiendo la acidificación de la laguna osteoclástica. Su disfunción puede provocar formas graves de osteopetrosis), las Integrinas (Moléculas expresadas en la membrana del osteoclasto y que facilitan su adhesión al tejido mineralizado, mediante su interacción con proteínas de la matriz ósea. La integrina a2ß 1se une al colágeno, mientras que la integrina avß3 lo hace con la vitronectina,

osteopontina y sialoproteína ósea), el ClC7 (canal de cloro 7, participa en el intercambio de cloro por protones, un proceso fundamental para la resorción osteoclástica) [14]

La resistencia ósea se mide en 2 componentes:

- Cantidad ósea: en la que influyen la masa, el tamaño y la densidad mineral ósea
- Calidad ósea: en la que están implicados la macroarquitectura ósea (o geometría ósea), la microarquitectura ósea (o conectividad trabecular), el remodelado óseo (formación más resorción) y las propiedades materiales (mineralización, microlesiones o microfracturas y puentes de colágeno) [16]

Existen dos tipos de estructuras óseas, el hueso cortical o denso, es el que está en la parte externa y confiere las propiedades mecánicas al hueso y el hueso trabecular o esponjoso, es la matriz del hueso. Ambos tienen una composición molecular muy parecida, pero difieren en su arquitectura. En adultos, aproximadamente, el 80% de los huesos es trabecular, mientras que tan sólo el 20% es hueso cortical. Con la edad, la capa cortical se hace más fina disminuyéndose la resistencia, fuerza y solidez del hueso. [13]

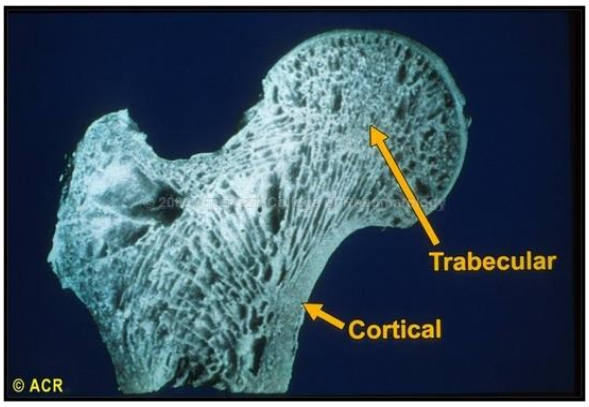
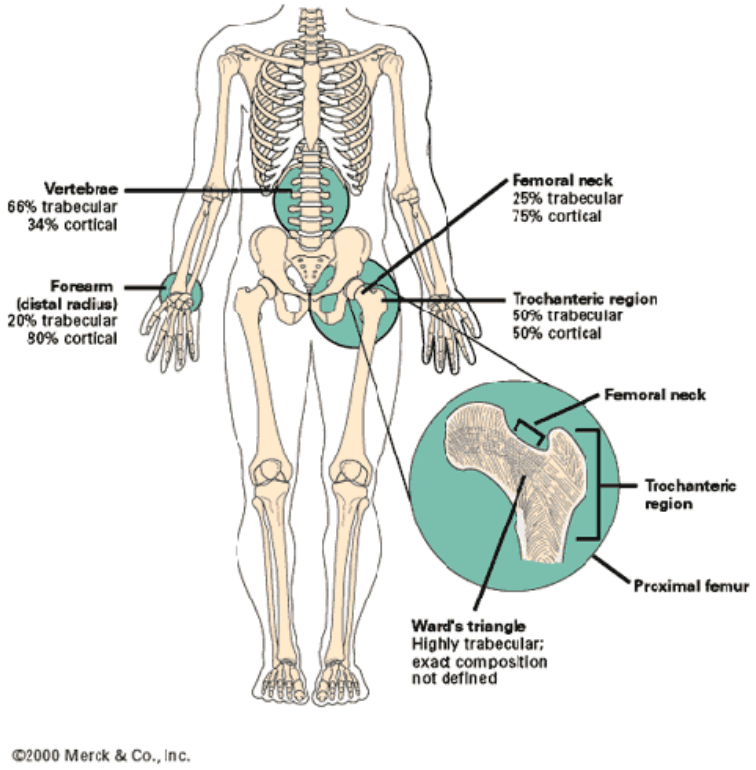


Figura 5.

Hueso cortical y trabecular. [15]

Figura 6.

Porcentajes de hueso cortical y trabecular en el cuerpo humano [17]



Entre los principales factores de riesgo asociados a un predominio de la actividad osteoclástica, y por lo tanto una mayor destrucción de hueso se encuentran:

- Edad: cada década de vida se incrementa un 1,4-1,8 el riesgo de padecer una fractura asociada a la osteoporosis post-menopáusica [17]
- Raza: las mujeres de raza blanca u oriental tienen mayores fracturas osteoporóticas que las de raza negra o polinesia [18] Tanto en Estados Unidos como en Sud-África, la osteoporosis en cadera es menos prevalente en las personas de raza negra, esto es debido en gran medida a que las mujeres blancas mostraron valores menores de DMO en cuello femoral [8]
- Bajo índice de masa corporal o baja actividad física, esto es debido a que los osteocitos, por ser receptores de presión, en estas condiciones no detectan suficiente gravedad, por lo que la resorción se ve incrementada respecto a la formación de hueso, por esto, se recomienda hacer ejercicio físico,

especialmente el relacionado con saltos, para ejercer mayor presión por golpeo. [20] La actividad física está íntimamente relacionada con la DMO, estudios epidemiológicos han concluido que si conseguimos aumentar un 10% el pico de masa ósea, es decir, la mayor cantidad de masa ósea que se alcanza al final de la etapa de crecimiento, entonces seremos capaces de disminuir el riesgo de fractura osteoporóticas post-menopáusica en un 50% [21-23]

- Antecedentes familiares directos de fractura de cadera, las mujeres con madres que han sufrido fractura de fémur tienen mayor probabilidad de padecer una fractura relacionada con la osteoporosis, de hecho entre un 60 y un 80% de variabilidad en el pico de masa ósea puede ser debido a factores genéticos [21]
- Fractura previa sin traumatismo severo, particularmente en la cadera, muñeca o columna, incluyendo las fracturas vertebrales en los adultos
- Tratamiento con Glucocorticoides (≥5 mg de Prednisona diarios o equivalentes durante 3 o más meses)
- Tabaco
- Alcohol, más de 3 unidades/día
- Causas de osteoporosis secundaria:
    - Artritis reumatoide
    - Hipogonadismo no tratado o nivel estrogénico bajo, como una menopausia prematura o menarquia tardía, una ooforectomía bilateral, anorexia nerviosa, quimioterapia para el tratamiento del cáncer de mama. Esto es debido a que una deficiencia de estrógenos provoca cambios tanto moleculares, porque desencadena un aumento del receptor RANKL en los osteoblastos, y por lo tanto una disminución de la OPG, resultando en un aumento en el reclutamiento de pre-

osteoclastos, así como en la actividad y vida media de los osteoclastos maduros. Además, en ausencia de estrógenos, las células T también

- promueven el reclutamiento, diferenciación y supervivencia de los osteoclastos vía IL-1, IL-6 y TNF-alfa.

Como cambios en la micro-arquitectura, ya que se disminuye el grosor y se incrementa la porosidad cortical, viéndose afectados también la arquitectura trabecular y consecuentemente la masa ósea.

- Déficit nutricional o inflamación intestinal, como enfermedad de Crohn o colitis ulcerosa. Calcio y vitamina D ayudan en el mantenimiento de la homeostasis ósea, cuando ingerimos o no asimilamos suficientes cantidades de calcio, se estimula la secreción de PTH, incrementándose la resorción ósea y disminuyéndose la excreción renal de calcio, esto se contrarresta con el incremento de la producción renal de 1,25-dihydroxyvitamin D (1,25[OH]2 D), la forma activa de vitamina D, la cual optimiza la absorción de calcio y fósforo, e inhibe la síntesis de PTH. Por tanto una ingestión adecuada de calcio y vitamina D son primordiales en la prevención de fracturas osteoporóticas.
- Anorexia, un estudio realizado en mujeres japonesas con anorexia nerviosa detectó que en dichas pacientes, la malnutrición había provocado una disminución en la formación ósea y una activación de la resorción ósea [24]
- Prolongación de la inmovilidad, como puede ocurrir tras daño en columna vertebral, enfermedad de Parkinson, ictus, distrofia muscular, espondilitis anquilosante
- Diabetes tipo 1 y 2
- Desórdenes tiroideos, como hipertiroidismo no tratado, o terapia hormonal supresora de la glándula tiroides

- Hiperparatiroidismo
- Enfermedad pulmonar obstructiva crónica [25]

DIAGNÓSTICO:

Por todo lo descrito, y porque la osteoporosis es una enfermedad silente que en numerosas ocasiones comienza a manifestarse cuando existe una fractura, un diagnóstico prematuro y acertado de la osteoporosis post-menopáusica es crucial para frenar en lo posible la enfermedad.

Siguiendo las recomendaciones de la WHO, un buen diagnóstico de la osteoporosis post-menopáusica debe realizarse entrevistándose con el paciente para determinar los factores de riesgo, determinando la DMO mediante DXA de columna lumbar, cadera total y antebrazo y adicionalmente es aconsejable el uso de la herramienta FRAX para determinar el riesgo de fractura en los próximos 10 años y así evaluar si la paciente necesita o no tratamiento. [26]

Junto a la determinación de los factores de riesgo y la medición de la DMO, es muy recomendable realizar una analítica de laboratorio que incluya los siguientes parámetros:

- Hematología, para descartar una anemia
- Bioquímica, para comprobar que los niveles de analitos son normales tal y como es esperado en la osteoporosis primaria
    - Una disfunción tiroidea ha estado asociado en ocasiones con osteoporosis
    - Una deficiencia en vitamina D puede ser un antecedente de osteoporosis, así como un déficit en calcio sérico

- Electroforesis de proteínas séricas para descartar un mieloma múltiple, el cual está estrechamente relacionado con la osteoporosis

- Creatinina y calcio en orina de 24 horas, puesto que una hipercalciuria en orina puede bien ser significativo de osteoporosis, o si esta va ligada a un déficit de vitamina D, quizá se trate de un síndrome de malabsorción [13]

Una vez asignado el tratamiento adecuado para cada paciente, es conveniente realizar test periódicos en orina y/o suero para determinar los niveles de biomarcadores de remodelado óseo y así conocer la efectividad del tratamiento elegido, pero también están resultando muy útiles para la medición de la velocidad de recambio óseo, ayudando algunos de ellos en la predicción del riesgo de fractura. [15]

En la tabla se enumeran los biomarcadores más utilizados en la determinación del recambio óseo, siendo los más específicos de formación ósea la fosfatasa alcalina, la osteocalcina y el propéptido N-terminal del procolágeno tipo I, mientras que los más sensibles y específicos de la resorción son los telopéptidos N- y C- terminal excretados por orina y el telopéptido C-terminal en suero [27, 28]

Tabla 2.

Biomarcadores óseos [27, 28]

BOMARCADORES DE FORMACIÓN ÓSEA	**BIOMARCADORES DE RESORCIÓN ÓSEA**
Productos procedentes de la síntesis del colágeno (determinación en suero): - Propéptido C-terminal del procolágeno tipo I (P1CP) - Propéptido N-terminal del procolágeno tipo I (P1NP)	Productos procedentes de la degradación del colágeno : - Hidroxiprolina (determinación en orina): - Piridinolina (determinación en suero y/u orina) - Deoxypiridinolina (determinación en suero y/u orina) (DPD)
Proteínas de matriz (determinación en suero): - Osteocalcina (ucOC)	Telopéptidos de colágeno tipo I (determinación en suero y/u orina): - Telopéptido N-terminal (NTX) - Telopéptido C-terminal (CTX) - Telopéptido C-terminal generado por poteinas de matriz - α-CrossLaps (α-CTX) (en suero) - β-CrossLaps (β-CTX) (en orina)
Enzimas osteoblásticas (determinación en suero): - Fosfatasa alcalina total (TAP) - Fosfatasa alcalina en hueso (BAP)	Enzimas osteoclásticas (determinación en suero): - Fosfatasa ácida tartrato-resistente (TRACP-5b) - Catepsina K

Los biomarcadores de formación ósea son productos de la actividad de los osteoblastos y son sub-productos de la síntesis de colágeno, proteínas de matriz y enzimas osteoblásticas. Los de resorción ósea son en su mayoría productos de degradación del colágeno tipo I y reflejan la actividad osteoclástica.

Un estudio realizado en 63 mujeres determinó incrementos en los niveles de DPD, Piridolina e Hidroxipiridolina del 40%, 61% y del 25% respectivamente en mujeres post-menopáusicas osteoporóticas respecto a mujeres post-menopáusicas sin osteoporosis, pero cuando se midió la osteocalcina, como indicador de formación ósea, también estaba ligeramente aumentado en las mujeres con osteoporosis (9,9 ng/ml versus 8,9 ng/ml), quizá justificable por el desajuste en el equilibrio formación-resorción ósea [29]. Otro estudio realizado en 587 mujeres, determinó mediante la técnica ELISA que los niveles de NTX variaban en función de si las mujeres tenían osteoporosis, osteopenia o no tenían enfermedad ósea, dichos valores fueron comparados con los obtenidos en las densitometrías realizadas a dichas pacientes. [30]

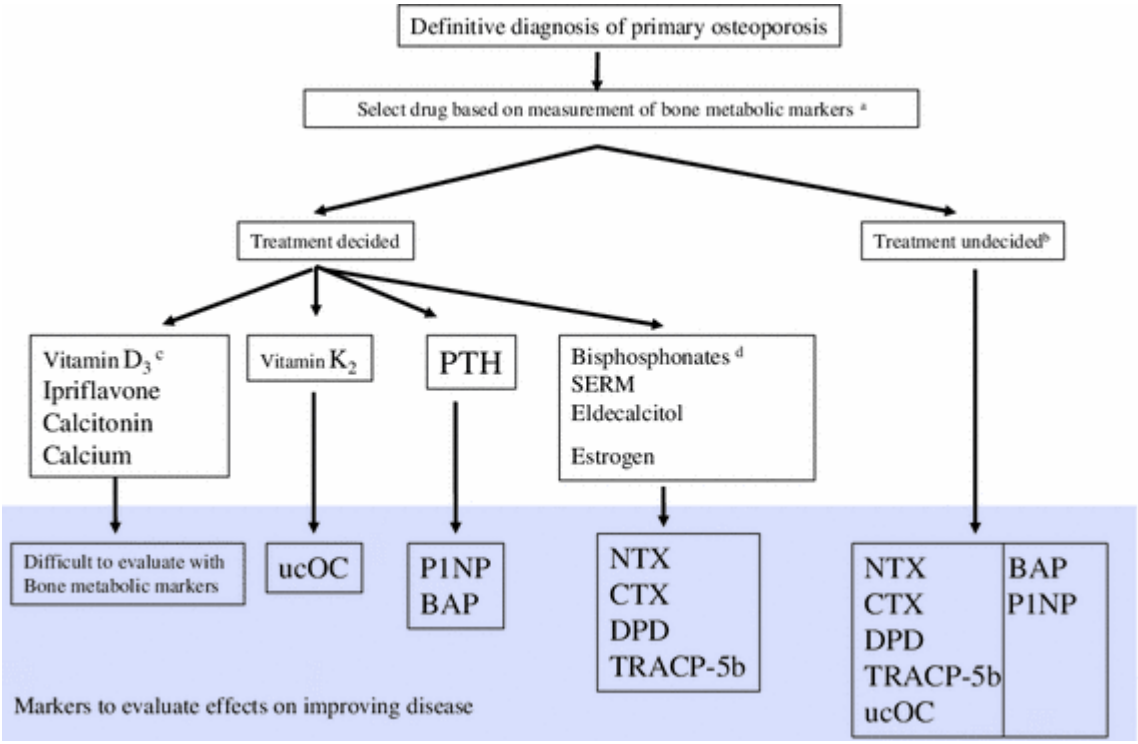
Respecto a la catepsina K, un estudio realizado en 21 mujeres post-menopáusicas osteoporóticas y 40 personas sanas, midió sus niveles usando un inmunoensayo enzimático específico (Biomédica, Viena), obteniéndose incrementos significativos en el primer grupo (11,3 pmol/l versus 3,1 pmol/l) [31]

Las DXA se planifican aproximadamente cada 2 años, tanto por el coste que supone un aumento de frecuencia, como para ver una evolución clara de la pérdida o ganancia de DMO, la ventaja de los biomarcadores es que no es necesario esperar este tiempo, lo que hace que estas mediciones tengan cada vez mayor interés, resultando imprescindible en ensayos clínicos y siendo altamente recomendable en la práctica clínica, tanto al inicio del tratamiento como en el seguimiento de la efectividad del mismo, aunque por el momento, es muy infrecuente su uso en la misma. [15]

Para cada tratamiento se recomienda la medición de determinados biomarcadores, por verse mayormente afectados sus niveles tras el inicio del mismo.

Tabla 3.

Algoritmo de decisión sobre qué marcadores determinar en función de los tratamientos osteoporóticos utilizados [32]



El uso de terapia antiresorptiva provoca una reducción de los niveles tanto de biomarcadores de resorción, en el plazo de 4 a 6 semanas, como los de formación ósea, en el plazo de 2 a 3 meses. [28]

En el caso del tratamiento con Bifosfonatos, se produce una disminución significativa de los niveles séricos de Catepsina K, produciéndose un cambio de hasta el 33% tras el mes del comienzo del tratamiento en mujeres post-menopáusicas osteoporóticas. [31]

Los telopéptidos se ven disminuidos entre el 50 y el 70% dentro de las 12 semanas de tratamiento, en orina el telopéptido N-terminal disminuye significativamente a las 8 semanas de tratamiento con Alendronato y un 20% de reducción se observa en los

niveles séricos de TRACP-5b. Y también se observaron disminuciones en los biomarcadores de formación ósea en respuesta al tratamiento de Bifosfonatos, por ejemplo, P1NP se redujo un 60% y la BAP en torno al 40%, siendo mayormente significativo en pacientes tratados con Alendronato que con Risendronato, a pesar de poseer eficacias similares en la reducción de fracturas.

El tratamiento con Raloxifeno (SERM) produjo disminuciones menores, quizá por tener menos acción anti-resorptiva que los Bifosfonatos. CTX disminuyó un 30-40%, TRACP-5b un 10%, P1NP un 30% y BAP entre un 15 y 20% [27, 28]

Respecto a las imágenes, existen diferentes técnicas que nos ayudan en la identificación de la osteoporosis, pero la única recomendada por la WHO para el diagnóstico de la misma es la **DXA** de cadera total, columna lumbar o antebrazo, zonas con mayor proporción de hueso trabecular versus cortical, en mujeres post-menopáusicas, en mujeres mayores de 65 años y en jóvenes o peri-menopáusicas que tengan factores de riesgo de fracturas de fragilidad [3]. Las densitometrías se introdujeron en la clínica habitual en 1987, miden la atenuación de los rayos X de 2 energías diferentes cuando pasan a través del cuerpo, midiendo la DMO en g/cm2. [1], siendo sus principales ventajas, la prácticamente nula exposición a radiación, el poco error (4-8%) y la gran precisión.

Figura 7.

Densitometría [33]

La osteoporosis se define como la DMO de la columna o la cadera 2,5 desviaciones estándar (DE) por debajo de la media de una población joven normal o como una fractura por fragilidad previa, con independencia de la DMO.

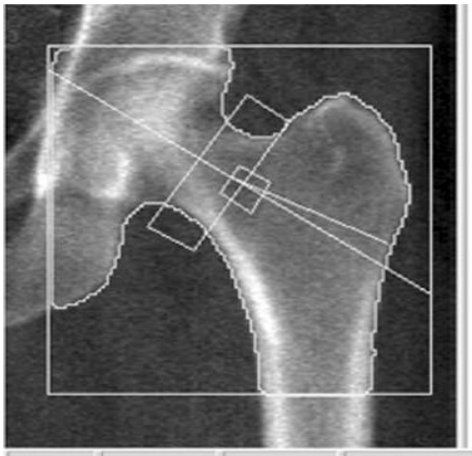
Las DE se miden mediante la puntuación T-score que compara los pacientes con los que están en su pico máximo de DMO:

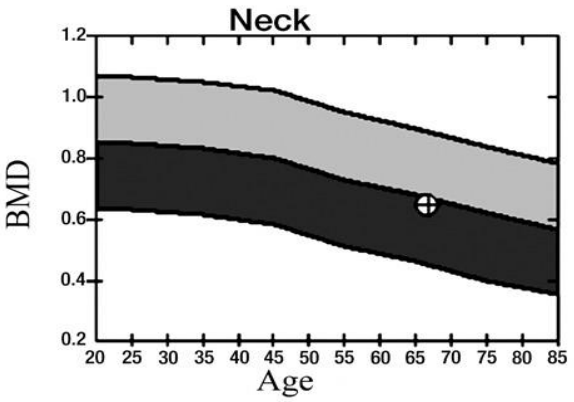
- WHO establece que 1 DE es un valor no patológico, que pertenece a personas jóvenes adultas
- T-score de –1 a –2.5 DE indica osteopenia
- T-score inferiores a –2.5 DE indica osteoporosis
- T-score inferiores a –2.5 DE junto a una fractura por fragilidad indica osteoporosis severa

Para mujeres pre-menopáusicas, hombres menores de 50 años y niños se utiliza el Z-score para ajustarlo a edad. [13]

Figura 8.

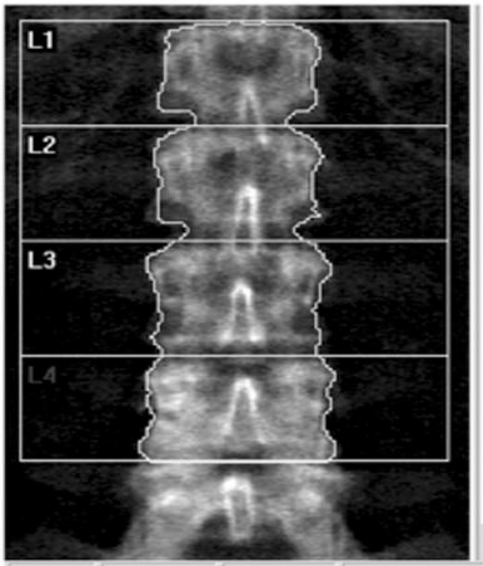
DXA de fémur proximal (imagen a) y de columna lumbar (imagen b) de una mujer de 66 años [34]

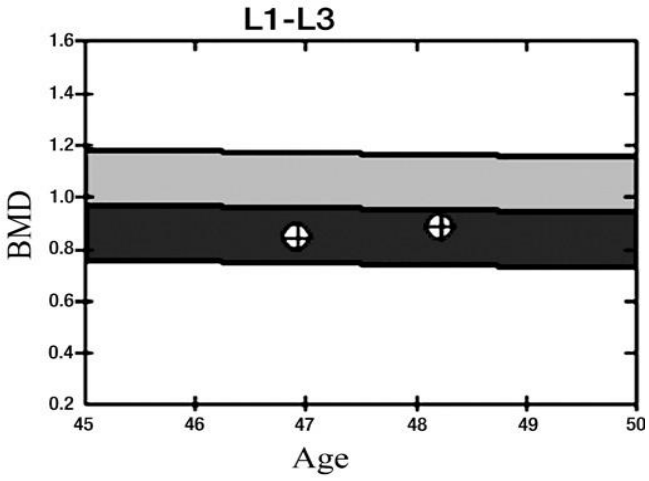




Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
Neck	**4.35**	**2.81**	**0.647**	**-1.8**	**76**	**-0.2**	**96**
Troch	12.91	6.58	0.510	-1.9	73	-0.8	87
Inter	19.28	18.29	0.949	-1.0	86	0.1	101
Total	36.54	27.69	0.758	-1.5	80	-0.2	97

a.





Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	12.10	9.51	0.786	-1.3	85	-0.7	91
L2	14.16	12.44	0.879	-1.4	85	-0.7	91
L3	15.77	15.27	0.968	-1.1	89	-0.4	96
Total	**42.03**	**37.22**	**0.886**	**-1.2**	**87**	**-0.6**	**93**

b.

Para la clasificación como persona con DMO normal, osteopénica u osteoporótica, la Sociedad Internacional de Densitometría Clínica recomienda utilizar el menor valor T-score del cuello femoral o el menor valor de cadera total, o cuando se mide la columna, como mínimo deben determinarse entre L1 y L4, como mínimo 2 vértebras deben ser medidas y deben incluirse las que difieran en más de 1,0 T-score respecto a la vértebra subyacente. [34]

Los principales inconvenientes cuando utilizamos DXA son:

- La incapacidad de distinguir entre hueso cortical y trabecular, al ser una técnica bi-dimensional, los huesos largos pueden dar falsos valores superiores de DMO respecto a los cortos
- Las áreas grasas pueden dar valores inferiores a los reales de DMO
- Mientras que los desórdenes degenerativos, calcificaciones vasculares, fracturas, deformidades o el uso de medios de contraste previamente pueden incrementar erróneamente los valores de DMO [8]

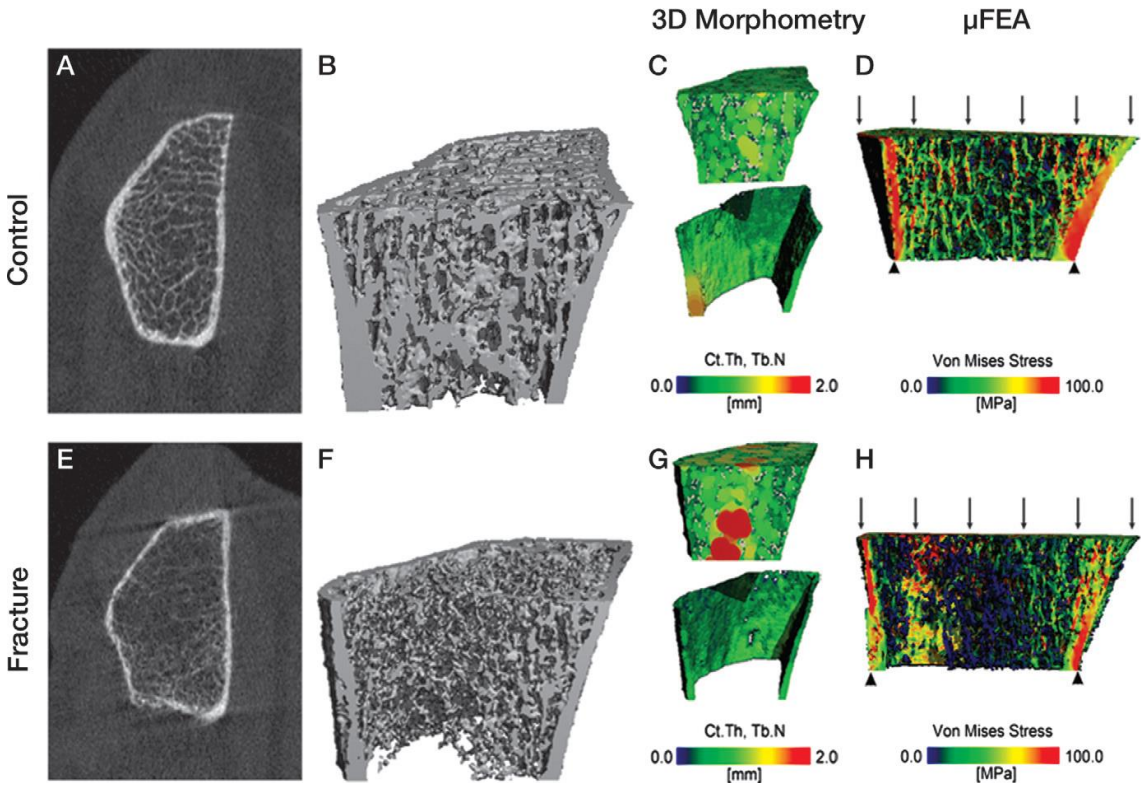
El **TAC** es una técnica con muy alta sensibilidad y que gracias a su lectura en 3 dimensiones proporciona valores volumétricos de DMO, pero debido a la gran radiación a la que están expuestos los pacientes, esta técnica se reserva exclusivamente al diagnóstico y seguimiento de enfermedades degenerativas en estado avanzado, también ha sido utilizado en pacientes con huesos especialmente cortos o largos o bien en pacientes obesos. [34]

El TAC cuantitativo periférico de alta resolución (HR-pQ CT) es mucho más rápido que el TAC convencional y emite menor radiación. Puede distinguir entre hueso

trabecular y cortical en 3 dimensiones, pero tan sólo de zonas periféricas, por lo que no pueden obtenerse imágenes de cadera ni columna.

Figura 9.

Imágenes realizadas con HR-pQ CT de radio distal en 2 mujeres post-menopáusicas de 63 y 68 años [34]



La primera imagen, control, muestra que una de las dos mujeres tiene los huesos sanos. La segunda imagen, fracture, es de la paciente con historia de fracturas de fragilidad en cadera. Las imágenes A y E son las capturas en 2 dimensiones del radio. Las imágenes B y F son en 3 dimensiones, en las 4 se observan claramente una disminución de la conectividad trabecular, así como un menor grosor del hueso cortical.

En las imágenes C y G se han separado hueso trabecular de cortical, Ct y Th determinan el grosor cortical, mientras que Tb.N mide las distancias intertrabeculares, mostrándose un cortex con mayor grosor y una parte trabecular más homogéneamente distribuido.
Las imágenes D y H simulan una carga compresiva del 1%, mostrándose una distribución más irregular de la misma en la mujer fracturada. [34]

Un nuevo TAC, el **Multidetector,** permite imágenes iguales a las obtenidas con el HR-pQ CT, pero además puede medir zonas centrales como cadera y columna, estudios han demostrado una mayor precisión que la DXA en la determinación de la DMO, pero el principal hándicap es la alta radiación que emite. [34]

La técnica de **Resonancia Magnética** ha sido mejorada en los últimos años para obtener mejores imágenes de la arquitectura trabecular, además con casi nula radiación emitida, el problema son los largos tiempos que se necesitan en cada evaluación y la facilidad con la que los artefactos volumétricos pueden alterar la calidad de la imagen. [34]

Se ha creado la **Resonancia Magnética ultrarápida (MR Ultrashort-echo-time (UTE),** la cual mide en microsegundos el contenido de agua en los tejidos ordenados, como es el caso del hueso cortical, para conocer la calidad de los mismos. [34]

La **Resonancia Magnética Espectroscópica de Protones** proporciona, además de la información cuantitativa del contenido en agua en los tejidos, también del contenido graso en la parte medular del hueso, siendo mayor dicha parte grasa en personas con osteoporosis. Se ha sugerido como técnica candidata en análisis rutinarios en la práctica clínica puesto que no es invasiva y muy fácil de utilizar. [35-37]

La detección de osteoporosis por **Ultrasonidos** se utiliza normalmente en centros de atención primaria midiendo la propagación de las ondas ultrasonidos a través del hueso calcáneo o de falanges, siendo más lenta en mujeres osteoporóticas. Tiene una precisión del 94,5% en la detección de fracturas por fragilidad y del 96,97% en la estimación del riesgo de fractura.

Es mucho más económico y rápido que la DXA, además es portátil y tampoco emite radiación alguna, pero la sensibilidad de la DXA es mucho mayor en el diagnóstico y monitorización de la respuesta a tratamientos. [8,34]

Las **radiografías** simples de columna siguen siendo las más utilizadas en la detección inicial de fracturas vertebrales, pero tan sólo se usa para esto en la osteoporosis post-menopáusica por la alta radiación que emite y el coste superior a la DXA. [8]

Recientemente se han evaluado un par de nuevas técnicas en mujeres post-menopáusicas, la que mide el **grosor del hueso cortical mandibular** y la que determina **el grosor del hueso cortical trabecular**.

La primera distinguió hueso de personas sanas, osteopénicas y osteoporóticas, pero con muy poca precisión entre las dos primeras, por lo que sólo resultaría útil para diferenciar mujeres sanas de osteoporóticas que tuvieran una radiografía panorámica bucal. [38]

El estudio que se realizó en la segunda se llevó a cabo en tan sólo 75 mujeres Árabes, resultando una muestra insuficiente para concluir resultados satisfactorios. [39]

En algunas pacientes que tienen fracturas de fragilidad se han obtenido DMO normales u osteopénicas, por esto, además de la imagen, la OMS recomienda determinar por la herramienta **FRAX** el riesgo de padecer una fractura osteoporótica de cadera, columna, antebrazo u hombro en los próximos 10 años.

Está alcance de cualquiera accediendo a la web: www.sheffield.ac.uk/FRAX/, en la misma nos pide que indiquemos la nacionalidad, puesto que está adaptada para personas Europeas, Asiáticas, del Medio Oeste, Africanas, Norte-Americanas y Latin-Americanas. A continuación debemos señalar los factores de riesgo que poseemos (historial conocido de fracturas, uso de tabaco y alcohol, consumo de glucocorticoides y padecimiento de artritis reumatoide). También se introduce la edad, el sexo, el peso, la altura y la DMO, si tenemos una DXA realizada.

Figura 10.

Página web de la herramienta FRAX [40]

Las principales limitaciones que posee, es que no tiene en consideración el nº de cigarrillos que se fuman diariamente, o la cantidad de alcohol que se consume, o el tiempo y la dosis de glucocorticoides tomados o el nº de fracturas previas. Todos estos factores no sólo se ven afectados por la existencia de los mismos, si no que también la

cantidad y el tiempo deberían ser factores determinantes en el cálculo de la mayor o menor probabilidad de padecer fracturas en un futuro. [34]

Tal y como se detalla en el primer artículo “Post-menopausal osteoporosis diagnosis around the world”, tras revisar las guías de actuación para el diagnóstico de la osteoporosis post-menopaúsica en los diferentes países, se ha llegado a la conclusión que todos aceptan las recomendaciones de la WHO, es decir, la utilización de la DXA como técnica de diagnóstico definitivo de la osteoporosis en mujeres post-menopáusicas. Pero las limitaciones para alcanzar las expectativas de un buen diagnóstico prematuro para evitar fracturas de fragilidad futuras, son fundamentalmente económicas, es decir, pocas instalaciones con DXA, distancia que tienen que recorrer los pacientes para realizarse una DXA, sistema de financiación de dichas imágenes por parte de los gobiernos y no menos importante, personal cualificado en los puntos de atención primaria que sepa realizar un buen cribado de las personas que necesitan o no la realización de una DXA.

TRATAMIENTOS FARMACOLÓGICOS:

El tratamiento de la osteoporosis post-menopáusica podríamos separarlo en dos grandes bloques:

- Los que poseen acción inhibidora de la resorción ósea, o catabólicos, entre los que se incluyen los Agonistas estrogénicos, los SERM (Bazedoxifeno y Raloxifeno), Bifosfonatos (Alendronato, Ibandronato, Risendronato y Ácido Zolendrónico), Denosumab y Odanacatib (no comercializado todavía)

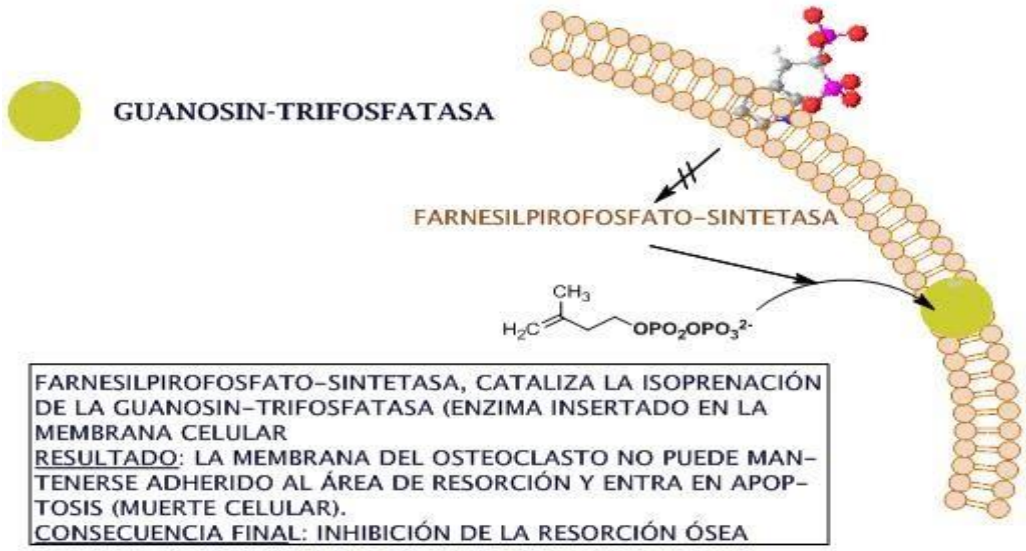
- Los que estimulan la formación ósea o anabólicos, y en este grupo encontramos a la Teriparatida , Ranelato de estroncio, y los nuevos fármacos, todavía en investigación, Romosozumab y Blosozumab

Los **Bifosfonatos** son, con diferencia, los fármacos con mayores prescripciones en el tratamiento de la osteoporosis post-menopáusica, los motivos son la gran eficacia en la reducción de fracturas, la seguridad, puesto que no provocan muchos eventos adversos y el bajo coste del tratamiento.

El mecanismo de acción de los mismos se basa en una inhibición de la enzima farnesyl pirofosfato sistasa, la cual está dentro del ciclo de la coenzima HMG-CoA reductasa. Esto conlleva a una reducción de la resorción ósea por pérdida de la función resorptiva osteoclástica y un incremento de la apoptosis osteoclástica.

Figura 11.

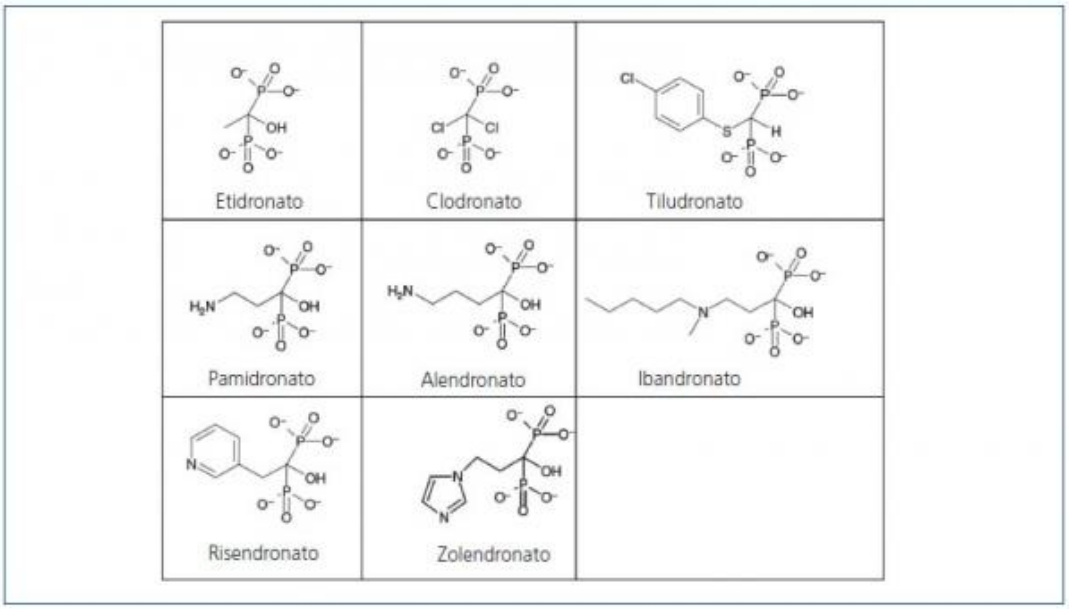
Mecanismo de acción de Bifosfonatos [41]



La afinidad y la potencia de acción de los diferentes Bifosfonatos (Zolendrónico > Alendronato > Ibandronato > Risedronato) es debida a los nitrógenos que contienen.

Figura 12.

Composición de los Bifosfonatos [42]



Los Bifosfonatos provocan una rápida disminución de los biomarcadores óseos, y tienen un efecto máximo a los 3-6 meses de tratamiento [43]

Pero se ha detectado que en los tratamientos a largo plazo con Bifosfonatos existe mayor incidencia de osteonecrosis mandibular y fracturas atípicas debido a la actividad resorptiva de los mismos, son eventos adversos muy poco frecuentes (aproximadamente 1/1000 mujeres post-menopáusicas pueden padecerlos), pero muy graves, por esto, la seguridad de los pacientes debe ser seguida estrechamente, la EMA recomienda que cada 5 años de tratamiento con Bifosfonatos los pacientes sean re-evaluados. [44-50]

Con toda esta información que se va recabando y tal y como se describe en el segundo artículo “Post-menopausal osteoporotic women’s treatments, what's new? How can we manage long-term treatments?, cada autor tiene su opinión que en

ocasiones discrepa de la formulada por la EMA, por ejemplo, el Dima et al. [51] propone que se prescriban Bifosfonatos a los pacientes con riesgo bajo de fractura durante 3-5 años, a los que tienen riesgo moderado durante 5-10 años y a los que tienen alto riesgo durante 10 años. Tras esto, sugiere discontinuar los tratamientos y re-establecerlos tan sólo si se produce una pérdida importante de DMO o una fractura. Durante el descanso de Bifosfonatos puede ser prescrito otro tratamiento aprobado para la osteoporosis post-menopáusica, y durante el mismo deben evaluarse periódicamente la DMO con DXA y los biomarcadores cada año para el tratamiento previo con Risendronato, cada 1-2 años para Alendronato, cada 2-3 años para Ácido Zolendrónico [52]

Bazedoxifeno y Raloxifeno pertenecen a los moduladores selectivos de receptores estrogénicos (SERMs), actuando como receptores agonistas o antagonistas, dependiendo del tipo de tejido, por ejemplo, Raloxifeno actúa como antagonista en útero y mama, y como agonista en hueso, produciendo una disminución en la resorción ósea y por lo tanto en los biomarcadores de remodelado óseo, alcanzándose niveles de los mismos comparables con los del periodo pre-menopáusico. [53-55]

La **Terapia Sustitutiva Hormonal (TSH),** es decir, los análogos estrogénicos se reservan exclusivamente a las mujeres que tengan un alto riesgo de fracturas y que no toleran otros tratamientos aprobados, esto es debido a los graves efectos adversos que provocan como acontecimientos trombo-embólicos, ictus, accidentes coronarios, complicaciones biliares, cáncer de mama o pulmón.[56]

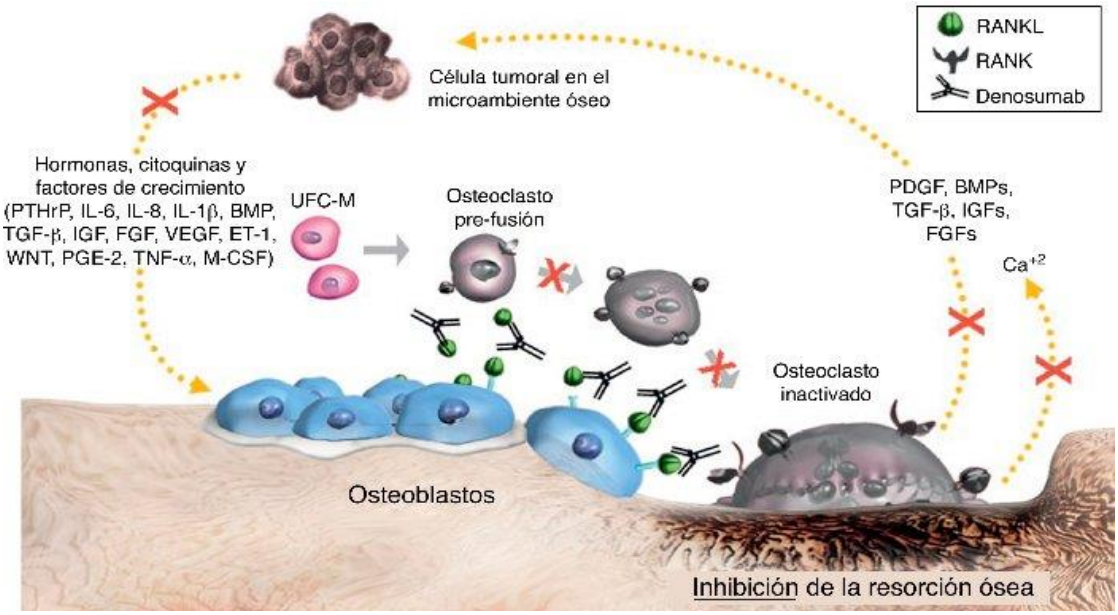
La **Calcitonina** también inhibe la acción osteoclástica, además de disminuir el calcio sanguíneo. Cuando existen altos niveles de calcio sanguíneo, se estimula la liberación de calcitonina, inhibiendo la liberación de calcio por parte del hueso, es decir,

paralizando la resorción. Es una hormona que se obtiene del salmón o recombinante humana, que . ha demostrado reducciones en fracturas vertebrales de un 33% cuando era administrada en dosis 200 IU/day durante 5 años, pero el problema es su acción carcinogénica a largo plazo, especialmente tumores de células basales. [57] Por esto, el 19 de Julio de 2012, la EMA desautorizó el uso de la Calcitonina para el tratamiento de la osteoporosis, y sólo aconseja su utilización en tratamientos cortos de la enfermedad de Paget, pérdidas agudas de hueso debido a inmovilizaciones repentinas o hipercalcemia de malignicidad.

Denosumab es un anticuerpo monoclonal totalmente humanizado con una gran afinidad por el RANKL, uniéndose al receptor humano y neutralizando su actividad, de forma similar a la OPG endógena, inhibiendo así la resorción ósea.

Figura 13.

Mecanismo de acción de Denosumab [58]



La eficacia de Denosumab reduce la incidencia de nuevas fracturas vertebrales, no vertebrales y de cadera en comparación con placebo [54, 59].

Comparado con los Bifosfonatos, ha demostrado ser superior a Alendronato en el porcentaje de DMO ganado de cadera tras un año de tratamiento (1,90% versus 1.05%) [54]

Otra ventaja con la que cuenta Denosumab reside en el cumplimiento en la terapia (auto-inyección subcutánea semestralmente en lugar de un comprimido por la mañana 30 minutos antes y después de ingerir cualquier alimento y permaneciendo también media hora derecho o sentado para evitar trastornos gastrointestinales superiores)
Denosumab es un fármaco relativamente novedoso, en 1995 se averiguó que la OPG era un importante regulador de la DMO, en 1997 se identificó y clonó el complejo del receptor RANK/RANKL, a mediados de 2001 ya se dio la primera dosis de Denosumab en humanos, es decir, primer ensayo clínico, en 2004 se realizó el primer estudio en mujeres post-menopáusicas, de 2006 a 2008 se realizaron estudios fase II y III, hasta que en 2010 se consiguió la aprobación en Europa con la indicación de osteoporosis en mujeres post-menopáusicas con aumento del riesgo de fracturas [53, 60]

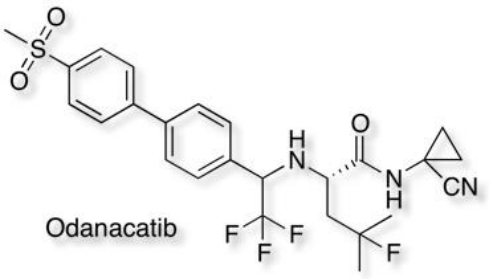
Al igual que en los Bifosfonatos, también se han notificado casos raros (igual o superior al 0,01% e inferior al 0,1%) de Osteonecrosis mandibular en pacientes tratados con Denosumab (60 mg cada 6 meses) para la osteoporosis. Y también se ha confirmado una fractura femoral atípica en ensayo clínico con denosumab. Como la experiencia con sujetos tratados con denosumab durante ≥ 6 años es limitada, un comité de adjudicación independiente se encarga de revisar todos los acontecimientos notificados como fracturas femorales atípicas.

Actualmente se está realizando un estudio para evaluar los efectos del tratamiento de Denosumab a largo plazo (7 años), del cual no se disponen datos por el momento

Una nueva vertiente en el área de búsqueda de terapias novedosas en el tratamiento de la osteoporosis post-menopáusica ha llevado a la síntesis de **Odanacatib.**

Figura 14

Odanacatib [61]



Odanacatib es un inhibidor potente, selectivo y reversible de la Catepsina K, proteasa cisteína que se encuentra predominantemente en osteoclastos adhiriéndose a los dominios de colágeno helicoidales. Su inhibición paraliza la resorción ósea, sin alterar otras funciones osteoclásticas, por lo que se espera que prevenga la pérdida ósea sin modificar la formación de hueso.

Odanacatib (Merck) es el único inhibidor de la catepsina K que a día de hoy sigue en investigación por sus buenos resultados en el tratamiento de la osteoporosis post-menopáusica en mujeres. [62]

Ranelato de Estroncio es un compuesto con dos átomos de estroncio no radiactivos y estables en un medio orgánico que es el ácido ranélico. El estroncio, al igual que el calcio y el magnesio, es un catón divalente que puede unirse a proteínas del plasma, además, al igual que el sodio y el plomo, puede sustituir al calcio en la hidroxiapatita del hueso.

Tiene un modo de acción mixto, por un lado actúa como precursor de la replicación de osteoblastos y estimula la síntesis de colágeno, y por otro disminuye la diferenciación de osteoclastos y la actividad resortiva. Esto produce un aumento del grosor del hueso cortical y del número de conectividades trabeculares, sin modificar la porosidad cortical.

La estimulación de osteoblastos se debe a la activación del receptor sensible de calcio (CaSR= calcium-sensing receptor), el cual es una proteína sensible a los niveles extracelulares de calcio, además el Ranelato de Estroncio produce una estimulación tanto a nivel de la replicación de células osteoprogenitoras como en la diferenciación de precursores osteoblásticos a osteoblastos maduros.

Su acción inhibidora de la resorción ósea se debe a su capacidad de incrementar los niveles de osteoprotegerina y disminuir los de RANKL

Ranelato de Estroncio (2 gramos vía oral diariamente) produce una reducción del riesgo de padecer fracturas vertebrales, de no-vertebrales y de cadera.

Pero el principal inconveniente de su uso son sus potenciales efectos secundarios como cardiopatía isquémica, enfermedad arterial periférica e hipertensión. [63]

Respecto a los fármacos que estimulan la formación ósea, **Teriparatida** es el primero que se comercializó para el tratamiento de la osteoporosis post-menopáusica en mujeres con alto riesgo de padecer una fractura. Teriparatida es una fracción de la hormona paratiroidea humana, por lo que estimula la formación de hueso mediante el incremento de la absorción intestinal de Calcio y la reabsorción tubular del mismo a nivel renal

Ha demostrado efectividad en la prevención de fracturas vertebrales y no vertebrales, pero no sobre las de cadera

Pero el principal problema de su uso, es que no se aconseja el administrarlo (1 inyección subcutánea diaria) durante más de 24 meses por carecer de datos de seguridad del tratamiento a largo plazo. [64]

Dentro del campo de estimulación de la osteoblastogénesis, actualmente la investigación está dirigida en fármacos inhibidores de la Esclerostina, son **Romosozumab** producido por Amgen Ilt y **Blosozumab,** producido por Eli Lilly,

ambos son anticuerpos monoclonales que están demostrando eficacia en la formación de hueso en los ensayos clínicos fase II y III

La esclerostina es una gluco-proteína codificada por el gen SOST en osteocitos (osteoblastos embebidos en la matriz ósea), dicho gen se encuentra mutado en algunas familias con huesos especialmente densos y fuertes. La esclerostina bloquea la ruta de señalización celular Wnt/ β-catenina, produciendo así, una inhibición de la osteoblastogénesis y una activación de la apoptosis de osteoblastos.

Romosozumab es un anicuerpo monoclonal humanizado que se une a la esclerostina específica del hueso inhibiendo así su acción. Romosozumab está actualmente en fase III de investigación clínica para el tratamiento de osteoporosis post-menopáusica en mujeres con baja DMO y por lo tanto alto riesgo de fracturas
Blosozumab también es un anticuerpo anti-esclerostina, que ha demostrado cambios de DMO tras 1 año de tratamiento en columna lumbar, cadera total y cuello femoral. [65-67]

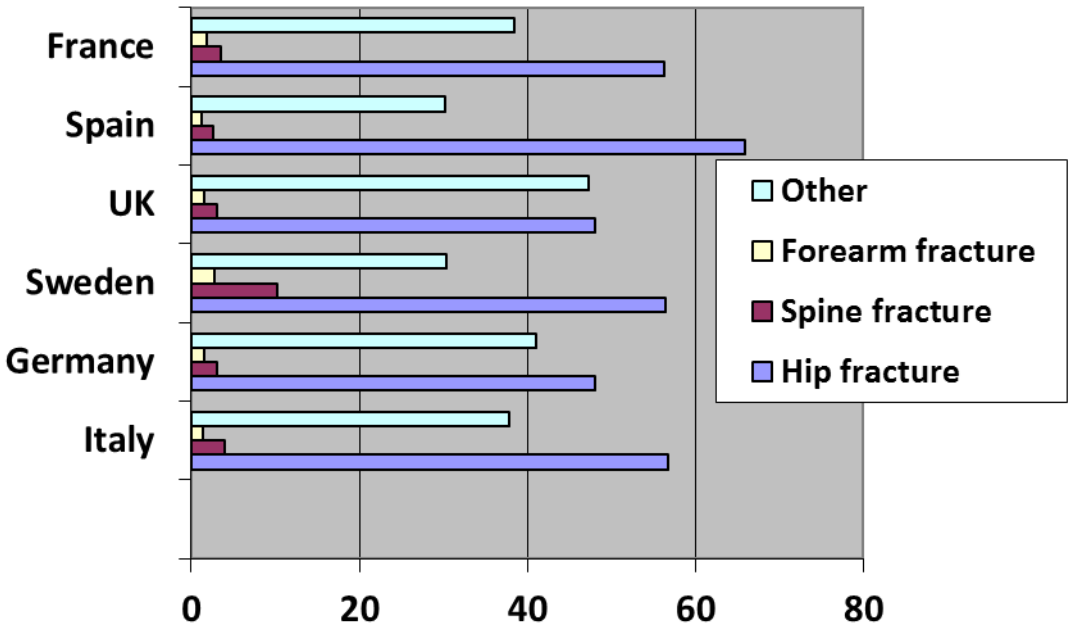
Tal y como se describe en el segundo artículo “Post-menopausal osteoporotic women’s treatments, what's new? How can we manage long-term treatments?, existen guías, las cuales difieren ligeramente entre países, para ayudar en la elección del tratamiento osteoporótico y cuándo comenzarlo, aunque todas ellas coinciden en que una fractura previa es suficiente factor de riesgo para comenzar el tratamiento osteoporótico en mujeres post-menopáusicas y todas ellas siguen la recomendación de la WHO, en la que indica que el T-score y la DMO se deben medir mediante DXA en cuello femoral, cadera total o columna lumbar. [68, 69]

Otro factor que no recogen las guías, pero que sí influencia en la prescripción de cada fármaco es el coste del tratamiento.

Como se puede ver en la tabla 4, dentro de Europa, España invierte más dinero en salud debido a las fracturas de caderas que Italia, Francia, Inglaterra o Suecia. Sin embargo, este último es el país que más invierte en fracturas de columna.

Tabla 4

Presupuesto (en millones de euro) invertido en fracturas osteoporóticas dentro de la Unión Europea en 2010 [70]



Tal y como se refleja en la tabla 5, que incluye el coste de fracturas más tratamientos en Europa, es Alemania el país que destina mayor presupuesto a las intervenciones y tratamientos de las fracturas osteoporóticas en mujeres post-menopáusicas y Suecia el que menos.

En el año 2000, en Europa se invirtieron aproximadamente 36 billones de euros en fracturas relacionadas con la osteoporosis, pero este gasto se vio incrementado a 77,7 billones de euros en 2010 debido a un mayor número de fracturas sucedidas ese año, quizá porque la población va envejeciendo paulatinamente. [71]

Tabla 5:

Costes de las fractura en la Unión Europea [70]

País	Coste de fracturas recientes	Coste de fracturas prevalentes	Coste del tratamiento+ administración del tratamiento	Total
Suecia	863	528	27	1,418
España	1401	1043	420	2,864
Francia	3266	1152	327	4,744
Inglaterra	4078	1315	121	5,515
Italia	4275	2386	348	7,010
Alemania	6854	2057	235	9,146

En las tablas 6 y 7 se muestra el precio de los fármacos aprobados en España para la osteoporosis. PTH y Teriparatida son los tratamientos más costosos, seguidos por la Calcitonina, Ranelato de Estroncio y Denosumab. Los Bifosfonatos son los más económicos y dentro de estos, es el Alendronato el más barato. [72]

Pero si se analiza el coste teniendo en cuenta el precio del tratamiento, la efectividad del mismo y el cumplimiento, los Bifosfonatos muestran una buena relación coste/efectividad en el tratamiento de mujeres osteoporóticas con alto riesgo de fractura, siendo Alendronato el de primera línea debido a su gran efectividad tanto en fractura vertebral como en fractura de cadera, además de su precio reducido. Risendronato podría ser una alternativa a Alendronato puesto que ya tiene comercializado su genérico.

Denosumab es una buena elección como segunda línea tras terapia con Alendronato o Risendronato.

Pero en pacientes con mal cumplimiento en el tratamiento con Bifosfonatos, el uso de Denosumab es la mejor opción puesto que resulta más económico a largo plazo. [73]

Tabla 6.

Coste (en euros) anual de los tratamientos de la osteoporosis post-menopáusica en España, actualizado en Octubre 2011 [72]

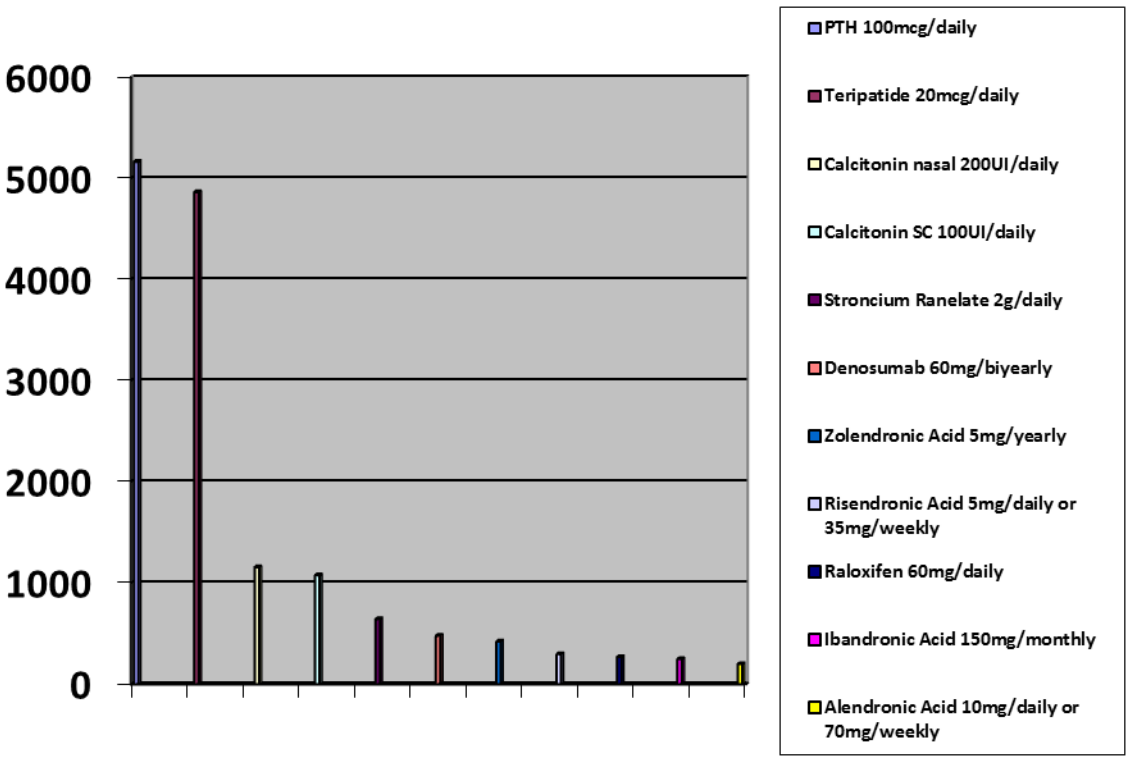


Tabla 7

Precio de los tratamientos osteoporóticos comercializados en España para el tratamiento de la osteoporosis post-menopáusica (Nov2012) [73]

Fármaco	¿Genérico disponible?	Precio por unidad (caja) (€)	Precio por dosis (€)
Alendronic Acid	Yes	12,49	0,45
Alendronic Acid plus vit D	No	28,01	1
Ibandronato	Yes	20,79	0,69
Risendronato	Yes	23,65	0,79
Ácido Zolendronico	No	417,40	1,17
Denosumab	No	240,15	1,32
Raloxifeno	Yes	20,64	0,74
Ranelate de Estroncio	No	49,39	1,76
Teriparatida	No	405,38	14,48

TRATAMIENTOS ALTERNATIVOS:

Debido a los efectos adversos potenciales que provocan los tratamientos farmacológicos y por no obtenerse en ocasiones los resultados esperados con los mismos, muchas personas optan por suplementarlos o por suplantarlos con terapias alternativas.

Dichas terapias se basan en las propiedades de los componentes de alimentos como:

- Los licopenos de tomates y zanahorias [74] y la vitamina C de cítricos como la naranja [75], los cuales han cobrado interés por su efecto antioxidativo asociado a una mejor salud ósea
- Las isoflavonas de proteínas de soja, por su similitud en componentes a los estrógenos [76]
- La Herperidina de cítricos como la naranja [77]
- El Ajo y la Cebolla [78, 79]
- El Colágeno [80]
- El aceite de oliva, también ha sido estudiado como preventivo de fracturas de fragilidad basándose en que en la región mediterránea existe una menor incidencia de la osteoporosis post-menopáusica. [81]
- Las Ciruelas [82]
- Los Polifenoles del Te verde [83]

La ventaja es la descrita arriba, es decir, no provocan apenas efectos adversos, los inconvenientes es que ninguno de ellos ha demostrado eficacia suficiente en la reducción del riesgo de fracturas osteoporóticas.

Los únicos que no sólo son aconsejables, si no que también altamente recomendados especialmente como tratamiento concomitante en el caso de recibir terapia resortiva, debido a que estos tienen alto riesgo de producir hipocalcemia, son los suplementos de Calcio y Vitamina D que La guía Europea para el diagnóstico y manejo de la osteoporosis recomienda que las mujeres post-menopáusicas ingieran al día como mínimo 1000 mg de calcio y 800 UI de vitamina D. [84]

METODOLOGÍA

METODOLOGÍA

Para conocer la última información publicada se ha realizado diferentes tipos de búsquedas:

- En PubMed, utilizando palabras clave como:

    - ***"Osteoporosis post-menopáusica"***, "***tratamientos a largo plazo"***, "***Bifosfonatos"***, "***Denosumab"***, "***Romosozumab"*** y "***Catepsina K ("Post-menopausal osteoporosis", "long-term treatments", Bisphosphonates", "Denosumab", "Romosozumab", "Cathepsin K")*** para acceder a publicaciones realizadas en revistas como Bone, Journal of Bone and Mineral Metabolism, Therapeutic Advances in Musculoskeletal Disease, Current Medical Research and Opinion, The American Journal of Medicine , Clinical Orthopaedics and Related Research, The New England Journal of Medicine, Arthritis & Rheumatology, Treatments in Endocrinology, Osteoporosis International, etc y poder conocer qué tratamientos son los que se están utilizando en el tratamiento de la osteoporosis post-menopáusica

    - ***"Osteoporosis post-menopáusica", "Densidad mineral ósea", "Ensayos clínicos", "Dieta", "Actividad" ("Post-menopausal Osteoporosis", "Bone mass density", "Clinical Trials", "Dietary", "Activity")***, y se accedieron a revistas científicas como British Journal of Clinical Pharmacology, Nutrients, the National Institutes of Health, the Journal of Nutrition, the Ontario Health Technology Assessment Series, Preventive Medicine and Nutrition, Metabolism and Cardiovascular Disease both from Elsevier, the Spanish Public Health Journal, etc para

estudiar las diferentes alternativas terapéuticas usadas en la prevención y/o tratamiento de la osteoporosis

- ***"Osteoporosis Post-menopáusica", "Europa", "Oceanía", "América", "África" y "Asia" ("Post-menopausal osteoporosis", "Europe", "Oceania", "America", "Africa" "Asia")*** se consiguió acceder a diferentes publicaciones científicas, incluidas entre estas guías de procedimiento para el diagnóstico de la osteoporosis menopáusica y para conocer las diferentes técnicas diagnósticas.

- En las páginas web de las Compañías Farmacéuticas como Amgen, Pzifer, Lilly, Merck y en la página www.clinicaltrials.gov se han buscado las moléculas que actualmente están en investigación y en qué fase de la misma. También los estudios que se están realizando para averiguar la seguridad, eficacia y tolerabilidad de los fármacos ya comercializados en el tratamiento a largo plazo para la osteoporosis post-menopáusica

- En las páginas web oficiales de la Agencia Española del Medicamento y Productos Sanitarios (AEMPS), Agencia Europea del Medicamento (EMA) y Agencia Americana de Alimentos y Fármacos (FDA) se han buscado las fichas técnicas de fármacos comercializados y usados para el tratamiento de la osteoporosis post-menopáusica, para conocer la fecha de aprobado por dichas instituciones, las indicaciones para las que han sido aprobados y las reacciones adversas notificadas hasta el momento, también se chequearon las alertas de retirada de indicaciones terapéuticas para determinados fármacos.

- la página web de la Organización mundial de la salud (WHO)se ha visitado para conocer los datos epidemiológicos de prevalencia, problemática global y mortalidad asociada a la osteoporosis post-menopáusica

- En la Sociedad Europea de Aspectos Económicos y Clínicos relacionados con la Osteoporosis y la Osteoartritis (ESCEO), la Sociedad Española de Investigación Ósea y del Metabolismo Mineral (SEIOMM), “National Osteoporosis Foundation”, y en la “International Osteoporosis Foundation” se buscaron las guías estandarizadas que deben ser utilizadas para la prescripción de tratamientos para la osteoporosis post-menopáusica

- Las guías institucionales de diferentes países de los 5 continentes, África, Europa, América, Oceanía y Asia se descargaron para conocer cuáles son las instrucciones que se dan en cada zona a los profesionales sanitarios para realizar un diagnóstico temprano de la osteoporosis post-menopáusica en mujeres. Dichas guías fueron localizadas en páginas web como:

    - África: http://www.iofbonehealth.org
    - Asia: http://www.iofbonehealth.org
    - Europa: http://www.esceo.org
    - América: http://nof.org.
    - Oceanía: http://www.osteoporosis.org.

RESULTADOS Y DESARROLLO ARGUMENTAL

Post-menopausal osteoporosis diagnosis around the world

Post-menopausal osteoporosis diagnosis around the world

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INTRODUCTION:

Osteoporosis develops low bone mass density (BMD) and micro-architecture bone deterioration that leads to high fracture risk. Approximately the 60% of vertebral fractures are asymptomatic, and the existence of one after the age of 50 increases the risk of having a new one on a 5-fold average. For these reasons, an early Osteoporosis diagnosis is crucial to reduce future fractures [85].

First, an interview with the patient is useful to identify the fracture risk factors, as advanced age, early menopause in women or men with low testosterone levels, 1 or more previous fragility fractures (non-traumatic bone fracture), corticosteroid's treatment, malabsorption illness, rheumatoid arthritis, hyper or hypo thyroidism or parathyroidism as well as kidney or liver disease. Laboratory tests, as Calcium, vitamin D or parathyroid hormone (PTH), to disregard other metabolic disorders or malignant illness also contribute important information. Furthermore, image techniques to identify fractures and to measure the bone mass density (BMD) are required. There are different image techniques, such as Dual X-ray Absorptiometry (DXA), X-ray, central quantitative Computed Tomography (CT), High-Resolution Peripheral Quantitative CT (HR-pQ CT), Multidetector CT, Magnetic Resonance (MR), MR Ultrashort-echo-time (UTE), Proton MR spectroscopy and Quantitative Ultrasounds (QUS). However, the World Health Organization (WHO) only recommend DXA for women aged 65 years and older, as well as in younger and peri-menopausal women with risk factors for fragility fractures. The mainly reasons for its election is that it is accurate, precise, safe, quick and easy to use.

Because osteoporosis in post-menopausal women (PMW) is closely related to the life expectancy, its early diagnostic is taking a special importance in developing countries [86]. Guidelines from South Africa, Morocco, Europe, Latin America, USA,

Australia, etc, have been reviewed to know how osteoporosis diagnosis is being managed in post-menopausal women around the world.

MATERIAL AND METHODS:

A literature searching in PubMed using the keywords “Post-menopausal Osteoporosis”, “Diagnostic”, “America”, “Asia”, “Europe”, “Africa” and “Oceania” was performed in order to know how it is being diagnosed women with post-menopausal osteoporosis around the world

OBJECTIVES:

How it is being managed the diagnosis of osteoporosis in post-menopausal women around the world has been the main objective to start this review. Because the high morbidity of this illness and because the effectiveness of the treatments already approved, an early diagnosed is a key point to avoid future fractures, and therefore to improve quality of life of patients and their surveillance.

RESULTS:

1. DIAGNOSTIC TECHNIQUES:

There are different techniques that help us in the Osteoporosis identification. The most important is the central DXA because is the only technique recommended by the WHO for osteoporosis diagnosis at hip (femoral neck or total hip) and lumbar spine or forearm in PMW or old men (50 years or older). DXA is indicated in women aged 65 years and older, as well as in younger and peri-menopausal women with risk factors for fragility fractures [87]

DXA was introduced for clinical routine in 1987 [3]. It computes the bone mineral content (BMC) in grams and the bone mineral density (BMD) in g/cm^2, of both, bone and soft tissue mass, because DXA measures the attenuation of X-rays of 2 different photon energies passing through the body. [85]

T-score is the standard deviation of the BMD of an individual patient compared to a young, healthy reference population, matched for sex and ethnicity. A T-score of -2.5 or lower standard deviation is diagnosed as osteoporosis, whilst a T-score between -1 and -2,4 as an osteopenia [87].

The International Society for Clinical Densitometry (ISCD) recommends using the lowest femoral neck or the lowest total neck when hip is measured in the osteoporosis diagnosis. Regarding spine, at least L1 to L4 must be measured, at least 2 vertebra should be measured and it should be excluded any vertebra that differs more than 1.0 T-score from an adjacent vertebra.

Because the rate of bone loss in PMW is between 1% and 2%, a DXA should be done at least each 2 years. The main advantages of DXA are accurately, only 4-8% of error, precisely, 1-3%, and safety, because the radiation exposure is close to zero. Also DXA is ease to use and it has shortly measurement times.

However, some disadvantages of DXA are that it cannot distinguish between cortical and trabecular bone, because DXA is a 2-dimensional technique, large bones could have higher BMD values than smaller ones, even though there are no differences between both. [85]

The fat in the lumbar region can underestimate the BMD, in contrast to degenerative disorders, vascular calcifications, previous contrast media, fractures or deformities can overestimate the BMD [85]

In addition, in some cases, women with 1 or more fragility fractures (osteoporotic), have normal BMD values when it was measured with DXA. For this reason, is always recommended to also use the Fracture Risk Algorithm **(FRAX™)** tool in order to evaluate fracture risk factors.

FRAX™ is available at www.sheffield.ac.uk/FRAX/ and it is adapted for African, North and Latin American, European, Asian and Middle Eastern populations [87]

CT is a very sensitive technique that provides volumetric BMD. However it is reserved only for those patients who have advanced degenerative disease, or very small or large bones, or obesity, because its high radiation dose [87].

HR-pQ CT is an equipment manufactured since 10 years ago with the name of XtremeCT that emits less radiation dose than CT to patient and each scan time is only 3 min for tibia and femur. HR-pQCT acquires both BMD of trabecular and cortical bones in three dimensions with high reproducibility (coefficient of variation, 1%), but it can only scan peripheral sites. Therefore, images from lumbar spine or proximal femur cannot be obtained. [87]

Other CT scan, the **Multidetector CT,** has the advantage over the previous one to scan central regions of the skeleton, such as lumbar spine or proximal femur both sites at risk for fragility fractures. However, its main disadvantage is the high radiation dose that emits. Last studies performed with Multidetector CT demonstrated greater sensitivity in fracture risk assessment than DXA [87].

MR technique has been modified in the last years to enhance the trabecular bone architecture imaging; it is very attractive for Clinical Studies because the lack of radiation dose, but it is only used for peripheral imaging as well as distal radius, tibia or calcaneus. The main disadvantages are that image can be affected by volume effects and the long acquisition times, making this device very susceptible to artifacts [87].

A new **MR UTE** imaging technique has been developed to know the bone quality by quantification of water content of ordered tissues as well as cortical bone in only a few hundred microseconds [87]

Proton MR Spectroscopy provides also quantitative assessment of water but also of fat content in bone marrow. It has been suggested as a candidate for routine clinical procedures because it is a non-invasively and easily technique. Some studies demonstrated that bone marrow fat measured with MR spectroscopy increased when BMD decreased (measured with DXA), and therefore it is elevated in PMW. [88-90]

QUS quantifies the propagation of the US waves through the bone, in osteoporotic bone; the speed of US is slowly than in normal ones. It is normally use close to the soft tissue surrounding the bone, and it is the case of the calcaneus bone and also of the phalanges. In contrast to DXA, QUS is portable, giving the opportunity to perform a bone density measurement to patients that cannot go to health centers. This technique does not need radiation source, is cheap and perform quick measurements [85]. QUS can differentiate subjects with fragility fractures from those without with a precision of 94-95% and can predict fracture risk with a precision of 96,97%, but these values are not as good as DXA as a technique either to diagnose osteoporosis or to monitor treatment response.[87]

Lateral **X-ray** of the spine remains the gold standard for initial vertebral fracture detection. It emits higher radiation dose and is more expensive than DXA. Nevertheless, X-ray provides better image resolution and identification of vertebral fractures grade 1 [85]. In poster anterior and lateral chest X-ray, there are 4 grades to differentiate the vertebral fracture severity, grade 0 (no fracture), grade 1 (mild

fracture, reduction in vertebral height of 20%–25%), grade 2 (moderate fracture, reduction in height of 25%–40%) and grade 3 (severe fracture, reduction in height of more than 40%).

Wedge-shaped and biconcave fracture deformities are most common in osteoporosis, while posterior vertebral fractures should always raise concern for neoplastic/metastatic vertebral body infiltration.

A web page (www.iofbonehealth.org/vfi/index-flash.html) was created to aid Radiologist in osteoporotic vertebral fractures detection by X-ray [85], because it was noticed that there were some reports where these fractures were not identified properly, for instance, the poster anterior and lateral chest X-ray performed to 934 women older than 59 years showed that 132 subjects had vertebral fractures, but only 17 of them had a diagnosis of vertebral fracture in the radiology reports. Similar results were obtained in 100 patients also older than 59 years old, in which the prevalence of moderate to severe fracture was 22%, but only the 55% of these were identified as vertebral fracture in the radiology reports [91,92].

A recent study was performed in 315 Greek women aged between 45 and 75 years testing **Mandibular Cortical Width** index as a new technique for osteoporosis diagnosis. The results showed differences in the values obtained between normal, osteopenic and osteoporotic women. However, the conclusion was that it cannot be an exclusively method for osteoporotic diagnosis that replace DXA. It could only be useful for diagnostic in those women who already have a dental panoramic radiography. The main reason was that the results were not enough different between normal and osteopenic women. [93]

The **Tibial Cortical thickness** was also measured in radiography from 75 Arabian women, as substitutive of DXA, when it is not available. However, the values

obtained did not achieve the main objective and new studies are needed including more patients of different geographical areas. [94]

New techniques are being studying to assess bone structure as micro-CT, high resolution magnetic resonance imaging (HRMRI), micro-MRI, and quantitative CT-based finite element analysis (FEA)

A new technique, the **Microdensitometry** bone measurement has been developed in Japan to measure BMD mainly cortical bone in the second metacarpal.

Despite of the availability of the different techniques described above, when the osteoporosis diagnostic guidelines created in different countries across the world are reviewed, we noticed that there are only a little bit of differences between these in the use of those techniques for the PMOW diagnosis.

2. POST-MENOPAUSAL OSTEOPOROSIS DIAGNOSIS AROUND THE WORLD:

2.1. AFRICA

2.1.1. SOUTH AFRICA

In South Africa, both state and private patients can access to DXA [87], in fact, post-menopausal osteoporotic women (PMOW) are considered for BMD measurement if they had had any prior osteoporotic fracture.

The main problem for the use of DXA is that the local reference values for BMD provided by manufacturers are normally not appropriate for African heterogeneous local populations. It is the same case of the FRAX ™ tool, useful for South Africans with ascendant British, German or Dutch, but that cannot be used for other South African ethnicities. Although an algorithmic tool was specially created for this population, the National Osteoporosis Foundation of South Africa (NOFSA)

recommends that this tool should never replace the good clinical judgment of a Health care specialist.

There are also other different techniques available to obtain the BMD, such as conventional X-ray, CT and QUS. Despite of the first one is the technique of choice when a vertebral fracture is suspected; the problem is that the 25% of patients with apparent radiographic osteopenia or vertebral fractures have a normal BMD. CT has more accuracy in BMD measurements, but this technique is not used for patient's follow-up because the higher cost and radiation dose. The problem of QUS is that the International Society for Clinical Densitometry (ISCD) only recommends it use in heel, as a predictable measurement of hip and vertebral fractures in PMOW. HR-pQCT is not available in South African Health Care Units yet.

Anyway, NOFSA only recommends DXA as technique for diagnosis of osteoporosis because its accuracy, precision, low radiation dose, shorts scanning time and the ability to predict fracture. It is a good technique for patient's follow-up.

NOFSA recommends that PMOW who have a T-score less or equal to -2.5 at the hip or spine measured with DXA should be considered to receive osteoporotic treatment, as well as those who have T-score between -1.0 and -2.5 added to other risk factors.

2.1.2. MIDDLE EAST AND NORTH OF AFRICA

In 2010 in Morocco, 2,137,410 people had osteopenia (about 39% of the population aged 50 years and over) and 984,730 had osteoporosis [86]. PMWs were estimated as 44.6% of the population. Although these high numbers, Physicians are poorly equipped and trained because Government does not considered osteoporosis as a major health problem. In fact, there is not local approved guidelines. Although DXA is also considered as the gold standard for osteoporosis

diagnosis, there are only 20 machines, located in big cities, and only 4 QUS machines. Private health care insurances reimbursed these exams, but only 17% of patients in Morocco have health insurance. Another problem related to PMOW is the prevalence of hypovitaminosis D that affects 91% of the female population, and in this case, there are no programs on lifestyle prevention yet [95].

The Endocrinology and Metabolism Research Center (EMRC) of Iran informed that 2 million people have osteoporotic fracture risk. This data put the osteoporosis on the top of health problems in the country [96].In addition, the life expectancy in Iran, as well as in other Middle East countries is growing, therefore, it is expected that osteoporosis morbidity will be increased.

Different studies performed mainly in women, in order to try to evaluate BMD and to adjust values to those obtained in the Western populations, showed that in Lebanon [97], Saudi Arabia [98], Kuwait [99], Qatar [100] and Iran [101] the BMD values were lower than those established as standard US/European reference data. The exception was in Kuwait, were data obtained was very similar to the standard reference. [86]

The global recommendations for Physicians in the Middle East and North Africa countries are:

1 Use evidence-based treatment.

2. Use fracture risk factors for requesting a test, mainly DXA. Only there are recommendations in the use of DXA as a diagnostic and follow-up technique of PMOW. However, there are not guidelines for men or pre-menopausal women.

3. Be aware of the Vitamin D deficiency. A study carried out in 316 people between 30 to 50 years old, showed that the 72.8% have Vitamin D insufficiency (defined by a 25(OH)D<15 ng/ml), and it was significantly more common in women than in men (83.9% vs 48.5%).

4. Establish in each country, the local BMD reference data and its relation to fracture risk.

5. Work, in each country, preferably with the WHO, to include the fracture registry program in the health system.

6. In the absence of prospective data on BMD and fracture risk, it is uncertainty to use local reference ranges when defining the prevalence of osteoporosis.

7. Use the Middle East website www.iofbonehealth.org to include your local data.

8. Share your experiences with other regional and international ones. [86]

2.2. OCEANIA

2.2.1. AUSTRALIA:

A study performed in 1494 Australian women showed that only the 0.9% had osteoporosis in spine, femoral neck or mid-forearm, but they are within the range of 40-44 years old, when BMD was measured in those older than 79 years, the results changed to 87.0% [102]

An additional National study was the Prospective Screening for Osteoporosis Australian Primary Care Evaluation of Clinical Test (PROSPECT) that tries to elaborate a protocol for primary care site in early diagnosis of osteoporosis mainly in older women [103]. In Australia, patients can be measured by QUS in some locations, as chemists or shopping centers, but this technique is not recommended for fracture risk prediction. DXA is also widely available, but in hospitals, specialists and radiology centers. The main problem is that the DXA cost only will be reimbursed by Australian's Medicare in those osteoporotic patients, already diagnosed, and with the following risk factors:

- Advanced age, defined as older than 69 years old
- Early menopause or men with low testosterone levels
- 1 or more previous fragility fractures

- Corticosteroid's treatment
- Malabsorption illness, rheumatoid arthritis, hyper or hypo thyroidism or parathyroidism, kidney or liver disease [104].

2.3. ASIAN COUNTRIES

2.3.1. CHINA, HONG KONG, SINGAPORE, SOUTH KOREA, MALAYSIA, TAIWAN AND THAILAND

The osteoporosis diagnosis is poorly evaluated in postmenopausal Asian women. After a data evaluation carried out using patient surveys and medical charts from 1122 PMW who were previously hospitalized due to a fragility fracture and who lived in China, Hong Kong, Singapore, South Korea, Malaysia, Taiwan and Thailand, (i) only the 51.5% of patients confirmed that they were informed about their osteoporotic status. This information was given by orthopedic specialists (76%) and general practitioner doctors (11%), suggesting that the last ones need more education regarding osteoporosis diagnosis. (ii) A BMD measurement was only performed in the 28.2% of the patients. (iii) Only the 33% of them received an osteoporotic treatment prescription within the 6 months after discharge.

The history of fracture, age or type of healthy payment (100% self-payment, partial self-payment or 100% social insurance) is closely related to the initial diagnosis, BMD measurement and osteoporotic treatment.

Thailand and Korea were the countries where the higher percentage of PMOW cases was diagnosed. BMD measurements are performed in PMW and treatments prescribed them yearly.

In Malaysia, there were most prescriptions of osteoporosis drugs than BMD measurements, therefore, there were patient who received medication without knowledge of their BMD. [105]

The osteoporosis diagnosis is described in the Taiwanese guidelines, based on an initial screening of the clinical risk factors, using the International Osteoporotic Foundation (IOF) One-Minute Osteoporosis Risk Test, which evaluates family, medical and drug histories as well as personal lifestyle. Although osteoporosis can be diagnosed by a physical examination, DXA is needed to confirm it.

Women older than 65 years, 3 or more centimeters of height lost and less than 18,5 kg/m^2 of body mass index are considered as fracture risk factors because people with lower weight or older has more risk of fracture related to osteoporosis. There is an easy tool, the Osteoporosis Self-assessment tool for Asians (OSTA) to determine these 2 last risks [106].

Other quick methods to screen osteoporotic patients are the wall-occiput distance measurement, in which if the horizontal distance between the patient's occiput and the wall when the patient is standing up an looking straight forward, is greater than 3 cm, then a latent thoracic vertebral compression fracture should be suspected.

And the method that measures the distance between inferior margin of the ribs and the superior margin of the iliac crest, in the pelvis, when patient is standing up and with the hands lifted. If the distance is less than 1 fingerbreadth, approximately 2 cm, a vertebral abnormality can be suspected. [107]

Traditionally, the simple X-ray detected more than 30% of BMD lost. In fact, it is still an important tool in osteoporosis diagnosis because, many patients with X-ray vertebral compression fracture confirmed present -2.5 or higher T-score using DXA. If a patient has 1 or more vertebral fracture, the risk of new fracture of adjacent vertebrae is increased and then patient needs an active treatment for osteoporosis.

Nevertheless, vertebral fracture assessment can only provide information regarding spinal compression; following WHO recommendations, DXA should be used to diagnose if these problems could be due to osteoporosis. In 2010, consensus was achieved on that WHO criteria for the osteoporotic diagnosis of Caucasian

postmenopausal women could be adapted for those Taiwanese women because there is no significant difference of fracture rate between both.

Following 2008 National Osteoporosis Foundation and 2010 Asia Pacific Consensus of ISCD official position, Taiwanese women candidates for a BMD measurement are:

- 65 years old or older
- Younger women than 65 years old who are postmenopausal and have at least 1 risk fracture factor.
- Women in the menopausal transition with clinical risk fracture factors, as well as low body weight, prior fracture or high-risk medication use.
- Fragility fracture.
- Disease or condition associated with low bone mass or bone loss.
- Medication associated with low bone mass or bone loss.
- Women who are receiving osteoporosis drugs and this treatment should be monitored

QUS (quantitative ultrasound) and peripheral DXA can be used for screening only, but not for diagnosis or monitoring since neither evidence-based diagnostic criteria nor consensus of interventional threshold have been well-established.

Regarding FRAX™, it is important to select the country-specific because it is available in Taiwan with the traditional Chinese format. However, this algorithm is only applicable for untreated patients between 40 and 90 years old. [106]

2.3.2. JAPAN:

The 2011 Japanese guidelines recommended that medical interview, physical examination, diagnostic imaging and lab test to measure bone biomarkers should be carried out for the osteoporosis diagnosis.

The osteoporosis screening is performed in Japanese women from 40 to 70 years old each 5 years-period by a medical interview and a bone mass measurement, thereafter they are classified as complete examination required, guidance required or no apparent abnormality.

Complete examination is for people who have a bone mass less than 80% of young adult mean (YAM), it is different from the diagnostic criteria of osteoporosis, that is when the bone mass is less than 70% of YAM in the absence of fragility fracture.

Physical findings are evaluated by the Female Osteoporosis Self-Assessment Tool for Asians, if the value obtained is -4 or less, then a potential osteoporosis should be suspected. The Japanese diagnostic criteria state that the presence of fragility fractures alone (non-traumatic bone fracture) confirms the diagnosis of osteoporosis. However, to diagnose a primary osteoporosis it is also necessary to determine either BMD or the osteopenia on spinal radiography.

It is recommended to perform a lumbar spine and a proximal femur DXA for the BMD measurement, but this technique cannot be used in case of prosthesis, surgery or deformities in the mentioned areas, if it happens, BMD can be measured at forearm bone.

As a difference from other regions, in Japan the parameters used in QUS were standardized by the QUS Standardization Committee of the Japan Osteoporosis Society in 2010. The bone mass measurement at the calcaneus using QUS is allowed for osteoporosis screening, but not for the osteoporosis diagnosis.

Radiography of the thoracic and lumbar vertebrae is useful for the assessment of fracture or deformity and also for exclusion of other similar disorders as lower back pain or low bone mass. The evaluation of osteopenia by spinal radiography should be used as supplementary means.

However, if the test is performed within 2 weeks of a fracture, MRI (Magnetic Resonance) provides better diagnostic than plain radiography. In fact, MRI is

recommended when it is necessary to distinguish between osteoporotic fractures, including those that are non-vertebral, from other diseases.

FRAX™ has been incorporated into the criteria for initiation of pharmacological treatment because it is a useful tool to identify people with high risk of fracture. [108]

2.3.3. INDIA:

It is estimated that Indian's women are 2 standard deviations (SD) lower than western population when BMD is measured.

Approximately, the 40% of women in the interval age 40-60 have low BMD, and this percentage is increased in women between 60 to 65 years old, the 62%, and it is 80% in women older than 65 years. These high numbers are due an early age of Indian's women natural menopause (46.7 years), nutritional deficiencies, physiological differences, genetic and environmental influences. In fact, Indians are deficient in some vitamins as vitamin D.

Recently, guidelines to aid Physicians in the diagnostic of some pathology, including PMOW have been developed. These guidelines recommend performing an initial Physical examination (height and weight) that should be repeated annually, it must be followed by a laboratory test to determine calcium, vit D and PTH and X-ray of thoracolumbar spine.

In addition, to know the 10 years fracture risk probability and whether treatment is recommended, WHO-FRAX™ is available on-line for Indian women, but it is important to note that the heterogeneity in different Indian's regions is not considered in the FRAX™ calculation.

The review of patient's history to identify risk factors is also important.

There is not a validated population screening tool for PMOW in India, then, DXA is carried out in:

- all women 5 years beyond the natural age of menopause
- women within 5 years after the menopause and with:
    - 1 high clinical risk
    - or more than 2 clinical risk factors, as well as, pharmacotherapy treatment already initiated for osteoporosis, fragility fractures, radiological evidence of osteopenia and presence of vertebral compression fracture.

The final diagnosis of osteoporosis will be based on central DXA of the spine, total hip and femoral neck, the interval of DXAs depend on the individual risk calculated and should be scheduled within 1 and 5 years [109]

2.4. EUROPE:

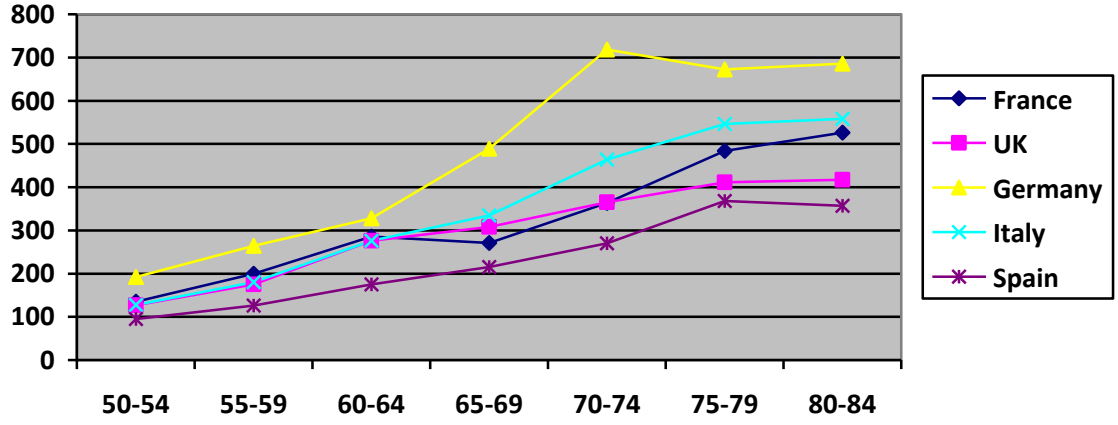
Regarding Europe, the International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published guidance for the diagnosis and management of osteoporosis in 2008 already updated in 2012. There are also different guidelines and publications in some countries, Germany, Bulgaria, Spain, Italy, UK, etc.

Using the WHO criteria, approximately, the 21% of women between 50 and 84 years old have osteoporosis in the largest European countries (Germany, France, UK, Italy and Spain)

In 2010, the number of deaths causally related to osteoporotic fractures was estimated at 43,000 in the European Union. Approximately 50 % of fracture-related deaths in women were due to hip fractures, 28% to clinical vertebral and 22 % to other fractures.

Figure 1.

Thousands of women with osteoporosis in femoral neck according to age [110]



The direct cost that develop these fractures was calculated in 2010 and it was of €38.7 billion in the European countries, and within it, €29 billion belongs to the 5 largest European countries

The diagnostic technique recommended in European guidelines is the same as described by the WHO, the DXA, although QUS showed similar results than DXA when the fracture risk were measured.

For instance, when a BMD is measured with DXA, the risk of fracture is increased by a factor of 1.5 to 3.0 for each standard deviation (SD) decrease in BMD. When it is measured by QUS, the fracture risk is increased by a factor of 1.5 to 2.0 for each SD decrease.

But the access to DXA varies between the different European countries, because it depends on some factors as the patient-cost reimbursement or the accessibility to the image's facilities. [110]

From 2006 to 2010, **Bulgarian** Government and Ministry of Health implemented an Osteoporosis program that included a pharmacoeconomic analysis of this illness, in it was detected that the main problem in Bulgaria was that 426 000 women (26.6 % ≥ 50 years of age) are supposed to have osteoporosis, and there are only 4 DXA devices per million population. Most of these are located in large cities.
The cost of each spine or hip DXA scan varies from €30 to 50, the public health system has not enough time to do it and the reimbursements is only €10 per scan, but only in patients either who have hypogonadism, or have a previous organ transplantation or have primary hyperparathyroidism [110]

In **Germany,** an analysis to evaluate if in some cases an osteoporosis diagnosis using only the clinical risk factors (CRFs) can be recommend was performed. Despite the incremented cost associated with the use of DXA (Cost-effectiveness of DXA plus CRFs compared with CRFs alone involves an extra-cost of 20,235 for 60-year-old women), the recommendation was that DXA should be the election technique in predicting women's fracture risk factors.

Other study performed in Germany evaluated if the use of QUS as a pre-screening technique of DXA would be cost-effective favorable. The results showed that it can be recommended for women between 60 and 70 years old. For other groups, this recommendation depends on different factors as the accessibility of a DXA or the global healthy budget. [111]

In **Spain**, the BMD measurement is part of the other fracture risks evaluations and is carried out by DXA following WHO recommendations, that is, in lumbar spine, total hip or radious. The frequency is established depending on the patient clinical situation. For instance, for patients that are not received any osteoporotic treatment, the DXA frequency depends on their BMD value, thus, if patient does not

have osteoporosis, then DXA could be repeated in 10 years, but if this patient has BMD close to osteoporosis, then DXA should be repeated in 2-3 years.

In osteoporotic-treated patients, DXA should be repeated in 1-2 years. In patients with especial circumstances, as an organ transplant, DXA frequency can be incremented to each 6-12 months.

Patients who should be candidates of a DXA measurement are:

- PMW 65 years or older
- PMW with a bone mass index less than 19 kg/m^2

X-ray is considered as a good technique for fracture identification, but not for BMD change detection.

- Patients with illness like rheumatoid arthritis, primary biliary cirrhosis, type I diabetes, mastocitosis, imperfect osteogenesis or malabsorption syndrome.
- Women with early menopausal status
- Women treated with corticoids
- In patients with hypertiroidism, type II diabetes or hypercalciuria renal litiasis, the DXA measurement will be performed after the evaluation of different illness factors as the gravity or the chronicity [112]

A study performed with 693 Spanish women between 30 and 93 years (mean age 58.2± 9.6 years) demonstrated that heel peripheral DXA can be used for initial osteoporosis diagnosis, because T-score values above +0.6 are very likely to be normal, whilst values bellow -1.3 are highly recommended to perform an additional central DXA because it is a symptom of osteoporosis [113]

In the **UK**, the BMD is measured by DXA at the femoral neck. Women with a prior fragility fracture are directly treated for osteoporosis, independently of their BMD value. The DXA is recommended mainly in younger PMW.

When there are other clinical risk factors that a previous fracture, FRAX™

is determined and the BMD measured. DXA is also recommended for the monitoring of the osteoporotic treatment. The age of the patient is an important factor to take into an account to perform or not a DXA, because the osteoporosis risk rise with the age, for instance, women in the UK potentially eligible for treatment rises from 20 to 40% with age. [114]

In **Italy,** the guidelines recommend performing a DXA for the PMOW diagnosis, and it can be use QUS as a complementary technique, because it is a valid option for the screening of patients depending of their osteoporosis risk.

DXA measurement is performed yearly for spine DXA and each 1.5-2 years for femur DXA. These times were calculated basing on data confirming that a PMW experience a reduction in BMD of 0.5-2% yearly and the common osteoporotic treatments increase it by 1-6%.

Lumbar spine DXA is recommended in the illness follow-up since it is more sensible to BMD changes caused by treatments. In the case of prolonged glucocorticoid treatment, hyperparathyroidism or malignancies, the frequency of lumbar DXA can be increased. [115]

The IOF recently identified some limitations in the FRAX™ as a tool of osteoporosis identification and the needed or not of treatment for it, it was noted that the number of risk factors are not taking into account, for example, 1 prior fracture develop less future fracture risk than 2 prior fractures. The same case is the number of cigarette smoked or the alcohol intake [116]

2.5. AMERICA

2.5.1. USA:

Based in National Osteoporosis Foundation (NOF) data, 9.9 million Americans have osteoporosis that causes 2 million of fractures and there are 43.2 million of

people with low BMD. [114]. In USA, as well as in other countries, osteoporosis is poorly diagnosed because its etiology as clinically silent before manifesting as fracture.

In North-America, the measurement of BMD it is highly recommended using central DXA in women (i) who are 65 or more years old, regardless of clinical risk factors, (ii) or those who are postmenopausal and between 50 and 69 years old , based on risk factor profile (iii) and in those who are postmenopausal age 50 and older who already had a fracture adult-age related, Peripheral DXA is used to measure the BMD at the wrist, but only it is useful in patients at very low fracture risk.

Despite of QUS is cheaper than DXA, portable and patient is not exposed to ionizing radiation, this device is not commonly used because no diagnostic criteria have been identified.

Following the NOF criteria, vertebral imaging using a plain radiography is recommended for all women:

- older than 70 years whose have BMD T-score -1.0 or lower,
- women aged between 65 to 69 years with T-score -1.5 or lower
- postmenopausal women who are:
    - 50 years old or older with low-trauma fracture,
    - height loss (at least 4 cm since the peak height at age 20 or at least 2 cm since a previously documented height measurement),
    - recent or ongoing long-term glucocorticoid treatment.

The NOF recommends that pharmacological treatment should be reserved for postmenopausal women 50 or more years old with:

- a hip or vertebral fracture,

- T-score -2.5 or less at femoral neck or spine,

- low bone mass, defined as T-score between -1.0 and -2.5 and at least 3% of probability to develop a hip fracture in 10 years or at least 20% of probability to develop a major osteoporosis-related fracture in 10 years, both based in the US-adapted WHO algorithm for FRAX™ [117]

2.5.2. LATIN AMERICA:

Fracture rates in Latin America are very similar to those determined in South Europe, but slightly lower than in North America or North Europe.

The main problem of Latin America is the lack of both medical resources to perform a osteoporosis diagnosis and policies of reimbursement for osteoporosis densitometry, bone markers measurements or treatments. In some cases, it is limited in the ones who have started some specific osteoporosis program.
Approximately from 12.1 to 17.6% of women 50 years or older have vertebral osteoporosis and from 7.9 to 22% have femoral neck osteoporosis. In **Brazil**, 1 of 17 people has osteoporosis, meanwhile in Mexico**,** 1 of every 4 people has osteopenia or osteoporosis. In **Chile,** the study of prevalence carried out on 1985 showed that 46% of population has osteopenia and the 22% osteoporosis. It is projected that by 2050, hip fractures will be increased by 400% in people from 50 to 64 years old and by 700% in people older than 65. In addition, the 17% of people who suffer a hip fracture died in the first fourth months after it. [118]

In **Mexico,** spine and hip DXA is the selected technique to diagnose PMOW. However, a cross-sectional study performed with 332 PMW to evaluate the efficacy of FRAX™ and of the heel peripheral DXA, and the low concordance between the results obtained from each one, (using the FRAX™, 13 (3.9 %) had an increased risk of osteoporotic fracture in a 10-year period and 40 (12 %) of hip fracture.

Meanwhile, using the heel DXA, 19 (5.7 %) women had osteoporosis (T-score less than or equal to -2.5), 171 (51.8 %) had osteopenia (T-score between -2.5 and less than or equal to -1) showed that maybe the use of only one of both techniques described could not be a good alternative for a good diagnosis. [119, 120]

Because the poorly information regarding rural areas, a study of the osteoporotic risk was performed in adults from rural Amazonian Ecuador, the technique used for BMD measurement was the Calcaneal Ultrasonometry. From the 74 females and 45 males older than 50 years who participated in it, the 33.6% had low bone density. As well as in other countries, in this area, it is expected that the life expectancy will be increased, and with this, the risk of fracture in elderly people, but, in zones as Amazonian the infrastructure of monitor this kind of patients is almost inexistent. [121]

CONCLUSIONS:

After an intensive review of different publications and guidelines regarding how osteoporosis diagnosis in PMW is managed through different countries, it is noticed that all of them agree with WHO recommendations. There are only differences in some fracture risk factors that can be included or not and in the use of other techniques than DXA as a complementary measurement.

The main discrepancies in diagnosing osteoporosis are not in the published guidelines, but in the daily clinical practice, because an early diagnostic is closely related to the country's resources. This means, availability of enough DXA devices, accessibility of patients to the diagnosis centers, reimbursement of the test cost, and very important to have staff properly trained in how to manage a good osteoporosis diagnostic in the primary health care points. These factors altogether help to achieve an early diagnosis and to derive patients to specialist doctors when it is needed.

Post-menopausal osteoporotic women's treatments, what's new? How can we manage long-term treatments?

Post-menopausal osteoporotic women's treatments, what's new? How can we manage long-term treatments?

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Abstract

Since middle 80's postmenopausal osteoporosis (PMO) was considered as a serious public health concern because the associated fractures. Pharmacological therapies that effectively reduce the number of fractures by improving bone mass have been and are being developed, continuously. Most current agents inhibit bone loss by reducing bone resorption, but emerging therapies may increase bone mass by stimulating bone formation. Furthermore, in this moment, the clinical practice with the most representative pharmaceuticals has been long enough to include the reporting of some adverse effects. This review discussed different osteoporotic drugs approved or under investigation for post-menopausal women (PMW) paying special attention to long-term treatments.

Keywords:

Postmenopausal-Osteoporosis; Long-term-Treatments; Bisphosphonate; Denosumab; Romosozumab; Cathepsin K

1. Introduction

Since post-menopausal osteoporosis (PMO) was considered as a serious public health concern [122], methodologies for its diagnostic and follow-up as well as new treatments are being investigated continuously, mainly to avoid derived fractures. According to the World Health Organization (WHO) definition, Osteoporosis is an illness that produces low bone mass density (BMD) and micro-architecture bone deterioration. It develops in a higher fragility and a high risk of bone fracture. [122]

By 2050, the worldwide incidence of hip fracture in women is expected to increase by 310 %, mainly by the ageing of population worldwide [123]. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe.

PMO treatments are focused on reducing the risk of fractures, because 1 in 3 women are at risk of osteoporotic bone fracture. In fact, an osteoporotic fracture is estimated to happen every 3 s [124]. The most common fractures are in (i) wrist (women older than age 65 years); (ii) spine (vertebral fractures develop height loss, intense back pain and sometimes deformity, 10% of vertebral fractures requires hospitalization), and (iii) hip (1, 7 million of fracture incidence in worldwide that requires surgery and may result in loss of independence or death, in fact, mortality is 10-20% higher than expected for their age).

The diagnosis of Osteoporosis in early stages is important to reduce the associated fracture risk. Women who already had an initial fracture have an 86% increased risk of any fracture [125]. Likewise, patients with a history of vertebral fracture have a 2.3-fold increased risk of future hip fracture and a 1.4-fold increase in risk of distal forearm fracture [126].

When a woman is diagnosed of PMO, different algorithms help to decide doctors whether to treat or not, and, on the best treatment. In this review, we analyzed how the PMO treatments are managed, which are the most prescribed and why, the duration of

each treatment and when it should be discontinued. We have pay special attention to new potential treatments that is expected will improve the women's quality of life.

2. Methodology

A literature searching in PubMed using the keywords "Postmenopausal-Osteoporosis", "Long-term-Treatments", "Bisphosphonate", "Denosumab", "Sclerostin" and "Cathepsin K" was performed. Not only publications regarding the management of bisphosphonate long-term treatments were searched, but also on the prescription of other approved osteoporosis treatments and on upcoming drugs for the treatment of osteoporosis in postmenopausal women.

Clinical trials already performed or still ongoing were searched in Pharmaceutical company's webpages and in www.clinicaltrials.gov. Guidelines on the treatments' prescription were reviewed in the websites of different organizations as the American National Osteoporosis Foundation, European Society for Clinical & Economic aspects of Osteoporosis and Osteoarthritis (ESCEO), International Osteoporosis Foundation (IOF), etc.

European Medicine Agency (EMA), Food & Drugs Administration (FDA) and World Health Organization (WHO) webpages were checked for treatment indications, adverse drug reactions, and data form prevalence of this important illness.

3. Results

3.1. PMO treatments:

There are two main groups of treatments [3]. One comprisses anti-resorptive agents, such as, estrogen, SERM (= Bazedoxifen, Raloxifen), Calcitonin, Bisphosphonates (Alendronate, Ibandronate, Risedronate and Zoledronic acid), Denosumab and Odanacatib (in phase III trials). The other includes those that stimulate bone formation

(anabolic), like PTH1-84 (full-length parathyroid hormone), PTH1-34 (Teriparatide), Strontium Ranelate and the new drugs Romosozumab and Blosozumab (not approved yet). (Table 1 and Table 2) [127]

In controlled clinical trials, Calcium and Vitamin D supplementation apparently reduce the risk of fracture [128], and the combination of both demonstrates to be more efficient than one alone. Ca and vitamin D can be administered in combination with any of the previously described treatments to improve its action by reducing the vertebral risk factor or to prevent hypocalcaemia developed by some of these treatments. The standard dose is 1000 mg of Calcium and 800 UI of Vit D daily. To aid Physicians to decide those cases that need treatment and the most appropriate one, there are different guidelines for PMO treatment [124].

In US, postmenopausal women with the following symptoms should be treated [129]:

- Vertebral or Hip fracture, because many studies demonstrate the effectiveness of osteoporosis treatments reducing the risk spine and hip fracture when there is already a fracture [130-137]
- T-score ≤ -2.5 at the femoral neck, total hip or lumbar spine by dual x-ray absorptiometry (DXA)
- Low BMD (T-score between -1.0 and -2.5 at the femoral neck, total hip or lumbar spine) and a 10-year probability of a hip fracture ≥ 3 % or a 10-year probability of a major osteoporosis-related fracture ≥ 20 % based on the WHO Fracture Risk Algorithm (FRAX) adapted to U.S. population, calibrated to U.S. fracture and mortality rates, because FRAX underestimates fracture risk in patients with recent fractures, multiple osteoporosis-related fractures and patients with increased risk of falling [127,138,139]

Treatments that must be prescribed are those already approved by FDA for Osteoporosis (Table 1 and Table 2) [140]. Non-pharmacological therapies can be considered as concomitant with the pharmacological treatment, and there are some

centers with fracture liaison service to take care of patients older than 50 years with recent fractures

In Europe [141], criteria for the treatment of PMO women differs in some aspects from one country to another, for instance,

- In France, patients are treated if they have a vertebral or hip fracture plus T-score ≤−1 or BMD≤−2.5 plus risk factors or a T-score ≤−3
- In Germany is recommended to treat patients who have a Vertebral fracture and a T-score ≤−2 or 10-year probability >30% (FRAX)
- In Spain, the last guidelines, reviewed on March 2014 by the Spanish society of mineral metabolism and bone investigation (SEIOMM) states that:
    - Patients with high fracture risk factor, that is, with 2 or more vertebral fractures should receive PTH for 24 months, followed by Alendronate or Risendronate, Zolendronic acid or Denosumab
    - Younger women with low hip fracture risk and moderate vertebral fracture risk (only vertebral osteoporosis without any previous fracture) will receive either, Raloxifene or Bazedoxifene, or if cannot comply with the special instructions for administering, other standard treatment (Alendronate or Risendronate). The main reason for no starting in this group of patients with Bisphosphonates or Denosumab is their long-term side effects as atypical fracture and osteonecrosis of the jaw.
    - Patients with other fracture risk factor would be candidates to receive either Alendronate, Risendronate, Zolendronic acid or Denosumab, depending on other patient's factors, such as age, compliance with tablet treatments, gastrointestinal or kidney problems, etc... [142]
- In the UK patients are treated when they are Women aged >75 with a fragility fracture or women aged <75 years with a T-score ≤−2.5 or lower.

Drug compliance should be reviewed periodically to assure complete adherence to the treatment prescribed [129].

3.1.1. Bisphosphonates:

Bisphosphonates inhibit bone resorption by binding to surface hydroxyapatite sites reducing osteoclast activity by decreasing the development and recruitment of the osteoclast progenitor and by promoting osteoclast apoptosis. [143]

3.1.1.1. Alendronate:

Alendronate has demonstrated a 50% of hip fracture reductions over 3 years in women with previous vertebral fracture and a 48% of reduction in those without. It is being prescribed as first line therapy in PMO women who had high hip risk but not vertebral risk [129].

The Fracture Intervention Trial Long-Term Extension *(FLEX)* study evaluated safety of long-term treatment with Alendronate in postmenopausal osteoporotic women [144, 145]. The measurement of adverse events (AE) in women who received a 5 years treatment with Alendronate and then, had 5 years of cessation showed significant lower risk of clinical vertebral fracture than in women that received 10 years of Alendronate therapy -relative risk of 2.4% vs 5.3% (95%CI). However, the risk was not affected by discontinuation regarding non-vertebral fractures.

A post hoc analysis showed that women with non-vertebral fractures at baseline and Tscore< or = 2,5 in femoral neck that were continuously treated with Alendronate for 10 years had less risk of new non-vertebral fractures. Regarding BMD, 1.94 % vs 3.74 % of increase was observed in DXAs performed to patients who discontinued treatment in the last 5 years against those who continued, in both groups, patients gained BMD in

total hip, femoral neck, trochanter, lumbar spine, total body and forearm since they started Alendronate therapy [130, 146-148].

To obtain more information regarding long-term alendronate treatment, the study *BILANZ* (= Comparison of the effect of an ongoing treatment with Alendronate or a drug holiday on the fracture risk in Osteoporotic patients with Bisphosphonate long-term therapy) started on January 2012 and it is expected to be ended by March 2015. In this study, safety and efficacy in long-term bisphosphonate therapy are evaluated by continuing the treatment with Alendronate for another 2 years after a preceding therapy (patients who have taken bisphosphonate of at least 4 years). The end point is observed whether the treatment reduces the incidence of new osteoporotic fractures in patients with high fracture risk compared with a therapy-free interval [148].

Both studies, FLEX and BILANZ will demonstrate the long-term Alendronate treatment efficacy in patients with post-menopausal osteoporosis, and whether a drug-holiday after 10 year-treatment is needed or not.

3.1.1.2. Risendronate:

There are two recent clinical trials providing interesting new information in Risendronate long-term treatments: The 3-years, 5-years and 7-years Vertebral Efficacy with Risedronate Therapy (VERT-MN) and the 2001079 studies.

VERT-MN [132, 138] evaluated the effects of Risendronate in vertebral and non-vertebral fractures after 5 years of treatment; PMO women who entered in the 3 years placebo-controlled vertebral fracture study were invited to receive 2 more years of Risendronate, or placebo according to original randomization. The results showed that the risk of new vertebral fractures was lower after 5 year-treatment than after 3 year-treatment (59% versus, 49% risk reduction 95% Confidence interval (CI), P=*0.01*). BMD in spine, lumbar and hip was increased in the first 3 years, and these values were maintained or increased at the end of 5 years treatment.

Thus, positive achievements in prevention of vertebral fractures and BMD with 2-years Risendronate therapy are maintained for 5-years treatment [138].

The five years study was extended for 2 additional years to evaluate the efficacy of long-term Risendronate therapy. In this case, all osteoporotic women enrolled received active Risendronate 5 mg/daily (no placebo used during the last 2 years study), and fractures risk reduction, BMD and bone biomarkers were measured comparing the 2 groups: (i) women who received placebo the first 5 years and (ii) women who received Risendronate the first 5 years. The results showed that the incidence of new vertebral fractures increased after 7-years treatment in the group that received previously placebo and did not change in the group that already received Risendronate. Non-vertebral fractures incidence after 7-years treatment was 7.4% in group who received placebo and 6.0% in group who received Risendronate. Therefore, Risendronate demonstrated to be efficient in fracture prevention.

The Study 2001079 that ended on May 2003, was performed to know the effect of stopping Risendronate after long-term treatment on the bone turnover. The study included 2 groups, the first one consisted of 30 Caucasian women who received placebo from years 1 to 5, Risendronate for years 6 & 7 and nothing for year 8 (Group 1) and the second of 31 caucasian women who took Risendronate from year 1 to 7 and nothing for year 8 (Group 2). The results summarized in Table 3 showed that BMD was always superior in the second group than in the first [149].

3.1.1.3. Ibandronate:

Monthly Oral IBandronate in LadiEs Long Term Extension study (MOBILE-LTE) and Dosing IntraVenous Administration Long Term Extension (DIVA-LTE) were 5 year long term Ibandronate studies that measured fractures as reported adverse event. First one covered oral treatment and second one intravenous (iv) treatment.

In MOBILE-LTE study, and after 3 years of treatment with Ibandronate, 6.1% of women who received 100 mg and 6.8% of women who received 150 mg reported osteoporotic fractures. After 5 year treatment, 10.3% of women that received 100mg and 9,1% of women that received 150 mg had clinical osteoporotic fractures. [150] In DIVA-LTE study, 11.0% of women who received Ibandronate 2 mg bimonthly iv and 8.5% who received 3 mg quarterly iv for 5 years reported fractures, the respective values for 2 years were 4.7% and 4.9%. Therefore, conclusion obtained for these data showed that fractures were increased in long-term treatments [146]

However data obtained from the study randomized, double-blind, placebo-controlled, parallel-group, in which 2946 postmenopausal women with prevalent vertebral fracture, were enrolled to receive placebo or oral Ibandronate administered either daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months), Ibandronate demonstrated a significant reduction of vertebral fractures after 3 years of treatment with oral daily tablets (4.7% rate of vertebral fractures happened and 62% of vertebral fractures risk reduction, P=0.0001), or with intermittent dose (4.9% rate of vertebral fractures happened and 50% of risk reduction, P=0.0006) versus placebo (9.6% rate of vertebral fractures). This trial was the first study that showed antifracture efficacy for the intermittent administration of a Bisphosphonate [131, 149, 151].

3.1.1.4. Zolendronic Acid:

The 3 year treatment of the Health Outcomes and Reduced Incidence with Zolendronic acid Once yearly Pivotal Fracture Trial (HORIZON PFT) was extended 3 more years to evaluate the long-term effects in Zolendronic acid at 5 mg/day in postmenopausal women.

The analysis of the data concludes that group who continued with Zolendronic acid for 6 years treatment had significant lower risk of morphometric vertebra fractures than those who discontinued it after 3 years treatment. In addition, the continuation of

treatment after 6 years was associated with a net gain of 0.24% in femoral neck and 3,20% in lumbar spine BMD, while discontinuation group had a net loss of 0.80% in femoral neck and a net gain of 1.18% in lumbar spine BMDs were obtained [137, 146].

Regarding adverse events (AE) reported in all types of Bisphosphonates [146, 152], the most important are:

- *Atypical fractures and osteonecrosis of the jaw (ONJ)* are caused because the prolonged antiresorptive action. Both have with very low incidence, but due to their relevance, women should be follow-up closely.
- *Renal deterioration*, mainly related to Zolendronic acid because it is administered intravenous (iv) for, at least 15 min infusion time, and it is contraindicated in patients with eGFR<35 ml/min.
- The most commonly reported in oral Bisphosphonate treatments are upper *gastrointestinal AEs.* In fact, because the high risk of esophageal ulceration, oral bisphosphonates must be taken fasting, with a glass of mineral water, 30 min before the first meal drink or drug. The patient should not lie down until 30 min later.

Last recommendations of the EMA established that the Bisphosphonate treatment should be re-evaluated after 5 years due to the AE reported in long-term use, ONJ, atypical hip fractures and esophagus cancer.

The cumulative incidence of ONJ in oncologic patients using Bisphosphonates ranged from 0.8 to 12% but there is no information on patients using them for PMO treatment. Estimations established that it would be 1/1000 from patients treated because the risk of ONJ is related to cumulative dose; therefore, the incidence could be higher in a future, because the increase of osteoporosis population with prolonged bisphosphonate therapies [127].

The most important advantage of Bisphosphonate showed in long-term clinical trials is to decrease *fracture risk* in PMO women (Table 4) [146, 148-150].

Despite of EMA recommendations, scientific data does not established when to stop the Bisphosphonate's treatment and if would be convenient or not to re-start therapy after drug holidays. With the information available, Dima et al. (2013) proposed to prescribe Bisphosphonate treatment to patients with mild risk of fracture for 3-5 years, with moderate risk for 5-10 years, and with high risk of fracture for 10 years, then stop, and only re-start if there is an important loss of BMD or a fracture. [153] During this Bisphosphonates' rest, another postmenopausal osteoporotic approved treatment could be prescribed. DXA and biomarkers should be evaluated periodically during the drug holiday to reassess the fracture risk, with a suggestion to do it at least after 1 year for Risendronate, 1–2 years for alendronate, and 2–3 years for Zoledronic acid [33]. However, always the decision of re-start or not Bisphosphonates' treatment should be based on Doctor's criteria. [153]

Etidronate, the first Bisphosphonate used for PMOW, have effect in the vertebral fracture risk reduction, because it low treatment cost, this drug was widely prescribed, but in the last years it is not currently used due to (i) the introduction of new drugs that reduce not only vertebral fractures, but also non-vertebral and hip fractures (ii) the decrease in the prize of Alendronate and Risendronate because the introduction of its generic's form

3.1.2. PTH-34=Teriparatide:

Teriparatide was approved as the first anabolic agent for the treatment of postmenopausal osteoporotic women. The drug, a portion of human-PTH, is indicated for the treatment of osteoporosis in PMO women who are at high risk of having a

vertebral and non-vertebral fracture, because Teriparatide stimulates bone formation with positive effect in BMD, but without effects in hip fractures [144].

Teriparatide is prescribed for PMO women because its efficacy in BMD at lumbar spine and in risk fractures reduction, but no longer than 24 months (1 subcutaneous (SC) injection daily) because there is not any study that demonstrates its long-term effectiveness and studies in rats indicate an increased incidence of osteosarcoma with long-term administration of Teriparatide. [152]

To solve this problem, some studies evaluated the effectiveness of combined therapies (e.g. Teriparatide followed by Antiresorptive medications [139, 155, 156]. The results demonstrated an increase or stabilization of BMD [155] with Alendronate or Risendronate followed by Teriparatide [156] and with the combination of both (Teriparatide plus Antiresorptive) [139]. In this last study [139], 93 postmenopausal women were randomized in 3 groups that received alendronate 10 mg daily (group 1), Teriparatide 40 µg SC daily (group 2), or both (group 3). After 30 months of treatment, BMD was measured in spine, where it was increased more in group 2 (18% +/-11%, P< 0.001) than in 1 (7% +/- 4%; P< 0.001) or 3 (12% +/- 9%; P= 0.045), similar results were obtained in femoral neck BMD (Group 2: 11 +/- 5 vs. Group 1: 4 +/- 4% and Group 3: 3 +/- 5%; P< 0.001). The study concluded that Alendronate reduces the ability of Teriparatide to increase BMD and bone turnover in women.

Another study evaluated the treatment with Antiresorptive medications followed by Teriparatide [156]. In it, 16 postmenopausal osteoporotic women were randomized to receive either Alendronate or Risendronate, at least, during 2 years and subsequently were treated 12 months with Teriparatide. Bone biopsy samples were taken from them to know the effects in bone mineralization density distribution (BMDD) in both trabecular and cortical bone.

At baseline, BMD values from women who have taken 2 years of either Alendronate or Risendronate treatments were similar and within the normal range. However, after 1 year of treatment with Teriparatide, values changed significantly, increasing both trabecular and cortical bone:

- At baseline for patients previously treated with Alendronate, the increase of BMD in low mineralized bone areas, was 25.9% in trabecular bone and 62% in cortical bone, both $P<0.05$. The heterogeneity of mineralization improved 22.8% ($P<0.001$) in cortical bone
- At baseline, the heterogeneity of mineralization for patients previously treat with Risendronate was also increased 14.8% in trabecular bone ($P<0.05$) and 15.8% ($P<0.01$) in cortical bone.
- After 1-year Teriparatide treatment, the increase of BMDD in low mineralized bone areas, was 18.2% ($P<0.05$) in trabecular bone and 36.6% ($P<0.01$) in cortical bone. The heterogeneity of mineralization improved 10.7%, ($P < 0.01$) in trabecular bone and 19.6% ($P < .001$) in cortical bone

This data indicates a significant effect of Teriparatide on BMD when administered subsequent to bisphosphonates in agreement with Teriparatide's anabolic action.

Eli Lilly and Company performed a *phase III study* to demonstrate effectiveness of Teriparatide in the treatment of post-menopausal women with osteoporosis. The endpoint observed was the reduction of new vertebral fractures after 3 years of treatment with Teriparatide at 20 and 40 mcg/daily plus calcium/vitD supplements against calcium/vitD supplements treatment alone [157]. Vertebral fracture was reduced in the group of Teriparatide vs that of placebo by 84% ($P<0.001$), the risk of 2 or more vertebral fractures was also significantly reduced by 94% ($P<0.001$), also severity of the fractures (if produced) was lesser in the Teriparatide group. Teriparatide was more effective in women with the highest number and severity of prevalent vertebral fractures. [158]

Teriparatide *AE* reported were pain in the limbs as more commonly (>1/10) and anemia, hypercholesterolemia, depression, dizziness, headache, sciatic, vertigo, palpitations, hypotension, dyspnea, nausea, vomiting, muscular cramps, asthenia, pruritus as commonly (from >1/100 to <1/10) [152]

3.1.3. Strontium Ranelate:

Strontium Ranelate presents mixed mode of action, increasing bone formation and decreasing bone resorption. The increase of bone formation together with osteoblast precursor replication and collagen synthesis was observed in bone cell culture. The reduction of bone resorption is produced by decreasing osteoclast differentiation and resorbing activity. Strontium Ranelate improves cortical thickness, trabecular number, and connectivity, without changing cortical porosity.

The absorption of Strontium Ranelate is reduced by food, milk and derivative products and therefore, it should be administered in-between meals. Given its slow absorption, this product should be taken at bedtime, preferably at least two h after eating. [152]

Effect of 2 g/daily oral administration of Strontium Ranelate for 5-years on non-vertebral and vertebral *fractures* in postmenopausal women with osteoporosis was evaluated in a double-blind, placebo-controlled trial. This clinical study confirmed that Strontium Ranelate reduces the risk of vertebral fracture by 24%, non-vertebral fracture by 15% and hip fracture by 43% [159].

Relative fracture risk reduction vs placebo was already evaluated in SOTI and TROPOS studies after 3 years treatment with Strontium Ranelate, in both, new vertebral fractures were reduced in a range of 39-41% (P<0,001, 95% CI) [149, 157].

No different *adverse events* to those reported in the first 3 years study were observed in the extension of the study. Hypersensitivity skin reactions (rash, urticarial,

angioedema and pruritus), muscle spasm, myalgia, bone pain arthralgia and pain in extremity as very commonly AEs happened (>1/10) [152].

However, on July 11th, 2014, AEMPS published a newsletter informing that Strontium Ranelate should be used only in PMO women with high fracture risk, and always as second line treatment because the ischemic cardiopathy, peripheral arterial illness and hypertension reported as potential related events [146]. This change in benefit-risk balance causes that Strontium Ranelate is only prescribed by Hospital Doctors.

3.1.4. Estrogens= Hormonal Substitutive Treatment (HST)

Estrogens have global efficacy in menopausal symptomatology. However, these substances are only recommended as a second line PMO treatment for patients with high risk of fractures that do not tolerate or have contraindicated any other approved drug. An important reason for this is the *potential serious drug reactions*, as breast or lung cancer, gallbladder disease, coronary events, stroke and venous thrombo-embolism. The therapy of combined estrogen+progestagen is associated with a breast cancer risk increase of 2,00 (CI 95%), the use of estrogens alone increase the risk in 1.30 and Tibolone treatment in 1.45, all of these compared with women who have never taken HST [146].

Studies Women Health Initiative (*WHI 1998)* and Heart and Estrogen/Progestin Replacement Study *(HERS 1998)* showed that HST produces significant decreased incidence of fractures with long term use (after 5.6 years of combined HST: Absolute Risk 86 ‰; after 7.1 years' use of estrogen-only HST: Absolute Risk 102 ‰). Risk of fracture was the only outcome for which there was strong evidence of clinical benefit from HST. [148, 149]

3.1.5. SERM: Raloxifene and Bazedoxifene

Selective estrogen receptor modulators (SERMs) are partial agonist/antagonist of estrogens. This mixed activity is either by blocking the estrogen action or by displaying estrogen like-actions through the estrogen receptors (ER) in a target gene-specific and tissue-specific fashion. Ideally, they should have a partial estrogen agonist activity in bone formation and lipid metabolism (decreasing total and LDL-chloresterol) and antagonist activity in the hypothalamus, uterus and breast. Raloxifene belonging to the second generation of SERMs, presents greater activity in bone but reduced estrogen agonist activity in the uterus, and antagonist action in breast showing positive effect on invasive estrogen-receptor positive breast cancer. Badoxifen is a third generation SERM designed for to prevent and treat postmenopausal osteoporosis with reduced negative effects.

Eli Lilly & Company performed an cross-sectional study to evaluate the long-term effects of *Raloxifene* treatment on bone quality of PMO women previously enrolled in the continuing outcomes relevant to EVISTA study, demonstrated that SERM prevent and reduce vertebral fractures, but no effects showed regarding hip fractures. [158] The efficacy of *Bazedoxifene* was established in two multicentre, double-blind, randomized, placebo and active-control, Phase 3 trials: 3-year osteoporosis treatment trial and a 2-year osteoporosis prevention trial. In this study, 7,492 postmenopausal women received Bazedoxifene (20 or 40 mg daily), Raloxifene (60 mg daily), or placebo to evaluate the incidence of new vertebral fractures over 3 years. This study was extended up to 7 years demonstrating a significant reduction in the incidence of new vertebral fractures. (Table 5) [134, 146]

Currently, Bazedoxifene is being studied in the post-marketing plan, VIOLINE study, which evaluates the treatment of long-term of Bazedoxifene in postmenopausal women. Currently, the study is in enrollment period and is scheduled to end by July 2016.

Important *adverse events* described for SERMs are the increase of thromboembolism and vasomotor symptoms. Furthermore, hot flushes and muscle spasms have been reported as very common (1-10%). Menopausal symptoms, effects on uterine and breast tissues and cardiovascular risks and benefits should be evaluated on an individual basis to decide whether to prescribe or not SERMs. [157]

3.1.6. Calcitonin:

Calcitonin is a hormone protein that lowers blood calcium and inhibits osteoclast action being obtained either, from salmon or from human-recombinant technology (less risk of intolerance). Calcitonin is approved for it SC administration and there are some studies demonstrating its efficacy in vertebral fracture reduction.

But on 19 July 2012, the European Medicines Agency (EMA) evidenced of a small increased risk of cancer with long-term use. The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that they should only be authorized for short-term use in Paget's disease, acute bone loss due to sudden immobilization and hypercalcaemia caused by cancer. And it should no longer be used for the osteoporosis treatment. [152]

Prevent Recurrence of Osteoporotic Fractures *(PROOF)* study, a 5-year double-blind, randomized, placebo-controlled trial showing that salmon calcitonin nasally sprayed at a dosage of 200 IU/day can reduce the risk of vertebral osteoporotic fractures by 33% ($P = 0.03$). It analgesic effect is appreciated in women with vertebral pain due to fracture. However, the main problem is the high risk of cancer (malignancy) when Calcitonin is used in long-term treatments, no specific type of malignancy was evident, but the most common was basal cell carcinoma, for this reason, it is recommended to use as short as possible and in the lowest efficacy dose. [161, 162]

3.1.7. Denosumab:

Denosumab, a fully-human monoclonal antibody (IgG2) was approved on 23-April-2013 by the FDA for PMO with osteoporosis who are at high risk for fractures because its antiresorptive effects when inhibits to Receptor Activator of Nuclear actor-KappaB ligand (RANKL), doing a similar action of endogenous osteoproteogerin. [140, 152, 161]

Denosumab's efficacy has been studied in 4 clinical trials randomized phase III:

- Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (*FREEDOM)*: pivotal study that evaluated Denosumb efficacy along 3 years in 3,902 women who received active treatment vs 3,906 who received placebo. The incidence of new vertebral fractures was 2,3% in Denosumab group against 7,2% in placebo group (P<0,001), non-vertebral fractures incidence was 6,5% vs 8,0% (P<0,01), regarding hip fractures incidence, denosumab 0,7% vs placebo 1,2% (P<0,04) and vertebral Clinical fractures denosumab 0,8% vs placebo 2,6% (P<0,001). The reduction in fracture risk was observed from the first year of treatment along the 3 years of duration of the study. [157]
- DEnosumab FortifiEs boNe Density (*DEFEND)* study demonstrated that denosumab 60mg produced in 332 women and important BMD increase compared with placebo (6,5 vs. -0,6%; P< 0,0001). [157]
- In Determining Efficacy: Comparison of Initiating Denosumab versus alEndronate (*DECIDE)* study, Denosumab was compared with alendronate to evaluate BMD in 1,189 women with low BMD values (T-score < -2.0 in lumbar spine or total hip). Denosumab non-inferiority was demonstrated, because the BMD percentage of change after 12 months was 3,5% vs 2,6% in alendronate group (P< 0,0001), also, Denosumab was superior to alendronate regarding BMD but it Clinical significance is unknown. [157]

- The Study of Transitioning from AleNdronate to Denosumab (*STAND)* was carried out in 504 postmenopausal women (treated in a previous study with alendronate, at least for 6 months) to evaluate changes in total hip after 12 months of treatment with alendronate or with Denosumab. This study demonstrated again superior performance of Denosumab obtaining 1,90% as BMD total hip change vs 1.05% in alendronate group. Similarly to DECIDE study, Denosumab demonstrated superiority against alendronate but without Clinical significance [157]
- As well as Alendronate, Risendronate and Zolendronic acid, Denosumab demonstrated versus placebo, an effect in new radiological vertebral fracture incidence. To know data for denosumab long-term treatment an extension study to evaluate the long-term safety and efficacy of Denosumab in the treatment of osteoporosis is performing and the results are expected to be published by June 2015

Regarding *adverse events* urinary tract infection, upper respiratory tract infection, sciatic, constipation, skin eruptions and pain in limbs were reported as frequents (1/100 to < 1/10). Despite of hypocalcaemia was identified in rare occasions Calcium/Vit D daily supplements are recommended concomitantly with Denosumab [140, 152, 157]. As in the case of Bisphosphonates, atypical fractures and ONJ were related to denosumab use, mainly in 120 mg dose in cancer patients. Maybe, the safety concern in Denosumab long-term treatment is regarding it immunity effect, because RANKL is expressed in both, osteoclast and immune cells. [140]

US FDA evaluated a risk plan in denosumab treatment and recommended to monitorize closely hypocalcemia, infections, including skin infections and ONJ. [140]

3.2. New potential PMO treatments:

3.2.1. Anti-Sclerostin's Antibodies

Sclerostin, a protein encoded by the SOST gene in osteocytes, inhibits osteoblastic bone formation because it blocks the canonical Wnt signaling by binding to LRP5/6, therefore, b-catenin is not accumulated in the cytoplasm and the following inactivation of GSD-3b is not produced, thus b-catenin is not translocated to the nucleus and the gene expression is not activated.

It was found that the mutation in SOST gene in some families develops dense and also strong bones, this observation reinforced the idea of compound that inhibit sclerostin could be effective in the osteoporosis treatment. [163]

An intermittent treatment with PTH is also associated with the sclerostin inhibition, but the results in BMD obtained with anti-sclerostin antibodies were significantly better that those obtained with Teriparatide. [164]

3.2.1.1. Romosozumab (AMG 785)

Romosozumab is a humanized monoclonal antibody developed by Amgen that targets sclerostin's specificity to bone. Its use has increased bone growth in preclinical trials in osteoporotic rats and monkeys. In a Phase I study, a single dose of Romosozumab increased bone density in the hip and spine in healthy men and postmenopausal women and the drug was well tolerated. [164]

Romosozumab phase 2 data show significant increases in BMD at both spine and hip in PMO women with low BMD. Romosozumab is under investigation in phase 3 clinical development for the treatment of osteoporosis in postmenopausal women with low BMD and therefore high risk of fractures.

Romosozumab is not currently approved in any country, phase 2 trial results showed that compared with placebo, it increased 11.3% BMD at lumbar spine, 4.1% at total hip

and 3.7% at femoral neck, all of these with P<0,001, the better results were obtained with 210 mg dose once a month.

When it was compared with 12 months therapy with Alendronate (Fosamax, 70mg oral weekly) and Teripatide (Forsteo, 20 micrograms SC daily) BMD was increased in 11.3% at lumbar spine after Romosozumab treatment, 4,1 % after Alendronate therapy and 7.1% after Teriparatide treatment. BMD at total hip was improved in 4.1% for Romosozumab, 1.9% for Alendronate and 1,3% for Teriparatide.

As AE, by the moment, only mild upper respiratory tract infection, pain in the back and joints and headache were reported as related with investigational product use. [164]

3.2.1.2. Blosozumab

Also an anti-sclerostin antibody, but developed by Eli Lilly, Blosozumab has demonstrated, in PMW with low areal BMD, that the mean changes at the lumbar spine, total hip and femoral neck, from baseline in areal BMD to Year 1 treatment with placebo vs 270 mg every 2 weeks (=highest tolerated dose) of Blosozumab were 1.6 vs.17.7%, 0.7 vs.6.7%, and 0.6 vs.6.3%, respectively.

But, non-significantly efficacy has been demonstrated in the radius (1.4 vs.0.9%, respectively)

Because radius is normally not exposed to high levels of mechanical strain, these values confirms the fact that sclerostin secretion is increased by osteocytes upon skeletal disuse and decreased by skeletal loading, therefore, anti-sclerostin antibodies dose should be increased in patients with reduced physical activity.[165]

3.2.2. Cathepsin K inhibitors:

Cathepsin K is a cysteine protease predominantly found in osteoclast, where it adheres to helical collagen domains. Its inhibition stopped the resorption without altering other

osteoclast functions suggesting that it could prevent bone loss while allowing bone formation. The inhibition of cathepsin K provides a novel mechanism of modulating bone remodeling. Preclinical and early clinical data support the potential effectiveness of these agents as treatments for osteoporosis. [166]

3.2.2.1. Relacatib: (SB-462795, GlaxoSmithKline):

This drug is a non-selectively cathepsins K, L and V inhibitor. Despite the good results in bone biomarkers levels and the reduction in both cortical and trabecular bone sites produced in monkeys, clinical trials with this drug were discontinued after phase I because of drug–drug interactions with the commonly prescribed medications acetaminophen, ibuprofen and atorvastatin. [167]

3.2.2.2. Balicatib: (AAE-581, Novartis):

In enzyme-base assays, this substance demonstrated to be a highly selective nitrile-based cathepsin K inhibitor but is not so selective in whole cell assays due its high concentration in lysosomes. After 18 months, histomorphometric analysis demonstrated that reduced indices of bone resorption at trabecular and cortical sites but this study was stopped because Balicatib developed skin-related complicated AE, as well as rashes and scleroderma-like lesion similar to morphea. [1689]

3.2.2.3. ONO.5334: (ONO Pharmaceutical):

This compound is a potent inhibitor of cathepsin K no longer under clinical development for the treatment of osteoporosis. Despite of, ONO-5334 showed significant increases in the BMD at lumbar spine, total hip and femoral neck, decreased serum and urinary resorption bone biomarkers levels with little increase in bone formation markers and there were no clinically relevant adverse events events, after

12 months of a trial in which 285 postmenopausal women with osteoporosis were randomized to receive either placebo, or alendronate 70 mg weekly, or one of three regimens of oral ONO-5334 (50 mg twice daily, 100 mg once daily or 300 mg once daily). [169]

3.2.2.4. Odanacatib, (MK-822, Merck):

Odanacatib is a reversible, potent and highly selective cathepsin K covalent inhibitor, and today, is the only remaining Cathepsin K inhibitor in development for osteoporosis treatment. Patients who received Odanacatib 50 mg orally once a week for 5 years at study phase II, showed prevention of bone loss without reduction of bone formation (almost linear increases in BMD from baseline at the lumbar spine (11.9%), total hip (8.5%) and femoral neck (9.5%) and biomarkers serum levels of bone alkaline phosphatase remained close to baseline while the level of urinary N-terminal telopeptide was decreased by 67.4%.) The phase II trial has been extended to 10-years to further assess the effects on safety and efficacy of the odanacatib treatment in osteoporotic postmenopausal women and phase III has been started as fracture outcome international trial for the treatment of PMO. [166]

4. Conclusions and Remarks:

Nowadays, developed countries have specific Health programs that perform a close follow-up of women in order to minimize their post-menopausal osteoporosis associated fracture risk. An early diagnostic and a good treatment election are key points to reduce this risk. Physicians evaluate the previous patient's medical history as well as parent's fractures, because the genetic burden of this illness, but also patient's previous fragility fractures, height, weight, sex, race and age, previous smoke and alcohol abuse, and concomitant estrogenic or steroid treatments, because their side-effects in bone resorption. If after this evaluation, patient is considering within the group of fracture risk, bone-biomarkers are determined in serum and urine and the most important diagnostic technique, DXA, is performed to conclude if woman needs or not a treatment for her osteoporosis. [132,170]

To determine the most suitable drug commercialized for each patient, other factors as gastrointestinal side effects, kidney illness, but also the patient's preference in the administration manner and the cost of each treatment are evaluated. This means that approved treatments are being administered in a personalized manner.

Alendronate and Risendronate, are the most commonly prescribed drugs for PMO women, it is because both have shown its effectiveness in reducing the risk of hip fracture. Alendronate showed a 55% in vertebral fracture reduction after 1 year-treatment, 47% in non-vertebral fracture reduction after 1 year-treatment and 53% in hip fracture reduction after 3 years-treatment. And Risendronate produced a reduction of 69%, 74% and 60% in the same 3 fractures measured. Whereas, other Bisphosphonate, as Ibandronate, did not obtain evidence in hip fracture reduction, being this kind of fracture the most commonly in elderly people and therefore, the associated with higher mortality rates.

The main disadvantage of both Alendronate and Risendronate is that tablets must be taken under especial conditions (fasting, with mineral water and 30 mins before any meal, drink or drug) and once intake, the patient should not lie down for 30 min). This makes that the compliance of these treatments could be compromised by some patients, mainly in elderly patients and in those with gastrointestinal problems. Therefore, Denosumab (1 SC administration each 6 months) and Zolendronic acid (1 IV administration yearly) treatments can be a good alternative. [170] The main problem of Zolendronic acid is its IV administration that requires Hospital's facilities and staff resulting in a very expensive treatment.

Denosumab has also demonstrated high efficacy in vertebral, non-vertebral or hip fracture risk reduction (Denosumab non-inferiority was demonstrated, because the BMD percentage of change after 12 months was 3,5% vs 2,6% in alendronate group (P< 0,0001)) [36] and without any adverse drug reaction in kidney, therefore, this drug would be the first option in patients with high hip fracture risk and renal disease or also gastrointestinal intolerance to Bisphosphonates since Denosumab is administered in a subcutaneous prefilled syringe biyearly**,** the main problem in the decision of prescribe or not this drug is the cost per dose, that is 1,32 euros vs 0,79 for Risendronate and 0,45 for Alendronate (Table 6) [171]

Last safety data obtained from studies performed in Bisphosphonates and Denosumab, showed a relationship between these and ONJ or atypical fractures in long-term treatments. For this reason, and only as a preventive measure, it is recommendable to discontinue them after 5 years-treatment and either change to another treatment available or discontinue but with exhaustive BMD follow-up

Because the effectiveness of osteoporosis treatments in the reduction of new fracture risk and also in the improvement of BMD values have been widely tested, nowadays, studies in course are being addressed in two mainly lines:

- The safety, security, tolerability and effectiveness of already approved drug used in long-term treatments. For instance, results published for some bisphosphonates showed that effectiveness is maintained after 10 years of treatment, but EMA recommends that it use for more than 5 years could be an important increased risk of osteonecrosis of the jaw for the patient.

  Therefore, after the review of those clinical trials that are being performed with osteoporotic treatments, it can be remarked that more of these are needed (i) to assured or not that Bisphophonates have enough safety to continue its treatment for more than 5 years (ii) to know the effectivity, tolerability and safety of Denosumab in long-term treatments.

- The searching of new drugs with different mechanism of action that get better BMD improvements and higher reductions in future fracture risk, as Odanacatib Blosozumab or Romosozumab. These new drugs are not approved yet and then, they are under investigation.

List of tables and figures:

Table 1:

Approved drugs and those newly developed and still under investigation, trademark and authorization date, dose, indications and main effects.

[127, 140, 152]

Dug	Trade mark (Marketing Authorization owner)/First authorization date	Dose	Indication approved/Effect
Anabolics (stimulates bone formation)			
Teriparatide	Forsteo (Eli Lilly Nederland Bv)/ Authorized on 24June2003	20 µg/80 µl, SC injection/daily	• PMO, osteoporosis in men and osteoporosis associated to glucocorticoid treatments • Reduction of vertebral & non-vertebral fracture risk • No hip fracture reduction risk effect
Strontium Ranelate	• Protelos (Les Laboratoires Servier)/ Authorized on 21September2004 • Osseor (Les Laboratoires Servier)/ Authorized on 21September2004	2 g daily, oral envelopes	• Severe osteoporosis at high risk of fracture in PMW and adult men that cannot be treated with other pharmaceuticals due to contraindications or intolerance. • In PMW reduces the risk of vertebral and hip fractures
Romosozumab	Non applicable, under investigation (Amgen Ltd)	SC injection, no approved yet	• Not approved yet
Blosozumab	Non applicable, under investigation (Eli Lilly and company)	SC injection, no approved yet	• Not approved yet
Antiresoptive agent			
Estrogens	Equin (Laboratorio Aldo Union, S.A.)/ Authorized on 26July1960	0.6 mg 1 tablet/daily	• Osteoporosis prevention in women at high risk of fractures that cannot be treated with other pharmaceuticals. • Symptoms associated to menopausal status caused by the lower levels of estrogens.
Bazedoxifen (Selective-	Conbriza (Wyeth Europe Ltd.)/ First authorization: 17 April 2009	20 mg tablet/daily	• PMO in women at increased risk of fracture. • Significant reduction in the incidence of vertebral

estrogen receptor modulator (SERM))			fractures. • Efficacy on hip fractures not established yet.
Raloxifen (Selective-estrogen receptor modulator (SERM))	• Evista (Daiichi Sankyo Europe Gmbh)/ First authorization: 5 August 1998 • Optruma (Eli Lilly Nederland Bv)/ First authorization: 5 August 1998 • Generic Raloxifen (Aurobindo, Cinfa, Kernpharma, Stada, etc)	60mg 1 tablet/daily	• Osteoporosis in PMW. • Significant reduction in the incidence of vertebral. • Efficacy on hip fractures not established yet.
Alendronate (Bisphosphonate)	• Fosamax (Merck Sharp and Dhome S.A.) Fosamax daily: First authorized on 26 June 1996 Fosamax weekly: First authorized on 01June2001	• Fosamax weekly: 70mg alendronate sodium trihydrate, 1 tablet/weekly • Fosamax daily: 10mg alendronate sodium trihydrate,1 tablet/daily	• Treatment of PMO • Reduces the risk of vertebral and hip fractures.
	• Fosavance (Merck Sharp and Dhome ltd) /Date of first authorization: 24 August 2005	70 mg as alendronate sodium trihydrate, and 70 µg (2800 IU) colecalciferol (vitamin D3). & 70mg as alendronate sodium trihydrate and 140 5600 IU of colecalciferol (vitamin D3). Date of first authorization: 24 August 2005 Dose: 1 tablet/weekly	• PMO in women at risk of vitamin D insufficiency. • Reduces the risk of vertebral and hip fractures
	• Generic Alendronate: Alendronic acid Accord, Acost, Actavis, Almus, Alter, Amneal, Apotek, Aurobindo, Bexal, Cinfa, Cinfamed, Cuve, Kern Pharma, Edigen, Cantabria,	• Alendronate weekly: 70mg Alendronic acid as Alendronate sodium trihydrate Dose: 1 tablet/weekly • Alendronate daily:	• PMO • Reduces the risk of vertebral and hip fractures.

	Davur, Qualitec, etc	10mg alendronic acid as alendronate sodium trihydrate Dose: 1 tablet/daily	
	Binosto (Lacer S.A.) / First authorized on June2012	70mg Alendronic acid as Alendronate sodium trihydrate Dose: 1 effervescent tablet/weekly	• PMO • Reduces the risk of vertebral and hip fractures.
	Adrovance (Merck Sharp and Dhome ltd)/ First authorized on 04January2007	70 mg Alendronic acid as Alendronate sodium trihydrate, and 70 micrograms (2800 IU) colecalciferol (vitamin D3). Dose: 1 tablet weekly	• PMO in women at risk of Vitamin D insufficiency. • Reduces the risk of vertebral and hip fractures.
Risendronate (Bisphosphonate)	• Actonel (Sanofi-Aventis S.A.)/First authorized on 07October1999	oral 35mg weekly & oral 5mg, 30mg, 75mg daily	• PMO for risk reduction of vertebral and hip fractures. • Prevention of PMO in women with increased risk of osteoporosis • For maintenance or increase the bone density in PMW with a corticoid prolonged systemic treatment (more than 3 months) with dose of Prednisone 7,5 mg/daily or its equivalent • Risendronate produces vertebral, non-vertebral and hip fractures risk reductions
	• Acrel (Warner Chilcott S.L.U.)/Authorized on 18Feb2004		
Ibandronate **(Bisphosphonate)**	• Bonviva (Roche Registration Limited)/ Date of first authorisation: 23February2004	150mg 1tablet/monthly	• Osteoporosis in PMW at increased risk of fracture. • Reduction in the risk of vertebral fractures Efficacy on femoral neck fractures not established
	• Generic Ibandronic acid (Actavis, Cinfa, Milan, Normon, Pensa, Stada, Sandoz, Ratiopharm, etc)	150mg 1tablet/monthly	
Zolendronic acid	• Zometa (Novartis Europharm Ltd) /authorized on 16Apr2001	5mg administered only once yearly or each 2 years in intravenous infusion	• Post-menopausal osteoporosis, for prevention of post-menopausal osteoporosis in patients with high

(Bisphosphonate)	• Zolendronic acid Swan Pond Investments Limited /authorized on 01April2014	for, at least, 15 min to prevent renal failure.	fracture risk , treated with glucocorticoid, for treatment of the malignancy bone disease and for the treatment of Multiple myeloma bone deterioration • Reduces the risk of Vertebral and hip fractures
Denosumab	Prolia (Amgen)/ authorized on 23Apr2013	60mg SC/6months	• Osteoporosis in PMW and in men at increased risk of fractures. In PMW significantly reduces the risk of vertebral, non-vertebral and hip fractures. • Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. • In men with prostate cancer receiving hormone ablation, reduces the risk of vertebral fractures. • Vertebral, non-vertebral and hip fractures risk reductions
Odanacatib	NA, under investigation (Merck Sharp and Dhome ltd)	Oral, no approved yet	• Not approved yet

PMO: Post menopausal osteoporosis

PMW: Post menopausal women

Table 2:

Mechanism of action, adverse drug reactions, contraindications, overdose and drug interactions of the PMO approved drugs. [152]

Drug	Mechanism of Action	Adverse drug reactions	Contraindications	Overdose	Drug interactions
Teriparatide	Identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone rhPTH(1-34), produced in E. coli, using recombinant DNA technology. Producing a stimulation of bone formation by direct effects on osteoblasts indirectly increasing the intestinal absorption of calcium and increasing the tubular re-absorption of calcium and excretion of phosphate by the kidney.	Very common side effects (seen in more than 1 patient in 10 (>1/10)): • Pain in the arms or legs • Anemia Common side effects (from >1/100 to <1/10) • Hypercholesterolemia • Depression • Dizziness • Headache • Sciatic • Vertigo • Palpitations • Hypotension • Dyspnea • Nausea • Vomiting • Muscular cramps • Asthenia	• Other bone diseases such as Paget's disease, bone cancer or bone metastases • Previous bone radiation therapy • Hypercalcemia • High levels of alkaline phosphatase - severe hepatic or kidney disease. • Children or in young adults whose bones are not yet fully mature, or during pregnancy or breast-feeding.	• Hypercalcemia • Orthostatic • Hypotension • Nausea • Vomiting • Dizziness • Headache In post-marketing spontaneous reports, there have been cases of medication error where the entire contents (up to 800 mcg) of the Teriparatide pen have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension	Transient elevations of serum calcium concentrations following Teriparatide injection and this event may predispose patients to digitalis toxicity Co-administration with Raloxifene or Hormone replacement therapy did not alter the effects of Teriparatide on serum or urine calcium or on clinical adverse events
Strontium Ranelate	• Stimulation of osteoblast precursor replication and	Very commonly (>1/10): • Hypersensitivity skin reactions (rash, urticarial,	• Current or previous venous thromboemboli	No clinically relevant events were observed in episodes of overdoses during clinical trials (up to	• Interferes with colorimetric methods for the determination of

	collagen synthesis in bone cell culture. • Inhibition of osteoclast differentiation and activity. Slight decreases in calcium and parathyroid hormone (PTH) serum concentrations • Increases in blood phosphorus concentrations and in total alkaline phosphatase activity	angioedema and pruritus) • Muscle spasm • Myalgia • Bone pain • Arthralgia • Pain in extremity Ischemic heart disease, peripheral arterial illness and hypertension have been reported as potential related events	c events, including deep vein thrombosis and pulmonary embolism. • Temporary or permanent immobilization • History of ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease. • Uncontrolled hypertension.	4 g/day for a maximal duration of 147 days), Administration of milk or antacids may be helpful to reduce the absorption of the active substance.	blood and urinary calcium concentrations. • Food, milk and derivative products, and medicinal products containing calcium may reduce the bioavailability of strontium Ranelate by approximately 60-70%. • Form complexes with oral tetracycline and quinolone antibiotics at the gastro-intestinal level and thereby reduce their absorption • The administration of antacids as aluminum and magnesium hydroxides either two hours before or together with strontium Ranelate caused a slight decrease in the absorption of strontium Ranelate.

Estrogens	• Proinflammatory effects by the inhibition of cytokines= Interleukines (IL-1 and IL-6), tumor necrotic factor (TNF-α), granulocyte macrophage colony-stimulating factor, macrophage colony-stimulating factor (M-CSF), and prostaglandin-E2 (PGE2). Inhibiting the pool size of pre-osteoclasts and therefore the bone resorption, in addition PGE2 increases RANKL and decreases OPG • Stimulation of TGF-β, which decreases activity and increases	Very common side effects (>1/10): • Nausea • Vomiting • Abdominal pain • Anorexia • Depression • Vaginal hemorrhage • Breast secretion • Gynecomastia • Amenorrhea • Dysmenorrhea • Cholestasis • Hepatitis • Jaundice • Dizziness • Headache • Alopecia • Endometrial hiperplasia • Increase in weight	• Breast cáncer • Estrogen-related malignancy. • Vaginal haemorrhage Non-treated endometrial hyperplasia. • Idiopatic venous embolism • Recent history of embolic illness • History of hepatic illness • Porphyria.	• Nausea • Vomiting • Bleeding Overdose can be reverted with gastric evacuation and administration of active coal	Metabolism can be increased with: • citocrome P450 induzed drugs (anticonvulsivants (Phenobarbital, Fenitoine, Carbamazepine), Meprobamate, Phenilbutazone and anti-infective drugs (Rifampicine, Rifabutine, Nevirapine, Efavirenz)). • Hypericum Perforatum. Estrogen decreases anticoagulant and hypoglycemic drugs.

	apoptosis of osteoclasts.				
Bazedoxifen (Selective-estrogen receptor modulator (SERM))	Developed in order to obtain favorable effects of the estrogens on the skeleton and lipid metabolism with the additional improvement of a neutral effect on hot flushes and without stimulating the uterus or the breast.	Very common side effects (> 1/10): • Hot flushes • Muscle spasms • Peripheral edema Common side effects (>1/100 to <1/10): • Hypersensitivity • Somnolence • Dry mouth • Urticarial • Rash, • Pruritus • Blood triglycerides increases, Alanine and Aspartate aminotransferases increases	• Active or past history of venous thromboembolic events • Unexplained uterine bleeding. • Patients with signs or symptoms of endometrial cancer	In the case of overdose, there is no specific antidote, and treatment should be symptomatic	• Increases hormone-binding globulin concentrations, including sex steroid, thyroxin and corticosteroid binding globulins, • The metabolism of Bazedoxifene may be increased by concomitant use of substances known to induce uridine diphosphate glucuronosyltransferase (UGTs), such as rifampicin, phenobarbital, carbamazepine, and phenytoin, because Bazedoxifene undergoes metabolism by UGT enzymes in the intestinal tract and liver
Raloxifen (Selective-estrogen	Reproduces the beneficial effects of estrogens on the	Very common (> 1/10): • Vasodilation (hot flushes)	• Active or past history of venous	• In adults, symptoms of leg cramps and	• Co-administration with Warfarin does not alter the

receptor modulator (SERM))	skeletal systems, without the negative effects estrogens on breast and endometrium.	• Gastrointestinal symptoms a such as nausea, vomiting, abdominal pain, dyspepsia • Flu syndrome • Increased blood pressure Common (>1/100 to <1/10): • Headache, including migraine • Rash • Leg cramps • Mild breast symptoms a such as pain, enlargement and tenderness • Peripheral edema	thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis. • Hepatic impairment including cholestasis. • Severe renal impairment. • Unexplained uterine bleeding. • Signs or symptoms of endometrial cancer	dizziness have been reported in patients who took more than 120 mg as a single ingestion. • In accidental overdose in children younger than 2 years of age, the maximum reported dose has been 180 mg. In children, symptoms of accidental overdose included ataxia, dizziness, vomiting, rash, diarrhea, tremor, and flushing, and elevation in alkaline phosphatase. There is no specific antidote for Raloxifene hydrochloride.	pharmacokinetics of either compound, however, modest decreases in the prothrombin time have been observed • Cholestyramine (or other anion exchange resins), reduces significantly the absorption and enterohepatic cycling of Raloxifene. • Peak concentrations of Raloxifene are reduced with co-administration with Ampicillin • Raloxifene modestly increases hormone-binding globulin concentrations, including sex steroid, thyroxin and corticosteroid binding globulins, with corresponding increases in total

					hormone concentrations. These changes do not affect concentrations of free hormones
Alendronate (Bisphosphonate)	Binding to bone-surface hydroxyapatite sites Bisphosphonates reduce osteoclast activity	Common (>1/100 to <1/10): • Headache • Abdominal pain • Dyspepsia • Constipation • Diarrhea • Flatulence • Oesophageal ulcer • Dysphagia • Abdominal distensión • Acid regurgitation • Musculo-skeletal pain Rarely (1/1000<1/10000): • Atypical femoral fracture • Osteonecrosis of the jaw	• Esophageal malfunction, stenosis, achalasia • Inability to stand up or sitting at least during 30 minutes • Hypocalcaemia.	There is no data of Alendronate overdose, but the expected symptoms are: • Hypocalcaemia • Hypophosphatemia • Stomach ache • Pyrosis • Gastritis • Esophagitis • Ulcer Never should it be reverted with gastric evacuation because the potential esophageal pain effect. The best option is the administration of milk or antacids.	• Water, other liquids, any food or any drug may interfere in the Bisphosphonate absorption if these are taken within 30 min of drug administration • Divalent cations may interfere in the Alendronate absorption • No other kind of interactions
Risendronate (Bisphosphonate)	Binding to bone-surface hydroxyapatite sites Bisphosphonates reduce osteoclast activity	Common (>1/100 to <1/10): • Headache • Constipation • Dyspepsia • Nausea • Abdominal pain • Diarrhea • Musculo-skeletal pain	• Esophageal malfunction, stenosis, achalasia • Inability to stand up or sitting at least during 30 minutes • Hypocalcaemia	There is no data of Risendronate overdose, but the expected symptoms are: • Hypocalcaemia Never should it be reverted with gastric evacuation because the potential esophageal pain effect. The best option is	• Water, other liquids, any food or any drug may interfere in the Bisphosphonate absorption if these are taken within 30 min of drug administration • Divalent cations

		Rarely (1/1000<1/10000): • Atypical femoral fracture • Osteonecrosis of the jaw	• Renal insufficiency (creatinine clearance< 30ml/min)	the administration of milk or antacids.	may interfere in the Risendronate absorption
Ibandronate (Bisphosphonate)	Binding to bone-surface hydroxyapatite sites Bisphosphonates reduce osteoclast activity	Very common (> 1/10): • Esophagitis • Gastritis • Gastroesophageal reflux • Dyspepsia • Diarrhea • Abdominal pain • Nausea • Headache • Face eruption • Arthralgia • Mialgia • Musculo-skeletal pain • Influenza like-illness Common (>1/100 to <1/10): • Asthma exacerbation • Dizziness • Ulcer • Oesophageal ulcerations or strictures and disphagia • Vomiting • Flatulence • Backpain • Fatigue	• Esophageal malfunction, stenosis, achalasia • Inability to stand up or sitting at least during 30 minutes • Hypocalcaemia.	There is no data of Ibandronate overdose, but the expected symptoms are: • Hypocalcaemia • Hypophosphatemia • Stomach ache • Pyrosis • Gastritis • Esophagitis • Ulcer Never should it be reverted with gastric evacuation because the potential esophageal pain effect. The best option is the administration of milk or antacids.	• Water, other liquids, any food or any drug may interfere in the Bisphosphonate absorption if these are taken within 30 min of drug administration • It is recommended to avoid milk and its derivate 6 hours before and 1 hour after Bisphosphonate administration • Intravenous Ranitidine administered concomitantly produced an increase of the Ibandronate biodisponibility • Drugs with divalent cations, like antacids or calcium supplements can decrease

		Rarely (1/1000<1/10000): • Atypical femoral fracture • Ocular inflammation Very rarely (<1/10000): • Osteonecrosis of the jaw • Anaphylactic shock			Ibandronate absorption
Zolendronic acid (Bisphosphonate)	Binding to bone-surface hydroxyapatite sites Bisphosphonates reduce osteoclast activity	Very common (> 1/10): • Hypophosphatemia Common (>1/100 to <1/10): • Anemia • Headache • Conjunctivitis Nausea • Vomiting • Anorexia Bone pain • Myalgia • Arthralgia • Generalized pain Renal insufficiency Fever • Flu-like syndrome (including fatigue, chills, malaise and flushing) • Increased blood urea and creatinine • Hypocalcemia Rarely (1/1000<1/10000): • Atypical femoral fracture • Atypical femoral fracture	No different from the usual of Bisphosphonates, as well as drug intolerance, pregnancy or lactation*	It has been reported the overdose of 48 mg of Zolendronic Acid by mistake, the symptoms observed were: • Renal function impairment • Serum calcium, phosphorus and magnesium levels alteration In case of hypocalcemia, it is recommended to perform calcium gluconate perfusions	• Aminoglucosides administered concomitantly with Zolendronic produce an additive effect developing a hypocalcaemia in long-term treatments • It must not be administered with other nephrotoxic potential drugs. • It has been reported cases of osteonecrosis of the jaw when Zolendronic has been administered with antiangiogenics agents

Denosumab	Human monoclonal antibody (IgG2) with high affinity to RANKL, inhibiting the action of RANK, and therefore the osteoclast formation, function and survival.	Very common (> 1/10): • Pain in extremity • Musculoskeletal pain Common (>1/100 to <1/10): • Urinary tract infection • Upper respiratory tract infection • Sciatica • Cataracts • Constipation Abdominal discomfort • Rash • Eczema Rarely (1/1000<1/10000): • ONJ • Atypical femoral fractures	Hypocalcaemia	There is no experience with overdose	There are no clinical data on the administration of Denosumab and oestrogen's therapy concomitantly, however the potential for a pharmacodynamic interaction is considered to be low. No other alterations identified.

*The use of all of these anti-osteoporotic drugs are not recommended in case of intolerance to either, the drug or some formulation excipient, also in pregnancy or breastfeeding women. These drugs are no clinically tested in children in any study.

Table 3:

2001079 Study, Long-term use of Risendronate, 2 groups, 30 women included in group 1 received placebo from years 1 to 5, Risendronate for years 6&7 and nothing for year 8, and the 31 women randomized into group 2 took Risendronate from year 1 to 7 and nothing for year 8 [149]

Change in BMD (%)	**Day1Year1-M6 Year8 in Group 1**	**Day1Year1-M6 Year8 in Group 2**	**Day1 Y1-M12 Y8 in Group 1**	**Day1 Y1-M12 Y8 in Group 2**
% in lumbar spine BMD (mean % of change+/- standard error)	6,2217+/- 1,82459	12,7784+/- 2,09663	5,5312+/- 1,66394	13,3472+/- 2,09761
% in femoral neck BMD	-1,0384+/- 2,19722	1,4797+/- 1,03811	-0,2530+/- 1,80000	3.2192+/- 3,55882
% in femoral trochanter BMD	1,6386+/- 1,39295	4,4060+/- 1,54420	1,9561+/- 1,37883	2,23334+/- 1,37500
% in total proximal femur BMD	-1,3867+/- 1,98837	3,3871+/- 0,9671	-2,2999+/- 1,67680	0,6672+/- 0,99708

Table 4:

Bisphosphonate long-term clinical trials reductions in risk fracture [146,148-151]

BISPHOSPHONATE	VERTEBRAL FRACTURE REDUCTION IN 1 YEAR	NON-VERTEBRAL FRACTURE REDUCTION IN 1 YEAR	HIP FRACTURE REDUCTION IN 3 YEAR
RISENDRONATE	69%	74%	60%
ALENDRONATE	55%	47%	53%
IBANDRONATE	49%	69%	NON SIGNIFICATIVE

Table 5:

Bazedoxifene and Raloxifene Incidence vertebral risk reductions compared with Placebo after 3, 5 and 7 years treatment [134, 146]

Vertebral fracture relative risk reduction compared with placebo	Bazedoxifene 20mg	Bazedoxifene 40mg	Raloxifene 60mg
3 years	42%	37%	42%
5 years	36%	NA	NA
7 years	30%	NA	NA

Table 6:

Price of Spanish Osteoporosis treatments commercialized (Nov2012) [171]

DRUG	GENERIC AVAILABLE	PRICE PER BOX (€)	PRICE PER DOSE (€)
Alendronic Acid	Yes	12,49	0,45
Alendronic Acid plus vit D	No	28,01	1
Etidronic acid	No	4,57	0,30
Ibandronate	Yes	20,79	0,69
Risendronate	Yes	23,65	0,79
Zolendronic Acid	No	417,40	1,17
Denosumab	No	240,15	1,32
Raloxifene	Yes	20,64	0,74
Strontium Ranelate	No	49,39	1,76
Teriparatide	No	405,38	14,48

Can healthy life prevent us from post-menopausal osteoporosis? Myths and trues

Can healthy life prevent us from post-menopausal osteoporosis? Myths and trues

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ABSTRACT:

Unfortunately, post-menopausal osteoporosis illness is closely related to heredity, raze, gender and age, all of these are factors that cannot be modified. However, factors such as activity, body mass, hormone and calcium levels and dietary habits are modifiable factors that can reduce fracture risk factors. Significant increases in bone mass density has been linked to physical activity in children, supplements of Vitamin C taken for more than 10 years, and high consumption of fish or olive oil or dried plums. This study is aimed at established the scientific rational that there is behind the recommended practices. The results showed an important lack of clinical trials in postmenopausal women to establish effective dose of alternative therapies regarding fracture risk reduction. Therefore, in some cases, conclusions are based on epidemiology studies and in others on the extrapolation of data obtained from those pre-clinical trials carried out in ovariectomized rats. Collagen, Lycopenes, Hesperidin and Green tea develop changes in bone biomarkers levels. Isoflavones prevent bone loss in studies with ovariectomized rats. Although some daily foods demonstrate positive effects in BMD and bone mineral content, food will never be as effective as drugs. However, they have the advantage of the lack serious adverse events.

Keywords: Post-menopausal Osteoporosis; Bone mass density; Clinical Trials; Dietary Activity;

1. Introduction

Despite of incident osteoporotic fractures has been stabilizing during the last years; hip and vertebral fractures are still associated with mortality risk, mainly in elderly. [172]. In fact, according to estimations, approximately 40% of women and 13% of men older than 50 years will have an osteoporotic related fracture in their lifetime. With these percentages, osteoporosis leads the cause of morbidity and mortality in elderly. [173]

Epidemiological studies showed that if we get a 10% increase in the peak bone mass (the maximum bone mass accrual achieved at the end of growth) then we are be able to reduce post-menopausal osteoporotic fracture risk by 50% [174-176]

Low Bone Mass Density (BMD) means higher risk of vertebral fractures, 1 T-Score standard deviation reduction reflects in 2 increases of percentage of fracture risk [177]

However, some post-menopausal osteoporotic fracture risk factors cannot be modified as well as:

- Age: each decade the risk of fractures as consequence of post-menopausal osteoporosis is increased in 1,4 - 1,8 [178] (Table 1)

Table 1:
Age-related osteoporosis in Spanish women [178]

Women-Years old	Lumbar Spine Osteoporosis (%)	Femoral neck Osteoporosis (%)
45-49	4,31	0,0
50-59	9,09	1,3
60-69	24,29	5,71
70-79	40,0	24,24

- Raze: White raze and Oriental raze have more risk of osteoporotic women fractures than Black raze or Polynesian raze [179]
- Family history: it has been demonstrated that women who had mother with femur fracture has more probability to have a fracture related to osteoporosis, in fact, between 60% and 80% of the variance in the peak bone mass can be explained by genetic factors [174]

- Estrogens: despite of we can intercede in the estrogen serum levels taking drugs to equilibrate hormone levels during the menopause, it is demonstrated that early menopause and late menarquia increased fracture risk factors, and we can't modified both factors on time [178]

Nevertheless, there are a large number of risk factors in fracture development associated to post-menopausal osteoporosis that can be affected by our habits. Some of these are the tobacco use and alcohol intake [178], weight [180], sedentary lifestyle [181], vitamin D and calcium deficit and hyper-protein diet [182]. In addition, some studies showed benefits in the daily consumptions of vegetables [183, 184], olive oil [185], orange juice [186], fruits [187], collagen [188], soy [189] and tea [190].

Despite there is an important lack of clinical trials that demonstrate the efficacy in humans, data obtained from pre-clinical trials and from epidemiology studies have been interpreted to recommendations for reducing fracture risk in PMW.

In this review, pre-clinical studies, clinical trials and epidemiological studies performed with the most popular alternative therapies used for the treatment of post-menopausal osteoporosis in women have been analyzed trying to find out if these have or not efficacy in the prevention or treatment of the illness.

Unfortunately, post-menopausal osteoporosis (PMO) illness development is closely related to heredity, raze, gender and age, all of these are factors that cannot be modified, but some studies demonstrated that activity, body mass, hormone and calcium levels and dietary habits are modifiable factors that can reduce fracture risk factors.

The objective of this review is to find out for results regarding fracture risk reductions in post-menopausal women (PMW) when dietary and/or activity were modified, and we try to conclude if these changes have really significance or not.

2. ***Material and Methods***:

We have reviewed information already published in Scientific Publications as the British Journal of Clinical Pharmacology, Nutrients, the National Institutes of Health, the Journal of Nutrition, the Ontario Health Technology Assessment Series, Preventive Medicine and Nutrition, Metabolism and Cardiovascular Disease both from Elsevier, the Spanish Public Health Journal, etc.

And this information has been searching using PubMed with keywords as Post-menopausal Osteoporosis, Bone mass density, Clinical Trials, Dietary, Activity.

3. Results

a. Physical activity

When a subject is immobilized, the stimulus for bone acquisition is insufficient and resorption gained to bone formation, it happens because osteocytes, as bone pressure receptors do not detect gravity properly. The same problem has thin or lean people. For this reason, it is very important to practice regular exercise, better hitting the ground. In fact, three controlled trials done in pre- and peri-pubertal American children showed that jumping several minutes three times a week stimulated bone formation. McKey demonstrated that trochanteric BMD increased in interventional group vs control group when jumps were tracked 3 times a week for 8 months in 144 children from 6 to 10 years old [191]. Mackelrie measured BMD in 177 children with ages between 8 and 11 years old, who jumped 10 minutes 3 times a week for 7 months, in these, femoral neck and spine BMD increased in interventional group vs control group in early puberty, but no effects were observed in pre-pubertal girls [191, 192]. Fuchs evaluated BMD in 89 children (5-9 years old) who jumped 100 times 3 times a week for 7 months, results showed that spine BMD increased more in interventional group vs

control group [193]. Another 6-year longitudinal study [194] demonstrated that the most active teenagers have more bone mineral content (BMC) in spine, femoral neck and whole body than those who are inactive. (Table 2)

Table 2:
Relationship between activity and fracture risk reduction in children [191-194]

Study main author	Fracture risk reduction measure	Population	Duration
Fuchs [194]	BMD spine increases	89 children (5-9 years old)	7 months
McKey [192]	BMD thochanteric increases	144 children (6-10 years old)	8 months
McKelrie [193]	BMD femoral neck and spine increases	177 children (8-11 years old)	7 months
Bailey [195]	BMC in spine, femoral neck and whole body	Teenagers	6 years

However, after menopause, there is no evidence that physical activity prevents bone loss or increases BMD. Possible reasons are (i) limitations of the skeleton capacity to adapt it to mechanical stress of exercise, (ii) altered hormonal status, (iii) inadequate calcium availability or (iv) low intensity of exercise in training studies [181]

In PMW, physical inactivity was associated with an increased risk of hip fracture but no with the risk of ankle and/or wrist fractures. The cumulative absolute risk for ages 50 to 84 was 2.5% for ankle fracture, 5.0% for wrist fracture, and 6.2% for hip fracture. [195]

Anyway regular exercise is strongly recommended suggesting dynamic exercise as more effective than static, better if it is intermittent and it exceed a threshold intensity and strain frequency, [181]

Increasing bone mass index is associated with a reduced risk of hip fracture but conversely the risk of injury may be increased while participating in physical activities. [196] The relationships of Body Mass Index (BMI) and physical activity to fracture risk were independent of one another for ankles, wrists, and hips.

Fracture risk is increased in people with weight less than 50 kilograms or with low BMI (<20.0 kg/m2), because at is has been described above due to “anti-gravity” effect and also because adipose tissue is a barrier that protects bone during a fall [198] and stimulates endogenous estrogen production [198]. In fact, increasing adiposity was associated with a reduced risk of wrist and hip fractures, but with an increased risk of ankle fracture (Table 3) [195].

Table 3:
Association between adiposity and relative risk (RR) fracture of wrist, hip and ankle [195]

Compared with lean women (BMI of <20.0 kg/m2)	**RR for ankle fracture**	**RR for wrist fracture**	**RR for hip fracture**
women of normal weight (BMI 20.0–24.9 kg/m2)	1.77 (95%CI 1.46–2.14)	0.88 (95%CI 0.80–0.97)	0.51 (95%CI 0.46–0.56)
overweight women (BMI 25.0–29.9 kg/m2)	2.62 (95%CI 2.16–3.17)	0.71 (95%CI 0.65–0.79)	0.34 (95%CI 0.30–0.37)
obese women (BMI of ≥30.0 kg/m2)	3.07 (95%CI 2.53–3.74)	0.57 (95%CI 0.51–0.64)	0.23 (95%CI 0.21–0.27)

Although the increase of adiposity could be a benefit to avoid fractures, the prevalence of obesity in children is an alarming fact that motivated to evaluate ***fatty diets*** in both skeletally immature (5 weeks old) and in mature (20 weeks old) male mice. Data obtained suggested that fatty diets can reduce bone, mainly femoral trabecular bone in children and that it is very difficult to recover this mass.

Immature mice who received high fat-content diet had greater decrease on femoral trabecular bone than mature mice (P=0.017 by 2-way ANOVA) and also immature mice who after 12 weeks of high fat-content diet switched to low fat diet did not recover the bone already loss. However, mature mice recovered their femoral trabecular bone. [199]

In the opposite side of high level of activity, there are persons with ***anorexia*** that carried out almost no physical activity. A study done with 34-year-old Japanese women

with anorexia nervosa demonstrated that bone mineralization is closely related to food intake. In these patients, the established malnutrition developed a reduction in bone formation and activation in bone resorption by osteoclast, because of previous formation of empty lacunae in bone. [200]

b. Calcium, vitamin D and Proteins

Despite of ***calcium, vitamin D and proteins*** are the most important nutrients for bone. However, in some countries where citizens have the adequate daily intake of calcium, the post-menopausal osteoporosis presents high rates.

In fact, BMD increases have been directly associated to a balanced dietary pattern consisting of the consumption of legumes, rice, seafood, nuts, vegetables and fruits [202]. European guidance for the diagnosis and management of osteoporosis in PMW recommends a daily intake of at least 1000 mg/day for calcium, 800 IU/day for vitamin D and 1 g/kg body weight of protein for all women aged over 50 years [182]

The intake of food as sardine, milk, yogurt and cheese ensure higher levels of calcium (Table 4), oily fish (mainly in salmon, tuna and sardine), liver, butter, fatty cheese, eggs and mushrooms guarantee a proper intake of vitamin D (Table 5).

Table 4:

Foods with higher content of Calcium [182, 201]

Food	Serving size	Calcium mg
Custard	100g	100
Almonds	50g	110
Tofu	100g	150
Salmon, tinned, red	100g	220
Sardines, canned	100g	380
Cheese, mild	40g	300
Yogurt, plain	200g	390
Milk, reduced fat (1%)	250ml	352
Milk, regular	250ml	285
Milk, skim	250ml	320

Table 5:

Foods with higher content of vitamin D [181, 201]

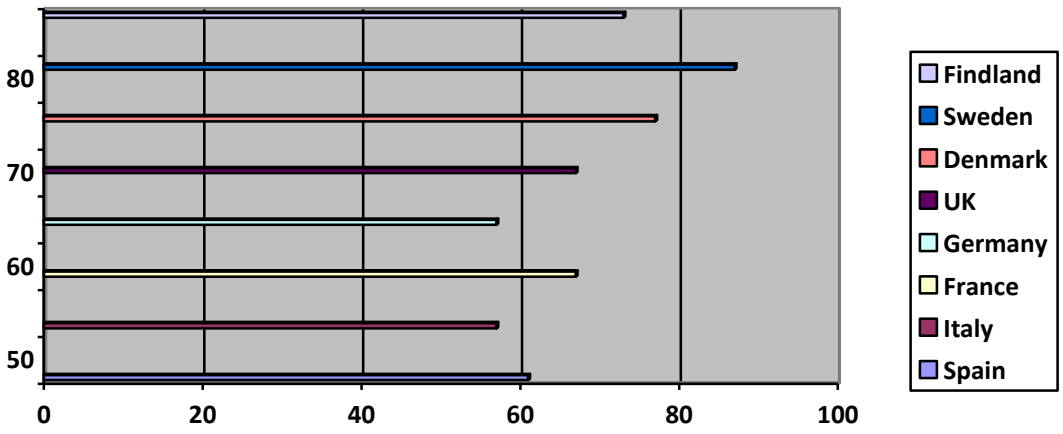
	Portion	Vitamin D quantity
Sockeye salmon	1 Fillet 3-ounces (= 85, 049 g)	450 IUs
Canned tuna	4-ounces (= 113,40 g)	150 IUs
Canned albacore tuna	4-ounces (= 113,40 g)	50 IUs
Canned sardines	2-units	40 IUs
Mushrooms (Dole's Portobello Mushrooms)	3-ounces (= 85, 049 g)	400 IUs
Egg (mainly in yolk)	1-unit	40 IUs
Beef liver	3.5-ounce (=99,223 g)	50 IUs
Cod liver oil	1-tablespoon	1300 IUs

However, the most important contribution of Vitamin D comes from 7-dehydrocholesterol in the skin that during the exposure to sunlight absorbs solar radiation with energies between 290 and 315 nm (ultraviolet B) transforming it into pro-vitamin D3 (cholecalciferol). Once in the human organism, cholecalciferol is hydroxylated into the liver to 25-hydroxyvitamin D3, which is transformed in the active metabolite, 1,25-dihydroxyvitamin D3, mainly in the kidney.

The optimal absorption of vitamin D is produced at high latitudes. In contrast, in these zones, there are less hours of sunlight per day. However, figure 1 shows that people who live in Nordic countries has better serum vitamin D levels than those who live in Mediterranean countries, maybe, because in the formers uses to take daily products as milk or orange juice fortified with vitamin D_2 (ergocalciferol) [202].

Figure 1:

Serum 25(OH) D levels (y= nmol/l) in people who live in different European countries (x=degrees North), relationship between vitamin D and latitude [202] P<0,001



Based on the results of 5 Randomized Controlled Trials involving 1237 elderly women and men can be established that vitamin D reduced the fracture risk by 22% (corrected odds ratio, 0.78; 95% confidence interval [CI], 0.64-0.92) compared with patients

receiving calcium or placebo. [203]. However, in the study carried out within the Women's Health Initiative, in with 36282 women were randomized to receive either calcium 1000 mg/day and vitamin D3 400 IU/day or placebo, the reduction on fracture incidence was not significant (RR: 0,88, 95% CI). [204]

In fact, reviewing those trials performed with vitamin D and calcium supplementation, doses of vitamin D 800 IU/day showed better results regarding fracture risk reduction than lower doses. Regarding to calcium supplementation, there is little evidence to suggest that countries with lower dietary calcium intakes are at higher risk of osteoporotic fracture, but it is more complex to determine which dose is the better because clinical trials and prospective studies did not show differences in fracture risk when the dose of calcium was increased. Europe guidelines recommends at least of 800 mg/day of calcium daily for women aged 50-65, whilst in US the recommendation is of 1200 mg/day. Nevertheless an Iceland study suggested that it is not necessary a daily calcium intake >800mg/day for preventing an increase of serum PTH when serum 25(OH)D > 25 nmol/l. [205]

c. Collagen

The native collagen from animal tissues is gelatinized and hydrolyzed to obtain the Collagen Hydrolysate that help to improve the intestinal incorporation of its amino acids. This collagen hydrolysate consists of small peptides with a molecular weight lower than 5000 Da. Collagen as a supplement food, can improve bone-biomarkers levels, as it was demonstrated in a clinical trial performed in 108 PMW, who were randomized to receive Calcitonin or Calcitonin plus Collagen hydrolysate 10g per day during 24 weeks. Spine and forearm BMD values (measured by X-ray) did not change significantly, but it did in urinary excretion of pyridoline and deoxypyridonoline, and it was more marked in those women who received collagen than in those who only took calcitonin, also the effect was maintained in the first ones until 3 months after treatment discontinuation. [206] (Table 6)

Table 6:

Collagen supplements effects in bone-biomarkers in postmenopausal women [188]

	urinary excretion of pyridoline **% declined from basal levels**	**urinary excretion of deoxypyridonoline** **% declined from basal levels**
Calcitonin group 24 weeks of treatment	63,51%	70,40%
Calcitonin+collagen 10g/day 24 weeks of treatment	56,22%	56,10%
Calcitonin+collagen 10g/day 3 months after 24 weeks of treatment discontinuation	54,02%	56,66%

d. Lycopenes

Tomatoes and carrots have lycopenes, carotenoids not synthesized by animals or humans [207] widely studied because its antioxidative effect, protecting against some chronic diseases, including osteoporosis [208]. Studies performed in ovariectomized rats who received 30 and 40 mg/kg of lycopene vs placebo [209, 210] established that the benefits obtained from lycopenes regarding bone health are the increase of BMD and BMC. These results were similar to those observed in 1 randomized controlled trial and 2 epidemiology studies done in PMW, in which neither BMD nor BMC were measured, but positive effects in bone protection were obtained in all of them. [208, 211, 212]

Tomatoes have a minimum of 4.6% and a maximum of 15% of lycopenes, it is equivalent to 70-130 mg/kg depending on the variety. Its absorption is greatest when it is processed as juice or sauce.

Lycopene is extracted from the pulp of tomato using ethyl acetate as a solvent and is used as colorant to change yellow to red color in foods as cereals, bread, baked goods, spreads and some drinks. These tomato extracts has content in Lycopene ranging from 150 to 250 mg/kg.

Safety of Lycopenes has been evaluated in different studies, and only in long-term use, histopathological alterations as basophilic concentrations were observed in rats. In humans, only in the long-term use of lycopene-rich food and supplements, some case of yellow-orange skin discoloration or gastrointestinal discomfort have been reported, all of them were reversible upon cessation of lycopene ingestion. For this reason, on 2007, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) agreed the Acceptable Daily Intake (ADI) of lycopene of 0-0.5 mg/kg/day, both natural and synthetic, this last one, should be produced by co-fermentation of the fungus *Blakeslea trispora*. [213]

Commercial lycopene from *B. trispora* is intended for use in certain foods and beverages as a color. [214]. However, it also can be taken as a food supplement only if ADI is not overdue.

In the randomized controlled trial, post-menopausal women with ages between 50 and 60 years old received lycopene-rich tomato juice, lycopene capsules or placebo for 4 months. The measurement of N-terminal telopetide crosslinks of type I collagen (NTX) showed a reduction in those women who took lycopene vs placebo, and also a lower protein oxidation and lipid peroxidation were observed in them. [211]

The epidemiology study done in PMW from 50 to 60 years old showed reductions in NTX levels and also lower protein oxidation as well as it was determined in the randomized trial described above [208]

In the epidemiology done by Shani et al on 2009, elderly men and women (75 years old) with higher lycopene intake was associated with lower risk of hip fracture [212]

e. Olive oil

Olive oil has been also studied as fracture prevention in PMW because the incidence of fracture is less within Mediterranean citizens, in fact, phenols containing in olive oil increase alkaline phosphatase activity and calcium ions in the extracellular matrix of osteoblasts, therefore, stimulating bone formation. [185]

High consumption of fish and olive oil was positively associated with better BMD at lumbar spine and BMC in total body in an epidemiology study done in 220 healthy pre-peri- and postmenopausal Greek women, [215]

Similar effects were previously identified in two pre-clinical trials with ovariectomized rats. In one of these, rats were dosed with either 2.5, 10 or 15 mg/kg mg/kg body weight per day for 100 days of oleuropein, an olive oil phenolic compound with anti-inflammatory and anti-oxidative properties. The measurement of BMD showed a reduction in the total femur, metphyseal and diaphyseal subregions. In the other study, ovariectomized rats were randomized during 3 months to receive either 25 g of peanut oil plus 25 g of rapeseed oil/kg, 50 g of olive oil/kg or 0.15 g of oleuropein/kg. Both, Oleuropein and olive oil prevented the bone loss happened in ovariectomized rats, but these had no effect on plasma osteocalcin nor on urinary hydroxipiridoline, both bone biomarkers. [216, 217]

However, no clinical trials with established dose have been found regarding olive oil benefits in PMW.

f. Isoflavones

Because of the important side effects of the Hormone Substitutive Therapy (HST), some women have decided to change it for Isoflavones (Soy protein) because they are

considered as estrogen-like compounds, but are there enough studies that corroborate the theory of isoflavones can be manage as a substitutive of HST?

The effects of isoflavones, such as bone loss prevention, were demonstrated in studies with ovariectomized rats [218]. However, there are some discrepancies in those performed last years in PMW randomized to receive either isoflavones or placebo. The majority of the studies showed improvements in BMD of women treated with isoflavones, but some studies did not find significance differences between both groups.

There are one study that compared isoflavones (84 or 125 mg/day) with estrogen therapy (2,5 mg/day) in 97 PMW for 24 weeks. Estrogen showed better results in BMD improvement, but isoflavones not only prevent the 4% of BMD natural loss estimated per year in the 5 first years of menopausal period, but also improve BMD in Femur's neck, Ward's Triangle and Lumbar Spine (Table 7) [189, 219-228]

Table 7:
Randomized, double-blind and placebo controlled trials done to evaluate effects of soy isoflavones in post-menopausal women [189, 228-237]

POSSITIVE STUDIES	POPULATION	COHORTS	DURATION	ENDPOINTS	RESULTS
SIRBL (Soy Isoflavones for Reducing Bone Loss study) [189]	43-63 years old healthy PMW (post-menopausal women)	-Soy isoflavones 80 mg/daily -Soy isoflavones 120 mg/daily -Placebo	3 years	BMD and strength (measured by peripheral quantitative computed tomography)	-120mg dose was protective of cortical BMD - 80mg dose was protective as bone turnover increase (p=0,011) - both doses showed modestly beneficial for midshaft femur BMD as time since last menopausal period increased and also for midshaft femur strength-strain index as bone turnover increased
Soy isolate protein and Resistance exercises [228]	60 PMW with osteopenia or osteoporosis and sedentary Mean age 54,55 years old	-Soy isolate protein -Soy+ exercise (progressive resistance exercises 4 times/week for 12 weeks) -Placebo	12 weeks	-Muscle performance (measured by isokinetic dynamometry) -Bone health (measured by ultrasounds densitometry)	-Significant changes were observed in the analysis of variance in both groups who received soy (p<0,5) in either muscle performance or bone health. -The best improvements were observed in the group who also do exercise
Soybean isoflavones extract attenuating bone loss [229]	97 healthy post-menopausal women	-Soy extract 84 mg daily –Soy extract 126 mg daily -Estrogen 2,5 mg per day. Women also took 250 ml of milk, 300 mg of calcium and 100 UI of vitamin D per day. Also women were advised to practice 30 to 45 minutes of mild exercise daily	24 weeks	BMD in femur's neck, ward's triangle and lumbar spine	Although estrogen gave the best results in bone healthy, soy extract showed not only prevention of bone loss but even increases of BMD, showing a dose-response curve, therefore, soy extract can be a good natural alternative to estrogen treatment

Soy isoflavones on bone mineral content [230]	175 post-menopausal Chinese women	-40 mg/daily of isoflavones -80 mg/daily of isoflavones -Placebo They also received 500 mg calcium and 125 IU vit. D per day	12 months	BMC and BMD of the whole body, lumbar spine, left hip and femoral's neck	-An increase of 1mg of isoflavones per day was associated with a yearly increase of 0.019-0.028% of BMC - The better results were obtained with the 80 mg daily dose and these were positive, taking into account that on average postmenopausal women lose 4% of bone mass yearly.
Soy isoflavone extract supplements on bone mineral density [231]	1240 PMW	-Soy Isoflavones from 47 mg/daily to 150mg/daily -Placebo	12 months	BMD (measured by DXA) in spine, femoral neck, trochanter and total hip	-A meta-analysis showed that daily ingestion of an average of 82 (47-150) mg soy isoflavones for 6-12 months significantly increased spine BMD by 22.25 mg/cm2 (95% CI: 7.62, 32.89; P=0.002), or by 2.38% (95% CI: 0.93, 3.83; P=0.001) compared with placebo. -But no significant increase was found on femoral neck, total hip or trochanter.
Osteoporosis Prevention Using Soy (OPUS) [232]	406 postmenopausal women in their early years of menopause from United States	- Isoflavones 80mg per day - Isoflavones 120 mg per day -Placebo	2 years	-Safety -Efficacy (BMD in whole body, BMC, serum bone metabolism biochemical markers)	-Reductions in BMD in whole-body were less in the group taking 120 mg than in those who were taking placebo. -Benefit was not observed regarding neither in the BMC nor in serum bone metabolism biochemical markers

NEGATIVE STUDIES	**POPULATION**	**COHORTS**	**DURATION**	**ENDPOINTS**	**RESULTS**
Soy isoflavones in the prevention of menopausal	45-60 years old women within 5 years of menopause with	-Soy isoflavones 20 mg daily (n=122)	2 years	-Bone loss measured by BMD (DXA) in lumbar spine,	- No significance changes in BMD between both groups were found it (BMD changes in spine -2,0% vs -2,3%; in total hip -1,2% vs -1,4% and in femoral neck -2,2% vs -2,1%)

bone loss and menopausal symptoms [233]	Tscores> or equal to -2.0 in lumbar spine or total hip	-Placebo (n=126)		total hip and femoral neck -Menopausal symptoms - Changes in vaginal cytology characteristics - Changes in serum and urine N-telopeptide of type I bone collagen - Changes in serum lipids and TSH	- There were more hot flushes reported in Soy group
Soy isoflavone on bone mineral density in postmenopausal Taiwanese women with bone loss [234]	431 Post-menopausal Taiwanese women from 45 to 65 years old	-Soy isoflavones 300 mg/daily (n=217) -Placebo (=214) Both groups also ingested 600 mg of Calcium plus 125 IU of vitamin D3 daily	2 years	-BMD ((DXA) in proximal femur and lumbar spine -Bone biomarkers (serum alkaline phosphatase and urinary N-telopeptide of type I collagen)	-Not statistically significant differences between both groups neither in BMD (P=0,42 in spine and P=0,39 in femur using generalized estimating equation) nor in bone biomarkers
Effect of milk product with soy isoflavones on quality of life and bone metabolism [235]	99 Post-menopausal Spanish women	-48 women consumed milk enriched with soy isoflavones (50mg/day) -51 women control	1 year	-BMD estimated by ultrasounds of the calcaneous -Bone biomarkers	-BMD increased in those women who consumed milk (P=0,040) and no significant differences were found it in women who participated in control group -There were no significant differences in serum bone biomarkers.

				-Quality of Life (QoL) using Cervantes Scale	
STUDIES WITH NO RESULTS PUBLISHED YET	**POPULATION**	**COHORTS**	**DURATION**	**ENDPOINTS**	**RESULTS**
(SPARE) Study--a clinical trial of the effects of soy isoflavones in menopausal women [236]	283 PMW from 45 to 60 years old, without osteoporosis and within 5 years from menopause, 66,1% of women were Hispanic white	-Soy isoflavones 200mg/daily -Placebo	2 years	-Spine and hip BMD -Urinary phytoestrogens -Serum lipids, TSH and estradiol -QoL -Menopausal symptoms, mood changes and depression	-It is expected that this trial will give us information still unavailable on the benefits of purified soy isoflavones in the prevention of bone loss and menopausal symptoms in the first 5 years of menopause
Bone response to soy isoflavones in women [237]	234 non-osteoporotic women from 45 to 65 years old within 10 years of menopause, they were from Iowa and California	-Isoflavones rich soy extract 80 mg /daily - Isoflavones rich soy extract 120 mg /daily -Placebo	3 years	-BMD lumbar spine -Bone turnover biomarkers -Serum levels of estrogens, sex hormone-binding globulin, insulin-like growth factor	It is expected that after 3 years treatment those women who received either 80 or 120 mg of soy extract will improve their BMD in lumbar spine without put into a risk their safety

		(IGF-I) and vit D -Safety

The most new regarding isoflavones for the PMW osteoporosis treatment is the study of a metabolite of the soybean isoflavone diadzein, it is theEquol (O-desmethylangolensin (O-DMA)). Depending of the intestinal bacterial profile, there are people who can produce or not equol. Last theories suggest that if habitual dietary patterns are modified, the intestinal bacterial profile can be influence in the isoflavones metabolism. [219] Therefore, the increase in the production of equol, also increase the estrogen effect and consequently the benefits of soy.

However, it is needed to do more studies regarding it because for example, it has been demonstrated that 5 g/day for 2 weeks of fructooligosaccharides does not modulate the capacity of intestinal microbiota to produce equol in Japanese PMW. [220]

a. Vitamin C

Because the antioxidative action of fruits and vegetables, these have been associated to better skeletal health, and ***vitamin C*** is responsible of an important part of this effect [187]. Some studies demonstrated its activity, and orange juice fortified with calcium and vitamin D could be a good option to increase these components in PMW daily intake [221]

A study done between 1892 post-menopausal women from Washington, determined that longer duration of vitamin C supplement intake, defined as more than 10 years, can be associated with higher hip BMD in those women aged between 55 and 64 years old, than in those who never used to took it (multivariate adjusted mean BMD 0.699 (0.017) g/cm2 versus 0.655 (0.007)g/cm2, P=0.02). There was no found it any association between vitamin C only obtained from diet and increases in BMD. The mean intake of vitamin C taken by women who took supplements was 407mg/day, and in women who only took vitamin C from the diet was 113mg/day. [222]

In the 5-years longitudinal study performed with post-menopausal Mexican American women, where diet was assessed using the modified National Cancer Institute Food Questionnaire, an evidence of a positive association between dietary vitamin C intake

and femoral neck BMD (measured by DXA) was found it (P=0.07), but vitamin C was not associated with lumbar spine BMD increases. [223]

b. Hesperidin

Citrus are rich in ***hesperidin***. Each orange has 31 to 43.2 mg/g of this flavonone. There is only one study in PMW available, in which, effects of hesperidin in BMD were evaluated after 1 year of treatment (500mg daily) vs placebo. The results do not show statistically significant differences were between both groups after 2 years of follow-up. However, women who were randomized to take hesperidin had better balance regarding bone turnover index (procollagen I N-terminal propeptide:carboxy-terminal collagen crosslinks type I ratio) [186]

c. Garlic and onions

Both, *Allium cepa* (Onion) [224] and *Allium sativum* (Garlic) [224] were studied in young ovariectomized rats to evaluate if its consumption could be related to positive effects in BMD. Bone resorption and loss were reduced in comparison with baseline values.

In the case of onion, its active ingredient, g-L-glutamyltrans S-1-propenyl L cystein sulfoxide (GPCS), inhibited osteoclastogenesis and had anti-reabsorptive effect because reduced deoxypyridinoline (Dpd) TRAP levels but does not changed alkaline phosphatase (ALP), TNF-α, or IL-632 levels in rats.

Allum sativum recovered BMD values significantly to baseline levels in ovariectomized –induced rats, but also, the levels of biomarkers like serum alkaline phosphatase, serum tartrate resistant acid phosphatase, urine hydroxyproline and urine calcium returned to normal values. These results give the option to take into consideration garlic as beneficial in bone resorption

d. Prunes

Prunes or dried plum are also considered as beneficial in the bone turnover, it was studied in 160 early osteopenic PMW (aged between 55 and 58 years old), they took

100 g daily of dried plums or a dried apple for control group. In addition, they were supplemented with 500mg of calcium plus 400 IU of vitamin D daily After 12 months, bone turnover biomarkers decreased significantly (BSLAP (=bone specific alkaline phosphatase), osteocalcin and TRAP (tartrate-resistant acid phosphatase-5b)) in women who took dried plum, as well as happened in BMD, that was increased in spine and ulna in comparison with dried apple group. [225]

e. Infusions

Common infusions that people use to take daily, such as Tea and *Angelica sinensis* (the most commonly herb taken in China) have been tested in rats to measure their anti-osteoporotic effects. A randomized controlled trial done in osteopenic women with ages between 56.5 and 58.3 years old, evaluate the effects of green tea polyphenols (500 mg/day vs. placebo). After 6 months, an increase in BSLAP was measured, but neither BMD nor BMC were determined [190]

Also green tea was evaluated in the epidemiology study done in men and women 50 years old or older, and a reduction of hip fractures were identified in this using a Questionnaire completed on health and lifestyle, but BMD was not measured in this study. [226]

Angelica sinensis extract demonstrated in ovariectomized rats that could be an effective natural alternative of oestrogens in PMO. In fact *Angelica sinensis* diels extract has also included in some dietary supplements for menopause in Europe and North America. Despite of *Angelica sinensis* has been widely studied in women, for both menopausal and breast cancer symptoms, there were not studies regarding its effects in bone mass protection. Therefore, it would be a promising filed for fully investigation that guarantee good results basing in those already obtained previously in rats. [227]

4. Conclusions

BMD increases when physical activity was stimulated, also BMC was increased in spine, femoral neck and whole body when active teenagers were studied. Vitamins as vitamin D demonstrated a reduction of fracture risk by 22%. Women who took vitamin C as a supplement for more than 10 years had higher BMD than women who never took it (multivariate adjusted mean BMD 0.699 (0.017) g/cm2 versus 0.655 (0.007) g/cm^2, P=0.02). High consumption of fish and olive oil was positively associated to better BMD at lumbar spine and BMC in total body. Collagen as a supplement had not any effect in BMD but developed changes in bone biomarkers levels. Lycopenes from tomato demonstrated positive effects in bone protection in post-menopausal osteoporotic women and hesperidin from citrus showed an improvement in the balance regarding bone turnover index. Isoflavones showed bone loss prevention in studies with ovariectomized rats, but after an intensive review of those clinical trials performed last years in PMW, we notice that there are some contradictions regarding if hormone substitutive therapy (HST) could be substitute by isoflavones or not. The intake of dried plums daily developed a reduction in bone turnover biomarkers. Green tea modified bone turnover biomarkers and its treatment developed a reduction in hip fractures, but no BMD was measured in both studies analyzed. Despite of post-menopausal osteoporosis illness have a big hereditary component, healthy life, involving equilibrate dietary patterns with daily aerobic activity, could help us in post-menopausal osteoporosis symptom reductions.

RESUMEN

RESUMEN:

1. Diagnóstico de la osteoporosis post-menopáusica alrededor del mundo

1.1. Introducción

El 60% de las fracturas vertebrales son silentes y no diagnosticadas, padecer una más allá de los 50 años incrementa 5 veces el riesgo de sufrir nuevas, por lo que un diagnóstico correcto prematuro de la osteoporosis es fundamental para frenar en lo posible la enfermedad.

Dicho diagnóstico debe comenzar por una entrevista con la paciente para identificar posibles factores de riesgo, como edad avanzada, menopausia temprana, fracturas de fragilidad previas o tratamiento con corticosteroides, y para descartar otro tipo de enfermedades como síndromes de malabsorción, artritis reumatoide, hiper- o hipo- tiroidismo o paratiroidismo, enfermedad renal o pulmonar.

Tras esto, una analítica ayudará a identificar si la fractura es debida a una osteoporosis o a otro tipo de enfermedad, puesto que por ejemplo, en el mieloma múltiple se produce osteoporosis.

Y siguiendo las recomendaciones de la WHO, el diagnóstico definitivo de la osteoporosis post-menopáusica debe realizarse mediante una DXA de cadera total y columna incluyendo L1-L4.

1.2. Objetivos

Establecer cómo están siendo diagnosticadas las mujeres osteoporóticas post-menopáusicas en distintos países ha sido el objetivo principal para iniciar esta

revisión bibliográfica. Debido a la morbilidad de la enfermedad y a la efectividad de los tratamientos comercializados, un diagnóstico temprano es un punto clave para evitar futuras fracturas, y por lo tanto mejorar la calidad de vida de las pacientes y disminuir la mortalidad.

1.3. Metodología

Para conocer cómo se está diagnosticando la osteoporosis en las mujeres post-menopáusicas alrededor del mundo se ha hecho una revisión exhaustiva de publicaciones en PubMed usando las palabras claves “osteoporosis post-menopáusica”, “ diagnóstico”, “América”, “Asia”, “Europa”, “África” y “Oceania”

1.4. Resultados

Se han desarrollado distintas técnicas para el diagnóstico de la osteoporosis post-menopáusica, siendo la DXA la única aceptada por la WHO para un diagnóstico concluyente de la misma en cadera total y columna lumbar de L1a L4. Los densitómetros se incluyeron en la práctica clínica en 1987 y miden la diferencia de energía en fotones cuando los rayos X atraviesan la zona corporal seleccionada, dando como resultado una medición de la DMO en g/cm2. Dichos resultados se transforman en la puntuación T-score para conocer el grado de osteoporosis de las pacientes respecto a la población joven y sana. Una desviación de -2.5 indica una osteoporosis. Entre las grandes ventajas de la DXA son su precisión, exactitud, 4-8% de error, velocidad, en aproximadamente un minuto se realiza un escáner completo y seguridad, puesto que la paciente se ve sometida a una radiación prácticamente nula.

Pero al tratarse de una técnica bi-dimensional, la DXA no es capaz de discriminar entre hueso trabecular y cortical, dando en ocasiones valores sobre-estimados en la medición de huesos largos e infra-valorados cuando se miden zonas grasas.

El TAC es una técnica con alta sensibilidad y tri-dimensional, pero que se reserva su uso para enfermedades degenerativas graves, para personas con huesos anormalmente largos o cortos y para personas obesas.

Variantes del mismo, como el HR-pQ CT fue creado hace 10 años, tiene una alta velocidad de escaneo en 3 dimensiones, con una altísima reproducibilidad y una baja emisión de radiación, el problema es que sólo permite la medición de zonas periféricas, no siendo viable el escaneo de cadera o columna.

Otra variante, el TAC Multidetector, permite medir zonas centrales con alta sensibilidad, incluso superior a las DXA, pero el problema es la emisión de radiación que origina.

La Resonancia Magnética fue modificada recientemente para obtener mejores imágenes del hueso trabecular, no emite apenas radiación, pero la larga duración de la prueba y la susceptibilidad de la misma a artefactos voluminosos la rechazan como técnica de elección.

Aunque la velocidad de la misma fue mejorada con la técnica de resonancia magnética de tiempos ultra-cortos, la cual mide el contenido acuoso del tejido óseo cortical ó compacto.

Es la Resonancia Magnética de Protones la que está barajándose como posible candidata a sustituir la DXA por su elevada velocidad de escaneo, ser una técnica no invasiva y medir tanto del contenido acuoso, como el graso de la médula ósea (que se incrementa a medida que disminuye la DMO).

La técnica de Cuantificación por Ultrasonidos es muy utilizada en centros de atención primaria, ya que el equipo puede transportarse con facilidad, mide el paso de los ultrasonidos a través de una zona poco voluminosa, como el calcáneo o las falanges, no emite radiación y es muy económica. Sin embargo, pesar de medir con una elevada precisión no es capaz de alcanzar la de la DXA.

Las radiografías simples siguen utilizándose en el diagnóstico de fracturas vertebrales porque es la técnica que mejor las identifica, a pesar de la alta radiación que emiten.

La revisión de las guías de diagnóstico de la osteoporosis en diferentes países del mundo muestran que en Sud África una fractura osteoporótica previa ya justifica la realización de una DXA. Los valores de referencia de BMD facilitados por los fabricantes del densitómetro no siempre pueden aplicarse a la población multirracial de Sud África, ocurre lo mismo con la herramienta FRAX™, por esto, la NOFSA ha creado un algoritmo para adaptar dichos valores a la población. Sin embargo, y debido a estas discrepancias las directrices establecidas siempre recomiendan basarse más en el criterio médico que en las herramientas de cálculo de riesgo de fracturas.

El problema de países eminentemente musulmanes como Marruecos, es que las autoridades sanitarias no consideran la osteoporosis post-menopáusica una enfermedad importante, por lo que el personal médico no está correctamente formado y se disponen de muy DXA localizadas en las grandes ciudades. Sin embargo algunos como Irán si se están tomando medidas en cuanto al diagnóstico de la osteoporosis puesto que la prevalencia de la misma aumenta cada año por el envejecimiento poblacional.

En Australia, al contrario que en Marruecos, las DXA están ubicadas en multitud de centros de especialidades, pero el problema aquí es el re-embolso de los costes por parte del gobierno, el cual sólo costea a los pacientes con un diagnóstico de osteoporosis previo y sumado a cualquiera de los siguientes factores de riesgo:

- Mayores de 69 años
- Menopausia temprana en mujeres o bajos niveles de testosterona en hombres

- 1 ó más fracturas osteoporóticas previas
- Tratamiento con Cortioides
- Síndrome de malabsorción, artritis reumatoide, hiper- o hipo- tiroidismo o paratiroidismo, enfermedad renal o hepática.

En los países Asiáticos el diagnóstico de la osteoporosis también es muy pobre, siendo la historia previa de fracturas, la edad de la paciente o el tipo de seguro de salud del que disponga factores determinantes de la realización de la primera DXA diagnóstica.

El seguimiento de la osteoporosis se realiza a las mujeres Japonesas entre 40 y 70 años de edad cada 5 años. En el mismo, se realiza una entrevista médica y una determinación de la DMO para evaluar si las pacientes necesitan o no un examen completo (bioquímica, biomarcadores, etc)

En India, la DXA se realiza a mujeres con una edad 5 años superior a la edad natural de la menopausia o que se encuentran dentro de los 5 años posteriores a la menopausia siempre que presenten alguno de los siguientes factores de riesgo:

- 1 riesgo de fractura clinic alto
- Más de 2 factores de riesgo, como tratamiento osteoporótico ya comenzado, fracturas osteoporóticas previas, evidencia radiológica de osteopenia y presencia de compresión vertebral. Las DXA se repetirán con una frecuencia de entre de 1 a 5 años dependiendo de los riesgos que presente cada paciente.

En Europa, aunque hay diferencias importantes entre países, sobre todo respecto al reembolso por parte de las autoridades sanitarias de los costes del diagnóstico, las directrices comunes establecen, al igual que en otras zonas, que la DXA debe ser la técnica usada para el diagnóstico definitivo de la osteoporosis post-menopáusica.

En Norte-América, la DXA se recomienda para mujeres post-menopáusicas mayores de 64 años, que tienen entre 50 y 64 años y presentan factores de riesgo, o bien mayores de 49 años pero con una fractura osteoporótica previa.

Respecto a Sud y Centro América los principales problemas en la utilización de la DXA como técnica de diagnóstico de la osteoporosis post-menopaúsica son los pocos densitómetros disponibles, la inaccesibilidad de muchos pacientes a éstos y la baja cobertura sanitaria.

1.5. Conclusiones

Tras revisar las directrices existentes para realizar un buen diagnóstico de la osteoporosis post-menopáusica en los diferentes países, se observa que todas ellas coinciden en utilizar la DXA como técnica determinante para el diagnóstico y en cumplir las recomendaciones de la WHO, habiendo tan sólo pequeñas diferencias respecto a los factores de riesgo considerados como importantes y a las técnicas complementarias utilizadas para la detección de fracturas.

Las mayores diferencias entre los distintos países se encuentran no en las directrices marcadas, sino en la práctica clínica, puesto que un diagnóstico temprano depende en gran medida de los recursos disponibles, es decir, existencia de suficientes densitómetros, accesibilidad de los pacientes a las instalaciones donde se ubican estos, un buen sistema de abono de los costes que suponen dichos procedimientos y también fundamental, una buena formación del personal sanitario que trabaja en asistencia primaria para que puedan realizar un cribado adecuado en la derivación de pacientes a especialistas.

2. Tratamientos para la osteoporosis post-menopáusica, ¿Qué novedades existen? ¿Cómo podemos manejar los tratamientos a largo plazo?

2.1. Introducción

La osteoporosis post-menopáusica ha cobrado especial interés para las Autoridades Sanitarias en los últimos años. Entre otras previsiones, se espera que para el 2050, la incidencia de fracturas de cadera consecuencia de la osteoporosis post-menopaúsica se incremente en un 310 %, principalmente envejecimiento poblacional.

Los tratamientos anti-osteoporóticos están dirigidos a la reducción del riesgo de fracturas, de hecho, aproximadamente cada 3 segundos ocurre una fractura osteoporótica, siendo las más comunes las de muñeca, pero las más graves las de cadera, puesto que implican hospitalizaciones, inmovilizaciones y un alto riesgo de muerte.

Por todo esto, el diagnóstico y la elección de un tratamiento adecuado en los estadios iniciales de la enfermedad es primordial para reducir el riesgo de dichas fracturas.

2.2. Objetivos

- Evaluar los riesgos de los tratamientos osteoporóticos cuando se administran a largo plazo y las opciones existentes en minimizar los mismos.
- Conocer las nuevas terapias, hacia dónde van dirigidas las investigaciones actualmente en el tratamiento de la osteoporosis post-menopáusica

2.3. Metodología

"Postmenopausal-Osteoporosis", "Long-term-Treatments", "Bisphosphonate", "Denosumab", "Sclerostin" y "Cathepsin K" fueron las palabras utilizadas para realizar la búsqueda on-line en PubMed.

Además guías de diferentes instituciones como la SEIOMM, ESCEO, WHO, etc fueron consultadas para conocer las recomendaciones respecto a la elección de los tratamientos más adecuados.

Páginas web de diferentes Compañías Farmacéuticas, así como la página www.clinicaltrials.gov fueron revisadas para conocer los ensayos clínicos realizados y en proyección con dichos fármacos.

2.4. Resultados

Existen varias directrices que difieren ligeramente entre países, para ayudar en la elección del tratamiento osteoporótico y cuándo comenzarlo en las mujeres post-menopáusicas:

- En España las guías de la SEIOM indican que deben ser 2 ó más las fracturas vertebrales existentes para comenzar con Teriparatida durante 24 meses, seguido de Alendronato, Risendronato, Ácido Zolendrónico o Denosumab.

  Las mujeres jóvenes en España son tratadas si tienen un riesgo de fractura de cadera bajo y un riesgo de fractura vertebral moderado, en este caso, se recomienda comenzar con Raloxifeno o Bazedoxifeno y después pasar a Bifosfonatos o Denosumab, no se aconseja empezar con estos por el riesgo de fracturas atípicas y osteonecrosis mandibular en el tratamiento a largo plazo de ambos.

  Las pacientes con otros factores de riesgo en España serán candidatos a ser tratados con Bifosfonatos o Denosumab, la elección dependerá de las comorbilidades de los pacientes, por ejemplo, no se administrará un

Bifosfonato si existen problemas gastrointestinales o se detecta un mal cumplimiento con el tratamiento.

En Inglaterra, las guías son más sencillas, las mujeres son tratadas cuando son mayores de 75 años con una fractura no traumática o si son menores de 75 años deberán presentar un valor de T-score ≤−2.5

- En Francia, las pacientes son tratadas cuando existe fractura vertebral o de cadera sumado a un T-score ≤−1 o una DMO≤−2.5 más factores de riesgo o bien un T-score ≤−3

- En Alemania se recomienda tratar a las mujeres post-menopáusicas cuando tienen una fractura vertebral y un T-score ≤−2 o una probabilidad de tener fractura en 10 años (FRAX) >30%

- En Estados Unidos, las mujeres post-menopáusicas son tratadas cuando existe una fractura vertebral o de cadera, o cuando el T-score ≤ -2.5 o si existe una baja DMO (T-score entre -1.0 y -2.5) sumado a un FRAX ≥ 20 %

Todas ellas siguen la recomendación de la WHO, en la que indica que el T-score y la DMO se deben medir mediante DXA en cuello femoral, cadera total o columna lumbar.

Los **Bifosfonatos** son, con diferencia, los fármacos más prescritos en el tratamiento de la osteoporosis post-menopáusica, los motivos son la elevada eficacia en la reducción de fracturas, la seguridad (prácticamente no provocan eventos adversos) y el bajo coste del tratamiento. Sin embargo, se ha detectado que en los tratamientos a largo plazo con Bifosfonatos existe mayor incidencia de osteonecrosis mandibular y fracturas atípicas debido a la actividad resorptiva de los mismos

Se han realizado diversos estudios para comprobar que efectivamente las mujeres post-menopáusicas osteoporóticas tratadas a largo plazo con **Bifosfonatos** tienen mayor riesgo de desarrollar dichos eventos y la relación beneficio-riesgo de dicho tratamiento.

- En el estudio “Fracture Intervention Trial Long-Term Extension” (FLEX) se observó que había un mayor riesgo de fracturas vertebrales en las pacientes que continuaron el tratamiento con **Alendronato** durante 10 años que en aquellas que lo tomaron 5 años y descansaron del mismo los 5 años siguientes. (riesgo relativo 5.3% versus 2.4%), aunque esto no afectó a las fracturas no vertebrales. Sin embargo, un análisis posterior de las mujeres que no tenían fracturas vertebrales y presentaban un T-score ≤ -2,5, demostró que las que habían discontinuado el tratamiento con Alendronato a los 5 años tenían mayor riesgo de fracturas no vertebrales que las que lo habían continuado durante 10 años, de hecho, se observó un incremento de DMO del 3.74% frente al 1.94%, medido con DXA en cadera total, cuello femoral, antebrazo y columna lumbar.

  El estudio BILANZ, todavía en curso, compara el efecto que tiene tratamiento discontinuo y continuo con Alendronato en el riesgo de fractura. Para ello se seleccionaron entre Enero 2012 y Marzo 2015 pacientes que hubieran estado como mínimo 4 años en tratamiento con Bifosfonatos y se les prescribió Alendronato durante 2 años más.

- En el caso del **Risendronato**, el estudio VERT-MN evaluó el riesgo de fracturas vertebrales en pacientes en tratamiento durante 3 años y durante 5 años, produciéndose una disminución del riesgo de las

mismas del 59% versus 49%. Dicho estudio se amplió a un total de 7 años, en el mismo, todas las mujeres, tanto las que habían estado tomando Risendronato como placebo en los primeros 5 años recibieron Risendronato activo 5mg durante 2 años. En el mismo se demostró que la incidencia de fracturas seguía siendo menor en el grupo de tratamiento activo que en el de placebo (7,4% versus 6,0%)

- Los estudios DIVA-LTE y MOBILE-LTE evaluaron el tratamiento de **Ibandronato** intravenoso y oral, concluyendo que la incidencia de fracturas observadas tras 5 años de tratamiento era considerablemente superior a la observada en tratamientos más cortos (6,8% a los 3 años de tratamiento oral con 150 mg frente a 9,1% a los 5 años del mismo y 8,5% a los 2 años de tratamiento intravenoso con 3 mg cada 3 meses frente a 4,9% para las que recibieron dicho tratamiento durante 5 años)

- El estudio HORIZON PFT fue ampliado 6 años para evaluar los efectos del **Ácido Zolendrónico** en el riesgo de fracturas a largo plazo, observándose no sólo la disminución del riesgo de fracturas vertebrales, si no también un aumento en la ganancia de DMO (0,24% en cuello femoral y 3,20% en columna lumbar en pacientes tratados con Ácido Zolendrónico versus 0,80% y 1,18% en los que recibieron placebo los últimos 3 años)

  Pero el principal problema del tratamiento a largo plazo con ácido Zolendrónico es el deterioro renal que puede producir, puesto que se metaboliza a este nivel.

Bazedoxifeno y Raloxifeno: Estudios realizados por Eli Lilly demostraron reducciones en fracturas vertebrales, pero no de cadera tras el uso de

Raloxifeno en el tratamiento a largo plazo en mujeres post-menopáusicas. Los mismos resultados se observaron para Bazedoxifeno en el estudio realizado tras 7 años de tratamiento. VIOLINE es un estudio post-marketing que actualmente está evaluando los efectos del Bazedoxifeno a largo plazo en mujeres post-menopáusicas.

La **Terapia Sustitutiva Hormonal (TSH)** se reserva exclusivamente a las mujeres que tengan un alto riesgo de fracturas y que no toleran otros tratamientos aprobados. Esto es debido a los graves efectos adversos que provocan como acontecimientos trombo-embólicos, ictus, accidentes coronarios, complicaciones biliares, cáncer de mama o pulmón

Respecto a su eficacia, estudios como “Women Health Initiative” (WHI 1998) y “Heart and Estrogen/Progestin Replacement Study” (HERS 1998) demostraron que la THS produce una disminución significativa de la incidencia de fracturas cuando esta es administrada en tratamientos a largo plazo, tras 5.6 años, una terapia combinada de THS disminuyó el riesgo en un 86 ‰ y tras 7.1 años, pero utilizando estrógenos únicamente como THS, el riesgo disminuyó en un 102 ‰.

Un estudio realizado tras 5 años de tratamiento con **Ranelato de Estroncio** (2 g vía oral diariamente) confirmó su efecto en la reducción en un 24% del riesgo de padecer fracturas vertebrales, en un 15% en el riesgo de no-vertebrales y un 43% en el riesgo de sufrir fracturas de cadera.

Los resultados de los estudios SOTI y TROPOS, que comparaban la eficacia en la reducción del riesgo de fracturas del Ranelato de estroncio frente a un placebo, fueron muy similares y en ambos las fracturas vertebrales se vieron reducidas de un 39 a un 41% tras 3 años de tratamiento.

Pero el 11 de Julio de 2014 la AEMPS estableció que este producto tan sólo debía ser utilizado en mujeres post-menopáusicas osteoporóticas con alto riesgo de fractura y siempre como segunda línea de tratamiento, debido a sus potenciales efectos secundarios como cardiopatía isquémica, enfermedad arterial periférica e hipertensión.

La **Calcitonina** es una hormona que se obtiene del salmón o recombinante humana,. En el estudio PROOF se demostró que las fracturas vertebrales se reducían un 33% cuando era administrada en dosis 200 IU/day durante 5 años, pero el problema es su acción carcinogénica a largo plazo, especialmente tumores de células basales., por lo que en Julio 2012, la EMA retiró su uso en el tratamiento de la osteoporosis.

La eficacia de **Denosumab** es similar a la de los Bifosfonatos, de hecho los ensayos clínicos en fase III demuestran que reduce la incidencia de nuevas fracturas vertebrales, no vertebrales y de cadera en comparación con placebo.

Además en el estudio DECIDE, el tratamiento durante un año con Denosumab o Alendronato mostró resultados similares en el porcentaje de cambio de DMO (3,5% frente a 2,6%) y en el estudio STAND el tratamiento durante un año con Denosumab produjo un incremento el porcentaje de DMO en cadera mayor que un tratamiento de la misma duración con alendronato (1,90% versus 1.05%)

Teriparatida es el primer fármaco que se comercializó para el tratamiento de la osteoporosis post-menopáusica en mujeres con alto riesgo de padecer una fractura. El estudio de fase III realizado por Eli Lilly demostró que las fracturas vertebrales se redujeron un 84% tras 3 años de tratamiento con este fármaco y el riesgo de padecer nuevas se redujo un 94%, por lo que funciona

perfectamente en las mujeres que ya tengan fracturas prevalentes, pero el principal problema de su uso, es que no se aconseja el administrarlo (1 inyección subcutánea diaria) durante más de 24 meses por carecer de datos sobre la seguridad del tratamiento a largo plazo.

Actualmente la investigación está dirigida hacia el desarrollo de:

- Fármacos inhibidores de la Esclerostina, son **Romosozumab** producido por Amgen Ilt y **Blosozumab,** producido por Eli Lilly, ambos son anticuerpos monoclonales que en la fase II están demostrando eficacia en el tratamiento de la osteoporosis post-menopáusica como fármacos estimuladores de la actividad osteoblástica. La comparación del tratamiento con Romosozumab durante 12 meses con tratamientos durante el mismo periodo de tiempo con Alendronato (Fosamax, 70 mg oral semanal) o Teriparatida (Forsteo, 20 µg Subcutáneo diario) mostraron que la DMO se vio incrementada un 11,3% en la columna lumbar tras el tratamiento con Romosozumab, un 4,1 % tras la terapia con Alendronate y un 7,1% tras el tratamiento con Teriparatida. La DMO de cadera total se vio incrementada un 4,1% con Romosozumab, 1,9% con Alendronato y un 1,3% con Teriparatida.

  Blosozumab también es un anticuerpo anti-esclerostina, que ha demostrado tras 1 año de tratamiento cambios de DMO en columna lumbar, cadera total y cuello femoral de 17.7 frente a 1.6% de placebo, 6.7 frente 0.7% de placebo, y 6.3 frente a 0.6% de placebo, pero no ha demostrado por el momento cambios significativos en radio (0.9 frente a 1.4%, respectivamente)
- Fármacos inhibores de la Catepsina K, es el caso del **Odanacatib,** estudios fase II demostraron que el Odanacatib 50 mg vía oral, 1 vez por semana durante 5 años, produjo un incremento casi linear en la

DMO de columna lumbar (11,9%), cadera total (8,5%) y cuello femoral (9,5%), además los niveles de biomarcadores NTx en orina disminuyeron un 67,4%, mientras que los de fosfatasa ósea alcalina en suero no se modificaron apenas respecto al nivel basal.

2.5. Conclusiones

Para tratar de elegir el tratamiento más adecuado para cada paciente, los Especialistas evalúan la historia médica previa de la paciente, las comorbilidades o incluso la vía de administración preferida por el paciente para intentar que los tratamientos sean totalmente personalizados, mejorando así el cumplimiento y la eficacia de los mismos.

Sin lugar a duda, el Alendronato es el fármaco más prescrito debido a su eficacia (comparable con otros fármacos como Denosumab) y a su coste considerablemente más bajo. Sin embargo, el inconveniente del Alendronato es la administración, ya que el paciente debe tomarse los comprimidos en condiciones muy estrictas, mientras que Denosumab se auto-administra subcutáneamente cada 6 meses.

Actualmente, se ha puesto de manafiesto que los tratamientos con bifosfonatos prolongados por más de 5 años incrementan los efectos adversos graves como la osteonecrosis mandibular o las fracturas atípicas. Denosumab ha demostrado en ensayos clínicos que presenta el mismo riesgo de que ambos eventos se produzcan, aunque que no lleva tantos años en el mercado como para obtener resultados de los estudios fase IV o post-comercialización. Todavía no hay un consenso claro en cómo manejar esta situación, aunque la EMA propone discontinuar tratamientos con Bifosfonatos tras 5 años y bien, cambiar a otro tratamiento o evaluar la progresión de la enfermedad estando la paciente un tiempo sin tratamiento.

Los nuevos avances en cuanto a fármacos anti-osteoporóticos están demostrando eficacias superiores a los existentes, aunque los riesgos a largo plazo no pueden ser evaluados por el momento.

3. ¿Puede una vida saludable prevenirnos de la osteoporosis post-menopáusica? Mitos y realidades

3.1. Introducción

Se estima que aproximadamente el 40% las mujeres y el 13% de los hombres mayores de 50 años tendrán al menos una fractura osteoporótica. De hecho, la osteoporosis lidera las causas de morbilidad en la vejez

Existen diferentes factores que no podemos modificar, como son:

- Edad: cada década se incrementa el riesgo de fracturas osteoporóticas en 1,4 - 1,8
- Raza: los datos epidemiológicos muestran que las personas de raza blanca y oriental tienen mayor riesgo de fracturas osteoporóticas que las de raza negra o polinesia
- Historial familiar: se ha demostrado que mujeres que han tenido una madre con fractura osteoporótica de femur tienen mayor probabilidad de desarrollar una fractura osteoporótica.
- Estrogenos: una menopausia temprana y una menarquia tardía están relacionadas con un incremento del riesgo de fracturas osteoporóticas.

Sin embargo, existen varios factores de riesgo en el desarrollo de fracturas que sí pueden disminuir variando hábitos de vida como el consumo de alcohol y tabaco, el peso, el sedentarismo, el déficit de vitamina D y calcio. Además varios estudios demuestran beneficios en el consumo diario de vegetales, de aceite de oliva, de zumo de naranja, colágeno, soja y te.

A pesar de la falta de ensayos clínicos que demuestren la eficacia de estas terapias en humanos, los datos obtenidos de estudios pre-clínicos y epidemiológicos se han extrapolado e interpretado como recomendaciones para la reducción del riesgo de fractura.

3.2. Objetivos

El objetivo principal de esta revisión fue la búsqueda de terapias alternativas, como la modificación de la actividad física o la ingestión de diferentes alimentos o complementos alimentarios. Y tratar de establecer si, con los resultados publicados, la efectividad de los mismos podría compararse con los tratamientos farmacológicos.

3.3. Metodología

Palabras como “Post-menopausal Osteoporosis”, “Bone mass density”, “Clinical Trials”, “Dietary” y “Activity” fueron utilizadas en PubMed para conocer la información publicada referente a tratamientos alternativos utilizados en la osteoporosis post-menopáusica.

3.4. Resultados

Debido a los efectos adversos potenciales que provocan los tratamientos farmacológicos y por no obtenerse en ocasiones los resultados esperados con los mismos, muchas personas optan por suplantarlos o suplementarlos con terapias alternativas.

Dichas terapias se basan en las propiedades de los componentes de alimentos como:

- Los **licopenos de tomates y zanahorias** han cobrado interés por su efecto antioxidativo. En estudios pre-clínicos con ratas ovariectomizadas que recibieron 30 y 40 mg/kg de licopeno frente a placebo, se observaron aumentos de DMO.

  Un estudio randomizado realizado en mujeres post-menopáusicas, las cuales recibieron zumo de tomate enriquecido en licopenos, cápsulas de licopeno o placebo durante 4 meses, demostró reducciones en el biomarcador de telopéptido N-terminal del colágeno tipo I y los mismos resultados se obtuvieron

en un estudio epidemiológico con mujeres también post-menopáusicas con edades comprendidas entre los 50 y 60 años

- **Vitamina C del zumo de naranja,** también por su efecto antioxidativo asociado a una mejor salud ósea. Un estudio epidemiológico realizado en Washington en 1892 mujeres post-menopáusicas concluyó que aquellas que habían tomado suplementos de vitamina C durante más de 10 años tenían DMO mayores que las que nunca los habían consumido. Otro estudio epidemiológico, pero en mujeres mejicanas, evidenció una asociación positiva entre la dieta suplementada con vitamina C y la DMO de cuello femoral

- Las **Isoflavonas de la soja**, son componentes similares a los estrógenos, de hecho dieron buenos resultados en ratas en la prevención de pérdida ósea. Sin embargo, en los ensayos clínicos realizados en mujeres post-menopáusicas existen discrepancias respecto si pueden o no sustituirse las isoflavonas por la terapia hormonal. Quizá sea porque en ratas la dosis administrada fue mucho más elevada que en mujeres, o bien porque se necesite evaluar el tratamiento a largo plazo y no a 3 años máximo.

  Los últimos avances se centran en un metabolito de la daizeína, una isoflavona de la soja. Dicho metabolito, el equol (o-desmetilangolensina), es producido por la flora intestinal de determinadas personas. Se cree que si estimulamos la producción de Equol por la flora bacteriana intestinal, se incrementará el efecto estrogénico de la soja. No existen estudios experimentales que confirmen esta teoría.

- **Herperidina de cítricos como la naranja**, en el único estudio realizado en mujeres post-menopáusicas, las cuales tomaron 500 mg diarios de hesperidina durante un año, no se observaron diferencias significativas entre el grupo de

tratamiento activo y el grupo placebo. Pero las mujeres que recibieron hesperidina sí mostraron un mejor equilibrio en los biomarcadores a través del índice de propéptidos de procolágeno N-terminal: C-terminal

- **Ajo y Cebolla**, el g-L-glutamyltrans S-1-propenyl L cystein sulfóxido (GPCS) provoca una reducción de los niveles de los biomarcadores deoxipiridolina y TRAP, sin alterar la fosfatasa álcalina, pero por el momento, tan sólo se ha determinado en estudios pre-clínicos en ratas.

- **Colágeno,** 10 g diarios de su hidrolizado en forma de complemento alimenticio fue tomado durante 24 semanas por 108 post-menopáusicas tratadas con Calcitonina, al igual que se observa en otros suplementos alimenticios, los niveles de biomarcadores se modificaron, en este caso la excreción urinaria de piridolina y deoxipiridolina disminuyeron en el grupo Colágeno más Calcitonina frente a placebo más Calcitonina, sin embargo la DMO no se vio alterada

- **El aceite de oliva,** también se ha estudiado para previnir fracturas de fragilidad basándose en que en el area mediterránea existe una menor incidencia de la osteoporosis post-menopáusica. Su efecto se atribuye a los fenoles que contiene. En estudios pre-clínicos con ratas ovariectomizadas se demostró un aumento de la DMO femoral. Y en estudios epidemiológicos se ha asociado con una mejor DMO en columna lumbar. No existen datos de ensayos clínicos.

- **Ciruelas**, tras 12 meses de tratamiento con 100 g diarios de ciruelas pasas, los niveles de biomarcadores osteocalcina, de fosfatasa tartrato ácido-resistente y de fosfatasa alcalina específica de hueso disminuyeron y la DMO de columna se vio incrementada en mujeres post-menopáusicas osteopénicas.

- **Polifenoles del Te verde**, un estudio randomizado realizado en mujeres mayores de 50 años demostró incrementos en el biomarcador fosfatasa

alcalina específica de hueso versus placebo, pero no se midió la DMO en ninguno de los dos.

- Los **suplementos con Calcio y Vitamina** D no sólo son aconsejables, si no que también altamente recomendados especialmente como tratamiento concomitante en el caso de recibir terapia resortiva, debido a que estos tienen alto riesgo de producir hipocalcemia. La directriz Europea para el diagnóstico y manejo de la osteoporosis recomienda que las mujeres post-menopáusicas ingieran al día como mínimo 1000 mg de calcio y 800 UI de vitamina D. Los alimentos con mayor contenido en calcio son las sardinas, leche, yogur y queso, mientras que los más ricos en vitamina D son pescados azules como salmón, atún y sardinas, hígado, mantequilla, quesos grasos, huevos y setas. Sin embargo, el principal aporte de vitamina D proviene de la exposición solar, siendo la absorción óptima de dicha vitamina a altas latitudes, pero en estas zonas hay menos horas de sol al día. Estudios randomizados realizados con aportes extraordinarios de calcio y vitamina D han dado resultados dispares, unos muestran una reducción en el riesgo de fractura de un 22% cuando se ingieren suplementos con vitamina D, mientras que otro en que se comparó el tratamiento de calcio+vitamina D frente a un placebo no obtuvo reducción significativa en el riesgo de fractura.

3.5. Conclusiones

Tras la revisión de diferentes estudios realizados con los tratamientos alternativos más utilizados en la osteoporosis post-menopáusica, llama la atención la falta de ensayos clínicos en mujeres post-menopáusicas para poder establecer una dosis adecuada de dichas terapias que produzca una reducción del riesgo de fracturas osteoporóticas.

Por lo tanto, las conclusiones establecidas se basan en unos pocos estudios epidemiológicos y en la extrapolación de los datos obtenidos en estudios pre-clínicos.

CONCLUSIONES FINALES

CONCLUSIONES FINALES:

Primera.- Las directrices existentes para realizar un buen diagnóstico de la osteoporosis post-menopáusica en los diferentes países coinciden en utilizar la DXA como técnica determinante para el diagnóstico y en cumplir las recomendaciones de la WHO, habiendo tan sólo pequeñas diferencias respecto a los factores de riesgo considerados como importantes y a las técnicas complementarias utilizadas para la detección de fracturas.

Segunda.-La osteoporosis post-menopáusica sigue siendo una enfermedad infravalorada en cuanto al diagnóstico, a pesar de la atención clínica que requieren las fracturas asociadas a la misma suponen un 40% del tiempo y recursos sanitarios totales, siendo equiparable al empleado en las enfermedades cardiovasculares. Las principales causas de la falta de diagnosis son la escasez de instrumental apropiado (no solo escaso, sino también concentrado en las grandes ciudades) y la falta de cobertura sanitaria para realizar las pruebas en los distintos países.

Tercera.- La terapia con Bifosfonatos es el tratamiento más prescrito para la osteoporosis post-menopáusica en mujeres, ya que poseen una alta eficacia: el Alendronato reduce en un 55% las fracturas vertebrales y en un 47% las no-vertebrales tras un año de tratamiento, y un 53% las de cadera tras tres años de tratamiento. El Risendronato proporciona incluso mejores porcentajes. Además los Bifosfonatos desencadenan pocos efectos adversos, los más comunes los relacionados con el tracto gastrointestinal.

Cuarta.-Actualmente se plantea insistentemente la necesidad de protocolos para gestionar los tratamientos a largo plazo, puesto que ya hay personas tratadas durante 10 o más años y no se disponen de suficientes estudios de seguridad a largo plazo. En tratamientos continuados, los pacientes tratados con Bifosfonatos tienen una mayor probabilidad de sufrir osteonecrosis mandibular y fracturas femorales atípicas. Ocurren en muy raras ocasiones, pero debido a la complejidad de dichas patologías, la EMA ha establecido que el tratamiento con Bifosfonatos debe ser re-evaluado a los 5 años, aunque no hay datos científicos que soporten dicha decisión.

Quinta.-Entre los fármacos actualmente comercializados para el tratamiento de la osteoporosis post-menopáusica, Denosumab es una alternativa interesante a los Bifosfonatos, ya que posee una eficacia similar, e incluso en varios estudios ha demostrado ser superior a Bifosfonatos en la reducción del riesgo de fracturas. Tiene la ventaja de administrarse bianualmente, mediante una auto-inyección subcutánea, pero los efectos adversos a largo plazo que está mostrando coinciden con los de los Bifosfonatos, es decir, osteonecrosis mandibular y fracturas femorales atípicas.

Sexta.-Los nuevos fármacos: Romosozumab, Blosozumab y Odanacatib, actualmente en investigación fase III, están demostrando efectividades superiores a los ya comercializados. Por ejemplo, en el caso de Romosozumab, la densidad mineral ósea medida, tras 12 meses de tratamiento con Alendronato, Teriparátida y Romosozumab, se incrementó 4,1%, 7,1% y 11,3% respectivamente cuando se midió en columna lumbar y aumentó un 1,9% tras terapia de Alendronato, un 1,3% tras la de Teriparátida y un 4,1% tras la de Romosozumab cuando la densidad mineral ósea se midió en cadera total.

No se ha comparado Romosozumab con Denosumab, pero los valores que se obtuvieron cuando este último se evaluó frente a Alendronato fueron que tras 12

meses de tratamiento, la terapia con Denosumab produjo una ganancia de un 1,90% de densidad mineral ósea en cadera total, mientras que Alendronato produjo un 1,05%.

No hay resultados publicados de Blosozumab y Odanacatib comparados con otros fármacos osteoporóticos, pero en fase II el primero demostró un aumento de densidad mineral ósea de columna lumbar y cadera total de 17.7% y 6.7% respectivamente, versus 1,6% y 0,7% que obtuvieron los pacientes que recibieron placebo durante 1 año de tratamiento.

Con Odanacatib se vió que tras 5 años de tratamiento, la densidad mineral ósea se incrementaba casi linealmente, obteniéndose aumentos de un 11,9% en columna lumbar y un 8,5% en cadera total.

Septima.-Aunque no se disponen de suficientes ensayos clínicos en mujeres post-menopáusicas para concluir si son eficaces o no en el tratamiento de la osteoporosis tratamientos alternativos, como los licopenos del tomate, la vitamina C de los cítricos, el colágeno hydrolizado, las isoflavonas de la soja, el te verde, el ajo, la cebolla, etc., administrados en forma de suplementos o ingeridos directamente de los alimentos, han demostrado efectividad en estudios pre-clínicos con ratas ovariectomizadas y algunos también en estudios epidemiológicos. La efectividad en gran parte de dichos estudios se ha evaluado mediante variación de los niveles de biomarcadores de recambio óseo, pero raramente se han obtenido resultados concluyentes respecto a las variaciones de densidad mineral ósea.

Octava.- Los suplementos que sí se reconocen como eficaces y de hecho se prescriben como tratamientos concomitantes a terapias aprobadas por las Autoridades Sanitariasson los de calcio y vitamina D, por ejemplo, para prevenir la hipocalcemia asociada al uso de agentes antiresortivos, se recomienda una ingesta diaria

suplementaria con 1000 mg de calcio y 400UI de vitamina D, aunque no existen recomendaciones estandarizadas de cuales deben ser las cantidades mínimas a ingerir por una persona adulta para minimizar el riesgo de fracturas.

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