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Physiopathology of osteoporosis and action mechanism of PTH

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Osteoporosis. Concept

There is no universally accepted definition of osteoporosis. One of the most convincing is that proposed by the NIH in 1993[1], according to which osteoporosis is a generalised disease of the skeleton, characterised by a reduction in bone mass and a deterioration in the microarchitecture of the bone, which results in an increase in bone fragility and a greater tendency to fractures. The loss of bone mass and the deterioration of the microarchitecture are consequences of an alteration in the phenomenon of bone renewal, whose fundamental protagonist is what is called a "unit of bone remodelling". Osteoporosis is therefore, ultimately nothing but a functional alteration in this unit.

Subsequent to the NIH definition, it has been felt necessary to introduce a new concept, that of bone quality[2], which was not reflected in it. This concept includes both those aspects related to bone structure as well as those related to the characteristics of bone tissue (intrinsic properties of bone material). It is possible that an alteration in the quality of bone material is involved in the tendency to osteoporotic fractures, but in general its importance –in relation to bone mass and to those structural aspects– is less. Thus it can be accepted that the definition indicated earlier continues to be valid.

Bone remodelling

The skeleton is an organ of support, and as such it is exposed to the processes of deterioration which all structures which have to bear mechanical load suffer. But differently from inert support structures (columns, beams, etc), bone is a living organ, with capacity for renewal, and for maintaining its conditions of resistance. This renewal takes place in a permanently and has been given the name "bone remodelling"[3,4]. The speed at which it occurs is known as "bone turnover".

The aforementioned unit of bone remodelling, and that responsible for this phenomenon, consists in a group of cells charged with destroying small portions of bone, which are subsequently substituted by new bone. These cells are of various types, but two of them are the principal protagonists of the process: the osteoclasts (charged with destroying the bone), and the osteoblasts (charged with forming it). They intervene by lending their support to other cells such as lymphocytes, macrophages, endothelial cells, neurones, etc. The volume of renewed bone for each unit is 0.025 mm³, and the annual rate of renewal of the skeleton is approximately 10% (25-30% trabecular bone and 3-4% cortical).

In the skeleton, at any one time, there are more than a million active units. These units are out of step: some are found in the initial phase, others in the final phase, and others in different intermediary phases. There is a temporal asymmetry between the intervention of the osteoclasts and the osteoblasts. The former carry out their destructive task in some 2-3 weeks, while the latter take 4-5 months to replace the destroyed bone. Between the action of both types of cells there is an intermediate "investment" phase which lasts some 2 weeks. In this phase, cells whose origin is not well determined –although probably from the osteoblastic line (not macrophagic, as had been thought previously)– clean the bone surface produced by resorption, preparing it for the formative phase.

The spatial organisation of the units of remodelling varied according to whether they are in the cortical or trabecular bone[5]. In the first case the osteoclasts act on the sinus of the bone, moving longitudinally as they carry out their resorptive activity. Therefore the result of their action is a tunnel-shaped cavity. After the osteoclasts, the osteoblasts advance, closing this cavity. They do this by forming cylindrical and concentric bone layers, disposed from the walls of the cavity to its centre. The result is what are called "osteones" or bone structural units, which in the case of cortical bone is also known with the name of "Havers' system".

In trabecular bone the osteoclasts act on the bone surface, and do not move in a longitudinal way, but in an erratic zig-zag, in which the cell returns to pass over the area on which it has already acted earlier. The final result of its action is a cavity with a morphology which resembles a laguna. The osteoblasts also fill this with layers from the bottom to the surface. The cavity, once filled, has in section, an aspect of a half-moon. This half-moon constitutes the bone structural unit or osteone of trabecular bone (some authors refer to these as "hemiosteones", to compare the half-moon shape with the cylindrical shape of the layers of the Havers' system). The endostic surface can also show units of remodelling with these characteristics.

The process of remodelling, together with its primary function of permitting the skeleton to maintain its characteristics as a support organ, is at the service of other biological phenomena of great interest. On the one hand, it allows the modification of the shape of the bone, to adapt it to changes in mechanical demands. In addition, it plays a role in the regulation of calcemia. On the other hand, it has shown its importance in the maintenance of the haematopoeietic stem cells, located in the bone medulla next to the trabecular surface. Finally, its intervention in the homeostasis of acid-base equilibrium, as been indicated.

Before leaving this section on of bone remodelling, we should indicate the existence of another process, known as "modelling"[6], essentially functioning during the development, and determining the morphological and structural transformation of bone throughout it. It consists of bone formation not preceded by resorption in certain places (fundamentally the periosteum, with which the external diameter of the bone increases) and with resorption in others (the endosteum, to increase the medullar cavity, and some zones of the periosteum –those that ought to transform metaphisis to diaphisis–). In adult life the subperiostic formation and the endostic resorption are maintained but with much lower intensity. This supposes a displacement of bone towards the outside (away from the central axis), which increases bone resistance and partly neutralises the deterioration which the bone suffers with aging. Some authors consider the concepts of "modelling" and "bone formation not preceded by resorption" as practically synonymous, and although this assertion is not always correct, it is most of the time.

In a healthy adult 97% of bone formation is due to remodelling, and only 3% to modelling.

Bone remodelling unit cells

We have already mentioned that the principal cellular protagonists of the units of bone remodelling are the osteoclasts and the osteoblasts.

1. Osteoclasts

The osteoclast is a multinuclear cell, the product of the fusion of mononuclear precursors (preosteoclasts), through the participation, amongst other factors of the protein DC-STAMP. Its origin is haematopoeietic, deriving from a cell which is the common precursor of the osteoclast and the macrophage. To destroy bone it adopts a special shape[7,8], by virtue of which the part of the membrane of the cell which comes into contact with something adopts a rugous character, which in histological images is described as a brush border. This border is made up of microvilli which discharge hydrogen ions and enzymes (principally cathepsin K) capable of destroying bone. The hydrogen ions eliminate the mineral component, and the enzymes the collagen. In order that these substances remain between the osteoclast and the surface of the bone developing their function, at the edge of the rugous zone they form a ring whose surface has the property of bonding closely with the bone; the result is that in the interior of this ring a sealed space is left, from which the hydrogen ions and the enzymes cannot escape. The ring is mainly made up of actin, and the reason why its surface appertains to the bone is that it possesses molecules of integrin $\alpha v\beta 3$, which tend to bond to RGD (arginine-glycine-aspartic acid) present in various bone proteins (vitronectin, fibronectin, osteopontin). In both the formation of the actin ring and that of the rugous surface, the cell cytoskeleton plays a key role. The configuration which this adopts, in addition, points the way to some cytoplasmatic vesicles which direct the microvilli to release their contents into the sealed space, where they will exert their bone-destructive effect.

In the development of the osteoclast and in its functional activation a surface receptor called RANK is key. On the action of a molecule known as the "RANK ligand" or RANKL[9], present in the membrane of osteoblastic line cells (precursors of the osteoblasts, and mesenchimal cells of the medullar stroma). The RANK-RANKL interaction involves therefore direct cell-cell contact. However, RANKL is occasionally present in soluble form. For the activation of the osteoclast it is necessary to combine RANKL with another molecule, M-CSF, for which the osteoclast also has a specific receptor (c-fms). M-CSF is also formed by ostebLastic line cells, but is not bonded to the cell membrane, but is a soluble factor. The osteoblastic line cells, in addition to these substances, produce others for which there are also receptors in the osteoclasts (e.g. OSCAR, TREM2)[10], which are

considered "co-stimulators" with respect to the RANK-RANKL system. On the other hand, also acting on the osteoclasts are substances originating in other types of cells; of these one type are activators (TNF, VEGF-C) and others inhibitors (calcitonin). The interaction of the osteoclast itself with the bone matrix increases its survival.

The stimulation of the osteoclasts by RANKL gives way to the activation of various intracellular signalling pathways (NFkB and various MAPK)[11,12], with the production of different factors, of which one, NFATc1[13] should be especially mentioned due to its importance. The action of the co-stimulators (ligands of OSCAR and TREM2) activates pathways in which there are present adaptor molecules such as ITAM, phospholipase C (PLC), calmodulin and calcineurin. Curiously RANKL can negatively regulate the formulation of osteoclasts.

A protein characteristic of the osteoclasts is tartrate-resistant acid phosphatase (TRAP), whose physiological role is not well defined.

The osteoclasts are involved in other functions, as well as, strictly, in osteoresorption. Some have to do with bone homeostasis itself, in their capacity to stimulate osteoblasts, to which we will return later. On the other hand they regulate the egress from the bone medulla of the haematopoietic stem cells (in which are involved certain receptors and the secretion of proteolytic enzymes), and may be involved in immune phenomena in inflammatory processes.

2. Osteoblasts

The osteoblasts have a mesenchymatous origin, and possess common precursors with cells such as fibroblasts, myocytes or adipocytes. The differentiation to osteoblasts from their precursors requires the presence in them of transcription factors runx 2, osterix, ATF4 (or CREB 2) and AP1 (heterodimeric transcription factor composed of proteins of the families Fos and Jun). They possess a powerful ribosomal apparatus, which is consistent with the intensive synthesis of protein which they perform. Of these, the most important, quantitatively, is collagen, but they also synthesise other proteins whose function is not always well known, among which should be mentioned, since it is the most known, is osteocalcin. As well as synthesising proteins the osteoblast drives bone mineralisation. The non-mineralised bone tissue, called "osteoid", is formed by layers which are synthesised from the bottom to the surface, defined by the different orientation of the collagen fibres in each of them. Their mineralisation is carried out progressively from the deepest layers to those on the surface, after a period of osteoid maturation. Alkaline phosphatase is an osteoblast protein which is involved in the process of mineralisation, destroying one of its inhibitors, pyrophosphate, by which it also increases the local concentration of phosphate.

Rather surprisingly, the osteoblast has, along with the bone forming function which we have just commented on, a regulatory function on bone destruction. According to what we have already said, the osteoblast –or its precursors– have the capacity to produce substances which stimulate the osteoclast. RANKL is the most characteristic, although not the only one. The osteoclast, in addition, produces a substance –osteoprotegerin (OPG)[9]– which has an affinity with RANKL itself, such that it binds with it, preventing it from accessing RANK, and, therefore, preventing the stimulation of the osteoclast. Ultimately, the behaviour of the osteoclast varies with the RANKL/OPG relationship. Many factors which act on the osteoclast (PTH, 1.25 (OH) 2D, oestrogens...) do so, at least in part, indirectly, through the osteoblast, modifying this RANKL/OPG relationship. The osteoblast does not only have the capacity to stimulate the osteoclast (a function which develops when the activity of a bone remodelling unit is initiated), but also to inhibit it (when the osteoclasts have to end their activity 2-3 weeks later), which they bring into effect through OPG, and the ephrin system[14], to which we refer in more detail later (the osteoblast has something in its membrane called EphB4, which, by bonding with the Ephrin B2 present in the osteoclast's membrane, slows it).

Now we intend to focus on the bone-forming aspects of the osteoblast. The principal signalling pathway involved in this –although not the only one– is considered to be the Wnt-βcatenin system[15,16]. The proteins Wnt have available a receptor on the surface of the osteoblasts, called Frizzled, for which there is a co-receptor (LRP5). When these proteins bond to the Frizzled-LRP5 complex, they are prevented from acting in a conjunction with cytoplasmatic proteins whose function is to phosphorilate the βcatenin, so that is degraded in the proteosome. By avoiding this phophorilating effect the βcatenin accumulates in the cytoplasm and passes into the nucleus. Here, an increase in the transcription factors "T cell factor/lymphocyte stimulator factor" (TCF/LEF) takes place, which stimulates the genes involved in bone formation, including runx 2. Other substances which stimulate bone formation by the osteoblast are the bone morphogenetic proteins (BMP), TGFb, IGFs, FGF, PDGF, endotelin, PTHrP, etc.

The Wnt-βcatenin pathway establishes a nexus between the bone-forming and anti-osteoclastogenic functions of the osteoblasts, since βcatenin is involved in the regulation of the RANKL/OPG equilibrium, biasing it in favour of the latter. In general terms it can be said that the activation of the pathway in early phases of the life of the line cells induces formation, whilst in the later phases it reduces osteoclastogenesis. It has been suggested that the ligand of LRP5 decides which of the two functions should predominate.

Along with the stimulatory signals for bone formation the inhibitors should also be mentioned, the first ones of note, being those which antagonise the Wnt-βcatenin pathway, such as SFRP-1 (Secreted Frizzled-Related Protein 1), Dickoppf 1 (DKK1) or schlerostin, to which we will return later. It should also be mentioned that they are

inhibitors of intestinal serotonin, a function which has recently been described, and whose synthesis is regulated by ligands which act on the LRP5 of the enterochromafin cells.

The osteoblast, after forming osteoid may remain carpeted to the surface of the recently synthesised bone (surface or coating osteoblasts), may stay buried in the sinus of synthesised bone in its surroundings (transforming itself into a cell called an "osteocyte", or dying by apoptosis. This last option is the one for which the majority of the osteoblasts are destined.

The osteocytes[17,18] have extensions which bind them to each other and with the surface osteobalsts by means of "gap junctions". It is considered that they perform a key role in bone remodelling, being involved both in setting in motion the bone remodelling units and in their termination. The former comes about by mechanisms which are poorly understood, but which are thought to consist in the detection of the changes produced in the bone (microfractures), due to which a signal is sent to the bone surface in order to activate the osteoclasts. The same thing happens in apoptosis. It is quite likely that the osteocytes are continuously sending to the bone surface inhibition signals for the osteoclasts (TGFβ and NO might carry out this function), and that what really happens is that after detecting a bone lesion they stop sending the signals. On the other hand, as we have said, the osteocyte seems also to be involved in ending the activation of the unit of bone remodelling once it has formed the necessary quantity of bone. This function would take place through the synthesis of schlerostin, a substance which would reach the bone formers on the surface where it would inhibit the Wnt-βcatenin system by binding with the LRP5 co-receptor or blocking it. However, there are still aspects to be clarified. For example, a rat model deficient in osteocytes has reduced bone formation, despite a lack of schlerostin cell formers.

Apoptosis of the osteocytes, as well as determining the initiation of bone resorption, itself causes an increase in fragility for poorly understood reasons. Among those phenomena determining apoptosis of the osteocytes which should be remarked upon, in addition to a lack of mechanical stimulus, is a lack of oestrogen and the glucocorticoids.

Regulation of bone remodelling

Bone remodelling is subject to regulation by a series of factors which stimulate or inhibit the osteoblasts or osteoclasts, some of which have been mentioned in the description we have just given of these cells. We are going to consider them then, systematised in three sections: 1) factors involved in what is called the "osteoclast-osteoblast dialogue" (that is to say, how both types of cells relate to one another)[19-22]; 2) other local regulatory factors (products of cells of the bone microenvironment other than osteoclasts and osteoblasts); 3) systemic factors.

1) Factors involved in the osteoclast-osteoblast dialogue (Figure 1)

The specific factors which connect both types of cells, and how they connect, are largely unknown and, therefore, their description is, to a certain degree, speculative.

The first idea which should be taken into account is that the relationship between the osteoclasts and the osteoblasts is not static or constant, but that it changes across the different evolutionary phases of the unit of remodelling.

a) Initiation of the unit of remodelling. Bone destruction

As we have already indicated, is considered to happen when the osteocytes detect the necessity that a part of the bone needs to be renewed[23], they send stimulatory signals (or stop sending inhibitory signals) to the bone surface, so as to initiate osteoclastogenesis. It is thought that these signals are received by osteoblastic line cells, which respond by synthesising chemotactic factors for osteoclast precursors (e.g. sphingosine-1-phosphate, osteopontin), producing RANKL and other substances which activate osetoclastogenesis and mature osteoclasts, and release collagenase which prepares the bone surface so that resorption can commence. The type of osteoblasts involved in these phenomena are not well known, but could be treated as coating osteoblasts or as mesenchymal cells; in either case it appears that they belong to a particular subtype of osteoblastic line cells which express ICAM-1. It is possible that RANKL and M-CSF could also be produced by their own osteocytes, and the possiblity has also been considered that apoptic bodies of the osteocytes may increase the formation of the osteoclasts

It has been suggested also that the preosteoclasts attracted by the chemotactic agents to those sites where a unit of bone remodelling is going to be initiated, can be found lodged, and partially activated, in niches near to them, from which they would move towards them.

b) Investment phase. Coupling phenomenon

Once a sufficient quantity of bone has been destroyed, the activity of the osteoclasts (which then finally die through apoptosis) needs to be slowed, , and the osteoblasts stimulated. The fact that the osteoblasts, and following them, are activated in the same place in which the osteoclast had previously acted, is a phenomenon known as "coupling", or a temporo-spatial fit between the action of the osteoclasts and that of the osteoblasts. The mechanisms responsible have not been established with certainty, but various possibilities have been considered, all compatible with each other:

I.- Substances released from the bone matrix

During the formation of the bone matrix, remaining buried in an inactive form, are substances synthesised by the osteoblasts themselves or from the circulation, which with bone resorption are released and activated, performing a modulating effect on the activity of the bone cells. The best known is TGFβ, which on the one hand inhi-

bits the osteoclasts, and on the other attracts (by a chemotactic effect) osteoblast precursors, and stimulates their proliferation. Other substances released from the bone matrix which are osteoblast stimulators are the IGFs, the BMPs, FGF and PDGF. There is disagreement about up to what point the proteolytic enzymes present in the sealed space contribute to their activation (acting on the inactive form) or to their inactivation (acting subsequently on their active form), such as is necessary to reach optimum levels.

II.- Release by the osteoclasts of substances which stimulate the osteoblasts

Although little known, included as a possible candidate in this section is cardiotrophin (which is indicated by glycoprotein 130).

III.- Mechanisms dependent on cell-to-cell contact

In the proximity of the osteoclasts there are osteoblastic line cells with which they establish contact. This contact appears to be supported by the existence of a layer of cells of this line (from the "coating" type of osteoblast) covering the space which the remodelling unit occupies, to which we usually refer as the "canopy". The cells of this canopy can be found near the osteoclasts. It is also possible that some canopy cells are precursors of the osteoclasts (a variety of macrophages which some authors call "osteomac" –from osteal macrophages–).

On the other hand, various blood vessels have access to the remodelling space bounded by the bone and the canopy, through which osteoblast precursor cells can access the central focus of resorption. It is possible, also, that they can do this directly from the bone medulla by means of these canopy cells, attracted by the factors which are released in the centre of resorption. Another factor which favours cell-to-cell contact comes from the fact that both the osteoclasts and the osteoblasts feature cytoplasmic extensions (similar to those of the osteocytes) which allows them contact even though their cell bodies are at a certain distance. Earlier we have indicated how, in the resorptive phase, the osteoblast-osteoclast connection results in the stimulation of the latter by RANKL produced in the former. In this second phase of evolution of the bone remodelling unit the RANKL/OPG relationship changes, and a displacement is produced in favour of the latter, in such a way that OPG is predominant and the osteoclasts are inhibited. This change is induced, at least partly, by the osteoclasts themselves. In fact,

Figure 1. Unit of bone remodelling indicating: A.- the successive intervention of osteoclasts (black) and osteoblasts (grey); B.- the canopy which covers the space being remodelled
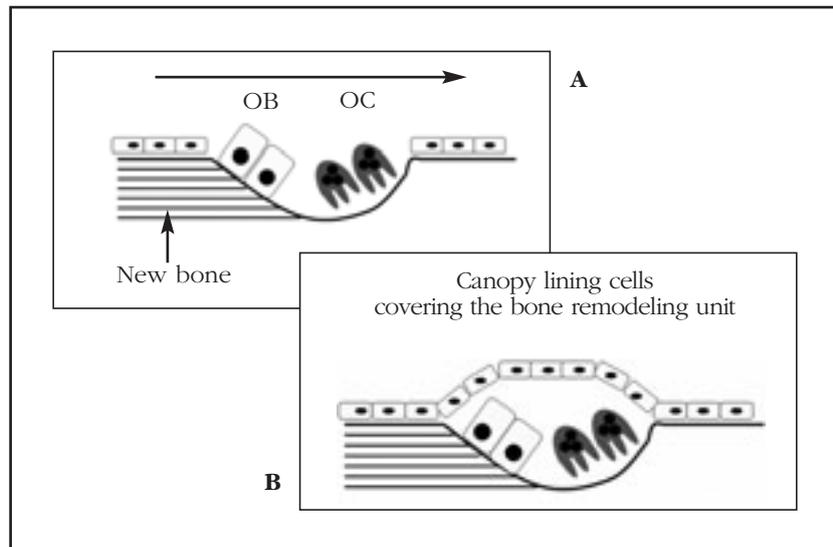
the osteoblasts have a receptor in the membrane (Notch) for which the osteclasts have various ligands, also situated on their membrane (Jagged and Delta). It is thought that the activation of the Notch receptor promotes the synthesis of Wnt proteins, which is probably stimulated also for other reasons not yet clear. The Wnt-βcatenin system determines the change in the RANKL/OPG relationship in the way we have already mentioned –in addition to stimulating osteblastic differentiation–.

A relationship is established between the osteoclasts and the osteoblasts, as well as through another ligand-receptor system in which the elements are found in the membranes of these cells. This is the system of ephrins[14]. What is interesting about this system is that, when its two elements bond, signals are not only sent towards the cell which contains the receptor, but also towards that which contains the ligand. In the case that we are now discussing, the osteoblast is stimulated and the osteoclast inhibited. The osteoclast presents ephrin B2 and the osteoblast its receptor EphB4.

c) Bone formation and ending of the action of the bone remodelling units

Once the osteoblasts are activated bone synthesis occurs. This process appears to be self-fed, since the osteoblasts synthesise substances which stimulate themselves in the form of autocrines (IGF, TGF, FGF, BMP...). One of the substances to which most importance is given today is PTHrP[24,25], for which the osteoblast has a receptor (PTHR1) which is common to this substance and to PTH. The bone stimulatory effect of PTHrP should be intermittent, for which its action needs to happen in a context of mechanism which is involved in determining this intermittence. Once the bone synthesis has produced an adequate quantity of bone, it must cease. This task appears

also to fall to the osteocytes. They receive some information (perhaps mechanical) by virtue of which they synthesise schlerostin which inhibits the action of Wnt proteins through their effect on the co-receptor LRP5. It is possible that other mechanisms are involved. Some of which may be of a physical nature: a mechanostat which detects when sufficient bone has been formed, or a topographic mechanism, to which we refer below, capable of detecting the fact that there are no longer any empty spaces on the bone surface.

IV.-Topographic mechanism

There are data which support the idea that the existence of a vacant space on the bone itself sets in motion the mechanisms for bone formation in relation to a phenomenon which detects the surface configuration or the spatial limits of bone tissues. Maybe aspects related to the distribution of mechanical load are involved.

2) Other local factors

At the margin of the factors involved in the osteoclast-osetoblast dialogue (local by definition), other factors synthesised in other types of cells also present in the bone microenvironment are involved in the regulation of bone remodelling: lymphocytes, macrophages, endothelial cells, and even the mesenchymal cells themselves (from which the osteoblasts derive). These factors are frequently co-determining. On the other hand, they can be capable of acting both on the osteoclasts as well as on the osteoblasts, in general in an opposing way (if they inhibit one, the other is stimulated), and therefore giving the same final result (either increasing or decreasing bone mass). Sometimes their action on the osteoblasts has repercussions on the osteoclasts by means of the RANKL/OPG system.

These factors are usually cytokines or growth factors[26-28]. Some cause a reduction in bone mass, as is the case with those called inflammatory cytokines – IL-1, TNF, IL-6 – which promote bone destruction , and others its increase, such as IL-4, the IGFs, BMP, TGFb, PTHrP, etc.

3) Other systemic factors

General factors which intervene in the regulation of bone remodelling are usually classified as humoral (hormones) and mechanical.

I.- Hormones

- PTH.- Endogenous PTH appears, essentially, to have a stimulatory effect on bone destruction. This is, at least, the effect which has been confirmed for PTH when it is administered continuously. Such an effect is performed through the osteoblasts and their production of RANKL. On the other hand its intermittent administration stimulates bone formation[29]. The reasons for this difference are not well understood. We will return to the anabolic effect of PTH later.

- Oestrogen.- The oestrogens have a positive effect on the bone through multiple mechanisms[30,31]. On the one hand, there are receptors for them in both osteoclasts and osteoblasts, in the second of which they bias the RANKL/OPG relationship in favour of the latter. On the other hand, they inhibit the production of osteoresorptive cytokines by the macrophages and the lymphocytes.

- Glucocorticoids.- The glucocorticoids, at physiological concentrations, have a permissive effect on bone formation. At pharmacological concentrations, however, they depress the activity of the osteoblasts and, initially, increase that of the osteoclasts, resulting in a reduction in bone mass[32]. The glucocorticoids reduce osteoprotegerin.

- Calcitonin.- Calcitonin is a powerful antiresorptive agent, although it may play some role in bone formation, since in knockout rats calcitonin results in an increase in bone formation[33].

- Serotonin.- We have already indicated that serotonin has been revealed as a powerful inhibitor of osteoblasts[34]. Its synthesis takes place in the enterochromaphine cell, from where it is released into the blood, of which 95% passes into the platelets. The remaining 5% has access to the osteoblasts, which have receptors for it. Our knowledge of the effects of serotonin on bone are still at a very early stage.

II.– Mechanical factors

Mechanical load exerts a positive effect on bone, and its absence (weightlessness, being bedridden), a negative effect, increasing bone turnover and encouraging bone destruction. The mechanisms through which these effects happen are not fully known, but appear to involved the osteocytes[35-36]. The osteocytes would detect changes in the mechanical load through changes in the flow of liquid which surrounds the extensions in the canaliculi where they are sited, and through the stimulation of structures which bond the surface of the extensions with the walls of these canaliculi, in which integrins are presumably involved. Other studies suggest the involvement of ionic channels present in the membrane of the osteocytes. In whichever case, the stimulus detected by the membrane structures should transcend the cytoskeleton and activate intracellular signalling pathways (MAPK).

An increase in runx 2 and osterix, as well as βcatenin, has been found in the osteoblasts of bone submitted to mechanical overload. This probably relates to the fact that the mechanical stimulus reduces the production by the osteocytes of schlerostin, antagonist of LRP5. The mechanical stimulus appears also to inhibit another antagonist of the Wnt pathway, Dkk1. In addition to the schlerostin-Wnt-βcatenin system, the response of the bone to mechanical stimulus appears to involve other substances, such as NO and the PGs. Also involved is the RANKL/OPG relationship, perhaps in relation to the modification in βcatenin. Finally, an increase in osteopontin has also been detected, in whose absence (KO rats) bone remodelling produced in response to mechanical changes is diminished, which has been related to a possible chemotactic effect of protein for the osteoclasts.

PTH sensitizes the bone to the mechanical sig-

nals, which is what the fact that the anabolic effect of the mechanical stimulus is lost in rats subject to parthyroidectomy, appears to indicate. PTH inhibits schlerostin, exerting on it a synergetic effect with βcatenin in response to mechanical stimulus. It should be taken into account that mechanical overload, although initially anabolic, when excessive can drive an increase in bone turnover with bone loss. This is because it can result in an accumulation of microcracks. Bone modelling (subperiostic formation) however, does not seem to be negatively affected in this situation.

The response to mechanical stimulus reduces progressively if it persists in a steady manner, thus mechanical overload is more efficacious from an osteogenic the point of view of if it occurs intermittently.

## Alterations in the units of bone remodelling in osteoporosis

We have indicated at the beginning of this chapter that osteoporosis is a dysfunction of the unit of bone remodelling[37]. This dysfunction is due, essentially, to two types of alteration. The first consists of the establishment of what we know as "negative balance"; the second in an increase in the number of units of bone remodelling, which gives way to what we call "increase in bone turnover". (Figure 2).

a) Negative balance

In the young adult the quantity of bone which makes up the osteoblasts in each unit of bone remodelling is equal to that which the osteoclasts have previously destroyed. The situation is known as "zero balance". However, at around 40 years of age, or perhaps a little earlier, the quantity of bone formed by the osteoblasts starts to be a little less than that destroyed by the osteoclasts. This situation is described as "negative balance". Given that, as we have already said, the number of units normally functioning in the skeleton is higher than a million, this means that from this age there are more than a million points in which bone mass is being lost. The result, logically, is the reduction in its total quantity. Depending on the initial bone mass, on the degree of negative balance, and the time during which it has been present (and certainly, the age of the person), this loss can take place at values of bone mass which qualify as osteoporotic. Negative balance is a sine qua non condition for the development osteoporosis.

Negative balance which develops with age is due fundamentally to a reduction in bone formation, probably related both to a decrease in the number of osteoblasts (due in part to a reduction in its precursors, in part to a diminution in their differentiation, and in part to a reduction in their survival) and in their individual activity. This, at least partly, is due also to falls in the bone microenvironment of the concentration of stimulator factors of these cells, which in one case (Wnt proteins) has been attributed to an increase in ROS radicals during aging. On occasion, an increase in bone resoprtion contributes to the negative balan-

Figure 2. Mechanisms involved in the bidirectional dialogue existing between osteoblasts and osteoclasts. See the text for a detailed explanation
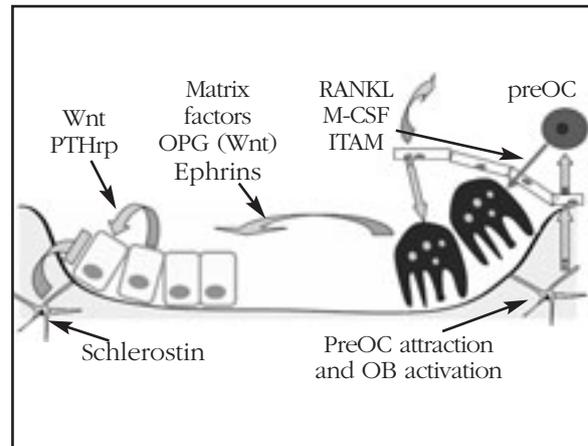
ce, due to an increase in osteoclastic activity. This increase could translate into a greater movement of osteoclasts, up to the point that the trabecular could become perforated. On the other hand, this increase in the activity of the osteoclasts is accompanied by the birth of a higher number of bone remodelling units, so that a phenomenon known as "increased turnover" takes place, which is commented on in the following section. As opposed to the reduction in activity of the osteoblasts due to age, the increase in osteoclasts is related to the reduction in oestrogens. The lack of these hormones probably also inhibits the formative activity by favouring osteoblast apoptosis, which intensifies the negative balance.

b) Increase in bone turnover

The increase in the number of bone remodelling units when these are found in negative balance supposes an increase in the number of points in the skeleton in which bone mass is lost, and therefore, an acceleration of this loss. In fact, although the negative balance could be an essential factor in the development of loss of bone mass, the factor which is usually responsible for the greatest quantity of loss of bone mass is an increase in turnover. The forms of osteoporosis in which this factor effectively plays the main role is known as "high turnover osteoporosis". The most characteristic example of increased turnover is that which constitutes the menopause, with the depletion of oestrogens which is brings. To this is due the acceleration of the loss of bone mass which follows it, and is ultimately the mechanism responsible for what is called "postmenopausal osteoporosis". There can also be an increase in bone turnover in later ages of life which is usually attributed to an increase in PTH in relation to a reduction in renal function and the endowment of vitamin D. There are some forms of osteoporosis –less frequent– in which turnover is not increased, such as, for example, idiopathic osteoporosis in males.

Consequences of alterations in bone remodelling units (Figure 3)

The differences in the structure and spatial positioning of the osteones in trabecular and cortical bone mean that the impact of the changes in the unit of remodelling on which we have just commented are different in the two section of bone.

a) Trabecular bone

As a consequence of the negative balance, a reduction in bone mass is established which is translated primarily into a thinning of the trabeculae. On the other hand, the increase in turnover intensifies this thinning, that, along with a greater movement of the osteoclasts due to this situation, tends to cause trabecular perforation. The accumulation of perforations makes a large part of the trabeculae start to disappear, such that the morphological aspect of the trabecular framework changes from what is called a "plate pattern" to a "rod pattern". That is to say, from walls with holes in them, like a sponge or a honeycomb, to a kind of tridimensional lattice, with less capacity to support mechanical load. On the other hand, the same loss of trabecular material results in a disconnection between trabeculae, which reduces their support for one another, which diminishes even more their ability to support load[38,39]. Specifically, most of the trabeculae which are lost are those which are horizontal, for which reason the vertical ones which have been preserved lose their buttressing effect which they shared with the horizontal trabeculae by bonding with them. This means that the residual vertical trabeculae are, in functional effect, longer, which facilitates their curvature ("buckling") and, in the long run, their fracture.

Added to the fact that the trabecular framework consists of trabeculae which are thinner and poorly interconnected, is another phenomenon of interest: that of the "concentration of tensions" at the level of active units of bone remodelling. From when a unit of remodelling initiates its activity until it ends, a vacant space in the bone (corresponding to the bone which has already been destroyed but has not yet been substituted by the new formation) is generated. Its presence in the thin trabecula produces weak points in which all the tensions in this trabecula has to support are concentrated (called "stress risers")[38]. At this point a fracture of the trabecula is easily established in the same way that if subject to a load, a structure (for example, a stick) which has been thinned at a certain point, will tend to snap at that point. In situations of high turnover, given that the number of active units of remodelling in them is greater, so also will be the number of "concentrators of tension", and thus, the points in which there is a risk of developing a fracture. The free spaces in the bone due to their being renewed, determinants of the concentrations of tension, frequently known jointly as "spaces in remodelling", in the literature written in English, tend to be described as "transient remodelling (spaces)"[40], to give an understanding that the loss of bone is reversible (transitory), given that it disappears once the osteoblasts fill the hole formed earlier by the osteoclasts.

In men, the reduction in bone mass with age is not established at the expense of an increase in turnover (possibly in relation to the absence of a phenomenon equivalent to the menopause), rather of the negative balance, in such a way that their trabeculae, rather than suffering a process of perforation and disconnection, undergo thinning.

b) Cortical bone

In the cortical bone the negative balance of the units of remodelling result in a thinning of the walls of the Havers' systems, which results in a widening of their channels. In the transversal histological cortex, this widening of the channels result in the presence of circular cavities, which give the bone tissue a porous aspect, which is why we talk of "cortical porosity".

On the other hand, in the osteones closest to the endosteum, the coincidence of thinning of the Havers' systems –due to the negative balance– with the greater movement of osteoclast –due to the raising of their activity– may result in a perforation in its wall, in such a way the Havers' channel makes contact with the tissue of the bone medulla. In such a case, this tissue enters towards the interior of the Havers' system, which ultimately suggests that the bone medulla gains space at the cost of what we could qualify as an endostial recess. The result, logically, is a thinning of the cortex.

c) Consequences common to trabecular and cortical bone: modification in the intrinsic properties of bone tissue

The increase in turnover, in addition to the inconveniences indicated, has the impact of negatively modifying the intrinsic properties of bone material, due to what is thought to be the existence of an excessive quality of juvenile and immature bone[41]. The ideal properties of bone tissue are those corresponding to mature bone. The maturation of bone tissue involves different phenomena, of which should be mentioned the development of collagen bridges of certain characteristics, mineralisation carried out in two phases (primary and secondary mineralisation), with the hydroxyapathite crystals reaching sufficient size. The too rapid renewal of the bone does not allow the maturation of the collagen bridges, the secondary mineralisation, or the formation of hydroxyapathite crystals of the correct size.

On the other hand, the increase in turnover could have a beneficial effect, in the first place by avoiding the accumulation of microlesions due to fatigue, which tend to increase as the bone ages, and secondly due to the difficulty of their propagation, given the greatest heterogeneity in the mineralisation of the osteones that this implies (the oldest more mineralised, the youngest, less). However, the reduction in bone mass implied by the increase in turnover means that the usual load is, in relative terms, an overload, which should lead to a greater number of microlesions. This, along with the fact that the exact implications of

the microlesions is not well known, especially within physiological levels[42], means that these comments should be considered as merely speculative.

d) Recapitulation

Therefore, the phenomena determining bone fragility as a consequence of an alteration in the functioning of the remodelling units characteristic of osteoporosis, are the following:

- Thinning of the trabeculae and of the cortex.
- Disappearance of part of the trabecular framwork with their disconnection.
- Increase in the number of tension concentrators in the trabeculae.
- Cortical porosity.
- Immaturity of bone tissue.

The consequences of the intermittent administration of PTH on the alterations in structure and bone quality characteristic of osteoporosis

We have indicated already that PTH administered continuously generally results in a reduction in bone mass, principally as a consequence of a stimulation in the activity of the osteoclasts, and therefore, bone resorption. However, administered intermittently it has a bone forming, also called anabolic, effect. The cellular mechanisms which drive this effect are dealt with later. Now we are going to focus on its repercussions on bone structure and bone mass[43,44].

It is possible to distinguish two phases in the effect of PTH administered intermittently: the first, of some months duration, in which only the activity of the osteoblasts is increased, with the consequent bone forming effects, and the second, in which there is an increase in the activity of both the osteoblasts and the osteoclasts, in such a way that what ultimately happens is an increase in bone turnover with a positive balance, whose result, as we will see, is also bone forming. The increase in the osteoresorptive activity is detected some months after the start of the administration of the hormone. In the first phase, both the osteoblasts which are acting on the active units of bone remodelling and some of those which are found on quiescent surfaces (possibly the "coating" osteoblasts themselves)[45], that is to say, those that have not undergone previous resorption: the osteoblasts of the external surface (periosteum), of the internal surface (endosteum), and of the trabecular surface which is not found in remodelling. In this final case, it appears that those osteoblasts found in proximity to the units of remodelling can be activated, while a possible alternative is that the active osteoblasts of those units themselves overflow their limits and occupy part of the surrounding bone. In whichever case, the possibility cannot be discounted that on the trabecular surface new bone is formed totally independent of the units of bone modelling, as has been argued[45] on the basis that the increase in volume of 35% at the end of the first year of administration of PTH could not be explained if it were only produced in

Figure 3. Negative balance of the unit of remodelling and increase in bone turnover as determining mechanisms in the loss of bone in osteoporosis

Mechanisms for loss of bone mass

Negative balance

Increase in turnover
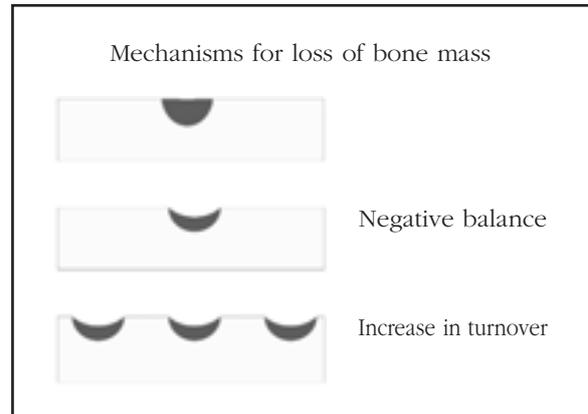
these units. The bone formed in sites previously subject to resorption (that is to say, in the units of remodelling) is sometimes called "remodelled bone" and that formed in places not subject to previous resorption (quiescent surfaces), as "modelled bone".

The stimulus of the osteoblasts of the internal and external surfaces produces an increase in the thickness of the cortex, and therefore, in bone resistance. In particular, the subperiostic deposition produces an increase in the external diameter of the bone, and it is worth noting that in this respect the mechanical efficacy given by a unit of bone tissue is higher the further its distance from the axis of the bone (greater module of inertia). Therefore, the bone tissue laid down below the periosteum is especially useful from a mechanical point of view. There are, however, doubts as to the exact extent of the subperiostic apposition of the bone, and in whichever case it seems to be heterogeneous, in the sense that it is developed more in some bones than in others (probably more so in the tubular bones, above all if a mechanical stimulus is added, such as supporting weight, which works with PTH in its anabolic effect.

The units of remodelling which are active when the administration of PTH starts –more abundant in the trabecular bone– are essentially in a forming phase, since the action of the osteoclasts is very brief (some two to three weeks) in relation to the osteoblasts (several months). The stimulus of these osteoblasts puts the units of remodelling in positive balance, which causes an increase in the thickness of the osteone. As we have just indicated, some authors have said that the stimulator effect of PTH on the osteoblasts of the unit of remodelling extends to the surface osteoblasts which surround them, in such a way that the positive balance overflows the strict dimensions of the unit. These phenomena are responsible for a clear increase in trabecular bone volume.

The effect of PTH in stimulating the osteoblast starts to become noticeable in the second phase of its activity, which from this moment gives way to the birth of new and more numerous units of remodelling. That is to say, a phase of increased bone turnover begins. Given that the stimulator effect of the osteoblasts is maintained, this second phase is characterised by the combination of high turnover with positive balance. This results in the existence a great number of points in which bone is formed, which again, gives way to an increase in bone volume. For not very clear reasons, it increases also the number of trabeculae (it is not known if they are newly formed or results of tunnelling of thickened trabeculae). Trabecular connectivity also appears to be increased. The stimulator effect of the subperiostic osteoblasts also appears to increase, so that the increase in cortical thickening continues. The increase in units of remodelling which characterise this phase, although favourable in the long term by increasing the number of places in which bone is formed by being in positive balance , could result in the fear of an initial transitory weakness in the skeleton by supposing places in which tension concentrations are established.

This is not confirmed in practice, which is probably due to the fact that the increase in bone volume makes the concentrations of tension at the points at which the units of remodelling are present, lower. However, we should point out that on occasions when the cortical bone near the endeostium, an increase in porosity can be observed on the administration of PTH, which definitely results in an increase in units of remodelling.

A theme frequently debated is if the increase in bone mass produced by the intermittent administration of PTH is contributed to more by remodelling bone, synthesised on earlier units of remodelling, or of modelling on previously quiescent surfaces. It seems beyond doubt that the former has much more importance. In any case, the relative importance varies from the former to the latter in the phases commented on. In the former, the modelled bone may be up to 30%;in the latter, much less: around 3-8%[44]. The reason for this is that in the latter case the number of units of remodelling is increased. In accordance with this, the principal bone forming effect of PTH takes place in the trabecular bone, which is where they are most abundant.
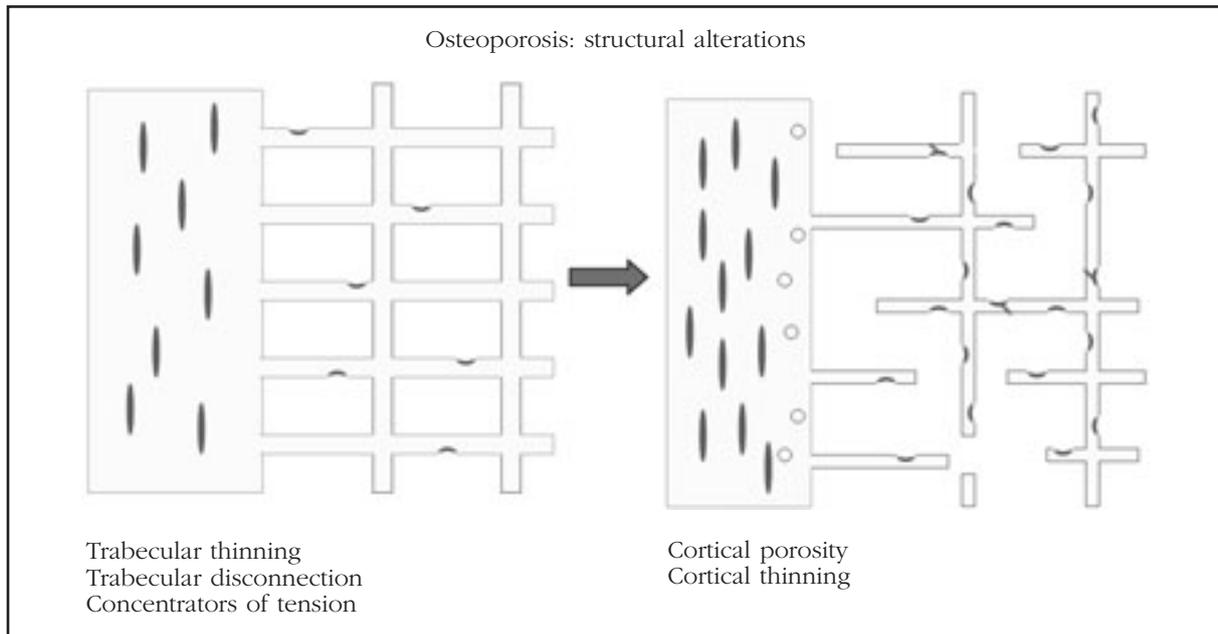
In summary, PTH administered intermittently modifies the bone structure in the sense of increasing the formation of bone on the trabecular, endocortical and periostic surface , both in trabecular and cortical bone (Figure 4). All this results in an increase in bone resistance confirmed in biomechanical studies. The intensity of this effect may vary from one place to another, depending, among other factors, on the mechanical load which is established in the different locations. The increase in subendostal porosity in some places, such as the radius, could raise a fear of a reduction in resistance, which however is not yet con-firmed, most likely by the compensatory effect of the bone's subperiostic growth.

During the first, solely bone forming, phase, an increase in markers for bone formation is detected in the blood. Later, to this increase in markers for formation is added an increase in those for resorption. The graphic representation (Figure 5) of this temporary behaviour of the two types of markers permits the observation of a space between the curves for each of them, before they finally join, once both are increased. This space corresponds to what we have just described as the first effect of the PTH, and was at one point called the "anabolic window". The term is a mistake, given that it may be interpreted as saying that only here does bone formation happen. This is clearly incorrect. In the second phase, although this stimulates resorption, formation predominates, given that there is a positive balance. What the resorption does is to mark the point of birth of the units of remodelling, and therefore the place in which the osteoblasts will act later. It should be noted that the osteoclasts contribute to the formation and activation of the osteoblasts (coupling) by means of various mechanisms (releasing substances from the destroyed bone, producing soluble factors which stimulate the osteoblasts, through membrane molecules such as the ephrins, etc.), some of which are stimulators of PTH (ephrins), which favour the positive balance of the units of remodelling. In fact, the lack of osteoclasts reduces markedly the effect of PTH. Some authors suggest that in order to activate this it is not necessary that the osteoclasts carry out their resporptive action, being present is sufficient, although they do not resorb bone.; in fact PTH itself could produce transitory action on the osteoclasts. However, others believe that in the absence of resorption the anabolic action of PTH cannot be fully expressed. The discrepancies in the results obtained when antiresorptives and PTH are administered in different patterns most likely have to do with these aspects, not yet sufficiently clarified.

The change in bone mass - defined by densitometry – shows a rapid increase in the first 6-12 months, becoming attenuated later. At one point it was thought that it would practically disappear after around two years, although a recent study of steroidal osteoporosis over three years confirmed a continuation of the increase in bone mass during the third year, although of lower intensity. The levels of markers, however, do appear to diminish progressively, as the image in Figure 5 indicates. The reason for this behaviour, and of this possible limitation in the bone forming effect of PTH after a certain period of intermittent administration, is not known, It is possible that once a certain bone mass is attained, a kind of mechanostatic mechanism makes difficult the later apposition of the bone. One cannot discount the phenomenon of cell desensitisation to hormones. It is also possible that, with the passing of time, in the unit of remodelling the resorptive activity increases compared to the forming.

Figure 4. Structural alterations in the bone determined by the negative balance of the units of bone remodelling and the increase in bone turnover

Osteoporosis: structural alterations

Trabecular thinning
Trabecular disconnection
Concentrators of tension

Cortical porosity
Cortical thinning

Before leaving this section it is worth giving some consideration to the quality of bone tissue formed under the action of PTH[43.44]. We refer here to the quality of the bone material, since that of bone as a whole –in which structural aspects ate predominant– is clearly improved by PTH, as has been deduced from the results of biomechanical studies already quoted. The characteristics of the bone material are essentially determined by the fact that they are found in a situation subject to high turnover. On average we are dealing here with younger bone before treatment, with collagen in which there is a high proportion of divalent bridges. The osteones are frequently renewed before they experience secondary mineralisation, for which reason the overall bone mineralisation is lower. On the other hand, in being renewed more quickly, the accumulation of microlesions in the bone tissue ought to be less (although this matter has not yet been confirmed). This is, without doubt, beneficial, as it is the heterogeneity of the mineralisation of the osteones which makes difficult the propagation of these microlesions. On the other hand, the lower mineralisation and the lack of maturation of the collagen may be unfavourable by reducing resistance. It is difficult therefore, to forsee the final result of these changes on the intrinsic biomechanical characteristics of the bone material.

Action mechanism of PTH at a cellular level

As we have seen, the aspect with defines the effect of the intermittent, as opposed to continuous administration of PTH, is osteoblastic stimulation. The hormone on the one hand increases the number of osteoblasts, and on the other, their activity. This is partly an indirect phenomenon, mediated through the osteoclasts, and simply represents the consequence of the phenomenon of coupling, with a higher production by these cells than stimulatory factors of the osteoblasts. But at the margin, PTH exerts a direct effect by means of various mechanisms. For example, it increases the number of osteoblasts, stimulating their differentiation and inhibiting their apoptosis. It may also increase the proliferation of their precursors, although this effect is disputed. On the other hand, it stimulates the activity of the mature osteoblasts. Of the two effects, the first appears to be the most important by far, judging by the histomorphometric studies (greater increase in the surface of mineralisation than of the speed of mineral apposition). The reduction in apoptosis seems less significant in the periostic bone than in the trabecular.

The action of PTH on the osteoblasts takes place through the receptor PTHR1, and its anabolic effects are principally mediated by the cAMP-PKA pathway[46]. It is possible that exogenous PTH, administered intermittently, may reproduce the effect of the endogenous PTHrP.

The end result of the action of PTH on the osteoblasts appears to be highly varied, and involve agents of different kinds[47-49]: osteoblast stimulatory factors, for which they have specific receptors, antagonists of the aforementioned ligands; certain receptors; various signalling pathways and transcription factors. Among the osteoblast stimulatory factors have been described some Wnt proteins, BMP2, the IGFs, FGF2, TGFβ –which would act in the form of autocrine or parahrine– as well as 1.25 (OH)2D, which, after being synthesised in the lower kidney stimulates the PTH, would be in the form of endocrine. At one point special impor-

Figure 5. Temporal relationship between the changes in markers for formation and resorption induced by PTH, which led to the (inexact) concept of a therapeutic window

Figure 6. Changes induced in bone structure by teriparatide

Basal · After 21 months
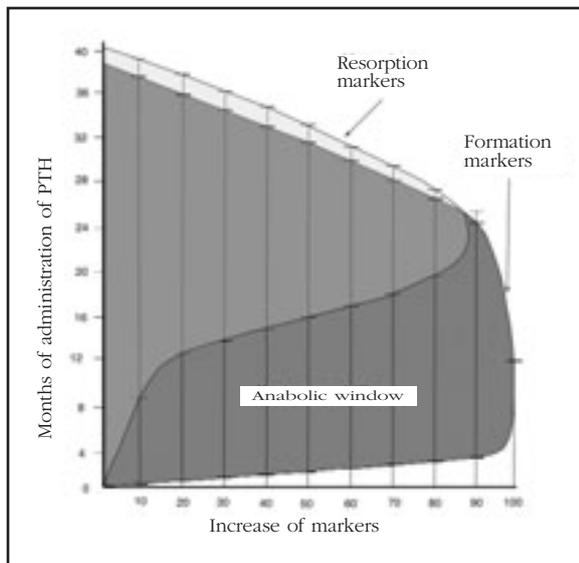
tance was given to IGF, proposing that in its absence PTH does not have an anabolic effect. Among the regulatory factors of these ligands, schlerostin should be mentioned, a substance produced by the osteocytes with an inhibitory effect on the action the Wnt proteins achieved by bonding to its receptor in the LRP5 component. The secretion of schlerostin by the osteocytes is slowed by PTH. PTH also suppresses other antagonists to the Wnt pathway such as DKK1 and SFRP-1. As receptors which can be modulated by the hormone, EGFR –whose ligands to these effects would be amphiregulin, RAGE– essentially in the spongy bone of the proximal femur, and the system of ephrins in the osteoblast, have been indicated. The intracellular agents (elements of the signalling pathways and transcription factors) which have been involved in the anabolic effect of PTH are also numerous: runx, osterix, ATF4 – stimulated by the hormone, PPARγ – all involved in osteoclast differentiation, or the protein Bad, with a proapoptic effect, and which is deactivated by PTH. Apoptosis is a critical factor in the determination of the number of osteoblasts.

In summary, PTH performs its bone forming effect by stimulating the osteoblasts through multiple mechanisms. It is appropriate to talk of the "pleiotropic effects of PTH". However, we do not know their details very well, nor do we know up to what point these mechanisms may be vicariant, or up to what point they are indispensable, being fundamental points of regulation. The absence of some of these factors block the bone forming effect of PTH, but the same does not happen with others. On the other hand, it appears that the effect of these various mechanisms varies from one place in the skeleton to another.
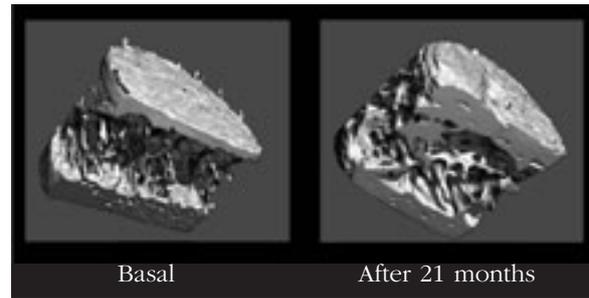
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Teriparatide in the treatment of postmenopausal osteoporosis

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Introduction

Nowadays there are many therapeutic options available for the treatment of osteoporosis. The objective of this treatment is to reduce the risk of fractures, both vertebral and non-vertebral. Fractures due to osteoporosis bring with them a high level of morbid-mortality[1], as well as the social and health costs they carry. In clinical trials the principal parameter for the measurement of the efficacy of treatment of osteoporosis is the reduction in risk of fracture. However, in clinical practice, a follow up after treatment is carried out with a series of measurements of bone mineral density (BMD). Although there is a clear relationship between BMD and the risk of fracture in patients without treatment, this correlation is not so clear in treated patients[2]. This is important because it should not be forgotten that the objective of treatment for osteoporosis is the reduction in fractures independently of any modification in BMD. This, although it may be an objective parameter for evaluating the response to treatment, never should be its aim.

Among the many therapeutic options teriparatide, or human recombinant PTH (1-34), has an outstanding position. It is classified in the group of bone forming or anabolic drugs in counterpoint to those called anticatabolics or antiresorptives[3]. It is administered as a daily self-administered subcutaneous injection, with an easily used preloaded pen, and induces the formation of new bone, increasing the rate of bone remodelling in favour of formation, with an increase in trabecular connectivity and thickening of the cortical bone[4]. Teriparatide improves the mechanical properties of bone[5], giving as a result a significant reduction in vertebral and non-vertebral fractures in postmenopausal women with osteoporosis[6], in men, and in those with corticoid osteoporosis[7,8]. It is for this reason that its use is considered appropriate fundamentally in patients at high risk of fracture and for those in whom there has been earlier failed treatment[9].

Physiological basis

The fundamental physiological action of parathormone (PTH) is the maintenance of the homeostasis of calcium, maintaining practically constant its concentration through the tubular reabsorption of calcium, and stimulating the absorption of calcium in the intestine by means of vitamin D, since it increases renal 1-a hydroxylase.

The effect which PTH exerts on the skeleton is complex. For example, a high and sustained level of PTH, observed in primary and secondary hyperparathyroidism, provokes an increase in bone resorption by its action on osteoclasts, producing secondary osteoporosis. On the other hand, high levels in intermittent peaks increases osteoblastic bone formation activity. This is the effect induced by administering PTH as a treatment for osteoporosis. In both schemes of stimulation of the receptor by the hormone, different genes are regulated which drive the stimulus for the resorption in the case of continuous exposure and formation with intermittent exposure.

The osteoblasts are the cells responsible for bone formation and principal protagonists of bone remodelling which the receptor of PTH expresses.

By means of growth factors modulated by PTH, the stimulation of the proliferation and the later maturation of the osteoblastic progenitors are produced[10]. Likewise, PTH induces the transformation of bone covering cells and of the osteocytes in active osteoclasts[11], and also increases the average life of the osteoblasts by a reduction in apoptosis[12]. The synthesis of PTH takes place in the parathyroid glands. Calcium is the most important signal in the regulation of the secretion of PTH. In the parathyroid glands, an increase in ionized calcium inhibits the secretion of PTH by increasing the intracellular calcium[13], whilst when it decreases an immediate response is produced with an increase in the secretion of the hormone and a reduction in its degradation and, subsequently, a late response with an increase in genetic expression and in the proliferation of parathyroid cells. This mechanism contrasts with that which happens in the majority of cells, where the secretion is stimulated by an increase in calcium.

The cells of the parathyroid gland have a receptor in their surface which acts as a sensor for levels of blood calcium[14] and also regulates the response of the C cells of the thyroid gland for the secretion of calcitonin. By means of a chain of intracellular signals the secretion of parathormone (PTH) will be produced.

Once released, PTH will increase the resorption of calcium, principally in the distal convoluted tube, and will inhibit the resorption of phosphate in the renal proximal tube, causing hypercalcemia and hypophosphatemia. Also produced is an inhibition of the Na^+/H^+ pump and the resorption of bicarbonate, causing mild hyperchloremic metabolic acidosis.

PTH receptor

PTH carries out its biological function by means of a receptor which is a membrane glucoprotein with a molecular weight of 80,000 Da. It belongs to the superfamily of transmembrane receptors linked to G proteins. It is formed of a circle of helices which surround a polarised centre and from which two chains split, one extracellular, aminoterminal, and one domain intracytoplasmatic carboxyterminal. The receptor for classic PTH recognises the extreme amino-terminal of the hormone and also of the protein related to parathormone (PTHrP) with a similar affinity in both cases, for which reason it has been called the PTH/PTHrP receptor[15].

The interaction of PTH or PTHrp with its receptor produces the activation of proteins Gs and Gq. In its turn, the activation of the G protein activates the production of adenyl cyclase and of the protein Gq activates phospholipase C. The adenyl cyclase pathway plays an important role in the induction of biological effects, while phospholipase would play a modulating role. Similarly, the activated receptor also induces the expression of the genes and induces growth factors like IGF-I, IGF-II, and TGF-β.

The action of PTH in resorption and mobilising calcium is mediated essentially by the RANK/RANKL system in response to a sustained exposure to the hormone. Experimentally, an increase in RANKL and an inhibition in osteoprotegerin (OPG) is observed, increasing its quotient. The addition of OPG to the medium blocks the hypercalcemic action of the hormone.

Here also, the intermittent administration of the hormone inverts the equation, since it induces an elevation of OPG with an inhibition of RANKL, again in favour of an anabolic effect. In addition the action of PTH on the osteocytes is transcended by this anabolic effect since it diminishes the expression of schlerostin (SOST). Given that this protein blocks the activation of the Wnt/LRP5-6 pathway, it has an inhibitory effect on osteoblast activation. Therefore, when PTH inhibits it, it "frees" the Wnt/LRP5-6 signalling pathway with the consequent stimulation of bone formation.

Preclinical basis for using PTH

The use of PTH was initiated in the first quarter of the 20th century. In 1925 an extract of parathyroid was purified which showed great anabolic bone activity. However, it has been in the last 30 years when its clinical use has been postulated definitely, following various studies using animal models (rats, rabbits and primates) highlighted its powerful anabolic action, although this had already been detected by Albright in the 40s.

It is in the 1970s when the fragment 1-34, or teriparatide, is synthesised. The first studies carried out in rats confirmed this action on bone. However, what was notable was the different response produced according to the method of administration – continuous or pulsed[16]. In both cases an increase in the formation of bone was produced, but a continuous administration also resulted in an increase in resorption and as a result, bone loss, as in the case of hyperparathyroidism. While an intermittent administration did not modify resorption, privileging the forming effect[16]. The mechanism by which this different response is produced is not well known. It is suggested, though, that when the administration of the hormone is intermittent the activation of the RANK/RANKL system produced is transitory and negligible. Thus it inhibits osteoblast apoptosis and stimulates its recruitment, which increases the bone-formative action. In animal models it has been shown that intermittent PTH would stimulate the differentiation and activity of the osteoblasts.

Animal models. Rat models

One of the first animal models, employed in the study of the effects of PTH on bone formation was the rat. The use of different types of rat (overiectomised, orchiectomised, or studies with young rats) allowed the discovery of what produced an increase in vertebral trabecular bone in which bone mass increased[17]. Studies were also carried out to analyse the change in the biomechanical properties of bone observed after treatment with PTH (1-34), an increase, dependent on dose, in the both the formation of cortical bone, and the circumference and resistance of the femur[18]. In these rat models it has been found that PTH induces an increase in both number

and activity of the osteoblasts, measured by the synthesis of collagen and osteocalcin in ovariectomised rats. PTH acts principally on trabecular bone, however, it has been observed that the action is different according to different bones. Thus, after 6 months of treatment, connectivity between trabelucae was re-established to a marginal extent in areas such the proximal tibia, while in the vertebral trabecular bone the recuperation was much greater[19]. The reparative effect of teriparatide is dependent on the dose, such that in the case of ovariectomised rats administration of 8 µg/kg would produce a recuperation of bone mass to the level prior to the oophorectomy, whilst a dose of 40 µg/kg increased it above the baseline level[20].

Animal model with rabbits

For the study of the behaviour of cortical bone after treatment with PTH the animal model with rabbits was resorted to, since they have a structure and remodelling most similar to humans.

It was observed how, after prolonged treatment with teriparatide at high doses (40 µg/kg), an increase in bone turnover was produced, as well as an increase in cortical porosity which could theoretically worsen the biometric parameters. However, these changes compensate for an increase in the formation of periostic and endostic bone, which brings with it an increase in bone resistance. However, at the start of treatment due to the this increase in porosity and turnover an increase in fractures could arise. Paradoxically, in studies designed to assess this extreme no such changes were found. The distribution of cortical porosity was studied, observing that this was higher in the two internal thirds. On the other hand, in the external third this increase in porosity was not found, which is also gave as a result an increase in resistance[21]. Subsequently these results have been confirmed in human cortical structure.

Animal model in primates

The last step in the study of the effect of antiosteoporotic drugs on the bone is the animal model with primates, with bone most similar to humans and a skeletal arrangement and share of cortical-trabecular bone also similar.

In these animals it is observed how teriparatide increases BMD in the axial and peripheral skeleton. In ovariectomised animals a dose of 5 µg/kg/d obtained an increase in trabecular bone without a significant change in phospho-calcium metabolism. This effect was maintained for 6 months after the withdrawal of treatment.

Clinical use of PTH

The first indication for teriparatide has been for the treatment of established osteoporosis in postmenopausal women. Of the different studies of this drug which exist, in those which analyse the reduction of fractures, one that stands out is a study called FPT (Fracture Prevention Trial), published by Neer et al.[6], which was the reference study for the drug, in which teriparatide at doses of 20 or 40 µg/day

were compared against a placebo in 1,637 postmenopausal women with vertebral fractures. In addition, all participants received calcium and vitamin D supplements. At approximately two years of treatment it was found that both doses of teriparatide achieved significant reductions in the rate of new vertebral (65% and 69% reduction respectively) and non-vertebral (53% and 54% respectively) fractures. The effect on the reduction in risk of multiple vertebral fractures was 77% and 86% respectively, and of moderate or severe vertebral fractures, 90% and 78% respectively. In increase in lumbar bone density was also produced (9.7% and 13.7%) and in the femoral neck (2.8% and 5.1%). Although with 40 µg/day greater effects on BMD were achieved the risk of fracture was not significantly different between the two doses, whilst the higher dose was less well tolerated (11% abandonment due to undesirable effects with 40 µg/day, as against 6% with 20 µg/day or placebo) for which reason 20 µg/day was selected for clinical use. This study was initially planned to have a duration of 36 months, but was suspended when the patients reached 21 months as a safety measure because in the study of the drug's toxicity in Fisher rats found cases of osteosarcoma. Subsequently in complementary studies there was evidence that this was only produced in young rats, with bone in full development and which had high doses of the drug[22,23]. Despite this precautionary suspension, subsequent exhaustive studies in animal models, as well as a detailed follow up of treated patients showed a reliably positive safety profile which allowed the drug's continued development and clinical use.

A subgroup of patients were followed over the long term, up to 18 months after the cessation of treatment. The subgroup of women who had received teriparatide continued to have a 40% reduction in the risk of vertebral fracture at 18 months in comparison with the placebo group. These results suggest that the benefit regarding the incidence of non-vertebral fractures after a year and a half of treatment with teriparatide would persist for three years after the treatment having ended[24,25].

Another trial has compared teriparatide (40 µg/dia) with alendronate[26] in a group of 146 postmenopausal women. After 14 months of treatment the BMD in the lumbar spinal column had increased significantly, more with teriparatide at 40 µg/day than with alendronate (15.1% vs 6.6%); the same happened for the BMD in the femoral neck. However, this study had a reduced sample size and an insufficient period of follow up, which meant that the number of fractures accumulated was also insufficient, for which reason it was not possible to draw conclusions from them as to the drug's antifractural efficacy.

Combined treatment

Nowadays the biphosphonates are the foundation for treatment of osteoporosis. There have been a number of trials to see if their association with teriparatide has a beneficial effect.

In a randomised trial carried out with 83 men affected by osteoporosis, the effects on bone of alendronate at a dose of 10 mg/day, of teriparatide at 40 µg/day, and a combination of both, were compared[27]. At the end, after 30 months of alendronate and 24 months of teriparatide a statistically significant increase in BMD in the lumbar spine was observed in the group who received only teriparatide as against those who received the combination. In addition, it was notable that the BMD in the femoral neck was higher at 30 months in the group which received only teriparatide. This might suggest that if both drugs are administered simultaneously, not only does it not strengthen them but it appears to inhibit them, and that their association would reduce the anabolic effect of the teriparatide in trabecular bone in the spine and would alter the capacity of the teriparatide to increase the cortical volume of the femur during the first months of treatment.

Recently, at the ASBMR congress the preliminary results of a study were presented in which it was observed that the combined administration of zoledronic acid and teriparatide resulted in a greater increase in BMD of the total femur than teriparatide alone[28], which suggests that when the cells have not yet received the inhibitory effect of the induced remodelling by the antiresoprtives the response the teriparatide. is maintained.

Teriparatide in previously treated patients

Seeing as these antagonistic effects which the combination of the two drugs appears exert one might ask if at the start of treatment with teriparatide when there has been previous treatment with antiresorptives, especially biphosphonates, the anabolic effect of teriparatide is influenced. For this reason, a study, the EUROFORS study, was carried out which evaluated the response in BMD and safety issues, in a group of 503 postmenopausal women with osteoporosis who received teriparatide for 24 months. They were classified into three groups: those who had not received previous treatment; those who, having been receiving treatment, did not show any evidence of its failure; and finally, those who had had an inadequate response to this treatment. Although bone mass increased significantly in all three groups, and in the group not having received previous treatment with teriparatide produced a higher increase in bone mass in the lumbar spine, there were also significant increases in the other groups[29], without statistically significant differences between them. These results guarantee that even in patients on prolonged treatment with antiresorptives, we could expect a powerful formative effect when changing over to teriparatide.

Sequential therapy

We have seen how the use of teriparatide after an antiresorptive treatment retains its full effect, whilst its concomitant use brings a somewhat limited benefit, in some studies, in relation to the use of teriparatide alone. However, starting antiresorptive treatment, after having carried out bone forming treatment with PTH 1-34, to consolidate the formed bone could have advantages. It is not clear what treatment should be started after having completed treatment with teriparatide in serious osteoporosis. There are clinical trials which show how the administration of an antiresorptives after having ended treatment with teriparatide has a protective effect on the gains in bone mass achieved. The most recent of all, an extension of the trial already cited, EUROFORS[30], a prospective, randomised and controlled trial, compared bone mass and clinical safety with three options for treatment after a year with teriparatide. These three options are: continue for a second year with teriparatide; start treatment with raloxifen; or do not carry out treatment. It was observed that in the group which continued to receive teriparatide bone mass in the hip increased by 2.5%, while the same increase was 2.3% in the case of raloxifen, and 0.5% in those patients who received neither drug, although the study was not strong enough to assess their effect on fractures. These results allow us to conclude that continuing therapy after completing treatment with teriparatide has a beneficial effect, since it consolidated the increase in bone mass achieved thanks to the bone forming treatment. Teriparatide, an anabolic agent, induces a period of formation or "recovery" which is then followed by the effect, by the antiresorptive, of "consolidation" of the gains in bone mass.

Osteoporosis induced by corticoids

There are, similarly, trials which show the efficacy of teriparatide in the treatment of osteoporosis induced by systemic corticoids[31,32]. In a randomised, double blind study 428 patients[28], of both sexes, with ages between 22 and 89 years, who had received corticosteroids for a period of at least 3 months, were allocated to two groups, one which received 10 mg/day of alendronate while the second was treated with 20 µg/day of teriparatide, both for a period of 36 months. Set as a primary objective was the change in BMD in the lumbar spine at 18 months, and as secondary objectives, markers for bone resorption, total BMD in the femur, and the incidence of fractures and safety. Statistically significant differences were attained with respect to BMD in the lumbar spine in favour of teriapratide at 6 months. At 12 months, the total BMD in the femur was higher in the teriparatide group, and at the end of the study, as well as the higher gains in bone mass, fewer vertebral fractures had been produced in the teriparatide group with respect to the alendronate group, the difference being statistically significant. Steroid osteoporosis, and male osteoporosis, will be commented on in more detail in other chapters of this monograph.

Treatment of male osteoporosis

Teriparatide has also been used in men with osteoporosis[33]. A group of 433 men with densitometric osteoporosis, of idiopathic origin, or due to hypogonadism, randomly received either placebo or teriparatide at 20 or 40 µg/day. They also received

calcium and vitamin D. After an average of 11 months of treatment the BMD in the spinal column increased by 5.9% and 9.0% for the doses of 20 and 40 µg/day respectively, both significantly different from the placebo group (p< 0.001). In the femoral neck the increases were 1.5 and 2.9% for the two doses, again, both significantly different from the placebo. The increases were independent of the state of the gonads and other factors, and of a similar magnitude to those observed in the FPT reference study in women.

Teriparatide and adverse effects

The most frequent secondary effects described in the clinical trials have been nausea, pain in the extremities, headache and dizzyness. There have been cases described of orthostatic hypertension, above all after the first dose, which do not require the interruption of treatment.

Treatment with teriparatide provokes a discrete raising of blood calcium which reaches a maximum at 4-6 hours after the subcutaneous administration of the drug, and which normalises itself after 16-24 hours. While it is not recommended to carry out a follow up of the calcemia, the presence of baseline hypercalcemia is considered to be a contraindication. As we have said earlier, in studies with Fisher rats, teriparatide has been associated with an increase in the incidence of osteosarcomas. This finding provoked an interruption of three clinical trials in humans which were under way, and the carrying out of experimental safety studies. The conclusions which were drawn from the results are that the dose and the duration of treatment are the main factors related to the appearance of sarcomas of this type specific to rats. However, there are notable difference between bone tissue of rats and that of humans. In addition, the study dealt with young rats in the full development phase, and the dose of teriparatide was extraordinarily high and administered during practically the whole life of the animal. All these factors put in doubt the validity of this Fisher rat model, since, in addition, the results of numerous studies in other animal models have been totally negative. In the studies carried out in primates with the administration of such high dose as 5 µg/kg over 18 months, not a single bone tumour has been seen. In the case of humans, not a single case of osteosarcoma has been observed after treatment with teriparatide over 18 months or in the three year follow up after the end of treatment. The exhaustive re-evaluation of the follow up data on all the patients treated, on the part of the evaluation agencies of North America and Europe, has concluded that the use of teriparatide is safe in human beings, there not having been observed a higher incidence of bone tumours than in the general population.

However, and as an additional precaution, teriparatide is formally contraindicated in those patients who present a high risk of osteosarcomas (Paget's disease, or inexplicably high levels of alkaline phosphatase), patients at an age of bone growth, those with systematically treated neoplasia, and those who have had skeletal X-rays.

Conclusions

Fractures are principal consequence of osteoporosis, both for their cost in terms of health and for their reduction in the quality of life of patients. The development of drugs which allow an ever greater reduction in the risk of fractures permits not only an increase in the therapeutic arsenal but one which diminishes the incidence of the most serious consequence of such a prevalent disease. For this reason, the appearance of this new group of treatments called bone formers or anabolics is important, since, specifically, teriparatide reduces vertebral and non-vertebral fractures, which on the one hand makes available a new anti-fractural option which acts specifically on the process of bone formation, and on the other, it reverses bone deterioration due to osteoporosis. This is so because teriparatide does not only produce a significant increase in BMD as a consequence of the net formation of bone, but it also improves the microarchitecture and the biomechanical properties of this bone. Comparative studies with other drugs have been favourable to teriparatide, both in terms of bone mass and in the reduction of risk of fractures. For all these reasons, teriparatide is a first line option in the treatment of patients with serious osteoporosis,such as those listed in the guide to clinical practice of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)[34] (http://www. seiomm.org/documentos/osteoporosis_es_en.pdf). This all means that we have available more therapeutic options in our fight against the most prevalent bone disease, osteoporosis.

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Osteoporosis in males. Treatment

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Introduction

Since the initial description of postmenopausal osteporosis in 1941, Osteoporosis (OP) has been considered a disease which appears in women. However, since a few years ago, it has been recognised that OP in men represents a significant problem in public health, since a seventh of vertebral fractures and a fourth to a fifth of all fractures of the hip occur in males, causing significant morbid-mortality[1].

Epidemiology of male osteoporosis

There are not many works on the prevalence of male osteoporosis in different populations. It is calculated that some 2 million American males may have OP and that it will increase 20% by 2015. In our experience, the percentage of densitometric OP in the Spanish male population is 4.15% (2.99%-5.31%), which would suppose that there would currently be between 418,000 and 743,000 Spanish males affected[2].

Incidence and prevalence of fractures in men

Incidence of hip fractures

The proportion of hip fractures in the male population represents 30% of all hip fractures in the world[3]. The life risk for hip fractures in men is 6% at the age of 50 years. In 1996 there were 80,000 hip fractures in American men. For the year 2025 an increase in these figures is foreseen.

The MEDOS (Mediterranean Osteoporosis Study) study[4], carried out in the Mediterranean basin, and in which this country participated, it was observed that the incidence of hip fracture due to OP in individuals of more than 45 or 50 years, varied in the case of men, between 50 and 100 cases per 100,000 inhabitants per year. In our

country it has been estimated that the incidence of hip fractures in those older than 50 years varies between the 127.8/100,000/year of Gran Canaria and the 267.7/100,000/year of Valladolid[5], with a female/male ratio of between 2.5-3 to 1.

The morbid-mortality of hip fractures is greater in men than in women. 36% of men with hip fractures die in the year following the fracture[6].

Prevalence of vertebral fractures

Vertebral fractures are more common now than was previously thought, although only 1/3 of them are symptomatic. In the EVOS (European Osteoporosis Vertebral Study) study, the standardised prevalence of vertebral deformity in people older than 50 years was similar in both sexes, with figures of 20.2% using the Eastell criteria and 12.0% using those of McCloskey, with significant variations between countries of similar latitudes, the rate in Spanish males being 572 per 100,000 inhabitants[7].

The vertebral deformities and their negative impact on health (back pain, reduced functional capacity, and global subjective feeling of health) was more significant in men than in women.

Mortality after vertebral fractures is higher in males. The work of Center et al.[8], showed that after the first year after fracture, the increase in global mortality was 1.66 for women and 2.38 for males. In patients clinically diagnosed with osteoporotic vertebral fracture there is an excess in mortality of 17% at five years[8]. It is possible that other risk factors are associated with this, such as age, smoking, alcohol consumption, immobility or, as well, chronic processes such as chronic obstructive pulmonary disease, gastrointestinal disease or infection.

Aetiology

From the clinical point of view, it is important to understand that roughly between 50-60% of men with OP have some dysfunction or condition which favours its appearance[9-11]. Standing out among these are hypogonadism[10,12,13], taking of steroids[10], hyperthyroidism, primary hyperparathyroidism, chronic alcoholism[13], gastrointestinal disorders, idiopathic hypercalciuria, malignant diseases and prolonged immobilisation.

In relation to hypogonadism, it is necessary to highlight the fact that long-term testosterone deficiency is typical in 30% of men with vertebral OP. It commonly appears in the sixth decade of life and the great majority have had symptoms related to hypergonadism for 20 to 30 years. Whilst deficiency in testosterone is related to a greater affectation in trabecular bone causing vertebral OP, the affectation of cortical bone may also be affected due to chronic testicular hypofunction, especially before the closure of the epyphises[14]. The androgenic deficiency reduces the synthesis of 1.25-dihydroxyvitamin D provoking a reduction in intestinal absorption of calcium (Ca) as well as provoking a reduction in bone formation[12]. Gonadal deficiency may be a risk factor for the appearance of hip fractures, and may also contribute to the reduction in bone mass associated with aging.

Pathogenesis of primary male OP

Although in women the ceasing of gonadal function during the menopause is the predominant pathogenic factor, this probably does not happen in men, where most important are the secondary causes and other risk factors. There are various published studies which relate risk factors with fractures in males[15-18]. Thus, the EVOS study[15], found a direct relationship with age, with the existence of a previous hip fracture, with lack of physical exercise or with excess physical activity in middle age, with a low body mass and with previous use of steroids.

The low incidence of male OP in relation to female, is related to different mechanisms which are summarised in Table 1.

Men have larger bones and the maturing of the axial and apendicular skeleton is faster in women than in men of the same chronological age[19], due to the greater speed of growth and the duration of the pubertal growth spurt. Hence, late or early puberty causes a deficit or excess of size, mass and density of bone (BMD) depending on when the disease occurs[20].

The growth phase is important, considering the different pattern of growth of the axial and apendicular skeleton and the changes in bone mass which occur during growth and aging. Men have a peak bone mass (PBM) higher than that of women[21] because they have a net gain of around 300 g more of bone Ca during growth, than women (1,200 g vs 900 g of total body Ca). The PBM in both sexes is influenced by different factors: nutrition, physical activity, genetic potential and other factors. Women show an increase in

Table 1. Mechanisms which contribute to lower bone fragility in males compared to women

- Greater size of bone structures
- Higher "peak bone mass"
- Lower loss of bone mass, over time
- Less trabecular perforation and disconnection with thinning of the trabeculas, as a result of a reduction in bone formation.
- Less thinning of the cortex, as a result of a higher periostic apposition and a lower endostal resorption

bone mass at the start of adolescence, completing it at the end of puberty. In men, as the start of puberty is later, PBM is reached later too. The differences in PBM and bone size explain the difference in the pattern of fractures which it produces in later stages of life. The loss of bone mass is later than in women, although the absolute quantity of loss of trabecular bone in the iliac crest is similar in both sexes. Men lose only around 100 g net of bone Ca during aging, while women lose nearly 250 g of Ca.

With aging there is a continuous growth in periosteum in men, but not in women, hence bone size is greater in males[22]. The mechanism of this continuous growth is unknown, but it is thought that it may be due to a phenomenon related to sex hormones. Men lose around 10% of their PBM during aging, while in women this loss can be up to 30%. These great differences in bone size and in BMD would explain the lower incidence of fractures in men compared to women.

The levels of blood testosterone reduce with age due to the reduction in the number of Leydig cells, to changes in hypothalamus/hypophysarial function and disease. There is an association between testosterone and BMD in men; in the institutionalised aged the levels of testosterone are correlated with BMD in the femoral neck, with low levels reported in 59% of patients with vertebral fractures compared to 18% in the control group[14].

The association between bone mass and testosterone has been reported in a minority of studies[22,23], while other studies have not found such a relationship[24].

On the other hand, the growth hormone (GH) and IGF1 can take a significant role in the reduction of bone formation during aging. Both hormones diminish with advancing age[25,26], it having been confirmed that IGF1 and IGF BP3 are positively associated with BMD. In fact IGF1 can be reduced in men with fractures. In addition, it is known that aging is associated with a reduction in blood levels of dehydroepiandrosterone sulphate (DHEA), with treatment with DHEA having been shown to increase levels of IGF1 and reduce IGF BP3, by which the ratio IGF1/IGFBP3 is increased by 50%, which increases the bioavailability of

IGF1. We also know that testosterone increases IGF1, from which it can be deduced that the effects of testosterone can be partly mediated through GH[27].

Diagnosis

The diagnosis of OP in men is established with a good clinical history, a physical examination, a lateral dorsal and lumbar X-ray, and the measurement of BMD. The majority of patients attend the clinic once an osteoporotic fracture has appeared, and there are only few occasions in which the diagnosis is performed before they occur[10]. The problem is to establish the etiological diagnosis to determine the appropriate treatment. An correctible cause of low BMD needs to be excluded, for which reason an analytical study is carried out which includes an elemental examination of the blood, with complete biochemical profile which includes blood proteins and protein immunoelectrophoresis, thyroid hormones, testosterone, luteinising hormone (LH), prolactin, urinary calcium excretion in 24 hours. The determination of cortisol is carried out in any man with OP when the aetiology is not apparent. Subsequent studies are carried out if anomalies are found in earlier analyses, for example, if there is hypercalcemia, the PTH is determined, if there is hypocalcemia, hypocalciuria and/or hypophospatemia with an increase, or not, of levels of alkaline phosphatase, levels of vitamin D will be determined. If there is diffuse bone pain, or any anomaly in the haematological profile, a bone X-ray and a biopsy of the bone medulla are carried out. In institutionalised patients it is recommended that a screening is carried out to determine vitamin D and evaluate its deficit. A diagnosis of idiopathic OP is carried out when a secondary cause of OP has been ruled out.

Treatment of osteoporosis in males

Although great advances have been made in the understanding of the epidemiology and pathology of male OP, this is not the case with treatment. Differently from female postmenopausal OP, there are few conclusive studies on the results of treatment of osteoporosis in males. The majority of studies have had as their primary objective changes in bone mass, and not the prevention of fractures, having small sample sizes. In addition, they include non-homogeneous populations, both in their aetiology –males with idiopathic OP and OP due to hypogonadism– and with different diagnostic criteria.

The treatment of OP in men consists fundamentally in identifying secondary causes, and maintaining a balanced diet, with an adequate intake of Ca, and in those cases where this may be insufficient, administering Ca and vitamin D, avoiding inactivity, taking adequate physical exercise or a programme of physiotherapy. In very old or frail males with OP, measures should be taken to minimise the risk of falls and to reduce their impact[28].

In patients with hypogonadism treatment with testosterone should be tried. Replacement with long-acting preparations of testosterone should be considered in all osteoporotic or osteopenic patients with low levels of blood testosterone. Generally this is well tolerated. The few available studies on the effects of androgens in older males with idiopathic OP do not allow a recommendation of their use in the absence of evident hypogonadism. A meta-analysis has been published on the effects of testosterone on males at risk of OP (hypogonadal men, very old men or those on corticoid treatment) which concludes that intramuscular testosterone –but not transdermic administration– moderately increases lumbar BMD without being able to infer results on fractures[29]. Precautions should be taken with patients with prostatic hyperplasia, since there is a risk of prostatic cancer, it being contraindicated in patients with prostate cancer. It is recommended that a digital rectal examination and prostate specific antigen (PSA) test be carried out in all men over 50 years of age who are going to receive androgenic therapy, as well as during the follow up period. Although no changes in levels of blood lipids have been shown, its use is not recommended in men with hypogonadism and a significant history of ischemic cardiopathy.

Calcium and vitamin D; vitamin D derivatives

As is the case with women, there is agreement in recommending the use of Ca and vitamin D supplements in male patients with osteoporosis, even when there is no clear proof available with respect to their efficacy, with the aim of avoiding negative consequences, in which, at least theoretically, a lack of them could result.

The scarce data available does not allow the establishment of recommendations on the use of alphacalcidiol, calcitriol or other derivatives of vitamin D for OP in males[30].

Calcitonin (CT)

The few available studies suggest that nasal CT (200 UI/day), continuous or intermittent, produces an increase in lumbar BMD and a reduction in markers for bone remodelling in males with osteoporosis[31]. The data on femoral BMD are contradictory. There are not sufficient quality data to pronounce on CT's effect on the reduction in the occurrence of osteoporotic fractures.

Etidronate (EDPN)

Not a single controlled clinical trial has been identified, so it is not possible to establish recommendations with respect to its use, although a recent publication shows that both EDPH and ALN are associated with gains in lumbar BMD (higher for ALN) and suggests a positive effect on femoral BMD and on fractures of both biphosphonates (BF)[32].

Alendronate (ALN)

The most important trial on the effect of ALN on males with primary OP (associated, or not, with low blood levels of testosterone)[33] included 241 males with an average age of 63 years (between

31 and 87 years). The primary objective was the change in lumbar BMD. More than 80% of the subjects completed the study (86% for ALN and 83% for the placebo). With the incidence of vertebral fractures measured by quantitative methods the difference was statistically significant: 0.8 vs 7.1% (-88.7%, ALN vs placebo; P= 0.02)). Those treated with ALN also presented a lower loss in height (0.6 vs 2.4 mm; P= 0.02).

This cohort was analysed again after 3 years of treatment[34]. 118 subjects (88%) finished the trial. Seven subjects treated with ALN (7/68, 10.3%) and 16 with alphacalcidiol (16/66, 24.2%) developed vertebral fractures, which suggests a significant reduction in risk of 57% (P= 0.04). Those treated with ALN also lost less height during the trial (7.1 vs 13.1 mm, P= 0.03). The difference in non-vertebral fractures (6 with ALN –8.7%–, and 8 with alphacalcidiol –12.1%–) and in vertebral pain was not significant. Adherence to both treatments was higher than 90%, and they were well tolerated.

Also assessed were the effects of weekly treatment with ALN in male idiopathic osteoporosis and that associated with hypogonadism (40% of the total number of subjects; 57% older than 65 years)[35]. This was a randomised placebo-controlled double blind trial of 12 months duration which included 167 males with T-scores <-2 and/or fractures (more than 60%) treated with Ca and vitamin D and randomly assigned (2:1) to either ALN (70 mg/week) or placebo. 86% of the subjects completed the study. Two subjects developed 2 non-vertebral fractures (one in each group). Nine subjects showed vertebral fractures 6 (7.5%) with ALN and 3 (7.3%) in the placebo group (4.6% of those treated with ALN and 5.2% of the placebo group suffered clinical fractures). Weekly ALN was associated with a significant increase in BMD in the lumbar region (4.3%), femoral neck (+2.1), trochanter (2.4%) and total body (1.4%) with respect to the initial value and the placebo group (P< 0.05), independently of gonadal state, weight or height.

In conclusion, ALN is associated with a significant increase in lumbar, femoral and total body BMD in subjects with idiopathic OP and with OP associated with hypogonadism, as well as a significant reduction in markers for remodelled bone. Daily ALN has shown, although a secondary objective, a significant reduction in risk of vertebral fracture.

Risedronate (RSN)
Sato et al.[36] assessed the effect of RSN on Japanese males of advanced age (> 65 years, average age 76 years) with hemiplegia due to cerebrovascular accident. Those subjects with previous fractures were exluded and the presence of densitometric OP as a criterion for inclusion, was not required. The primary objective was the incidence of hip fractures. 280 subjects were randomly allocated to receive 18 months of treatment with RSN. There were 10 hip fractures in the placebo group (10/133, 7.5%) as opposed to 2 in the RSN group

(2/134, 1.5%). The relative risk was 0.19 (interval of confidence of 95% 0.04-0.89). All the fractures occurred on the hemiplegic side. The bone mass assessed by radiogrammetry increased by 2.5% with RSN, while it was reduced by 3.3% in those receiving the placebo (P <0.001).

An open study which analysed the effects of RSN vs placebo over 12 months in males with OP or secondary OP showed a reduction of 60% in the appearance of vertebral fractures[37].

Ibandronate (IBN)
We did not find in the bibliographic search a single controlled trial on the effects of IBN on males with OP. One open study, not controlled, with intravenous IBN (2 mg/3 months) along with calcium and vitamin D, showed an increase in lumbar BMD of 6.7% and of 3.2% in the femoral trochanter at 2 years[38].

Thiazides
Despite not having been able to identify a single clinical trial on its effects on males with osteoporosis, the available evidence suggests an interest in the use of the thiazides in osteoporotic males with concomitant hypercalciuria[39].

Fragment 1-34 of PTH (PTH 1-34) or teriparatide
One of the first studies carried out to evaluate the potential anabolic effect of fragment 1-34 of PTH in males with idiopathic OP was a placebo-controlled double blind trial carried out in 23 males (average age 50 year, range 30-68 years)[40], in which were included subjects with values of BMD of OP in the lumbar spinal column or femoral neck. All had either previous osteoporotic fractures (78%) or vertebral pain (22%). The subjects were randomly selected to receive 18 months of treatment with 400 UI of PTH 1-34/day subcutaneously (n= 10) or placebo, also subcutaneous (n= 13). Only one subject, (4.3%), (in the placebo group) abandoned the trial. All received daily supplements of Ca and vitamin D to reach an intake of 1,500 mg and 400 UI respectively. Seven subjects had receive other treatments earlier (3 in the placebo group (23%) and 4 (40%) in the PTH 1-34 group).

All the markers for remodelled bone analysed in the study increase significantly in the patients treated with PTH 1-34. The most marked changes were those of bone alkaline phosphatase which reached its peak at 9 months (+168%, P= 0.053), remaining increased until the end of the trial (43%; P< 0.005), and those of osteocalcine (BGP) which showed changes of the greatest magnitude (%, P< 0.001) after 12 months of treatment (+150% at 18 months, P< 0.005). Among the markers for resorption, urinary NTX reached a peak at 12 months (+375%, P< 0.001) remaining elevated at 18 months (+261%, P< 0.005). Two subjects treated with PTH 1-34 (2/10, 20%) showed hypercalcemia which disappeared as the dose of PTH 1-34 was reduced. No increase in calciuria was detected.

The treatment with PTH 1-34 was associated with a progressive increase in lumbar BMD of 13.5% in 18 months, as opposed to a stabilisation of BMD in the placebo group (P< 0.001). In the femoral neck a significant increase in BMD was also produced (2.9%; P> 0.05 vs placebo). The BMD of the total femur did not change significantly, whilst in the third distal radius, even without significant changes from initial values, there was a reduction compared with the placebo group (-1.2 vs + 0.5%, P< 0.05).

The most important trial carried out in males with teriparatide[41] includes 437 caucasian subjects with osteoporosis (T-score <-2 in the spinal columns and/or proximal femur, total hip or femoral neck). Around 50% of the patients had low blood levels of testosterone. The average age was 59 years, and intake of calcium 0.8 g/day. 15% had received previous treatment for osteoporosis. No information was given on the prevalence of osteoporotic fractures. The subjects were randomly selected (the design was controlled double blind) to receive treatment with placebo (n= 147) or with 20 (n= 151) or 40 (n=139) mcg/day of teriparatide subcutaneously. All the subjects received 1 g/day of Ca and 400-1,200 UI/day vitamin D. In cases presenting with hypercalcemia, hypercalcuria, nausea or headache, the supplements of Ca may be reduced or stopped –which is what was done with 16 patients treated with teriparatide– and this dose can even be reduced to half –which was done with 7 patients treated with 40 mcg/day–. Compliance was estimated at 77% and 81 of the 437 subjects (18.5%) abandoned the trial before its completion. The duration foreseen of the trial was 2 years, but the development of osteosarcoma in an experimental study in rats who had been treated almost all their lives with teriparatide resulted in the organisers stopping the trial prematurely, which meant that the average exposure to teriparatide was 11 months, slightly less in those treated with teriparatide (15 to 26 days less, P< 0.05).

The markers for remodelled bone increase dose-dependently. Bone FA increased 30 and 60% at the end of the study (for 20 and 40 mcg/day P< 0.001 vs placebo, peak between 6 and 12 months), the blood PICP showed a maximum peak at the month of treatment (+35 and + 75 for 20 and 40 mcg/day) and later decreased until it reached initial values. The markers for bone resorption increased significantly in the groups treated with teriparatide later than those for formation (by the end of the NTX trial: 50 and 120% and D-pyr: 40 and 75% for 20 and 40 mcg/day, respectively).

The patients treated with teriparatide showed an increase in lumbar BMD of 5.9 and 9.0% (for the doses of 20 and 40 mcg/day respectively, P> 0.001 vs placebo), the increase was evident after three months of treatment. Femoral BMD increased by 1.5 and 2.9% (for 20 and 40 mcg/day, P< 0.05 and 0.001, respectively), while that of the whole body increased 0.6 and 0.9% (for 20 and 40 mcg/day, P< 0.05 and 0.01, respectively). There were no significant changes in the BMD in the dis-

tal radius. The increases in BMD were independent of the functional state of the gonads, age, initial BMD, body mass index, tobacco smoking or alcohol intake.

Only non vertebral fractures were noted, which showed no significant difference between the groups (3,2 and 1 for the placebo group, and those on 20 and 40 mcg/day respectively).

Hypercalcemia was present in 0% (placebo), 6.2% (20 mcg/day) and 16.8% (40 mcg/day) of patients, respectively, at 4-6 hours after the injection, but none presented with hypercalcemia at 16-24 hours after the dose. No patients in the placebo group and only 1.4% of those males treated with teriparatide presented hypercalciuria in 2 consecutive samples. One patient in the placebo group, one in the group on 40 mcg/day of teriparatide and two in the group on 20 mcg/day needed adjustments to the dose of Ca, whilst none from the three groups required a reduction in the dose of the drug being administered. One male (0.7%) from the group on 20 mcg/day was withdrawn from the study due to the presence of hypocalciuria.

The levels of abandonment due to adverse effects were similar in the placebo group and in that on 20 mcg. These were 4.8% (placebo), 9.3% (20mcg/day) and 12.9% (40 mcg/day) (P= 0.052). The most frequent of these effects were nausea (3.4% (placebo), 5.3% (20 mcg/day) and 18.7% (40 mcg/day); P< 0.001, 40 mcg/day vs placebo) and headache (which was also most frequent in the group on 40 mcg/day at 10.8%).

More recently Kaufman et al.[42] have published the results of a study of a follow up of up to 30 months after treatment of the same group of patients (42 months of observation in total). 355 males with an average age of 59 years and of whom 41% had previous fractures, participated. Even though the primary objective was the safety of the drug, the change in BMD was assessed at 6,12 and 18 months and spinal X-rays were carried out at 18 months. The study consists, therefore, of a follow up of the subjects who, after having completed the study, were treated according to usual clinical practice, meaning that 25 and 29% were in treatment with other drugs (75% BP) for 18 to 30 months of follow up. At the last visit, the use of treatment for OP was significantly higher in those subjects who had been receiving the placebo in the original study, compared with those who had received teriparatide (n= 46; n= 58, 25% respectively; p= 0.03).

A progressive reduction in BMD was obtained during the follow up, however, both the lumbar BMD and that of the total hip remained significantly higher than the initial value (4-6% in the spine and 1-3% in the hip, in those individuals previously treated with 20 and 40 mcg/day, P< 0.001). The subjects who were treated with antiresorptives showed an additional increase in BMD.

Among those 279 males for whom were available the lateral spinal X-ray at the start of the original trail and at 18 months from the discontinua-

Figure 1. Treatment algorithm for osteoporosis in males. The secondary causes of osteoporosis in males are more frequent, for which reason this population requires an adequate examination
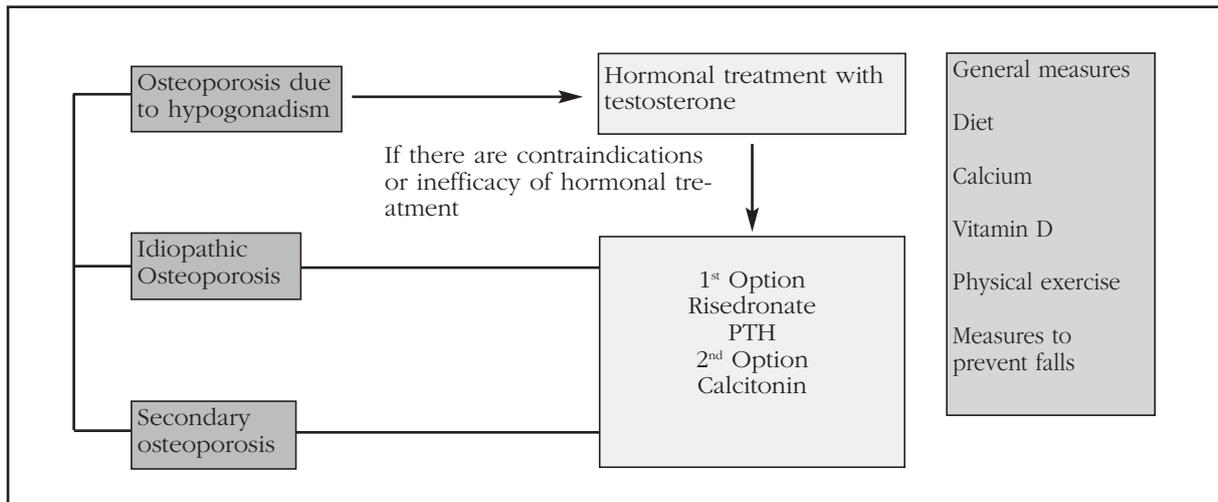
tion of the teriparatide, 22 (7.9%) subjects developed new vertebral fractures (11.7% of those initially treated with placebo, 5.4% of those treated with 20 mcg/day of teriparatide and 6.0% of those previously treated with 40 mcg/day, reduction of risk of those of those treated with teriparatide of 51%, P= 0.07). The reduction in the incidence of moderate or severe vertebral fractures in those treated with teriparatide considered as a single group was significant (reduction in relative risk 83%, reduction in absolute risk 5.7%; p= 0.01). The analysis of those subjects with previous vertebral fractures at the start of the study (n= 114) showed a reduction in absolute risk of new fractures in those treated with teriparatide of 13.1%, with a notable absence of moderate or severe fractures in these subjects (P= 0.002 vs placebo). There were no differences in non-vertebral fractures. Neither were there any safety problems among those patients previously treated with teriparatide. The authors conclude that the anti-fractural efficacy of teriparatide in males is similar to that in women.

Another study analysed the effect of teriparatide after suspending the recommended treatment during 18 to 24 months with teriparatide[43]. They studied 21 subjects up to 2 years after the withdrawal of treatment with teriparatide. This study has 2 phases, one in which out of 24 subjects who were randomly chosen for treatment with teriparatide or placebo over 18 months[41], 22 accepted participation in an extension. Those who received the placebo were treated subsequently with teriparatide over 18 months (n= 11), while those receiving TRTP in the original study (n= 11) received an additional year of treatment (the total duration of treatment with teriparatide being 30 months). At the end of this period, of 21 who continued and who were offered continued treatment with a BP, and Ca and vitamin D, 12 subjects accepted (57%; 10 of those with ALN), whilst 9 (43%) initially declined the offer, although 6 of those (67%) finally agreed to take it,

2 after 6 months of halting the teriparatide and 4 after a year. Therefore, a year after halting the teriparatide 7 subjects had received neither BF nor any other active medication against osteoporosis save calcium and vitamin D, and 11 had received BF and, even if it was not a randomised study, both groups were similar in terms of age, BMI, duration of treatment with teriparatide, BMD and change in BMD after teriparatide.

After a year of follow up the group treated with BF increased their lumbar BMD by an additional 5.1%, while those who did not take medication lost 3.7% (P< 0.002). The 6 subjects who continued treatment with BF for a second year (but not during the first) increased their BMD by 2.6%, although this increase was less than that observed at the end of treatment with teriparatide. Those subjects who started treatment with BF after the end of the teriparatide obtained an additional increase in BMD after 2 years of follow up of 8.9%. Thus, the total increase over the 4 years of the study was 23% for those treated for 2 years with teriparatide and subsequently for 2 years with BF, as opposed to 11.1% in those treated for 2 years with teriparatide followed by 1 year without treatment and another year with BF. The 3 subjects who only received teriparatide showed an increase after 4 years of 5.5%. Despite the limitations of the study (not randomised nor controlled with placebo, low number of cases...), this study suggests that the immediate use of BF after the withdrawal of teriparatide may optimise the increase in lumbar BMD, and that this therapeutic scheme results in a higher increase in BMD than concomitant treatment with teriparatide or PTH and BF.

In conclusion, teriparatide produces an increase in BMD in the lumbar spinal column, in the femur and total body in males with idiopathic OP and increases, dose-dependently, the concentrations of markers for bone formation and resorption. The

non-controlled follow up of patients who previously received teriparatide and treated according to usual clinical practise, suggests in post-hoc analysis, the permanence of the effect of teriparatide up to 30 months after its withdrawal and a lower prevalence of vertebral fractures among those who had a previous vertebral fracture, especially moderate and severe. Non-controlled studies also suggest that the immediate use of BF at the end of treatment with teriparatide is advisable with the aim of maintaining or increasing BMD.

Teriparatide is the only specifically bone-forming drug approved in Spain for the treatment of OP in males.

A possible protocol for the intervention in the treatment of male OP is represented in Figure 1[44].

Conclusions for the treatment of OP in males

- According to clinical guides and the experts, the drug of choice in the treatment of male osteoporosis is risedronate. Cases of osteoporosis with high risk of fracture or where there is an intolerance or contraindication to treatment with biphosphonate would indicate the use of teriparatide, as well as in cases where here is a high risk of fracture.

- For the same reasons as in the case of women, the administration of calcium and vitamin D to all patients is advisable.

- When hypercalciuria is detected the use of a thiazide (Grade C) can be considered.

- Androgens are only justified if there is clinical hypogonadism. Even in this case, they should probably be associated with aminobiphosphonates or teriparatide if the risk of fracture is very high despite androgenic substitution.

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Osteoporosis induced by corticoids

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1. Introduction. Osteoporosis induced by corticoids

The adverse effects of glucocorticoids (GC) on the skeleton have been known since Cushing's description in 1932, who observed the decalcification which accompanied suprarenal hyperplasmia due to a hypophysary adenoma which produces adrenocortitropic hormone[1]. The wide use nowadays of these drugs has made osteoporosis induced by glucocorticoids (OIC) the most frequent cause of osteoporosis associated with drugs[2], constituting, therefore, a health problem of great magnitude. So, for example, it has been estimated that 0.5% of the general population, and 1.7% of women over 55 years receive oral steroids[3]. This means, paradoxically, that, given that we now have the necessary means for the diagnosis and prevention of OIC, fewer than 14% of patients according to some series[3], and 7% according to others[4], receive any type of treatment to avoid the loss of bone mass when they are prescribed GC orally. The recognition of this problem and early action are fundamental, given the deleterious consequences of the GCs on bone[5-8].

Given the characteristics of this monograph and the limitations of space, we focus, in this chapter, on the effect of the oral corticoids, not including inhaled steroids, on bone mineral metabolism.

2. Epidemiology of osteoporosis induced by corticoids. Its importance

The true incidence of OIC is not known, being dependent on various factors, such as the underlying disease and individual susceptibility. Fractures can occur in up to 30-50% of patients receiving chronic therapy with GC[3,8,9]. These occur more frequently in postmenopausal women and in men, in the skeleton where spongy bone predominates, such as the vertebrae and femoral neck[10]. As happens with vertebral fractures which are observed in postmenopausal osteoporosis, vertebral fractures induced by chronic treatment with GC are often asymptomatic[11]. Vertebral fractures are produced just after exposure to GC, at the moment in which bone mineral density (BMD) diminishes rapidly[12]. The rapid loss of bone predisposes fractures, even in people whose densitometric values are only in the osteopenic range. The fact that in patients with OIC fractures appear with higher levels of BMD than those seen on patients with osteoporosis is indicative of the existence of qualitative changes, which drive a reduction in bone quality and an increased risk of fractures. The T-score threshold recommended by the clinical guides for the initiation of prevention or treatment is higher than that for postmenopausal osteoporosis.

A study carried out in Great Britain in 65,786 outpatients showed a prevalence of the use of corticotherapy of 0.5% in the general population and 1.4% in those patients older than 55 years[3,13]. The spectrum of indications for treatment with GC is very broad, but only 14% of those subjects treated, according to the most favourable observations, and at risk of OIC, receive active treatment for this condition[3,8,13].

In all the available studies, doses higher than or equal to 7.5 mg/day of prednisone produce a loss of BMD, although lower doses can drive a rapid loss of bone mass and an increase in the risk of fracture[9]. The subjects who receive this daily dose have an increased risk of loss of BMD (which occurs mainly in the first six months), of vertebral fracture (RR= 2.86: 95% CI, 2.54-3.16) and of hip fractures (RR= 2.01; 95% CI, 1.74-2.29) 9. The risk of fracture increases especially from the third month of treatment. There is a clear dose-depend-

ent relationship to risk of fracture. It has been established that 30-50% of subjects treated chronically with oral GCs will suffer fractures[8,14]. The data available suggest a prevalence of osteoporotic fractures in subjects with OIC of, at least, double that which might have been expected[15,16].

A meta-analysis carried out by Van Staa et al.[9] gathered all material written to date around the epidemiology of the loss of bone associated with the use of corticoids and offered a complete review of information around the risk factors for loss of bone mass and fractures. To do this, the authors gathered data from 66 studies in which were available the measurements of BMD in 2,891 patients treated with corticoids, the majority being women (71.5%) with an average age of 55.2 years. The average dose of corticoids was 9.6 mg of prednisolone (or equivalent) with an accumulative dose of 17.8 g approximately 5.4 years on average.

Among those studies collected, the one which evaluated fractures in most detail was called "General Practice Research Database" or GPRD[17]. However, all the studies which offered information on this issue concluded that the use of corticoids increased the risk of fracture even though in those smaller studies this was not statistically significant. So, the RR of fracture in patients treated with corticoids in the GPRD study was 1.33 (95% CI 1.29-1.38)and 1.91 (95% CI 1.68-2.15) in the rest of the studies. Similarly, those patients with COPD treated with corticoids showed a higher risk of fractures than those treated for arthropathy[18,19].

It is very important to establish a relationship between the dose of corticoids administered and the incidence of fractures. The GPRD study thus indicated that the risk of fracture for patients treated with less than 5 mg of prednisolone remained stable at around 20% but that it was raised to 60% in patients on doses of 20 mg in non-vertebral fractures. In terms of the accumulative doses of corticoids, a lower correlation was found in this study, although in others[18-20] this correlation was positive and was an even stronger predictive factor than the daily dose[18,20]. Looked at in detail, the GPRD study revealed an increased risk of non-vertebral fractures in 54% of patients treated with 7.5 mg or more of prednisolone daily over the first year, although therapeutic continuation at high doses did not substantially change this percentage[21]. The interruption of therapy with corticoids reduces both the risk of developing steroidal osteoporosis as well as its complications. Thus, the GPRD study showed strong evidence of a reduction in risk of fracture in the year following the ceasing of therapy with corticoids, more evident in vertebral fractures, but also in hip fractures[21].

3. Physiopathology

The mechanism for the development of OIC is unknown, although it appears to be different to that of postmenopausal osteoporosis. The loss of bone mass happens, above all, in the trabecular bone, where it reaches 30% in some studies, and

in the first months after the start of treatment[5-7]. The most significant changes observed in OIC are a reduction in osteoblastic activity, producing a suppression of bone formation[22], as well as a reduction in the levels of osteocalcin, which is observed already within the first 24 hours of treatment with corticoids[23], and which reverts very rapidly with the cessation of the therapy[24], as well as the induction of osteocytic apoptosis induced by the corticoids[25] and a reduction in the average life of the osteoblasts[26,27]. It seems also that there is an increase in bone resorption[28,29], through an increase in the average life of the osteoclasts[12], although it is not known how much these changes reflect the action of the GCs on the bone, or are due to the underlying disease, since in other studies the results are contradictory[30-32].

Other related factors are of a hormonal type. The GCs can produce secondary hyperparathyroidism, induced by a decrease in the intestinal absorption of calcium and greater urinary elimination[33,34], or even due to the direct effect of the GCs on the glandular secretion of the parathyroid hormone (PTH)[15,35]. The sex steroids, which intervene in bone remodelling, can be altered by treatment with GCs, with a dose-dependent decrease in blood testosterone 34 through an alteration in the secretion of hypothalamic hormone liberating gonadotropine[36], by the direct effect on the production of testosterone in the testicles[37], or through suprarenal suppression[38]. They also inhibit the secretion of oestrogens stimulated by the follicle-stimulating hormone[39]. Another mechanism which contributes to the resorptive action of the GCs is the reduction in the synthesis of osteoprotegerin[40]. The glucocorticoids also have deleterious effects on the muscle cells, producing myopathy, with an increase in the risk of falls. Similarly, they influence the hormonal axis, reducing the production of sex hormones, including the oestrogens and testosterone, which affects the bone cells.

4. Treatment of osteoporosis induced by corticoids

4.a General non-pharmaceutical measures

Among the general measures should be considered those non-pharmaceutical measures for the prevention of fractures[41-43], which are valid both for osteoporosis in general and for secondary osteoporosis, in which OIC is included.

Those patients receiving GC should follow a diet rich in calcium and protein[41], and carry out exercise which their underlying disease allows to maintain bone mass, since prolonged treatment with GC tends also to affect muscles, producing the aforementioned steroidal myopathy[44]. GCs should be prescribed at the lowest dose and for the shortest period possible, since the risk of fracture increases with daily administration[8], with the accumulated dose and with the duration of treatment[2,3,8,10,15,16,18,21,33,34,41,42,45]. Given that the loss of bone mass and the incidence of fractures increases rapidly after the start of treatment with GCs, therapeutic intervention should start as soon as possi-

ble, ideally from the start of the steroid therapy if it is suspected that the treatment with GC is going to last for more than 3 months.

4b. Biphosphonates

Alendronate (ALN)

Saag et al.[46] carried out a study in 477 patients who were taking GC, to whom were randomly administered alendronate (ALN) at a dose of 5 mg/day or 10 mg/day, or a placebo. To another 83 patients, coming from different centres, a dose of 2.5 mg/day of ALN was administered. All the groups were given a supplement of calcium (88-1,000 mg) and vitamin D (250-500 UI). After a follow up of 48 weeks, an increase in lumbar BMD was observed in those patients taking ALN at a dose of 5 mg/day and 10 mg/day, with respect to the placebo (2.1 and 2.9% respectively), whilst the group who took 2.5 mg/day obtained only a slight increase which was not statistically significant. The increases in BMD in the femoral neck were in the order of 1% in patients who took ALN at a dose of 5 mg/day and 10 mg/day with respect to the placebo (1.2 and 1% respectively), but again, these were not statistically significant on the 2.5 mg/day group. No statistically significant reduction was seen in the risk of fractures, either vertebral or non-vertebral, in any of the groups treated with ALN.

The study was extended for another year[47] with 208 patients, who were those who completed the earlier study and who continued the corticoid treatment. The patients who had been receiving 2.5 mg/day were changed "blindly" to taking 10 mg/day of ALN, and the groups taking the placebo, ALN at 5 mg/day and ALN at 10 mg/day, were maintained (with calcium and vitamin D at the same doses). A statistically significant increase in lumbar BMD was obtained in all the groups taking ALN (2.77, 3.85 and 3.69 respectively in the groups receiving 5 mg/day, 10 mg/day and in those who had passed from 2.5 to 10 mg/day of ALN), whilst in the group that only received calcium and vitamin D it reduced by 0.8%. The differences were statistically significant. A significant reduction was also observed in the incidence of vertebral fractures in the combined group being treated with ALN, in relation to the placebo group (0.7% as opposed to 6.8%; p= 0.026), but not in the incidence of non-vertebral fractures.

Risedronate (RIS)

Eastell at al.[48] carried out a study in 120 women affected by rheumatoid arthritis who were following treatment with GC, at a minimum of 2,5 mg/day for at least 6 months, with risedronate (RIS)being administered in two ways: either a daily dose of 2.5 mg, or 15 mg given cyclically (15 mg daily for 2 weeks followed by placebo for 10 weeks). The study was prolonged for 3 years, so that in the end both groups received the same quantity of RIS. At 97 weeks, in those patients who had received 2.5 mg/daily of RIS, BMD in the lumbar spine increased by 1.4%, and in the femoral neck it fell by 1.0%, while in the placebo group

the fall in BMD was statistically greater (-1.6% in the lumbar spinal column and -3.6 in the femoral neck). No statistically significant differences were observed between the results of the two groups which received RIS. With respect to the incidence of vertebral fractures, which were recorded as adverse effects, the differences were not statistically significant: in the placebo group new vertebral fractures were seen in 3 of the 33 patients, in the group which received 2,5 mg/day of RIS they were observed in 7 of the 31 patients and in the group receiving 15 mg of RIS cyclically they were produced in 2 out of 30 patients.

In a co-operative multicentric study, Cohen et al.[49] included 224 males and females who had started prolonged treatment with corticoids, carrying out a follow up over one year. In this first study of prevention it was observed that after 12 months no significant changes in BMD were produced in the spine, with either a dose of 2.5 mg or 5 mg, with respect to the baseline, although the average of the differences in BMD in the spine and femoral neck with respect to the placebo were significant (p< 0.001) and the reduction in incidental vertebral fractures which were observed in the risedronate group has no statistical significance (these were observed in 5.7% of patients receiving 5 mg daily of RIS as opposed to 17.3% in the group who had taken the placebo, p= 0.072).

The data from this study were combined with those of another study carried out with the same methodology, but directed at treatment, in which Reid et al.[50] studied 290 patients of both sexes who had been receiving at least 7.5 mg of prednisone for 6 months. The follow up was extended for a year and an increase in BMD was observed in the lumbar spinal column (2.9%), in the femoral neck (1.8%), and in the trochanter (2.4%), as well as a reduction of 70% in vertebral fractures. Although not initially planned, the researchers in both studies decided to combine their data with the objective of obtaining a sample size which allowed them the statistical power to confirm the reduction in the incidence of fractures.

This drove the publication of a third study[51] with a population of 518 men and women who received either placebo or RIS (in two groups: at doses of 2.5 mg and 5 mg per day, respectively), along with a supplement of 500-1,000 mg of calcium and 400 UI of vitamin D. In the joint population a statistically significant increase in BMD in the lumbar spine (1.9 ± 0.38%), the femoral neck (1.3 ± 0.40%) and in the trochanter (2.0 ± 0.37%). In the group which took 5 mg daily of RIS the difference with respect to the placebo group at 12 months was 2.9% in the lumbar spine (p< 0.001), and 2.8% in both the femoral neck and the trochanter, p< 0.001 in both cases. With 2.5 mg of RIS daily, the increase was statistically significant only in the lumbar spine (1.3 ± 0.41%, p< 0.001). A reduction in risk of vertebral fracture was observed in both the group receiving 2.5 mg a day of RIS and in those who received 5 mg daily, since after a year of follow up new vertebral fractures appeared in

16% of those patients who took the placebo, in 7% of the group on 2.5 mg of RIS daily and in 5% of the group taking 5 mg of RIS daily. No statistically significant differences were observed in the incidence of non-vertebral fractures between any of the groups. Level of evidence 1b.

In a sub-group of 184 males from the earlier study, Reid et al.[52] showed an increase in BMD with RIS at a dose of 5 mg/day of 4.8% in the lumbar spine, of 2.1% in the femoral neck, and of 2.6% in the trochanter compared with baseline values, in the treatment group (corticoids for more than 6 months). In considering in general the group of those treated with RIS as against those not treated, a reduction in risk of vertebral fracture of 82.4% (95% CI, 36.6-95.1%) was observed at the end of a year of follow up (p= 0.008).

Zoledronate (ZOL)
The efficacy of ZOL in steroidal osteoporosis has been studied in a non-inferiority trial[53], of a year's duration, which compared the effects of ZOL, administered at a dose of 5 mg/year intravenously, with those of RIS, administered orally at a dose of 5 mg/day. The population of the study consisted of 383 women who were in treatment with 7.5 mg of prednisone. The intervention qualified as "treatment" when the women had been receiving the corticoid for more than three months, and "prevention" when they had been receiving it for a shorter time than that. The primary objective constituted the changes in BMD in the lumbar spine, and the limit of margin of non-inferiority was established at -0.70% for treatment, and at -1.12% for prevention. The secondary objectives were the changes in apendicular BMD and the incidence of vertebral fractures. All the CI points of the differences for the treatment group (limits 0.67-2.05), and for that of prevention (limits 1.04-2.88) were within the margin of non-inferiority. In fact ZOL determined increases in BMD significantly higher than RIS in the lumbar spine, both in treatment (4.06 ± 0.28% vs 2.71 ± 0.28%; p< 0.0001) and in prevention (2.60 ± 0.45% vs 0.64 ± 0.46%; p< 0.0001). They were also higher in the femoral neck (1.45 ± 0.31% vs 0.39 ± 0.30%; 1.30 ± 0.45% vs -0.03 ± 0.46%; p< 0.005 in both cases). No differences in the incidence of fractures were observed. The trial permits the recommendation of ZOL for osteoporosis due to glucocorticoids.

4.c PTH 1-34 in the treatment of osteoporosis induced by steroids

Up to now only studies on the fraction 1-34 of PTH (teriparatide) have been published. Lane et al.[54,55] carried out a study in 49 postmenopausal women affected by chronic inflammatory diseases having corticoidal treatment (prednisone 5-20 mg/day, or equivalent for more than a year) and densitometric osteoporosis, who were randomly assigned to a control group or to a group which received treatment with teriparatide for a year. All the women received hormone replacement treatment (HRT). After a year of treatment with teriparatide the BMD in the lumbar spine, estimated by QCT (Quantitative Computed Tomography), increased by 35% compared with 1.7% (p< 0.001) in the control group, and by DXA, by 11% compared to 0% (p< 0.001) in the control group. Similarly, an increase in the transversal vertebral area was obtained of 48% (p< 0.001), while the control group showed no changes[56]. However, the changes in BMD in the hip and the forearm were not statistically significant. In the group treated with teriparatide there was not a single vertebral fracture, while in the control group there was one fracture.

The study was extended for one more year[57], after suspending the treatment with teriparatide, and it was observed that the BMD in the lumbar spine and in the femoral neck continued to increase, which did not happen in patients who received only THS.

Another clinical trial of 36 months, randomised, multicentric, double-blind, with active control, compared the effects of 20 µg of teriparatide daily with 10 mg alendronate daily in men and women with high risk of fracture and secondary osteoporosis due to glucocorticoids. This study included 428 men and women from 22 to 89 years of age with osteoporosis, who had received glucocorticoids at a dose equivalent to or higher than 5 mg daily of prednisone for at least 3 months. The primary objective was the evaluation of changes in BMD in the lumbar spinal column at 18 months of treatment[58]. The secondary objectives were the changes in BMD in total hip, femoral neck at 18, 24 and 36 months, as well as lumbar BMD at 24 and 36 months, changes in markers for remodelled bone at 18 months, incidence of fractures and safety data. At 18 months of treatment the increase in BMD in the teriparatide group was 7.2+/-0.7% vs 3.4%+/-0.7 in the alendronate group (p< 0.001), at 36 months the changes in BMD were 11.0% vs 5.3% in the lumbar spine, 5.2% vs 2.7% in the total hip, and vs 3.4% in the femoral neck respectively (p< 0.001). At 6 months of treatment there were already significant differences between the two groups (p< 0.001). At 18 months of treatment the percentage of patients who experienced a new vertebral fracture in the group assigned to teriparatide was 0.6% vs 6.1% in the alendronate group (p= 0.004), at 36 months 1.7% of those receiving teriparatide had vertebral fractures compared with 7.7% of the alendronate group (p< 0.007). There were no significant differences in non-vertebral fractures. This study suggests that teriparatide possesses a higher efficacy than alendronate in the reduction of vertebral fractures as well as higher increases in the BMD of patients treated with oral glucocorticoids[59,64]. The results have also been analysed according to sex and menopausal state[65]. At 18 months of treatment the increases in BMD were significantly higher in the teriparatide group than in the alendronate group in postmenopausal women (7.8% vs 3% p< 0.001), premeonopausal women (7.0% vs 0.7% p< 0.001) and in men (7.3% vs 3.7 p< 0.03).

5. Recommendations of the clinical guides for the prevention and treatment of osteoporosis induced by steroids

5.a Recommendations of the Working Group on Osteoporosis of the Spanish Society of Internal Medicine (GTO-SEMI)[60]

The GTO-SEMI published in 2008 a position document on the prevention and treatment of osteoporosis induced by corticoids, after a revision of the existing bibliography, making some recommendations in accord with the available evidence, and making a separation between "who to treat" and " with what to treat" (Table 1).

Regarding "with which drug to treat", the panel of experts considered that in all cases supplements of calcium (500-1,000 mg/day, dependent on diet) and vitamin D (800-1,000UI/day). With respect to specific drugs, starting with the anti-resorptives, they considered that RIS and ALN are the drugs of choice, recommending that before the start of treatment with biphosphonates, the clearance of creatinine is estimated with the Cockcroft-Gault formula; when this is under 30 ml/mn the dose should be reduced to 50% or the interval between doses doubled. At the time of production of the document, the results for zoledronate had not yet been published, for which reason they were not included. With respect to bone forming drugs. The committee was of the opinion that teriparatide could be indicated in especially serious cases (multiple fractures or extreme drops in BMD).

Finally, among other aspects to consider, they recommended that the treatment should be maintained while the steroidal treatment is maintained, carrying out as developmental controls an annual densitometry, as well as a lateral dorsal and lumbar spinal X-ray in all patients who have had 3 consecutive years of steroidal treatment, and if before this period of time there was a reasonable clinical suspicion of the presence of a vertebral fracture, such back pain which had recently started, or loss of stature. Finally, they recommended the use of thiazides in cases of hypercalciuria and/or coexistence of arterial hypertension.

5b. Recommendations of SEIOMM[61]

The Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) produced some guides to clinical practice in postmenopausal, glucocorticoidal, and male osteoporosis. The second edition of these was published in 2008 in the section on steroidal osteoporosis. Their conclusions were:

1) Alendronate and risedronate are efficacious in the prevention of osteoporotic fractures in patients treated with corticoids and constitute the drugs of choice (recommendation A)

2) Along with the biphosphonates, calcium and vitamin D should be administered. The active metabolites of vitamin D in themselves have a preventative action on bone loss, but there is a lack of data on the prevention of fractures.

3) The data obtained in the studies commented on earlier have resulted in the experts advising the primary prevention of osteoporosis due to GC in persons treated with 7.5 mg or more of prednisone a day (or the equivalent of another corticoid) when it is expected that this medication will be maintained for more than 3 months, and to whom one of these circumstances apply: being more than 65 years old, or having a T-score lower than -1.5 (recommendation D). The treatment should be maintained as long as the patient is receiving a dose equal to or higher than 7.5 mg/day of prednisone; it should also be maintained if the osteoporosis persists after it ceases, or if other risk factors continue (recommendation D). Given that one cannot exclude the fact that lower doses than those signalled can also provoke a reduction in BMD and fractures, above all if it is administered over a long term, in such cases the prevention or treatment can also be considered, particularly if to this other risk factors are added. In patients with normal BMD and whose intake of GC is less than 5-7 mg/day of prednisone or equivalent, some authors recommend treatment with calcium (1,200 mg/day and vitamin D 800 UI/day) only.

4) There are no studies which asses the efficacy of non-pharmacological measures, such as physical exercise, diet rich in calcium, quitting tobacco and moderation of alcohol intake, but all the guides on osteoporosis due to GC advise these measures, extrapolating the recommendations which have been given in postmenopausal osteoporosis. One should take into account the fact that the possibility of a patient carrying out physical exercise may be restricted by their underlying disease. Similarly, instructions should be given to avoid falls, trauma and excessive effort. It is necessary to follow the general rule that when starting a treatment with GC it should be administered at the lowest efficacious dose and for the shortest time possible.

These guides were subsequently updated and published in 2009. With reference to steroidal osteoporosis, the recommendations of SEIOMM were to maintain the earlier recommendations and specify the existence of 2 new drugs: teriparatide and zoledronate. Taking these into account the recommendation of the panel of experts was to maintain alendronate and risendronate as drugs of first choice, while also including as such zoledronate, if it is considered preferable in the specific circumstances of a case, and to use teriparatide if the risk of fracture is high or if the response is not considered adequate[62].

5c. Recommendations of other international guides

The American College of Rheumatology and the Royal College of Physicians at an international level have formulated a series of recommendations for the prevention and treatment of osteoporosis induced by glucocorticoids. Among these are included a higher awareness of general health, the administration of calcium and vitamin D supplements, the reduction in the dose of glucocorti-

coids to a minimum and, when it is indicated, therapeutic intervention with biphosphonates and other drugs indicated in this therapy.

The guides of the UK's Royal College of Surgeons recommend that primary prevention be carried out in all men, and in women more than 65 years old, in individuals with a previous history of fractures, and in younger people with a BMD T-score of ≤-1.5, who are going to follow a treatment with oral corticoids for at least 3 months[63].

However, the American College of Rheumatology recommends carrying out prevention in those patients being treated with glucocorticoids with a dose equivalent to 5 mg of prednisone, or higher, a day. These measures include changes in lifestyle, such as quitting smoking or reducing alcohol consumption, carrying out exercise, restricting sodium intake when there is hypercalciuria, and the intake of calcium and vitamin D supplements. The directors of the ARC recommend that treatment with biphosphonates is initiated in those patients whose T-score is equal to, or less than, -1.0[42].

6. Conclusions

Prolonged treatment with oral corticoids increases the risk of fragility-related fractures at doses as low as 5 mg/day of prednisone or equivalent, and already at 3 months from the start of treatment. Thus it is necessary to act to prevent the appearance of these fractures.

At the start of a treatment with corticoids one should take into account how much time and at what dose, approximately, the treatment with oral steroids is going to last, as well as the clinical state of the patient.

In all cases it is advisable to indicate general measures, such as the maintenance of physical activity as adequately as possible, a balanced diet with an abundant quantity of milk products, and exposure to the sun for at least 10 minutes a day. If the corticoids are going to be given for more than 3 months and the dose used is at least 7.5 mg/day, a supplement of calcium and vitamin D should be administered.

Alendronate and risedronate are drugs which should be used in the first instance, above all if used as prevention and if the patients do not have fractures or densitometric osteoporosis. There were no available studies which advised on the duration of treatment, but it appears reasonable to maintain it while the patient is taking oral corticoids. Zoledronate is also an excellent initial option, its annual administration being convenient and permitting an adherence to treatment higher than that of other drugs. But its intravenous administration and its use restricted to the ambit of a hospital limits its use.

PTH 1-34 (teriparatide) constitutes an interesting alternative, since it has been shown to be superior to alendronate in the reduction of risk of vertebral fracture. The indication for which it has been approved by the European Medicines Agency is the treatment of secondary osteoporosis

Table 1. "Who to treat". Recommendations of the GTO-SEMI[60]

a) Postmenopausal women: - In general, patients who are going to receive or are receiving more than 5 mg/day for more than 3 months - Patients with BMD (measured by DXA) with a T-score lower than -1.5 who are going to receive or are receiving more than 2.5 mg/day for more than 3 months b) Premenopausal women or males: - In general, patients who are going to receive or have received more than 7.5 mg/day for more than 3 months - Patients with BMD (measured by DXA) with a T-score lower than -1.5 who are going to receive or have received more than 5 mg/day for more than 3 months c) All patients with previous fractures due to fragility

due to glucocorticoids in men and women, pre- and postmenopausal, with a high risk of fracture. Its price, and the necessity of parenteral administration makes its use recommendable as a second line drug, when it is not possible to use biphosphonates, and when the clinical results have not been what was expected. However, in patients with vertebral fractures already present at the time of initiating the steroid treatment, or in those who have a very low BMD and require a long period with oral corticoids at doses higher than 7.5 mg/day, or in premenopausal women who are not able to take other treatments, the initial use of PTH 1-34 could be considered, to be continued later with a biphosphonate[59].

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