Cardiovascular disease, diabetes mellitus type 2 and osteoporosis

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Summary
In recent years various epidemiological studies have shown an independent association of age between type 2 diabetes and osteoporosis, as well as an increase in cardiovascular mortality in patients with a reduction in BMD and/or osteoporotic fracture. The most recent research has focussed on factors involved in the physiopathology of the two diseases. In general, the studies which have investigated the relationship between cardiovascular risk factors, bone metabolism, bone mass and risk of fracture have shown inconclusive and contradictory results. In patients with DM2 there is an increase in risk of fractures in spite of a higher BMD, caused essentially by an increased risk of falls associated with the presence of vascular complications, although changes in bone quality are also a determining factor. Knowledge of the physiopathological mechanisms common to these pathologies will not only help better management of patients, but also could contribute to the development of drugs which would act on the two processes.

Key words: Type 2 diabetes mellitus, Osteoporosis, Cardiovascular disease.
The levels of TC, LDL-C and TGs were lower than postmenopausal women with vertebral fracture of the studies differ as a function of sex. Thus, in between lipids and vertebral fractures, the results for the association of dyslipidemia with bone mass and risk of fracture, have shown inconclusive and contradictory results in most cases.

Dyslipidemia
In *in vitro* studies, HDL-C appears to show an inhibitory effect on osteoblast activity induced by inflammatory cytokines in the vascular wall, and raised concentrations of oxidised LDL-C has an apoptotic effect on osteoblastic cells, inhibiting their differentiation and promoting osteoclastic activity. Most of the studies carried out have not found a relationship between LDL-C and BMD, although in a recent study the values of TC and LDL-C showed a positive correlation with hip and lumbar BMD in males. In addition, high values of TG after adjusting for BMI have been positively associated with BMD. In terms of the association between lipids and vertebral fractures, the results of the studies differ as a function of sex. Thus, in postmenopausal women with vertebral fracture the levels of TC, LDL-C and TGs were lower than in those women without fracture, although in other cases no association has been demonstrated. Studies carried out in males have not shown an association between lipids and vertebral fracture. In the study carried out by Hernandez et al. in a Spanish cohort of males, levels of LDL-C and TC were lower in those subjects with non-vertebral fractures. The discrepancy between studies could reflect the influence of genetic, dietary or geographic factors on this association.

Arterial hypertension
In AHT, a higher rate of bone loss in relation to an increase in the excretion of calcium in the urine has been described, which raises the levels of PTH. A positive relationship has been proposed between BMD and the presence of AHT, while other authors describe a negative or independent association. In respect of fractures, the data are more consistent, and we know that AHT is a risk factor for hip fractures in women, and for other locations in both sexes, with one of the possible pathogenic factors being the increased risk of falls caused to a great extent by the hypotensive effect of the antihypertensive drugs. Other authors have described, as a class effect of hypotensive drugs, a discrete reduction in the global risk of fractures which could be related to a reduction in the urinary excretion of calcium.

The influence of different hypotensive treatments on BMD and other related factors has also been evaluated. Thus, in postmenopausal women with AHT in treatment with tiazides, the levels of markers for remodelling were lower with respect to the control group, and the lumbar BMD, higher.

Obesity
The pathogenic mechanisms responsible for the relationship between fat and bone are multiple: gastrointestinal peptides such as GLP-1 and GIP, levels of insulin in circulation and adipokynes. On many occasions this relationship is complex and discordant results have been found. Leptin, the adipokine increased in obesity, in the hypothalamus slows the formation of bone by inhibiting the proliferation of the osteoblasts, whilst in the bone it stimulates osteoblastic, and inhibits osteoclastic, differentiation. The results of clinical trials are also contradictory, finding a positive relationship between blood levels of leptin and BMD in women, and negative in males. On the other hand, adiponectin halts osteoclastogenesis in *in vitro* studies, and in DM2 its blood levels are negatively related to BMD.

Different studies have shown a positive relationship between body weight and BMD. This relationship is greater in women, both postmenopausal and sedentary. Similarly, a recent meta-analysis shows a protective effect of obesity on the global risk of fracture. Analysing the different types of fracture, this protective effect is shown on hip and vertebral fractures, but not in distal radius fracture.
**Hyperhomocysteinemia**

Hyperhomocysteinemia is a marker for cardiovascular risk which has been associated with a higher rate of bone resorption, and a higher risk of fractures. However, active therapy to control its blood levels was not able to reduce the incidence of fractures.

**Metabolic syndrome**

One of the fundamental components of metabolic syndrome is hyperinsulinemia and insulin resistance. Insulin has been demonstrated to stimulate the proliferation of osteoblasts and the secretion of other factors implicated in bone formation, such as BMPs and IGF-1, from which one would expect a higher BMD in these patients. Thus, in patients with metabolic syndrome a higher BMD in the hip has been described. The presence of metabolic syndrome has also been related to a lower risk of non-vertebral fractures, both in men and women in a transversal study, while in a prospective study incidental clinical fractures were 2.6 times more frequent in those patients with metabolic syndrome compared with the controls. In patients with DM2, the added presence of other components of metabolic syndromes was associated with a lower prevalence of vertebral fracture.

**1.2. Factors involved in bone metabolism and cardiovascular disease**

**Oestrogens**

The protective effect of oestrogens on the vascular system of postmenopausal women, and the increase in vascular disease after menopause suggests a role for oestrogenic depletion in the development of atherosclerosis in women. In relation to this fact, it has been observed that the gene for the alpha oestrogenic receptor is associated with a higher risk of cerebrovascular disease, and in turn, certain polymorphisms of the beta receptor appear to be a risk factor for acute myocardial infarction in Spanish males.

**Vitamin D**

The relationship between vitamin D and vascular disease has been studied in depth, with contradictory results. In experimental animals high concentrations of vitamin D in the diet favoured the development of coronary and aortic arteriosclerosis. In humans, various studies have found an association of risk between certain variants of the vitamin D receptor gene and the presence of coronary disease, while others show no such association. An epidemiological study in the US showed that supplementing foods with vitamin D increased the incidence of arteriosclerotic disease. However, other works have put the relationship the other way round, and have associated the deficit in vitamin D with the presence of peripheral arterial disease and myocardial infarction, thus, as an inverse relationship between 1-25 dihydroxyvitamin D and the degree of coronary calcification.

**Parathormone (PTH)**

Receptors for PTH have been confirmed in cardiac and smooth muscle cells, attributing to them a trophic effect and suggesting that it could be responsible for the hypertrophy of the left ventricle observed in patients in dialysis. On the other hand, in mice with acute myocardial infarction treatment with PTH favours the migration of angiogenic progenitor cells to the damaged area, which could attenuate the ischemic damage, and recently it has also been found that PTH increases the endothelial expression of NO.

**Parameters of remodelling**

A deficit in MGP encourages the presence of vascular calcification in experimental animals and specific polymorphisms are associated with a high risk of myocardial infarction in humans, which suggests that it has a role in the inhibition of vascular calcification. In turn, osteocalcin is expressed in the vascular tissue and its blood levels have been related with parameters for arteriosclerosis in patients with DM2. Osteopontin (OPN) is expressed in calcified athromatous lesions, and mice with high levels of OPN have a higher IMF. The type 2 bone morphogenetic protein and its osteogenic mediator CbFa-1 (core-binding factor α 1) are increased in human arteriosclerotic lesions, but not in healthy vessels. Catepsin K, the main enzyme involved in bone resorption, could be involved in the destabilisation of the plaque, since it has been observed that in ApoE knockout mice the cathepsin K deficit preserves arterial stability and integrity, and diminishes vulnerability to arteriosclerotic plaques.

**OPG**

OPG is expressed in the smooth muscle cells and in the endothelial cells of the arterial wall where they appear to be an autocrine survival factor of the endothelial cells. The increase in the levels of OPG in blood have been associated with the presence and severity of arterial calcification in various locations and in different pathologies: renal insufficiency in haemodialysis, coronary calcification in rheumatoid arthritis and abdominal aortic calcification in peripheral arthropathy. If the raise blood levels of OPG is simply a marker for vascular damage, represents a defence mechanism or, on the contrary, is an active mediator for the progression of the disease, remains to be clarified.

The predictive value of blood levels of OPG in the incidence and mortality of CVD has been confirmed in different populations studied. Thus, it has been shown that the increase in blood levels of OPG is a risk factor for cardiovascular morbidity in conditions of accelerated arteriosclerosis such as in women of advance age, haemodialysed patients, and diabetes type 1, but also in the general population. Raised blood levels of OPG are associated with the presence and severity of coronary disease, and with the severity of peripheral arthropathy. OPG has also been related to...
surrogate markers for sub-clinical arteriosclerotic disease. In postmenopausal women without CVD high levels of OPG are positively related to endothelial dysfunction, arterial rigidity and ITM.

1.3. Surrogate markers for CVD and osteoporosis

The majority of transversal studies carried out have described an inverse association between the presence, severity and progression of arterial calcification and BMD, both in menopausal women and, in males, as well as an increased risk of fracture in postmenopausal women with aortic calcification. Carotid atheromatosis, another surrogate marker for CVD, is associated with a lower lumbar bone mass in postmenopausal women, and a higher risk of fracture. The presence of osteoporosis and/or fracture have also been related to an increased risk of sub-clinical arteriosclerotic disease.

1.4. Cardiovascular events and osteoporosis

In osteoporotic women or those with vertebral fracture there has been described a relative risk of 3.9 and 3, respectively, of cardiovascular events, this risk being proportional to the severity of the osteoporosis at diagnosis. In the same way, the lumbar BMD is reduced in patients with cardiovascular disease independently of age, and the presence of peripheral arterial disease and/or ischemic cardiopathy is associated with a higher risk of hip fracture. There has also been a significant association found between the presence of myocardial infarction and low bone mass, and between the presence of osteoporosis/osteopenia and an increased risk of obstructive coronary disease in both sexes. On the other hand, a decrease of 1 SD in the BMD in the calcaneum and femoral neck increases the risk of cerebrovascular disease by 1.3 and 1.9 respectively.

2. Diabetes mellitus type 2, osteoporosis and risk of fracture

2.1. Diabetes and bone mass

The deleterious effect of DM on the bone varies as a function of the type of diabetes. In patients with DM2, although the results are odd, there appears to be an increase in the risk of fractures despite a higher BMD, caused fundamentally by an increased risk of falls associated with the presence of vascular complications, as well as alterations in bone quality, which are also a determining factor.

Studies which have assessed BMD in patients with DM2 show discordant results. In the lumbar region, positive, negative, and neutral effects have been described. In the hip, the results are somewhat more uniform, with a higher BMD for both sexes being observed in the majority, and in the distal third of the radius, negative, or neutral, effects have been described. The result in the studies indicated above mostly confirm that the main determinants of BMD in patients with DM2 are age and BMI. Although not all, some of these studies have found a negative relation between the degree of metabolic control and the duration of the disease. In the Spanish population with DM2 exercise, BMI and the adequate consumption of calcium appear to be factors protective of osteoporosis, on the other hand, age, and the consumption of zinc are risk factors.

2.2. Risk of fractures in patients with DM2

Most of the studies show an increase in risk of fracture in spite of a higher BMD. Thus, an incidence of fractures in patients with DM2 has been described which is similar to the control group despite a higher BMD. And an increase in the risk of non-vertebral fractures of 69% for both sexes in the diabetic population. The fact that in this study the increase in risk is circumscribed in those patients with DM2 in treatment, and that they suffered a higher percentage of falls, makes one think that the higher risk of fracture in these patients is due to a higher rate of falls. In fact it has been corroborated that the risk of falls is increased only in those patients treated with insulin (OR 2.76) and that the principal risk factors for this increase are age, alterations in balance, diabetic neuropathy and retinopathy, and coronary disease. Another risk factor for falls in this group of patients is the high prevalence of hypovitaminosis D which they suffer. A recent review has demonstrated a global increase in the risk of any fracture of 30%, and 70% for hip fractures. The results were consistent in Europe and the US, and there was a relationship with the follow up, since those with disease of more than 10 years standing had an even higher risk of hip fracture. On the other hand, no increased risk of vertebral, proximal humeral or in the distal third of the radius was found, although there was a 30% increase in risk for the bones of the feet. Against these results, a retrospective cohort study did find an increased risk of vertebral and proximal humeral fracture, the main risk factors being age, previous fracture, neuropathy and treatment with insulin, with exercise, BMI and the use of biguanides being protective factors.

The same as with BMD, the majority of the studies did not observe an association between the degree of metabolic control, determined by HbA1c, and the risk of fracture, save for one Japanese study where the presence of HbA1c > 9% was associated with an increase in the risk of vertebral fractures. On the other hand, blood levels of pentosidine (a product of non-enzymatic glycation) is an independent risk factor for vertebral fracture in both women and men with DM2. In Spain, the GIUMO study carried out in postmenopausal women with obesity and DM2 did not observe an increased prevalence in vertebral or hip fractures, nor in conjunction with non-vertebral fractures. Finally, a biphasic effect has been proposed regarding the risk of having a hip fracture, since patients with hydrocarbonate intolerance, or with a recent diagnosis of DM2, have shown a lower risk of fractures, while those with disease of longer duration have an increased risk.
On the basis of this theory, initially overweight and obesity will play a protective role, while subsequently the development of complications due to diabetes will raise the risk of fracture.

2.3. Potential pathogenic mechanisms of osteoporosis in DM2

Hyperglycemia has direct adverse effects on bone metabolism in both types of DM (Figure 1). In being the principal source of energy for the osteoclasts, it increases, dose-dependently, their activity *in vitro*. On the other hand, non-enzymatic glycosylation of various bone proteins, including collagen type 1, alters and reduces bone quality. Thus, in animal models of diabetes, the content of pentosidine in bone increases during the course of the disease, reducing the biomechanical properties of the bone, in spite of maintaining a stable BMD. The increase in glyceria also has indirect effects on the skeleton since it favours hypercalcuria and interferes with the PTH/vitamin D system. On the other hand, the improvement in glycemic control in poorly controlled DM2 reduces the urinary excretion of calcium and phosphorus. In addition, in recent years, interest has grown in researching into the effect of the incretins on bone metabolism. It has been suggested that GIP and GLP-2 could be responsible for the inhibition of bone resorption after the ingestion of food, and it has been observed that those patients with DM2 have a reduction in this effect after an oral overload of glucose. A Spanish study, carried out in diabetic rats has found that GLP-1 has an anabolic effect on bone, independently of insulin. However, if the alterations in the incretin system present in DM2 are responsible for the changes in BMD in this group of patients, it is still to be elucidated.

3. Conclusion

Atherosclerosis and osteoporosis are chronic degenerative diseases with a high incidence in developed countries and whose prevalence increases with age. Both are silent processes with a high economic cost, especially when there are acute complications which include cardiovascular disease and fractures. The OPG/RANKL system has been suggested as a common mediator for both processes, but its precise significance is unknown. Knowledge of the common physiopathological mechanisms of these two pathologies will not only help in better management of patients but it could also contribute to the development of active drugs for both processes. Research into type 2 diabetes may bring important data regarding this complex association.

Figure 1. Potential mechanisms responsible for osteoporosis and osteoprotic fracture in both types of diabetes (adapted from Hofbauer et al. 2007)

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