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Review

Bone health in Down syndrome☆

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ABSTRACT

Patients with Down syndrome have a number of risk factors that theoretically could predispose them to osteoporosis, such as early ageing, development disorders, reduced physical activity, limited sun exposure, frequent comorbidities and use of drug therapies which could affect bone metabolism. In addition, the bone mass of these people may be affected by their anthropometric and body composition peculiarities. In general terms, studies in adults with Down syndrome reported that these people have lower areal bone mineral density (g/cm^2) than the general population. However, most of them have not taken the smaller bone size of people with Down syndrome into account. In fact, when body mineral density is adjusted by bone size and we obtain volumetric body mineral density (g/cm^3), the difference between both populations disappears. On the other hand, although people with Down syndrome have risk factor of hypovitaminosis D, the results of studies regarding 25(OH)D in this population are not clear. Likewise, the studies about biochemical bone markers or the prevalence of fractures are not conclusive.

Salud ósea en el síndrome de Down

Palabras clave:
Masa ósea
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RESUMEN

Las personas con síndrome de Down podrían tener un mayor riesgo de osteoporosis debido a un envejecimiento precoz, alteraciones en el desarrollo o la presencia de factores de riesgo como baja actividad física, menor exposición solar, elevada comorbilidad o el uso de tratamientos que afectan al metabolismo óseo. Además, tienen peculiaridades antropométricas y de composición corporal que podrían influir en su masa ósea. Los estudios en adultos vienen a decir que tienen una densidad mineral ósea en g/cm^2 inferior a la de la población general, pero la mayoría no tienen en cuenta el menor tamaño de sus huesos, de tal manera que cuando se ajusta por el mismo (densidad mineral ósea volumétrica g/cm^3), estas diferencias se reducen o desaparecen. Los estudios sobre niveles de 25(OH)D, parámetros de remodelación ósea o prevalencia de fracturas no son concluyentes.

Down syndrome (DS) or Langdon Down syndrome is the most frequent chromosomal abnormality among live births.[1] Several studies have found that people with DS have a lower bone mass. Its causes are not well known, but they may contribute to premature ageing, abnormalities in development or the presence of risk factors for osteoporosis reported in this group.[2–4]

Risk factors for osteoporosis in Down syndrome

People with DS are known to engage in low-intensity physical activity. Vigorous physical activity,[5,6] especially in the case of women,[7] less commonly performed. A study of 75 people with DS of both sexes found that they had less total exercise determined by metabolic expenditure (MET-minute/week) and less vigorous exercise than their control group.[8] This fact may be important, since physical activity positively influences bone mineral density (BMD), both in the general population[9] as well as in the one with DS,[10] although the benefit in this group seems to be somewhat lower than expected according to a recent study.[11] In addition, people with DS seem to use more protective measures regarding sun exposure, using more sunblock lotions and wearing items like a cap,[8,12]

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perhaps because they often have skin disorders.[13] On the other hand, physical limitation and institutionalisation (up to 12%, especially at more advanced ages)[14] could influence lower sun exposure and thus favour a vitamin D deficiency, increasing the risk of osteoporosis, falls and fractures.[15,16]

It is estimated that 30% of children and 60% of adults with DS are obese or overweight, which can also determine their bone mass. The cause is not known, but it seems to be related to factors such as the presence of a slow basal metabolism, frequent hypothyroidism or poor eating habits.[17,18] In this sense, some studies have found that these people ingest more macro and micronutrients,[19] although other authors do not report it.[20] On the other hand, adults with DS have a high comorbidity. A recent study[14] performed on 144 people with DS (70 female and 74 male) described a prevalence of thyroid disorders of 81% (75% hypothyroidism and 6% hyperthyroidism), gastrointestinal disorders of 50.7% (constipation 33% and gastroesophageal reflux 14%), and 26% epilepsy. They also present cardiac diseases, mainly at the expense of congenital heart diseases, skin (palmoplantar hyperkeratosis and seborrheic dermatitis), visual and hearing disorders.[8,21] Frequent use of drugs that affect bone metabolism (levothyroxine 48%, antipsychotics 31% and antidepressants 32%)[8] may be another risk factor to consider.

Anthropometric parameters and body composition

People with DS have anthropometric and body composition peculiarities. They have a short stature due to retarded growth since childhood,[22,23] and often obesity.[24] A study of 39 adults with DS and 78 controls showed that people with DS had a lower height (151 ± 8 cm in DS versus 172 ± 9 cm in controls, $p < 0.001$) and had a lower weight (60 ± 10 versus 68 ± 12 kg; $p < 0.001$), but their body mass index (BMI) was higher (26.3 ± 4.2 versus 23.1 ± 3.0 kg/m^2; $p < 0.001$).[12] Another study[24] conducted in 38 people of both sexes with DS (16–38 years) found a percentage of obesity (BMI 30–39.9 kg/m^2) of 36.8%, similar to that of overweight (BMI of 25–29.9 kg/m^2), being higher in women (29.1 ± 4.3 kg/m^2) than in males (27.9 ± 4.6 kg/m^2) ($p < 0.001$).

Some studies analyse body composition by dual energy X-ray absorptiometry (DXA). People with DS seem to have a higher percentage of fat than their controls, especially in the case of women (30% in DS vs 27% controls; $p = 0.007$), as well as a smaller muscle component, both in absolute terms (39,522 [6925] vs 47,791 [10,602] g; $p = 9.6 \times 10^{-}$) as well as percentage (67 versus 70%; $p = 0.03$).[8] Another study,[25] performed in 67 people with DS of both sexes and a control group (mean age 14–40 years), also concludes that women with DS have a higher percentage of fat than their controls (38.7 ± 8.7 vs 27.4 ± 6.5%; $p = 0.001$) and men had lower muscle mass (22.9 ± 3.5 versus 30.5 ± 4.3 kg; $p = 0.001$). Table 1 shows a summary of body composition studies in DS.

Body composition parameters are positively related to BMD in numerous studies in the general population,[26,27] although its relationship in DS has not been clearly analysed (Table 1).

Bone mass in Down syndrome

In general, studies analysing bone mass in adults with DS conclude that DS subjects have a BMD lower than that of the general population. A study[28] performed in 22 people with DS showed that males had a lumbar spine (LS) BMD 25% lower than their controls (0.931 ± 0.114 versus 1.243 ± 0.072 g/cm^2; $p < 0.001$) and in the case of women a 14% lower (1027 ± 0.132 versus 1.197 ± 0.081 g/cm^2; $p < 0.001$). This same working group[29] later confirmed that adults with DS had a lower LS BMD than the BMD of people with disabilities or the general population (BMD L2-L4 0.926 ± 0.07 g/cm^2 DS, 1.228 ± 0.14 g/cm^2 disability and 1239 ± 0.06 g/cm^2 control group; $p < 0.001$). A study[25] in adolescents and adults with DS showed a LS BMD 10% lower in men than that of their controls (0.893 ± 0.111 and 0.988 ± 0.156 g/cm^2; $p = 0.02$) and 12% lower in women (0.961 ± 0.113 versus 1.094 ± 0.104 g/cm^2; $p = 0.001$), but found no differences in the femoral neck (FN) or in males (0.857 ± 0.168 versus 0.929 ± 0.111 g/cm^2; $p = 0.23$) or in women (0.862 ± 0.156 versus 0.926 ± 0.104 g/cm^2; $p = 0.49$). A later work,[12] performed in 39 people with DS of both sexes and 78 controls (older than 18 years of age), also concludes that people with DS have lower BMD in LS (L2-L4 0.919 vs 1.056 g/cm^2; $p < 0.001$), in FN (0.815 vs 0.908 g/cm^2; $p < 0.001$) and in total hip (0.872 versus 1.023 g/cm^2; $p < 0.001$). This same group analysed a greater number of people with DS with similar results.[8] The prevalence of osteoporosis in this group (defined as an Z index below -2 in LS or distal radius or FN) is 53% in some studies.[30]

Thus, it appears that people with DS have lower BMD in g/cm^2; however, some authors consider that this fact may be due to the smaller size of their bones. It is known that the BMD obtained by DXA (BMD according to the area in g/cm^2) is influenced by the size of the bone, being lower in smaller bones and greater in larger bones (Fig. 1). This fact is corrected when volumetric BMD is calculated (vBMD in g/cm^3), since it allows adjustment by size.[31] Thus, the study by García-Hoyos et al.,[8] after adjusting for size, found that the vBMD of people with DS is similar to that of the control group in both LS ($0.244 \pm 0{,}124$ g/cm^3 in DS versus 0.255 ± 0.033 g/cm^3 in controls; $p = 0.061$) and FN (0.325 ± 0.073 versus 0.309 ± 0.043 g/cm^3; $p = 0.10$). Another study[32] in children and adolescents with DS confirms that they have a vBMD similar to that of its control group in both LS (0.26 ± 0.05 versus 0.27 ± 0.05 g/cm^3; $p > 0.05$) and in FN (0.32 ± 0.04 versus 0.32 ± 0.05 g/cm^3; $p > 0.05$). Wu's study[33] does not describe significant differences in LS vBMD between DS and controls (0.149 ± 0.015 g/cm^3 in DS versus 0.152 ± 0.012 g/cm^3 in controls; $p > 0.05$). Other studies report similar results.[25] Therefore, although there are few studies that analyse vBMD in DS, it seems that, when adjusted for bone size, differences in BMD are reduced or disappear (Table 2).

Another approach to these people's bone health is given by calcaneal ultrasound (US), as they provide us with information about bone quality. We only found one related study in the medical literature which reports high US values in this group.[8] On the other hand, the *Trabecular Bone Score* (TBS) is a computer program that analyses the trabecular bone in lumbar spine densitometry based on the number of trabeculae, connectivity, and space between them. It is considered a surrogate marker of bone quality and is useful for stratifying the risk of fracture in postmenopausal women regardless of BMD.[34,35] There is only one study analysing the TBS in a group of 75 people with DS and the values were similar to those in the control group (1.456 ± 84 in DS and 1.474 ± 84 in controls; $p = 0.18$). Only 1% had a degraded microstructure (TBS < 1200).[8]

Bone metabolism in Down syndrome

As for bone metabolism, it is interesting to note that people with DS have risk factors for the development of hypovitaminosis D, among them, less physical activity, high comorbidity and the use of medication that affects bone metabolism.[40] Low levels of 25(OH)D have been associated with osteoporosis, risk of falls and fractures,[13] in addition to autoimmune diseases,[41] cardiovascular diseases,[42,43] tumors[44] and infections.[45] Vitamin D deficiency is common in neuropsychiatric disorders such as autism[46] and other intellectual disability.[47] Low levels of 25(OH)D have been reported in children and adolescents with DS,[48] but adult studies are inconclusive, and although the prevalence of hypovitaminosis D