COMPLEX TREATMENT OF OSTEOPOROSIS IN PATIENTS WITH 2 TYPE DIABETES MELLITUS IN COMBINATION WITH NON-ALCOHOLIC FATTY LIVER DISEASE

Ju. A. Titova
SI V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine, Kharkiv, Ukraine
julia_tit@ukr.net

At present, diabetes mellitus (DM) is recognized worldwide by the World Health Organization (WHO), one of the most serious non-communicable diseases, which occupies a leading position among all causes of death in most countries. The number of patients with diabetes in the world is constantly increasing, due to the global aging of the population. Thus, according to the International Diabetes Federation (IDF), 2017, there are 425 million patients with diabetes in the world and by 2045 this number is expected to increase by 48% to 629 million. The largest number of patients was recorded at the age from 40 to 59 years [1].

Osteoporosis (OP) is a chronic systemic metabolic bone marrow disease characterized by low bone mass, quality impairment and bone marrow microarchitectonics, decreased density and increased bone fractures, and increased risk of fractures. The problem of this pathology is very relevant. Thus, according to WHO, OP is one of the four diseases that occupy leading positions in the structure of disability and mortality of a large population cohort [2].

Today, according to experts from the International Foundation for Osteoporosis, it affects every third woman and every fifth man after 50 years [3]. The social significance of OP is determined not only by high prevalence but also by its consequences, that is, the fractures of the vertebral and peripheral skeletal bones, which cause high levels of disability and higher material expenses for treatment [4, 5].

In recent years, the features of osteopathy and OP for type 2 DM have been actively discussed. An important aspect of this problem is the combination of several diseases against the background of increasing life expectancy.
The relationship between type 2 DM and OP is actively considered recently, and there are different data on the development and progress of OPs, depending on gender, age and racial belonging. As mechanisms that determine the interconnection of diabetes with OP, not only consider the direct pathophysiological effects of diabetes itself, but also diabetic complications that participate in the development of pathological process [6].

Determination of bone mineral density (BMD) indices in patients with diabetes mellitus with the purpose of predicting the risk of pathological fractures may be limited by factors that provoke a decrease in the quality of bone tissue and high risk of falls. The quality of bone tissue is influenced by microvascular complications of DM [7]. Patients with type 2 DM often have an increased risk of falls because of the presence of peripheral neuropathy, hypoglycemia, nocturia and disorders of the vision. It should be taken into account that patients with type 2 DM have an overweight or obesity, and therefore a sedentary lifestyle. A sense of equilibrium and coordination that would help avoid falls are often disturbed, and as a result, patients with type 2 DM and obesity with a relatively large bone mass have a high risk of fractures and the interpretation of normal BMDs is often biased and low-informative [8, 9].

Hyperinsulinemia with type 2 DM can contribute to the formation of bone tissue [10]. Lowering the same level of insulin with the progression of type 2 DM can lead to a decrease in BMD. Thus, Majima and colleagues have shown that in elderly people with type 2 DM, there is a loss of cortical bone and a positive correlation between levels of insulin secretion and BMD.

In addition, support for satisfactory glycemic control is a key factor in preventing loss of bone tissue in type 2 DM [11].

Hyperglycemia, which promotes collagen glutening, leads to impairment of interaction with cells and other components of the intercellular matrix with the formation of glucose-dependent intermolecular bonds [12]. These processes adversely affect the strength of the bone and lead to the development of OP, and the final products of germination can stimulate apoptosis of osteoblasts [13].

Studies have shown that a more expressive reduction in BMD was observed in patients with poorly controlled type 2 DM, and improved glycemic status reduced bone loss over a short period of time and, as such, satisfactory glycemic control could protect patients with type 2 DM from loss of bone mass [14]. Another effect of hyperglycemia is glycosuria, which promotes hypercalciuria and leads to the mobilization of calcium from the bone depot, as well as the reduction of the BMD [15].

Bone tissue is a kind of depot of various minerals. On the one hand, it provides the strength of the skeleton, and on the other allows you to continue to maintain mineral homeostasis in the face of a shortage of mineral substances from the outside [16]. There is virtually no physiological or biochemical process that passes without the participation of calcium ions [17]. Excitation and transmission of nerve impulses, muscle contraction, blood clotting processes, hormonal exocytosis, activation of enzyme systems, cell division, acid-base balance regulation are not a complete list of calcium's participation in normal physiological processes [18].

An open question regarding the recognition of calcium of a special physiological role as a universal regulator of almost all metabolic processes is precisely chosen calcium, with the fact that the human body is not able to independently synthesize it and fully depends on the provision of an element from the outside [19, 20]. Probably this is due to the fact that calcium is readily contacted with proteins, carbohydrates, lipids. It can form stable, poorly soluble conjugates with phosphate and carbonate ions, which are the basis of bone tissue. With the exchange of calcium is tightly bound to exchange phosphorus. The functions of phosphorus and calcium are extremely diverse. Phosphorus is a structural element of bone tissue. Along with calcium, the stimulating effect on absorption of phosphorus is made by vitamin D. One of the main mineral components of the bone is magnesium. Its content in the human body is also significant and in number occupies the fourth place after calcium, potassium and sodium. More than half of magnesium contained in the body (60 %) is in the bones, which increases the strength of the spine. Due
to the multifaceted effects of the organism, it is similar to calcium, although it is its functional antagonist. In relation to bone tissue, magnesium affects the processes of bone remodeling, stimulating the activity of osteoblasts and increasing osteogenesis. Magnesium promotes bone sensitivity to the action of parathyroid hormone (PTH), which is likely to reduce the secretion of the hormone.

In addition, magnesium has a controlling effect on vitamin D, stimulating the formation of active metabolites [21]. Lack of magnesium is accompanied by a decrease in the activity of enzymes (phosphatase, ATP-az), reduces the formation of active forms of vitamin D, and therefore, reduces the absorption of calcium in the intestine [22–24].

Significant changes in the blood markers of bone metabolism in the patients with gonarthrosis are observed, at the same time it reveals itself in the imbalance of osteoassociated macroelements (calcium, magnesium, phosphorus) with the development of hypocalcemia, which was detected in 98%, high activity of alkaline phosphatase (47% of the cases), signs of hyperparathyroidism and hyperosteocalceemia. The bone metabolic disturbances have clinical and pathogenetic significance in gonarthrosis [25].

An important step of GA treating is the use of drug therapy, physical therapy and correcting orthopedics. However, despite the progress in medical science, the efficacy of GA treatment is still insufficient and the task of finding new therapeutic approaches has remained open. Morphological and functional feature of an articular cartilage is a small number of chondrocytes in a large volume of intercellular substance, absence of vascularization and innervation, that is one of the reasons for low repair capacity of cartilage. In a number of studies, morphological assessment was carried out. Changes in the tissues of the knee joint in rats under the conditions of modeling of osteoarthritis and treatment of cryopreserved serum of cord blood. The results of morphological study of knee joints of the rats with induced GA indicated that the treatment with CCBS reduced an inflammation activity and slowed-down degeneration of articular coating that was estimated at cell and tissue levels, prevented pannus formation. Increasing the number of chondrocytes in articular cartilage was accompanied with their functional activity recovery, as evidenced by a rise in refraction of type 2 collagen [26].

The main purpose of treatment of OP is to prevent bone fractures, and the most reliable criterion for the effectiveness of therapy is the lack of new fractures in the background of treatment [27, 28]. Modern pharmacotherapy OP has a good arsenal of drugs that have a positive effect on bone metabolism [27, 29]. Since the disease is polyethiologic and multifactorial, with the clarification of additional factors that negatively affect the bone mass, the methods of treatment of OP.

The modern pharmacological preparations for treating OP include bisphosphonates, strontium renalat, hormone replacement therapy by sex steroids, calcitonin, selective estrogen receptor modulators, PTH, calcium and vitamin D [29, 30].

The action of all drugs is aimed at inhibiting increased resorption and enhancing the formation of bone tissue, that is, to maintain the balance between the destruction and synthesis of bone [27, 30, 31]. As the bone remodeling process is long lasting, the question of the available quality assessment and the effectiveness of the therapy is being raised before the clinicians. The results of dynamic laboratory observation can be informative after 3–6 months. after the start of therapy and to a greater extent this refers to the levels of bone markers markers [32–34].

Much more slowly, the BMD changes according to X-ray densitometry data [35]. Despite the advancement of pharmacotherapy OP, the effect of treatment in some patients is not sufficient — there are new fractures, persistent pain syndrome, significantly reduced motor activity. This fact suggests the presence of additional negative factors that affect the bone and to this day remains poorly understood. Therefore, the multifaceted treatment is very important in determining the tactics of management of patients with type 2 diabetes with OP.

The aim of the study. Determination of the treatment strategy for patients with type 2 DM with NAFLD.
MATERIALS AND METHODS

During the study, 37 patients with type 2 DM with OP and NAFLD were examined and treated. Men were 15 (40.5%), women were 22 (59.5%).

The average age of patients was (55.9 ± 2.33) years, the duration of the disease type 2 DM was (5.69 ± 0.51) years. Women were not in menopause. BMI — (32.84 ± 1.29) kg/m². All patients were in the state of subcompensation of carbohydrate metabolism according to WHO criteria [2013].

Diagnosis of NAFLD was established in accordance with the Order of the Ministry of Health of Ukraine dated November 6, 2014, No 826 «On Approval and Implementation of Medical-Technological Documents for the Standardization of Medical Aid in Chronic Non-Infectious Hepatitis», namely: «Unified Clinical Protocol for Primary, Secondary (Specialized) Medical Aid «Non-alcoholic steatohepatitis»».

Supervised patients were prescribed therapy with the following drugs: magnesium, vitamin D, calcium in daily doses, depending on gender, age, detected pathology and laboratory abnormalities, and all patients received hypoglycemic therapy (metformin, glimepiride, dapaglifosin, glyclazide, saxagliptin). A study of glycosylated hemoglobin (HbA1c) by colorimetric method was conducted.

The determination of 25-hydroxycholecalciferol was carried out by the immuno-enzymatic method (normative values: <10,0 ng/ml — deficiency; 10–29 ng/ml — insufficiency; > 30.0 ng/ml — sufficiency); levels of Sa (norm — 2,15–2,57 mmol/L), Ca²⁺ (the norm is 1,12–1,32 mmol/L) and Mg (norm — 0.77–1.03 mmol/L) by colorimetric method.

Statistical data analysis was performed using Microsoft® Excel 2003 software, «Statistica 6». The significance of the differences for normally distributed data was assessed according to the Student criterion (t). The received results in tables and text are presented as relative values — (%), as well as x ± Sx, where x is the arithmetic mean, Sx is the statistical error of the arithmetic. Disparities were considered statistically significant at indicators at the level of significance p < 0.05.

RESULTS
AND THEIR DISCUSSION

When questioning patients, attention was drawn to the following complaints: dry mouth, visual acuity, frequent urination, limb pain, headache, fatigue, poor portability of oily food, discomfort and pain in the right hypochondrium, and decreased fertility.

Patients were interviewed to record all symptoms.

At examination of patients with type 2 DM with OP and NAFLD, vitamin D deficiency was observed prior to treatment, that is, none of the patients had adequate levels of vitamin D,

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Patients with type 2 DM and OP with NAFLD, n = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>Ca, mmol/l</td>
<td>2.35 ± 0.03</td>
</tr>
<tr>
<td>Ca²⁺, mmol/l</td>
<td>1.09 ± 0.01</td>
</tr>
<tr>
<td>Vitamin D, ng/ml</td>
<td>17.52 ± 0.91</td>
</tr>
<tr>
<td>Mg, mmol/l</td>
<td>0.8 ± 0.02</td>
</tr>
<tr>
<td>HbA₁c%</td>
<td>7.93 ± 0.27</td>
</tr>
</tbody>
</table>

Note:  
α — Data are presented as Mean+SD  
p — the likelihood of changes between indicators before and after treatment.
Fig. 1. Total serum Calcium levels after Combined Therapy patients with type 2 DM and OP with NAFLD:
* $P_{value}$ lower then 0.001 was considered as statistically significant.

Fig. 2. Ionized Calcium levels after Combined Therapy patients with type 2 DM and OP with NAFLD:
* $P_{value}$ lower then 0.001 was considered as statistically significant.

Fig. 3. Rapid Normalization of Vitamin D levels after Combined Therapy patients with type 2 DM and OP with NAFLD:
* $P_{value}$ lower then 0.001 was considered as statistically significant.
while Ca levels were within the normal range, and Ca\(^{++}\) values were lowered. The average level of Mg was on the lower bound of the reference values. The average level of HbA1c was (7.93 ± 0.27) %.

All patients received comprehensive treatment. Depending on the initial levels of vitamin D, calcium and magnesium, for 3 months, patients received medications: vitamin D (cholecalciferol) in daily doses of 2000 d 4000 IU; calcium (calcium carbonate) — 1000–2000 mg/day; Magnesium (magnesium orthoate dihydrate) — 1 tablet. 2 times a day (1000 mg/day).

Comparison of the above mentioned indicators before the beginning of treatment and after 3 months of the application of therapy (table).

Thus, in the treatment process, there was a significant improvement in the Ca\(^{++}\), vitamin D and Mg, relative to the reference values, and also a significant decrease in the HbA1c indices was observed, which beneficially affected the bone tissue according to the laboratory data, but still can not be very informative because the process of bone tissue renewal is sufficiently prolonged (Fig. 1–5).

At the same time, patients noticed improvement in state of health, reduction of general weakness, improvement of quality of life.
CONCLUSIONS

1. The expediency of assigning preparations of magnesium, vitamin D, calcium in daily doses, depending on gender, age, degree of the revealed violations and deviations of laboratory parameters for patients with type 2 DM with OP for the improvement of bone tissue condition, is substantiated.

2. It is proved that the improvement of the bone state positively affects the state of carbohydrate metabolism in the examined patients.

3. The results of a dynamic laboratory examination obtained in patients with type 2 DM with OP need further monitoring with densitometry in dynamics for the final determination of improvement of bone tissue condition against the background of treatment.

4. There was an improvement in health and quality of life by improving the condition of bone tissue and compensation of carbohydrate metabolism.

REFERENCES

An actual problem of modernity is the relationship between type 2 diabetes mellitus (DM) and osteoporosis (OP), as well as type 2 DM with non-alcoholic fatty liver disease (NAFLD), which are actively considered by scientists. There are different data on the development and course of OP, depending on gender, age and race. So the aim of the study was to determine the tactics of treatment of OP in patients with type 2 DM with NAFLD. 37 patients with type 2 DM with OP and NAFLD (15 men and 22 women) were examined and treated. When examining patients with type 2 DM with OP and NAFLD before treatment, there was a deficiency of vitamin D, that is, none of the patients had an adequate supply of vitamin D, while the indicators of the level of CA were in the normal range, and the indicators of Ca$^{++}$ were reduced, so they were prescribed therapy with magnesium, vitamin D, calcium in daily doses, depending on gender, age, revealed pathology and laboratory abnormalities, and all patients received individually selected therapy with sugar-lowering. To assess the degree of compensation of carbohydrate metabolism was carried out to study the level of glycosylated hemoglobin (HbA$_{1c}$) and further correction zakreslajac therapy. According to the results of the study, the expediency of prescribing drugs that affect the improvement of bone structure in patients with type 2 DM with OP in daily doses depending on gender, age, degree of detected violations and deviations of laboratory parameters was proved, and it was determined that the improvement of bone tissue has a positive effect on the compensation of carbohydrate metabolism in the examined patients. It was found that patients with type 2 DM with OP and NAFLD require monitoring with densitometry and laboratory diagnosis in dynamics against the background of treatment.

**Key words:** type 2 diabetes mellitus, osteoporosis, non-alcoholic fatty liver disease, calcium, magnesium, vitamin D.

**Комплексне лікування остеопорозу у хворих на цукровий діабет 2 типу в поєднанні з неалкогольною жировою хворобою печінки**

**Тітова Ю. О.**

ДУ «Інститут проблем ендокринної патології ім. В. Я. Данилевського НАМН України»,
м. Харків, Україна
julia_tit@ukr.net

Актуальною проблемою сучасності є взаємозв’язки між цукровим діабетом (ЦД) 2 типу та остеопорозом (ОП), а також ЦД 2 типу з неалкогольною жировою хворобою печінки (НАЖХП), які активно розглядаються вченими. Існують різні дані щодо розвитку та перебігу ОП в залежності від статі, віку та расової принадності. Отже метою дослідження було визначити тактику лікування ОП у хворих на ЦД 2 типу в НАЖХП. Було обстежено та проведено лікування у 37 хворих на ЦД 2 типу з ОП та НАЖХП (15 чоловіків та 22 жінки). При обстеженні хворих на ЦД 2 типу з ОП та НАЖХП до початку лікування спостерігався дефіцит вітаміну D, тобто ні у одного з хворих не спостерігався адекватного забезпечення вітаміном D при цьому показники рівня Са були в діапазоні норми, а показники Са$^{++}$ — нижні, тому ім була призначена терапія препаратами магнію, вітаміну D, кальцію в добових дозах західно від статі, віку, виявлена патології та відхилень лабораторних показників, а також всі хворі отримували індивідуально підібрану цукрознижуючу терапію. Для оцінки ступеня компенсації вуглеводного обміну проводилось дослідження рівня глюкозильованого гемоглобіну (HbA$_{1c}$) і в по- дальшому корекція цукрознижуючої терапії. За результатами дослідження доведено доцільність призначення препаратів, що впливають на поліпшення структури кісткової тканини хворим на ЦД 2 типу з ОП в добових дозах західно від статі, віку, ступеню виявлених порушень та відхилень лабораторних показників, а також всі хворі отримували індивідуально підібрану цукрознижуючу терапію. Для оцінки ступеня компенсації вуглеводного обміну проводилось дослідження рівня глюкозильованого гемоглобіну (HbA$_{1c}$) і в по- дальшому корекція цукрознижуючої терапії. За результатами дослідження доведено доцільність призначення препаратів, що впливають на поліпшення структури кісткової тканини хворим на ЦД 2 типу з ОП в добових дозах західно від статі, віку, ступеню виявлених порушень та відхилень лабораторних показників, а також визначено, що покращення стану кісткової тканини позитивно впливає на компенсацію вуглеводного обміну у обстежених хворих. Встановлено, що хворі на ЦД 2 типу з ОП та НАЖХП потребують контролю з проведенням денситометрії та лабораторної діагностики в динаміці на тлі проведенного лікування.

Ключові слова: цукровий діабет 2 типу, остеопороз, неалкогольна жирова хвороба печінки, кальцій, магній, вітамін D.
Актуальной проблемой современности является взаимосвязь между сахарным диабетом (СД) 2 типа и остеопорозом (ОП), а также СД 2 типа с неалкогольной жировой болезнью печени (НАЖХП), которые активно рассматриваются учеными. Существуют различные данные по развитию и течению ОП в зависимости от пола, возраста и расовой принадлежности. Целью исследования было определить тактику лечения ОП у больных СД 2 типа с НАЖХП. Было обследовано и проведено лечение 37 больных СД 2 типа с ОП и НАЖХП (15 мужчин и 22 женщины). При обследовании больных СД 2 типа с ОП и НАЖХП до начала лечения наблюдался дефицит витамина D, то есть ни у одного из больных не наблюдалось адекватного обеспечения витамином D при этом показатели уровня Са были в диапазоне нормы, а показатели Са$^{++}$ — снижены, поэтому им была назначена терапия препаратами магния, витамина D, кальция в суточных дозах в зависимости от пола, возраста, выявленной патологии и отклонений лабораторных показателей, а также все больные получали индивидуально подобранную терапию сахароснижающими препаратами. Для оценки степени компенсации углеводного обмена проводилось исследование уровня гликозилированного гемоглобина (HbА1c) и в дальнейшем коррекция сахароснижающей терапии. По результатам исследования доказана целесообразность назначения препаратов, влияющих на улучшение структуры костной ткани больным СД 2 типа с ОП в суточных дозах в зависимости от пола, возраста, степени выявленных нарушений и отклонений лабораторных показателей, а также определено, что улучшение состояния костной ткани положительно влияет на компенсацию углеводного обмена у обследованных больных. Установлено, что больные СД 2 типа с ОП и НАЖХП требуют контроля с проведением денситометрии и лабораторной диагностики в динамике на фоне проводимого лечения.

Ключевые слова: сахарный диабет 2 типа, остеопороз, неалкогольная жировая болезнь печени, кальций, магний, витамин D.