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## **Diabetes mellitus may be one of the risk factors of osteoporosis – there is more and more proof**

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### **Summary**

**Osteoporosis is characterised by reduced bone density, changes in the fine structure of the bone tissues and by increased fragility. Osteoporosis is the most frequent metabolic-type clinical picture. Since the 1960's – 70's, studies have been carried out about its link with diabetes. Since then many research teams around the world examined the reasons why osteoporosis develops earlier in the case of diabetic patients than in those with normal carbohydrate metabolism.**

**IGF-1 is considered to be playing an important part in the growth of bones. IGF-1 and the receptor level of IGF-1 decrease with age, which then, in time, leads to reduced bone density. In the case of patients with Type 1 diabetes, elevated IL-6 level has been measured, but further studies are being carried out in respect of its link with osteoporosis. Some believe that the accumulation of metabolic products generated by the non-enzymatic glycation of molecules affects normal bone metabolism and reduces bone formation.**

**A number of test results showed that a lower bone density is detected in the case of patients with Type 1 diabetes at the end of their teenager years, their peak bone mass is lower than their healthy peers, which then causes earlier development of osteoporosis. Structural difference in bones can also be detected in the case of patients with Type 2 diabetes. However, increased bone density can be measured in most of the patients, which, then, may delay the detection of osteoporosis.**

**A number of international studies on the current medications available for the treatment of osteoporosis confirmed that they are also successful in the treatment of diabetic patients.**

Since the 1950's, the close link between a number of rheumatic illnesses and diabetes mellitus has been confirmed. Most of them develop concurrently with the delayed complications of diabetes, and the accumulation of AGE (advanced glycation end products) as a result of non-enzymatic glycation of proteins and lipids subjected to glucose exposition, in addition to the diabetic micro and macro angiopathy and neuropathy, is one of its obvious reasons.

During the past few years, researchers showed increased interest in the link between diabetes mellitus and osteoporosis. The prevalence of osteoporosis and diabetes mellitus shows an increased tendency. Further similarities between the two clinical pictures are: their frequency of occurrence increases with age and their joint development becomes more frequent with the ageing of the population. The question

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is whether we should fight the two illnesses independently, or is there one or even a number of mutual points what we can jointly attack to combat these illnesses.

In 2002, as an enthusiastic medic, I was browsing the medical literatures searching for mechanisms behind this link. Three years later I came back to the question and I was surprised to see the number of significant developments in this subject. The careful hypothesises have now been supported by studies undertaken with the participation of a large number of patients, and animal studies and in-vitro studies offered proof on the molecular level.

### **The characteristics of osteoporosis**

The osteoporosis is the most frequent metabolic-based bone problem. No symptoms can be detected in its early stage. It is, therefore, often referred to as a clinical picture causing a silent epidemic. It is very difficult to estimate its exact occurrence rate, but on the basis of the frequency of fractures we can suppose that this illness may even affect 10% of the population.

According to the WHO definition, osteoporosis is characterised by low bone mass and the changes in the fine structure of bone tissues, which causes increased fragility of the bones. The bone mass gradually changes with age. This change is the result of the interaction of a number of factors, including genetic reasons, hormonal changes and external factors.

Osteoporosis, that is causing clinical symptoms, shows microscopic and macroscopic fractures. The physical deformities, that develop, cause sterile inflammation, muscle-spasms, radical symptoms and pain. Pain usually develops gradually, but in the event of a fresh compression, sudden, unbearable pain may develop in the affected region. The development of physical changes, for example reduction in body height, the characteristic deformation of the spinal column, kyphoscoliosis, the reduction of the distance between the pelvic bone and the lower ribs, the characteristic pine-tree stretch lines of the skin on the back, the flattening of the upper edge of the Michael-type rhombus indicate an already advanced osteoporosis. In addition to physical examination, the diagnosis is established by laboratory and radiology methods. The measure of bone density plays a determining factor in the diagnosis, but the illness does not equate to low bone density. If reduced bone density is confirmed, it is necessary to clarify the reasons behind the bone loss in order to select the correct treatment.

### **The role of insulin in the metabolism of bones, the molecular mechanisms**

In vitro tests confirmed the presence of insulin receptors in the bone cells. Insulin acts as a bone growth factor, encourages the reception of amino-acids and collagen synthesis. Reduced bone-change and increased bone fragility were detected (1) in diabetic animal test models on Streptozocin-induced diabetic rats. The No. 1. insulin growth factor (IGF-1) enhances both bone building and bone decomposition. Stabnov et al (2) investigated this process in IGF-1 deficient mice during bone absorption inhibition treatment, in the case of IGF-1 and/or Alendronate administration to puberty-age test animals. The two substances independently have increased the

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periosteal and endosteal circumference and the bone density, but the best result was achieved during their concurrent administration. It was an important finding that only the IGF-1 has increased the length of bones, whilst Alendronate did not.

Niu and Rosen (3) have recently published their report on the complex role of the IGF-1 gene. It was discovered during tests on mice that in addition to the direct effect of the IGF-1 genes on the bone structure, apart from the OPG/RANKL/RANK cytokine system, the parathormone and the growth hormones, the gene influences the metabolic processes via the sterane-structured sex-hormones, which may become new therapeutic goals in the future.

The protein level of IGF-1 is less in older age patients, just like the hormone sensitivity of tissues with the reduction in the expression of IGF-binding proteins. These all jointly contribute to the development of involutional osteoporosis (4).

The role of IL-6 cytokine in osteoporosis has also been studied. Rachon et al measured an increased level of IL-6 in Polish post-menopausal women with Type 1 diabetes, but they were not able to detect its link to low bone density (5).

The IL-6 plays a part in the inflammation processes as a mediator, several clinical pictures (osteoporosis, dementia, diabetes, Alzheimer-disease) may be mentioned as examples in addition to arteriosclerosis. Isoprenoid, one of the metabolites of cholesterol, appears at one of the stages of the metabolic process, the level of which may be influenced by statins and bisphosphonates. In the clinical pictures listed, Omoigui and his American team have selected the process transmitted by the IL-6 as a therapeutic goal (6).

The increased serum glucose level initiates a non-enzymatic glycation and then these products (AGE) increase. The AGE's create increased osteoclast-induced bone absorption under test conditions in mice cell cultures. The AGE's and their receptors induce the apoptosis of in vitro human mesenchymal cells. Therefore, they do not differentiate into bone, cartilage or fatty tissues. According to Mr. Yamagishi, those anti-diabeticums that inhibit the formation of AGE's, may also be able to reduce the relevant risk of osteoporosis originating therefrom (9).

#### **Hormonal effects**

Not irrespective of the above, by influencing the level of parathormone, the kidneys affect the bone metabolism. As nephropathy diabetes is a frequent latent complication, its role must not be disregarded in the development of diabetes-linked osteoporosis. Secondary hyperparathyreosis developing for renal reasons may be treated by external Calcium and Vitamin D replacement, together with the normalisation of glucose-metabolism. Following a simultaneous pancreas and kidney transplants, Smets et al examined the osteoporosis developed due to secondary hyperparathyreosis. Prior to the operation, hyperparathyreosis has been detected in 68% of the patients, and half of these patients have already been diagnosed with osteoporosis. Within six months of the transplant, the bone density was reduced, but during the next six months thereafter, this process came to a halt and the commencement of an alpha Calcitriol therapy started to increase the bone density (7).

**When is the first time when osteoporosis must be considered in the case of a diabetic patient? Osteoporosis develops faster than in the case of non-diabetic patients, does it start already in childhood?**

More and more data supports the fact that the osteoporosis process starts already at the end of puberty in the case of patients with Type 1 diabetes, and as a paradox, patients with Type 2 diabetes are more prone to an increased risk of bone fracture due to their high bone density. The assessment of bone density, in itself, may show a misleading result, if no consideration is given to the changes in the bone quality, especially in the case of patients with Type 2 diabetes.

By ultra-sound examination of the small tubular bones in the hand, Italian scientists established that the bone structure of 10.5% of children with Type 1 diabetes is significantly different from their healthy peers. (The Z-score at times has exceeded 2.5D) (9). In an earlier publication, the authors described the link between reduced bone density and incorrectly established sugar-metabolism (high HbA1C) in the case of teenager patients with Type 1 diabetes. Later, by optimal glucose-control, it might be possible to delay the development of osteoporosis in these patients (10).

Liu et al have measured relatively lower bone density values, when compared to a control group, in the case of 20 – 37 years old patients with Type 1. diabetes, which then may lead to a reduced peak-bone mass and a higher risk of bone fracture in post menopause (11).

In the Rotterdam-Study (12), the bone densities of 6655 patients with Type 2 diabetes over the age of 55 years have been compared with that of the non-diabetic patients. They made a difference in respect of the long-term treated, the freshly diagnosed patients with Type 2 diabetes and the reduced glucose tolerance (IGT) patients. They measured higher bone density in both the diabetic patients and IGT patients than in the normal glucose tolerance control group. They found a significant difference in respect of fracture risk between patients with Type 2 diabetes and the IGT patient group. In the former, the fracture risk was significantly higher, than in the control group, whilst the lowest risk was detected in the case of IGT patients.

**Therapeutic aims and results**

The treatment of osteoporosis in secondary osteoporosis is based on the treatment of the underlying illness. The aim is to optimise the serum-glucose level in known and treated diabetic patients. Changes may be anticipated during the selection of the correct medication, if it is proven that certain effective ingredients are significantly more capable of slowing down the development of certain complications.

Japanese scientists observed that the Thiazolidinedione antidiabeticum has an inhibiting effect on the osteoblasts under in-vitro conditions, and the bone absorption marker levels have been reduced in in-vivo conditions during the treatment (13). They felt that Metformin also reduces the development of AGE's and consequently, this may delay the onset of osteoporosis.

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Alendronate is widely used in the treatment of osteoporosis. In the treated population we have found a significant number of diabetic patients also. In women with Type 1 diabetes over the age of 70, Maged et al (14) observed that a daily 10 mg dosage of Alendronate with a D3 Vitamin and Sodium supplement made a significant improvement in their conditions. In addition to the increase in bone density, the patients' insulin requirements have been reduced by 21.6% after the treatment of 12 months and by 36.2% after the treatment of 24 months. The authors feel that the more the osteoporosis symptoms are reduced with the treatment, the more the patients' physical activity improves. Physical activity had a positive effect on the glucose metabolism, and, therefore, it was possible to reduce the insulin dosage.

The Fracture Intervention Trial (FIT) was carried out in 11 centres with the study of 6458 patients. They studied the daily 5 and then 10 mg Alendronate treatment of the participants for a period of 3 years. In the case of 297 women with Type 2 diabetes, the EMD has significantly increased in the lumbar spine and hips, on the basis of which it can be stated that the Alendronate treatment is just as successful in the case of patients with Type 2 diabetes as in the case of non-diabetics (15).

Daly and his Australian colleagues reported the beneficial effects of diet and physical activities in the treatment of osteoporosis patients with Type 2 diabetes. The results did not indicate that the bone density of the elderly and the obese patients was reduced during the application of this method, whilst their carbohydrate metabolism improved (16).

The connection between diabetes and osteoporosis seems very complex. More and more up to date results are published all over the world. The routine screening of diabetic patients for osteoporosis is not yet recommended. However, a large proportion of diabetic patients are affected by other illnesses, for which the patients regularly attend check-ups and various screenings. Therefore, the likelihood of these patients being diagnosed for osteoporosis in time is quite high. Irrespective of the fact whether it is possible to find a solid proof for diabetes as one of the risk factors of osteoporosis, the main aim in the treatment of diabetic patients remains the same: to establish the correct level of carbohydrate metabolism. According to studies to date, all the other, already proven and effective osteoporosis therapies are also right for diabetic patients.

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