

## ANNOTATION

of PhD thesis by Issayeva Samal Mukhametkaliyevna on the topic «**Clinical profile and risk assessment of osteoporotic fractures in patients in the Republic of Kazakhstan**», submitted for the degree of Doctor of Philosophy (PhD) in the specialty 6D110100 – «Medicine»

### **Relevance of the research topic.**

Osteoporosis (OP) is a multifactorial systemic skeletal disease characterized by a decrease in bone strength, namely, a decrease in bone mass and impaired quality of bone tissue, which lead to an increased risk of fractures (NIH Consensus, 2001). There is reason to believe that Kazakhstan belongs to countries with a high prevalence of OP. According to the results of a screening osteosonometric study of bone tissue conducted in the adult population of the country ( $\geq 40$  years), the signs of OP varied from 14.7% to 29.4% depending on the region (Sharmanov, T.Sh., 2012).

Bone fracture is the main clinical manifestation of OP. The most significant «major» osteoporotic fractures (OP-fracture) are fractures of the vertebral bodies, of hip (HF), of distal forearm and of the proximal humerus (Kanis J.A., 2001). Worldwide, an OP fracture occurs every 3 seconds (Johnell O., 2006), and every third woman and fifth man aged 50 and over will suffer at least one fracture in their lifetime (Melton L.J., 1992; Melton L.J., 1998; Kanis J.A., 2000). The global burden of disease associated with OP fractures occupies a leading position in the structure of disability and mortality worldwide (Johnell O., 2006; Hernlund E., 2013; Borgstrom F., 2020), and the economic burden is much higher compared to the costs due to myocardial infarction, stroke and breast cancer in postmenopausal women (Singer A., 2015). Due to the ongoing aging of the world population, a significant increase in patients with OP is predicted (Oden A., 2015), and more than half of all OP fractures of the hip by 2050 are expected in Asia (Gullberg B., 1997; Cooper C., 1992).

HF is the most severe complication of OP and causes high disability, mortality, and high medical and economic costs (Borgstrom F., 2020; Kanis J.A., 2012). The excess mortality within 1 year of a hip or pelvic fracture was higher than the excess mortality within 5 years of a diagnosis of breast cancer in women and prostate cancer in men (Tran T., 2018; de Lacerda G.F., 2019). According to single studies conducted in Kazakhstan (Amrayev S., 2018), there was also a high mortality and low functional activity after HF, especially in patients who did not receive surgical care. It should be noted that in the Republic of Kazakhstan (RK), as well as in other countries of Central Asia and Eastern Europe, there is no standard for entire emergency hospitalization and prompt care for patients with a fracture of this localization. In this regard, the official statistics do not provide full incidence rates.

The incidence of HF varies depending on the geographic location, ethnicity, gender, socioeconomic status, lifestyle and environment of the population. In addition, the difference in epidemiological data may be the result of different life expectancy of populations, as well as the level of organization of both medical care and statistical registration for fractures in individual regions of the world (Kanis J.A.,

2012; Cauley J.A., 2014; Curtis E.M., 2016; Aamodt G., 2020; Elffors I., 1994; Cheng S.Y., 2011). For example, according to J.A. Cauley et al. (2014), the countries with the highest and lowest levels of age-standardized incidence rates of HF differed more than 200-fold among women and 140-fold among men. Regional studies in Kazakhstan were conducted (Botabayeva A.S., 2009; Turekulova A.A., 2008), and generally confirmed the general epidemiological characteristics of HF. However, from a methodological point of view, these studies had certain shortcomings both in the methodology for collecting information on fractures and in the analysis of the obtained data. In foreign studies, information about fractures is based on data from State registers and official statistical reports. In Kazakhstan today there is no National register of fractures. The official statistical reports present fractures of the upper and lower extremities, and do not distinguish the specific location of the fracture, do not indicate the level of injury, so it is not possible to separate high- and low-energy fractures. Also, there is a lack of specially planned epidemiological studies that would allow to determine a reliable incidence of "major" OP fractures, and, as a result, to study the socio-economic consequences of this disease in the country. Given the above, at the time of planning this study, there was no reliable information on the incidence of major OP fractures in Kazakhstan.

The diagnosis of OP is based on low bone mineral density (BMD), but DXA (dual energy X-ray absorptiometry) is still not a widely used diagnostic method. The provision of these devices should be 10.6 per 1 million population (Kanis J.A., 2005). Meanwhile, according to the International Audit conducted in 2020 (Audit of the problem of osteoporosis, 2020), in the Republic of Kazakhstan in 2019 there were only 12 DXA, that is, the provision with devices was 0.7 per 1 million population, which is significantly below the recommended amount. Despite the fact that this method has a high specificity, is the "gold standard" for diagnosing OP and predicting the risk of fracture, it is not advisable to use densitometry as a mass screening due to the low sensitivity and high cost of this method (WHO, 1994). Moreover, low BMD is an important but not the only risk factor (RF) for fractures. Since OP is a multifactorial disease, more fractures may occur with normal BMD or a decrease to the level of osteopenia (Kanis JA, 2007).

There are less expensive and equally effective methods for predicting the risk of OP fracture, recommended in many clinical guidelines, which estimate the individual probability of future fractures based on RF (Compston J., 2017; Rabar S., 2012; Papaioannou A., 2010). The most widely used tool in the world is the Fracture Risk Assessment Tool (FRAX®) (Kanis JA, 2007), which estimates the individual probability of a OP fracture over the next 10 years. Since it is known that low BMD is one of the many risk factors for OP fractures, for more accurate prediction, the most significant clinical risk factors (CRFs) were selected in the FRAX tool: age (Kanis J.A., 2001), gender (Kanis J.A., 2001 ; Kanis J.A., 2011), body mass index (BMI) (De Laet C., 2005), BMD in the femoral neck (Johnell O., 2005), previous fracture (Kanis J.A., 2004), parents HF (Kanis J.A. , 2004), current smoking (Kanis J.A., 2005), long-term use of oral glucocorticoids (GCs) (Kanis J.A., 2004),

rheumatoid arthritis (RA) (Kanis J.A., 2004), secondary OP, alcohol intake more than 3 units (U) per day (Kanis J.A., 2005).

Sarcopenia is a risk factor for falls, fractures, disability and mortality (Harvey N.C., 2021; Veronese N., 2019). The studies that have appeared in recent years on the study of muscle tissue as a RF for OP fractures have not yet found due attention in Kazakhstan, and this problem has not been studied. The database of fracture risk factors increases every year, and over time, the list of CRFs in the FRAX algorithm can be supplemented.

A distinctive and important feature of the FRAX model is that this algorithm was developed separately for each population based on reliable data on the epidemiology of fractures and life expectancy in the country, since in different regions of the world the incidence of fractures in different age groups (Kanis J.A., 2012; Kanis J.A., 2002; Cauley J.A., 2011) and mortality differ significantly. Prior to this study, the FRAX model for the Republic of Kazakhstan had not been constructed.

**The aim of the dissertation research** is to provide a comprehensive clinical and epidemiological characteristics of manifest osteoporosis in the Republic of Kazakhstan as a basis for organizing medical care for patients with osteoporosis, including early detection using the FRAX calculator and the provision of modern specialized care for patients with osteoporotic fractures.

**Research objectives.**

1. Analysis of the general morbidity and primary incidence of osteoporosis according to official statistics in the Republic of Kazakhstan.
2. To study the incidence and other epidemiological characteristics of the major non-vertebral osteoporotic fractures in a specially designed population-based study and provide the construction of a FRAX model for the Republic of Kazakhstan
3. To study the state of care and outcomes in older people who have suffered a hip fracture.
4. To compare the risk factors for osteoporosis and fractures in older patients with hip fracture of the Kazakh nationality with patients of other nationalities.
5. Determine the possibility of applying the FRAX model and the intervention threshold developed for the Republic of Kazakhstan to residents of the country who do not belong to the Kazakh nationality.

**Object and subject of research:**

To solve the set objectives, a study was conducted, united by a common aim, and consisting of 5 stages.

*1st stage.* To study the trends in the prevalence of Musculoskeletal Disorders (MSDs) and OP, the annual official statistical data of the Ministry of Health of the Republic of Kazakhstan (MH RK) and documents of application to primary health care (PHC) from 2012 to 2018 were analyzed. (Health of the population of the Republic of Kazakhstan and the activities of healthcare organizations, 2012-2018; Medstat. Form 12, 2012-2018).

*2nd stage.* The study of the incidence of OP fractures was carried out as part of the multicenter multinational population study "Epidemiology of osteoporotic

fractures in the countries of Eurasia" (EVA), at the initiative of the Russian Association for Osteoporosis (project leader - Doctor of Medical Sciences, Prof. Lesnyak O.M.) with the support of the International Osteoporosis Foundation, which was carried out according to a similar design in the Russian Federation (Lesnyak O., 2012), the Republics of Belarus (Ramanau H., 2018), Armenia (Lesnyak O., 2017), Moldova (Zakroyeva A., 2020), Uzbekistan (Lesnyak O., 2020).

In order to obtain data for the further possibility of extrapolating them to the entire general population (residents of the Republic of Kazakhstan aged  $\geq 40$  years), the conditions for ensuring the representativeness of the sample were met: the use of a cluster representing the general population and compliance with the required sample size. So, the city of Taldykorgan was chosen due to its remoteness from other large cities of the republic and the availability of highly specialized trauma care for all residents of the city, where a entire study of all observation units was carried out. The data of the residents of the city were representative of the population of the Republic of Kazakhstan in terms of gender, age and ethnic structure.

For a certain period (01.01.2015 – 31.12.2016) a retrospective study of the incidence of fractures of various localization of residents of Taldykorgan aged 40 years and older was carried out (ICD-10 code: S72.0, S72.1, S72.2, S52.5, S52.6, S42.2) from outpatient and inpatient medical records («Taldykorgan City Multidisciplinary Hospital», «Regional Hospital of Taldykorgan», medical center "KhAK" and trauma center).

*3rd stage.* The prospective stage of the study was carried out for 12 months. (from March 1, 2017 to February 28, 2018). At this stage, an active search for new cases of HF (ICD-10 code: S72.0, S72.1, S72.2) was assumed in all available medical institutions, including the same sources as in the retrospective part and additionally from general practitioners (GPs) from 2 city polyclinics, 2 private centers, traumatologists at the PHC level, emergency medical care (EMC station) with mandatory subsequent verification.

At the time of the study, a register of patients with fractures was created, and all data were reconciled to exclude repeated registration of the same fracture. Incidence rates for HF (2015-2017) were standardized by age and gender for the population of the Republic of Kazakhstan in 2015 to estimate the number of femoral fractures throughout the country. Additionally, future projections were estimated up to 2050 assuming that the age- and sex-specific incidence remained stable. Population demography was taken from the United Nations using the medium variant for fertility (UN, Profiles of Ageing, 2017). The adjusted data on hip fracture were used to construct the FRAX model. The construction of the FRAX model was carried out by the working group of the International Osteoporosis Foundation and the University of Sheffield (UK) consisting of: J.A. Kanis, E. McCloskey, N.C. Harvey, M. Lorentzon, E. Liu, H. Johansson.

*4th stage.* As part of an observational study, the state of medical care and outcomes in patients were studied 1 year after undergoing PPBP, identified during the prospective phase of the study: mortality and functional activity.

*5th stage.* In order to study the clinical risk factors for OP and OP fractures, a cross-sectional case-control study was conducted in individuals aged 50 years and older with HF (ICD-10 code: S72.0, S72.1, S72.2) of Kazakh nationality in comparison with patients of other nationalities living in the Republic of Kazakhstan. The study took place in the traumatology departments of the «Almaty Multidisciplinary Clinical Hospital» and «City Clinical Hospital No. 4» in Almaty. For this study, an individual registration card (IRC) was specially developed, which was filled in by the researcher during a clinical examination and interview of respondents and analysis of patients' medical documents.

#### **Scientific novelty.**

On the basis of a specially planned population study, for the first time, the incidence rates of the major non-vertebral osteoporotic fractures in the Republic of Kazakhstan (fractures of the hip, proximal humerus, distal forearm) were obtained. It has been proven that their basic epidemiological characteristics are consistent with those in other countries: the predominance of women among patients and the increase in incidence with age. Similarly to the countries of Eastern Europe, the incidence of HF among people under 70 years of age was higher in men. The highest incidence figures were registered in the fractures of distal forearm. For the first time, the analysis of the structure of the main nonvertebral OP fractures in men and women of the Republic of Kazakhstan demonstrated a decrease in the proportion of fractures of distal forearm with age and an increase in the proportion of HF, while the proportion of fractures of proximal humerus remained stable.

For the first time, on the basis of the obtained data, a model of 10-year probability of osteoporotic fractures FRAX for the Republic of Kazakhstan was constructed, which was placed in the public domain.

For the first time, it became possible to compare the risk of OP fractures in residents of the Republic of Kazakhstan with the population of other countries, and it was shown that in residents of the RK the probability of HF exceeds that of the countries of Eastern Europe and China, and the probability of major non-vertebral OP fractures is similar to the population of the Russian Federation (RF) and higher than in China.

For the first time in a population-based study, the outcomes of HF were studied, including patients who did not seek specialized trauma care. The association of mortality and functional limitations within 12 months after the fracture with the patient's age, female sex and lack of surgical treatment has been proven.

In a comparative clinical study of older patients with HF admitted to a trauma hospital, it was shown for the first time that the main risk factors for osteoporosis and fractures in Kazakhs did not differ from those of other nationalities, except for less frequent smoking. HF in the Kazakhs was at an older age, which was associated with a higher frequency of clinical signs of sarcopenia. At the same time, in patients with HF of Kazakh nationality, the immediate outcomes of treatment did not differ from those of other nationalities.

It has been proven that the FRAX model and the intervention threshold developed for Kazakhstan can be equally applied to both Kazakhs and people of other nationalities living in Kazakhstan.

**Provisions to be defended.**

1. In the Republic of Kazakhstan, the registration of osteoporosis in medical statistics is not established, and the number of registered cases lags far behind the expected number of patients with osteoporosis.
2. The basic epidemiological characteristics of the major non-vertebral osteoporotic fractures in the Republic of Kazakhstan coincide with those in other countries. Life-time probability of hip fractures among residents of Kazakhstan who have reached the age of 50 years exceeds that for the countries of Eastern Europe and China. In the future, there will be a significant increase of the cases of hip fractures.
3. Specialized medical care for patients with a hip fracture in the Republic of Kazakhstan does not meet modern standards, which has a pronounced impact on outcomes.
4. Kazakhs suffer a fracture of the proximal femur at an older age, and therefore, they have more signs of sarcopenia than people of other nationalities. The main risk factors for osteoporosis and fractures occur with the same frequency in them, with the exception of rarer smoking in Kazakhs.
5. FRAX model and the intervention threshold developed for Kazakhstan can be equally applied to both Kazakhs and people of other nationalities living in the Republic of Kazakhstan.

**Practical significance of the obtained results.**

The work revealed a low level of registration of cases of osteoporosis in the official statistics of the Republic of Kazakhstan, which requires attention not only from healthcare organizers, but also from medical educational institutions, which should expand the training of students and doctors in the basics of diagnosing and treating osteoporosis.

Developed on the basis of the data of this study, the model of 10-year probability of OP fractures - FRAX, specific for the Republic of Kazakhstan, makes it possible to start a wide screening of the country's population aged 50 years and older. This will allow timely identification of patients with a high risk of fractures, diagnosis of osteoporosis in them and the appropriate start of adequate pathogenetic therapy aimed at reducing this risk. The introduction of the FRAX calculator throughout the Republic of Kazakhstan will make it possible to obtain registered cases of osteoporosis close to real numbers.

The design of the study made it possible to demonstrate the shortcomings in the organization of medical care for elderly patients with HF, when a large proportion of them are not hospitalized and do not receive modern surgical care. Some patients were observed only by primary care physicians. People aged 70 years and older had the greatest risk of being hospitalized and not operated on. This fact makes it necessary to make changes to the existing procedure for providing medical care to older people with HF.

### **Personal contribution of a doctoral candidate.**

The results submitted for defense were obtained by the author personally, are original and reliable. The PhD candidate independently performed an analysis of modern literature, prepared a literature review, statistical processing, interpretation of the data obtained, and on the basis of which the text of the dissertation was written and the main publications based on the results of the work (including those in the Web of Science list) were prepared for their implementation in educational and clinical diagnostic activity. During the epidemiological study, the author organized and carried out the collection and analysis of information according to the study plan. The PhD candidate developed individual patient records and conducted a clinical examination of patients. The author has created an electronic database with the necessary information.

### **Implementation of research results into practice.**

A tool for assessing the 10-year probability of OP fractures - the FRAX@ model for the Republic of Kazakhstan has been introduced into clinical practice at the University Clinic of NJSCA «Asfendiyarov Kazakh National Medical University», «City Rheumatological Center of Almaty», polyclinics «ZHANUYA», Taraz (acts of implementation). The main provisions of the dissertation are used in the educational process at the Department of Rheumatology of the NJSC «Asfendiyarov Kazakh National Medical University» (acts of implementation).

### **Approbation of the results of the dissertation.**

The main provisions of the PhD thesis work were reported: Second and Third Republican Congresses on osteoporosis (Almaty, 2017, 2019); Winter School of Rheumatologists of Kazakhstan (Almaty, 2018, 2019, 2020, 2021); Summer School of Rheumatologists of Kazakhstan (Almaty, 2019); World Congress on Osteoporosis, Osteoarthritis and Other Skeletal Metabolic Diseases (WCO-IOF-ESCEO) (Florence, Italy - 2017; Krakow, Poland - 2018; Paris, France - 2019; Barcelona, Spain - 2020); II International Forum of General Practitioners/Family Doctors (N. Novgorod, 2019); VII Russian Congress on osteoporosis, osteoarthritis and other metabolic diseases of the skeleton with international participation (Yaroslavl, 2020); XIV International Congress "Man and medicine - Kazakhstan" (Almaty, 2021); Scientific and practical conference "Modern approaches in the diagnosis and treatment of rheumatological diseases" (Taraz, 2021).

The PhD candidate participated in competitions for young scientists:

- 1) Diploma of the 1st degree - in the Young Scientists Competition within the framework of the III Republican Congress on Osteoporosis with international participation (Almaty, Kazakhstan, 2019);
- 2) Diploma 2020 ESCEO-IOF Young Investigator Award - for scientific achievements in the competition of young scientists of the world at the World Congress on osteoporosis, osteoarthritis and other metabolic diseases of the skeleton, (Barcelona, Spain, 2020);
- 3) Diploma of the 1st degree - in the Young Scientists Competition within the framework of the VII Russian Congress on Osteoporosis, Osteoarthritis and Other

Metabolic Skeletal Diseases with international participation (Yaroslavl, Russia, 2020).

### **Publications.**

As a result of the study, 21 scientific papers were published: 2 of them - in an international peer-reviewed scientific journal with an impact factor according to JCR (indexed in the Web of science Core Collection, science Citation Index Expanded, CiteScore percentile indicator of at least 50 in the Scopus database ), 1 - included in the international database Web of Science Core Collection (Clarivate Analytics) and Scopus; 5 - in journals, according to the recommendation of the Committee for Quality Assurance in the Sphere of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan; 11 abstracts in the materials of foreign international conferences, 9 of them in English; 2 - in other scientific publications.

From publications:

1. S. Issayeva, O. Lesnyak, A. Zakroyeva, B. Issayeva, D. Dilmanova, H. Johansson, E. Liu, M. Lorentzon, N.C. Harvey, E. McCloskey, J.A. Kanis. Epidemiology of osteoporotic fracture in Kazakhstan and development of a country specific FRAX model // Archives of osteoporosis. – 2020, №15 (30). – P. 1-8. <https://doi.org/10.1007/s11657-020-0701-3> (Q2 WoS, 70th percentile by CiteScore).

2. O. Lesnyak, J. P. Bilezikian, A. Zakroyeva, on Behalf of the Working Group for the Audit on Burden of Osteoporosis in Eurasian Region. Report on the Audit on burden of osteoporosis in eight countries of the Eurasian Region: Armenia, Belarus, Georgia, Moldova, Kazakhstan, the Kyrgyz Republic, the Russian Federation, and Uzbekistan // Archives of Osteoporosis. – 2020, №15(175). – P. 1-8. <https://doi.org/10.1007/s11657-020-00836-y> (Q2 WoS, 70th percentile by CiteScore).

3. A. Zakroyeva, O. Lesnyak, S. Sahakyan, G. Ramanau, V. Kazak, S. Issayeva, M. Shakirova. Multicenter Epidemiological Study of Osteoporotic Fractures in Eurasia (EVA Study). A step towards reducing the burden of age-related diseases // BIO Web of Conferences, EDP Sciences. – 2020, №22. – P. 01019. <https://doi.org/10.1051/bioconf/20202201019>.

4. Gabdulina G.Ch., Issayeva B.G., Kulshimanova M.M., Erlepesova A.T., Issayeva S.M. Proximal femoral and distal forearm fracture frequency among people of almaty region (post-hoc analysis) // Meditsina (Almaty) = Medicine (Almaty). – 2017. – №. 9. – P. 192-196 (In Russ.).

5. Issayeva B.G., Sapparbayeva M.M., Khabizhanova V.B., Gabdulina G.Kh., Esirkepova G.S., Kaiyrgali Sh.M., Issayeva S.M., Nurgaliyev K.Zh., Kulshymanova M.M., Atasheva A.A., Dalibayeva G., Beisen A. The dynamics of prevalence of main rheumatic diseases in the Republic of Kazakhstan for 2012-2016 years // Meditsina (Almaty) = Medicine (Almaty). – 2018. – №3(189). – P. 17-22 (In Russ.).

6. Issayeva SM. Some questions of epidemiology and diagnostics of osteoporosis. Meditsina (Almaty) = Medicine (Almaty). – 2018. – №. 3. – P. 154-158 (In Russ.).



7. Issayeva S.M., Issayeva B.G., Lesnyak O.M. Morbidity of osteoporosis of the Kazakhstan population and the incidence of osteoporotic fractures in Taldykorgan // Vestnik KazNMU. – 2018. – №. 4. – P. 249-255 (In Russ.).

8. Issayeva S.M., Bissembay M.A., Burakhanova G. Contemporary view at sarcopenia (literature review) // Meditsina (Almaty) = Medicine (Almaty). – 2019. – 3(201). – P. 61-65 (In Russ.).

**The scope and structure of the thesis.**

The dissertation work is presented on 137 pages of a computer text, consists of an introduction, 4 chapters (literature review, materials and methods, research results; discussion of the results); conclusions; practical recommendations; list of references from 358 sources and 4 appendices. The dissertation is illustrated with 13 figures and 19 tables.