Summary of professional accomplishments

Self presentation

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Łódź, 2014

1. **First and last name**: Agnieszka Joanna Rusińska

2. **Diplomas, scientific/artistic degrees – with name, location, year of acquisition and title of doctoral dissertation**

- **2005** – diploma in pediatrics, Medical Examination Centre in Łódź, specialization under the direction of Professor Danuta Chlebna-Sokół, MD, PhD
- **2002** – doctor of medical sciences, diploma with distinction, Medical Academy of Łódź, promoter: Professor Danuta Chlebna-Sokół, MD, PhD, doctoral dissertation title: „Evaluation of the participation of selected cytokines in etiopathogenesis of idiopathic osteoporosis and osteopenia in children and adolescents"
- **1997**- doctor of medicine diploma with a very good grade, Medical Academy of Łódź

3. **Information on the previous employment in scientific/artistic units.**

- **2006**-until present – assistant professor at Department of Pediatric Propedeutics and Metabolic Bone Diseases of the Medical University of Lodz
- **2002-2006** – assistant at Department of Pediatric Propedeutics and Metabolic Bone Diseases of the Medical University of Lodz
- **1998-2002** – PhD studies at Department of Pediatric Propedeutics and Metabolic Bone Diseases of the Medical University of Lodz
- **1997-1998** – post-graduate internship at Independent Public Health Care Facility (SPZOZ) Maria Konopnicka memorial University Clinical Hospital No. 4 of Medical University of Lodz

4. **Presentation of achievements pursuant to article 16 paragraph 2 of the Act of 14 March 2003 r. on the Academic degrees and the academic title as well as on the degrees and the title within the scope of art. (Journal of Laws no. 65, item 595 as amended):**

a) **Title of scientific/artistic achievement:**

Publication series entitled:

„Uwarunkowania nawracających złamań i zaburzeń gęstości mineralnej kości u dzieci"

["Causes of recurrent fractures and mineral density disorders in children"]

b) **Author/authors, title/titles of publication, year of publication, publishing house**

1. **Rusińska A.**, Chlebna-Sokół D.: Evaluation of interleukine –1 and –6 in etiopathogenesis of idiopathic osteoporosis and osteopenia in children. *Archivum Immunologiae et Therapiae Experimentalis, 2005, 53, 257-265* **(MNiSW points: 20, 2005: 10; IF: 2,818,** 5Y IF: 2,810, **IF 2005: 1,000)**
2. **Rusińska A.**, Chlebna-Sokół D.: Insulin-like growth factor-I and mineral metabolism markers in children with idiopathic decrease in bone mass. *Clinica Chimica Acta 2006, 336 (1-2): 257-263* **(MNiSW points: 35, 2006: 24; IF: 2,764,** 5Y IF: 2,748, **IF 2006: 2,328)**
3. Chlebna-Sokół D., **Rusińska A.**, Michałus I., Lewiński A., Zygmunt A.: Ocena znaczenia osteoprotegeryny w etiopatogenezie niskiej masy kostnej u dzieci i młodzieży [Evaluation of the importance of osteoprotegerin in etiopathogenesis of low bone mass in children and adolescents]. *Endokrynologia Pediatryczna 2006, 5, 1(14): 39-47* **(MNiSW points: 6, 2006: 3; IF:0)**
4. Chlebna-Sokół D., **Rusińska A.**, Michałus I., Frasunkiewicz J.: Evaluation of vitamin D metabolites concentrations in children with low bone mass. *Polish Journal of Environmental Studies 2006, 15, 2b: 1029-1033* **(MNiSW points: 15, 2006: 10; IF: 0,600,** 5Y IF: 0,762, **IF 2006: 0,353)**

5. **Rusińska A.**, Chlebna-Sokół D., Frasunkiewicz J.: Evaluation of the influence of state of nutrition and body composition on skeletal mineralization in children with body mass deficiency and body mass excess. *Polish Journal of Environmental Studies 2006, 15, 5b: 754-759* **(MNiSW points: 15, 2006: 10; IF: 0,600,** 5Y IF: 0,762, **IF 2006: 0,353)**
6. **Rusińska A.,** Chlebna-Sokół D., Lewiński A., Golec J., Woźniak E., Zygmunt A.: Ocena zależności między densytometrycznymi i ultradźwiękowymi wskaźnikami gospodarki mineralnej kości a występowaniem złamań u dzieci [Evaluation of the relationship between densitometry and ultrasound indicators of bone mineral balance, and bone fractures in children]. *Przegląd Pediatryczny 2007, 37, 4: 369-376* **(MNiSW points: 5, 2007: 4; IF:0)**
7. **Rusińska A.**, Chlebna-Sokół D., Michałus I., Prochowska A.: Environmental determinations of multiple bone fractures in children. *Polish Journal of Environmental Studies 2008, 17, 4A: 367-372* **(MNiSW points: 15, 2008: 10; IF: 0,600,** 5Y IF: 0,762, **IF 2008: 0,963)**
8. Michałus I., Chlebna-Sokół D., **Rusińska A.**, Jakubowska-Pietkiewicz E., Kulińska-Szukalska K.: Ocena gęstości mineralnej i metabolizmu kostnego u dzieci z wielokrotnymi złamaniami kości [Evaluation of bone mineral density and bone metabolism in children with multiple bone fractures]. *Ortopedia Traumatologia Rehabilitacja 2008, 6(6), 10, 602-612* **(MNiSW points: 9, 2008: 6; IF:0)**
9. **Rusińska A.,** Świątkowska M., Koziołkiewicz W., Skurzyński S., Golec J., Chlebna-Sokół D.: Proteomic analysis of plasma profiles in children with recurrent bone fractures. *Acta Biochimica Polonica 2011, 4(58), 553-561* **(MNiSW points: 15, 2011: 15; IF: 1,389,** 5Y IF: 1,558, **IF 2011: 1,491)**
10. **Rusińska A.,** Dzwonek A.B., Chlebna-Sokół D.: Recurrent fractures as a new skeletal problem in the course of Angelman syndrome. *Bone 2013, 55, 461-464* **(MNiSW points: 35, 2013: 35; IF: 4,461,** 5Y IF: 4,587, **IF 2013: 4,461)**

The total IF of the series of papers reported as an achievement: 13,232, by year of publication: **10,949,** including in reviewed supplements: **1,669, MNiSW points: 170,** by year of publication: **127,** in supplements: **30.** As first author IF: 12,632, by year of publication: 10,596, including in reviewed supplements: 1,316, MNiSW points: 140, by year of publication: 108, in supplements: 20.

c) **Discussion of scientific/artistic purpose of the above mentioned works and the achieved results, along with the discussion of their possible use**

Bone fractures in children are a common and significant health problem. Only in women after 85 years of age their occurrence is greater than in the developmental age. It is known that about ¼ of children suffer injuries, and in the USA about 20% of patients at the age of 5-21 are hospitalized because of injury effects. In 10-27% of them bone fractures are diagnosed, and their frequency over the last few decades has been rising. Scandinavian scientists' reports show that the risk of bone fracture from birth to 16 years of age in boys may even reach 42%, and 27% in girls. It is commonly thought that such frequency is related to childhood behaviors that promote injuries. However, the peak of fracture occurrence does not coincide with child's greatest physical activity but rather with the growth spurt, and occurs in girls at the age of about 10-12 years, and in boys around 13-14 years of age. Like in adults with osteoporosis, 50-60% of cases are low-energy fractures related with falling from the body-level height. Repeating and recurrent fractures are a specific and difficult problem. They occur in about 10-12% of all children 1/3 of which have already had a fracture. It is estimated that 40-66% of the total number of fractures occur in children with recurrent fractures. The etiology of the recurrent fractures is very unclear. The most common suspicion is the presence of bone mineral density disorders and these are searched for in the first place. However, it often appears that despite a normal bone mass the patient suffers fractures, thus other abnormalities have to be taken into consideration. **Consequently, the scientific purpose of the works presented in the discussed publication series was a multi-direction research of the causes of the recurrent fractures and of mineral bone density disorders increasing the risk of fracture in children.**

The series of the presented works is opened by publications referring to the search of etiopathogenetic factors of the of idiopathic bone mineral density lowering in children (**publication 1, 2, 3, 4**). These were patients in which chronic diseases that could lead to secondary bone metabolism disorders were excluded.

In the first of these works, published in 2005 (**publication 1**), considering the results of *in vivo* studies indicating the participation of proinflammatory cytokines in the stimulation of resorption and bone remodeling processes, an attempt was made to assess the possible relation between serum interleukine -1 and -6 level and bone metabolism indicators as well

as the occurrence of idiopathic bone mineral density disorders in children. Until now no such studies have been conducted in the developmental age. IL-1α, IL-1β, IL-1ra and IL-6 receptor antagonist, as well as IL-6sR solvent receptor levels were measured in patients with idiopathic osteoporosis, osteopenia and in the comparison group. It needs to be emphasized that these were children with no clinically apparent inflammatory state, and the classical indicators of the inflammatory state such as CRP, ESR and peripheral blood leukocyte count were within the limits of normal. Based on these studies it was stated that IL-6 level was statistically much higher in children with idiopathic osteoporosis and osteopenia as compared to the comparison croup. Moreover, a negative correlation was demonstrated between IL-6, IL-1α and cytokine/receptor rates (IL-1/IL-1ra, IL-6/IL-6sR), and bone mineral density measures: Z-score and BMD, in Spine projection. A positive correlation was also stated between IL1α, IL-1/IL-1ra rate and parathormone level, as well as between IL1α, IL-6sR and bone formation rates (IL1α correlated positively with osteocalcin, and IL-6sR with alkaline phosphatase bone isoenzyme). Prospective studies revealed that mineral bone density improvement after 1 year of treatment was accompanied by an important decrease of the initial high IL-6sR level. To summarize, the results of these studies showed that there is a relation between proinflammatory cytokines and bone metabolism as well as bone mineral density in children with mineral density disorders; to date no such observations have been presented for this age group. Based on the performed studies a hypothesis was made that it is probable that a chronic latent inflammation, even with mild intensity, may promote bone mass lowering, which means bone fractures in children.

In the next work which was issued in 2006 (**publication 2**), a reach for molecules involved in etiopathogenesis of idiopathic mineral bone density disorders was continued. Considering the results of experimental studies indicating the effect of growth factors on the bone formation processes, as well as publications regarding the role of these factors in physiology and pathology of body growth and ageing, studies were performed to verify the hypothesis that there is a relation between insulin-like growth factor 1 (IGF-1) and the occurrence of idiopathic skeletal calcification in the developmental age. To date, no such study results have been publishes in this age group. IGF-1 and its binding protein IGFBP-3 level was analyzed as compared to mineral balance in patients with idiopathic osteoporosis, osteopenia and in the comparison group. It needs to be stressed that the treatment group did not include children with somatic development disorders, including nanism, sexual

maturation disorder, growth hormone deficiency and other endocrinopathies, in order to avoid an error related with the known impact of these disorders on IGF-1 level and mineral balance. Based on these studies it was demonstrated that mean IGF-1 level was statistically significantly lower in children with decreased bone mineral density as compared to comparison group. This difference was also observed when analyzing results of children in the subsequent puberty phases. Moreover, IGF-1 level positively correlated with bone mineral density in Total body and Spine projection expressed in absolute BMD values as well as using Z-score. Additionally, in the subgroup of children with osteoporosis, the following inversely proportional dependence was observed: the lower IGF-1 serum level was, the stronger bone resorption processes were - they were visible as higher urine pirydynolin and desoxypirodynolin level. These tests results indicated that IGF-1 may be a significant factor involved in the etiopathogenesis of idiopathic bone mineral density in children; to date such tests results have not been presented in this age group. Maybe in the future it will be justified to use a recombinant IGF-1 or other agents with stimulating effect on its secretion in the body for treatment of severe types of osteoporosis; this issue requires further scientific research.

In the following work, which was published in 2006 (**publication 3**), the subject of searching for molecular etiopathogenetic factors of idiopathic bone mineralization disturbances in the developmental age was continued. This time, pioneer tests in children were performed to assess the importance of the newly discovered polypeptide composition involved in osteoclastogenesis and mutual relations between osteoblasts and osteoclasts - osteoprotogerin/RANK/RANKL system. Until now, no such studies have been performed in children. Ostoclastogenesis inhibitor – osteoprotegerin level was analyzed as well as its soluble ligand sRANKL level, in patients with idiopathic bone mineral density disorders and in the comparison group. A statistically significant difference was recorded between the groups as regards the osteoprotegerin/sRANKL receptor rate; in children with osteoporosis it was 9.4 on average, with osteopenia 21.6, and in the comparison group 14.2 ($p<0.05$). In children with a low bone mass, a positive correlation was demonstrated between OPG, OPG/sRAKL rate and bone mineral density expressed as Z-score in Spine projection. Moreover, in this group of patients significant dependencies were demonstrated between OPG, sRANKL and tested calcitrope hormones and bone turnover markers. Based on the conducted studies a conclusion was made that osteoprotegerin system is an important factor taking part in the

formation of idiopathic skeletal mineralization disturbances in children. Studies of this problem are now being conducted at our Clinic. Results of these scientific observations may have serious practical implications as pharmacological intervention into osteoprotegerin/RANK/RANKL system has recently become possible through biological treatment and denusomab use. It is a human monoclonal antibody directed against RANKL and preventing from RANK receptor activation at the surface of osteoclasts and its precursors, at the same time inhibiting osteoclastogenesis, like osteoprotegerin. Denosumab is already used in treatment of osteoporosis in adults; studies of its efficacy and safety in children with osteogenesis imperfecta are about to start, and maybe it will be used in the future for severe forms of osteoporosis in children.

The following two works that were published in 2006 (**publication 4 and 5**) concerned more recognized bone mass modifying factors, i.e. serum vitamin D level assessment in children with low bone mass, and the assessment of the nutritional status and body composition impact on skeletal mineral density. In the publication with the assessment of vitamin D importance (**publication 4**), the relation between 25OHD, 1,25OH_2D levels and mineral density and fracture occurrence was evaluated in children with idiopathic mineral density reductions, as compared to children with normal bone mass. An unexpected observation was that the 25OHD and 1,25OH_2D levels were not significantly different between the groups, and D vitamin deficiency with 25OHD level <20 ng/mL was present in children with lowered as well as with normal bone mass. A trend was observed for lower 25OHD levels in children with recurrent (3 and more) fractures and fractures of vertebras as compared to those with single fractures or without such symptoms. Based on the performed studies a conclusion was made that these results may indicate a relationship between the recurrent fractures and vitamin D deficiency. However, lack of dependencies between 25OHD and mineral density in the studied children may be the result of the common vitamin D deficiency in developmental age population in our geographical zone.

In the publication concerning the effect of nutritional status and body composition on the skeletal mineral density (**publication 5**), a relationship between anthropometric parameters, indicators of nutritional status, body composition assessed in densitometry assessment and bone mass indicators in the group of 327 patients was evaluated. The analysis was performed separately in the subgroup of children with the low, greater and normal body mass. A statistically important positive correlation was demonstrated between

the values of most anthropometric measurements, especially the height, body mass, fat-free body mass, and mineral density indicators; the most significant one in case of the total calcium content in bones, BMC and BMD as well as the volumetric bone mineral density (vBMD). It was also observed that the best nutritional status expressed by a higher BMI and a higher body mass index was associated with a higher mineral bone density, and the correlation was the most strongly expressed in children with body mass deficiency. It confirms the hypothesis that the nutritional status is an important bone mass modeling factor, especially in patients with body mass deficiency. Among relationships for Z-score, an important correlation was stated only in children with excess body mass in which fat-free body mass correlated with Spine Z-score, and thigh circumference with Total body Z-score. These measures were connected with the muscle mass, i.e. the greater the muscle mass was, the higher the Z-scores were. On the other hand, attention was drawn to a negative correlation of Z-scores with anthropometric parameters and indicators of nutritional status in children with body mass deficiency, which proves that lower mineral density occurred more often in the case of higher absolute values of anthropometric measurements. In this group of patients it was also observed that the higher the age of the child was, the lower Z-scores were. It may suggest that the negative effect of body mass deficiency on skeletal mineralization status increases with age, and is higher in older children as compared to the younger ones. This conclusion has also a practical meaning as, on the other hand, it means that in the process of treating bone mineral density disorders of the developmental age, body mass normalization plays a key role mainly in patients with body mass deficiency.

The purpose of the next work published in 2007 **(publication 6)** was to identify the relation between the occurrence of fractures in the developmental age and densitometric and ultrasound mineral density indicators, as well as to attempt to answer the question whether children with fractures have disorders within the scope of the studied parameters. Studies that simultaneously analyze densitometric and ultrasound assessment of bones as compared to fractures occurrence, were previously conducted mainly in adults. Single publications analyzing children with fractures concerned only the ultrasound assessment of phalanges, or densitometric assessment alone; until now, those two methods have not been combined in one study. The studies involved a group of 380 children of 5-18 years of age. To assess the mineral density a densitometric dual energy X-ray absorptiometry (DXA) was performed, using DPX device, in Total body and Spine projection. Moreover, a quantitative

ultrasound (QUS) of calcaneus was performed with Achilles Plus Solo device assessing Stiffness, SOS and BUA parameters. A positive correlation was stated at a high statistical significance level between DXA and ultrasound parameters; the highest correlation coefficients were demonstrated for Stiffness and BUA parameters as referred to mineral density in Total body projection. When analyzing the relation between skeletal calcification indicators and the occurrence of fractures, significantly lower mean values of Z-scores were stated in children with vertebral fractures (Z-scores were of: -1.48 in Total body projection and -2.75 in Spine projection). A trend for lower values of all parameters in the ultrasound assessment in this group of patients was also observed; however, the differences were not statistically significant. As for long bones fractures, no statistically significant differences were stated for mean values of all tested parameters of mineral balance between patients with and without fractures, also after considering a detailed analysis of individual age groups. Maybe it resulted from the fact that in this paper, mainly patients with fracture history were analyzed, and not with a new diagnosis of fractures, and moreover, no children with recurrent fractures were isolated which could affect the results of the presented work. Based on the conducted studies a conclusion was made that significant differences within the range of Z-scores in Total body and Spine projection between patients with vertebral fractures and without fractures allow using these parameters for the assessment of vertebral fracture risk in children. This conclusion had also important practical implications – it was determined that patients with lowered Z-score Spine values <= -2.0 should have lateral X-rays of the Th/L spine in order to detect vertebral fractures that are frequently asymptomatic, and to implement appropriate treatment. The next practical conclusion resulting from high correlation coefficients between the results of DXA and QUS, was the confirmation of diagnostic value of the quantitative ultrasound scan in the initial assessment of skeletal calcification status in children. It was stated that this testing method is relatively inexpensive, easy to perform and may be commonly used in the initial screening diagnosis of mineral density disorders, especially in children, mainly because it is safe as it does not use X-radiation. As there were no value differences of mean densitometric and ultrasound parameters between children with and without fractures of long bones, it was suspected that there is another, apart from mineral density, reason of fractures, including structure disorders of the protein part of the bone, that cannot be detected by densitometry or

ultrasound test. This hypothesis was further investigated in the next publication of this series (**publication 9**).

The following two works of the series (**publication 7 and 8**) involve a comprehensive assessment of 81 children with recurrent bone fractures (3 or more) and 31 in the comparison group. In the first work (**publication 7**) the relation between selected environmental factors and fracture occurrence was analyzed. Based on the thorough questionnaire surveys, it was determined that in the test group more children lived in cities as compared to the reference group. Among patients exposed to cigarette smoke at home, the mean number of fractures was greater than in the unexposed individuals. No relation between the mean time of sun exposure or number of children in the family and fracture occurrence was observed. In children with fractures, fathers had usually a vocational education level, in the reference group secondary technical education level was dominant; a negative correlation between father's education and the number of fractures was stated. Statistically significant positive dependence was observed between the number of physical education classes at school and mineral density Z-score, as well in Spine as in Total body projection. Moreover, a negative correlation between the time of physical activity at home and the number of fractures was demonstrated. Based on the performed studies, a conclusion was made that recurrent bone fractures in children may be affected by environmental factors – among the tested factors the strongest relation was demonstrated for the decreased physical activity at home, father's education level and exposure to cigarette smoke. Our studies confirmed the positive role of physical activity in prevention of fractures, mainly by affecting mineral density, because the higher the number of physical education classes at school was, the better the mineral density Z-score was; the lower the physical activity at home was, the more fractures there were, and additionally the number of fractures was greater in children living in the city than in children living in the country which is probably related to the lower daily physical activity of children living in cities. It should also be assumed that father's education and corresponding economic status of the family play an important role in the creation of a healthy lifestyle and appropriate eating habits among children. In our studies it was also demonstrated that children exposed to passive smoking had bone fractures more frequently. These observations were in compliance with the reports of authors of studies conducted in adults, who demonstrated that smoking cigarettes is an osteoporosis and femoral bone fracture risk factor in adults, and that the risk

increases with the number of smoked cigarettes. To sum up, clinical risk factors are an important element that has to be considered when estimating fracture risk in the patient, irrespective of bone mineral density value. It seems that teaching principles of healthy lifestyle and eating habits and knowledge of child's physical activity as well as eating needs in the period of intensive growth may be the basis for the prevention of bone fractures in adolescents. Results of these observations may be practically used to determine recommendations concerning prophylaxis of the recurrent fractures in the developmental age.

In the second work (**publication 8**), studies regarding the causes of recurrent fractures were continued by analyzing mineral density and bone metabolism indicators in the same patients with 3 or more low-energy fractures. In 64% of patients (52/81) in the DXA test a lowering of bone mineral density was stated. 28% of patients (23/82) were diagnosed with osteoporosis according to ISCD criteria, because fractures were accompanied by mineral density measure Z-score <= -2.0. Mean values of Z-score for densitometric test parameters, both in Total body and in Spine program, as well as of Z-score for ultrasound Stiffness and SOS were statistically lower in children with recurrent fractures as compared to children from the reference group. Among children with fractures, increased frequency of hypercalciuria, hypocalciuria, hypermagnesuria, hyperphosphaturia and lowered vitamin D liver metabolite level was observed. Moreover, bone metabolism disorders were stated – increased NTx level, increased activity of alkaline phosphatase bone isoenzyme and increased osteocalcin level, which proves the increased bone turnover in these patients. In this group, significant, negative relationships were also stated between biochemical bone formation and bone resorption indicators and the bone mass, and also lower DXA Z-score values in children with higher calciuria. Based on the conducted studies, a conclusion was made that lowering skeletal mineral density was the most frequently occurring (because stated in 2/3 of patients) factor predisposing to recurrent fractures in children. Moreover, increased bone turnover and abnormalities in calcium and phosphorous balance indicate bone metabolism disorders as another factor promoting fractures. Therefore, a practical implementation conclusion was made – a recommendation that repeating bone fractures in the developmental age are an indication for quantitative assessment of bone mass and calcium and phosphorous balance indicators, as well as for bone turnover markers in order to exclude disorders within this scope, and to determine further treatment.

In the next work published in 2011 (**publication 9**) a search for ethiopathogenetic factors of recurrent fractures was continued using qualitative analysis of serum proteins with a proteomic method. The reason to undertake such studies were the conclusions from the **publication 6** previously presented in this series, in which an assumption was made that in children with bone fractures and normal bone mineral density there may be disorders of the structure of the protein part of the bone. These studies were conducted in cooperation with Maria Świątkowska, MD, PhD and her collaborators form the Institute of Molecular and Medical Biophysics of the Medical University of Lodz. This analysis included patients with recurrent low-energy bone fractures in which the available research methods did not state skeletal calcification disorders, and thus a supposition of protein part of the bone disorder was made. Moreover, patients with osteogenesis imperfecta, i.e. a genetic disease usually related to a qualitative and/or qualitative defect of collagen, were studied. In order to analyze serum protein profile, the tested samples were divided using two-dimensional electrophoresis with Amersham Biosciences Ettan DALT II device. Next, proteins with the expression changed as compared to control group samples (after previous removal from the gel) underwent analysis of amino acid sequence using mass spectrometry (Waters Q–Tof Premier™ API mass spectrometer with quadrupole-time of flight hybrid analyzer) in order to identify them. In the studied group of patients, proteins were detected whose expression was changed as compared to the control, and also such proteins occurred only in sick individuals. Among the tested proteins the most frequently repeating peptides were those corresponding to alpha and beta chains of human haptoglobin in all six children with severe osteogenesis imperfecta. In one child with osteogenesis imperfecta, peptides corresponding to human alpha-1-acid glycoprotein were also discovered. It turned out that results of these studies corresponded with the results of the first work of the presented publication series because haptoglobin and alpha-1-acid glycoprotein belong to acute-phase proteins and their production in liver increases in inflammatory states, and is directly stimulated by proinflammatory cytokines such as IL-1, IL-6, whose relation with bone metabolic disorders was the subject of the earlier discussed studies (**publication 1**). It is possible that in the patients that we studied, an increased haptoglobin expression was accompanied by the increase of other proinflammatory factors, thus increasing bone resorption and the risk of fracture. It is also probable that hepatoglobin directly affects bone resorption stimulation because such an activity was demonstrated in *in vitro* studies, and that it indirectly affects

bone tissue by controlling the levels of iron that is essential as a cofactor of enzymes responsible for collagen and bone matrix synthesis, and as a cofactor of 25-hydroxylasis – enzyme involved in vitamin D activation and consequently intestinal calcium absorption. An interesting inflammatory state-related protein is human serum amyloid P discovered in a patient with osteogenesis imperfecta. It belongs to pentraxin family and shows 51% homology with C-reactive protein which is a classic acute-phase protein. It is detected in amyloid deposits and plays a role in immunity mechanisms. However it has not been yet determined what is its contribution to bone metabolism; this issue requires further scientific research. The next protein with an increased expression in three of our patients was transthyretin – it was detected in 2 children with recurrent fractures of an unknown etiology, and in one child with osteogenesis imperfecta. It is a serum transport protein with a structure that was discovered a long time ago and that remains unchanged, but its function is constantly being updated. It was called prealbumin, and then thyroid hormone-binding protein. It is essential for growth and development processes, especially of the central nervous system. Innate or acquired transthyretin defects result in amyloidose, they may also cause hyperthyroxinemia. Inversely to the previously discussed proteins, its level decreases in the inflammatory state, so pathogenesis of fractures in these children does not seem to be related with the inflammation. Maybe it is related with thyroid hormone disorders because literature data indicate that both their excess and deficiency may cause bone metabolism disorders. The last protein with increased expression in children with fractures that we studied was aplolipoprotein A-I in 2 patients. It is a protein that takes part in reverse cholesterol transport to liver, as an element of HDL lipoprotein. It is a cofactor of lecithin-cholesterol acyltransferase (LCAT) and therefore increases cholesterol elimination from tissues. Its defect may cause a number of unfavorable changes in lipid balance, especially it may increase atherogenesis. In the inflammatory state aplolipoprotein A-I level decreases which is most probably related to the increased production of the previously discussed haptoglobin which can bind it and block access to tissues and LCAT. The direct relation between aplolipoprotein A-I and fractures has not yet been determined. Perhaps, an important element is osteoprotegerin system discussed in **publication 3**, since studies conducted in post-menopausal women show that the increased aplolipoprotein A-I level was associated not only with the lower sclerosis risk but also with the reduction of osteoprotegerin level which is an important osteoclastogenesis inhibitory factor. It seems

that this dependence may also intensively reflect close relations between bone metabolism and lipid balance of the body that have been studied in the last years, that were seen from a new angle because of the discovery of osteogenesis regulating Wnt/β-catenin pathway. Its activation via LRP5 receptor inhibits differentiation of the mezanchymal stem cells toward adipocytes, at the same time stimulating differentiation and proliferation of osteoblasts and bone mineralization. Based on the pilot proteomic analysis, a conclusion was made that an increased expression of some proteins being indicators of the acute phase suggests a participation of the inflammatory component in the severe osteogenesis imperfecta; however, it was not present in children with normal bone mass and recurrent fractures of an unknown etiology. Further studies and follow-up of patients with an increased expression of transthyretin and apolipoprotein A-I are necessary to explain reasons and possible relation of these proteins with recurrent bone fractures. This problem requires further research; as these were pilot studies, they require a follow-up in bigger groups of patients.

The series of publications ends with a casuistic paper (**publication 10**) in which a patient with recurrent low-energy bone fractures in the course of Angelman syndrome (AS) was discussed. It is a genetic group of symptoms including severe psychomotor retardation and speech impairment with concomitant seizures and typical dysmorphic features, and also several skeletal symptoms; however, no fractures have been described until now. It is usually caused my microdeletion in 15q11-13 region resulting in the loss of *UBE3A* gene function. The aim of the work was to present new possible skeletal symptoms in Angelman syndrome based on a description of an 8-year-old girl with the confirmed 15q11;12 deletion and recurrent low-energy bone fractures. It was the first presentation in the world of fractures as bone symptoms in this group of patients and arose great interest among readers. It is known from the literature that the most common bone symptom in children with AS is microcephaly and skull disorders such as occipital flatness, prominent jaw, abnormal tooth development and scoliosis. Several authors describe other skeletal symptoms such as brachydactyly and deformities of long bones of extremities. During the last years a possible reduction of bone mineral density in about 40% of patients was also pointed out, which usually was translated by calcium and phosphorous balance disorders as a result of chronic anti-seizure treatment. It is known that low bone mass is an important low-energy fracture risk factor; however, in the discussed patient no mineral density was diagnosed. Despite a chronic anti-seizure treatment, calcium and phosphorous balance

indicators were also within the limits of normal, including vitamin D liver metabolite level, probably because of the regular supplementation with calcium and vitamin D. Nevertheless, between 6 and 8 years of age, she had six low-energy fractures which was the reason for the extended diagnostics of bone metabolism disorders. The examinations showed a faster bone resorption with low level of osteoclastogenesis inhibitor – osteoprotegerine, and also reduced parameters of quantitative ultrasound indicators, which confirmed a lower quality of bones in this patient and greater predisposition to fractures. Until now no such disorders have been described in patients with AS. A question arose whether it was an effect of the disease or of valproic acid and clonazepam treatment. It was demonstrated that chronic anti-seizure treatment may cause falls as well as fractures in post-menopausal women, although no such dependencies have been described until now. Anti-seizure treatment, especially with the group of medications inducing liver enzymes, has usually a negative effect on the skeleton because of calcium and phosphorous balance disorders and 25OHD level as well as bone mineral density lowering; however, such abnormalities have not been demonstrated in the girl presented in the elaboration. Instead, it was demonstrated that she had increased bone turnover indicators which is listed in the literature as negative effect of anti-seizure treatment. Nevertheless, until now no recurrent low-energy fractures have been described in children receiving anti-seizure treatment, not only in AS but also in epilepsy with another etiology. Therefore, perhaps in the etiology of recurrent fractures in the presented patient a genetic factor lying at the origin of AS could have a certain meaning. It was proved that *UBE3A* gene which plays an important role in the development of phenotypic features of this syndrome encodes E6-AP protein. It appeared that this protein has two independent functions: ubiquitin protein ligase and nuclear hormone receptor cofactor. Owing to the latter function, E6-AP can modify the biological response of the body i.a. to circulating steroid hormones and vitamin D, and these, as it is commonly known, play an important role in skeletal development. It is thus probable that *UBE3A*/E6-AP gene function disorders affect bone development and the process of bone formation and resorption in patients with AS, and also the occurrence of fractures, like in the presented patient. Moreover, perhaps bone fractures in these patients are also promoted by the excessive body mass and abnormal movement patterns with muscle tension disorders that were also diagnosed in the discussed girl. Based on the above elaboration a conclusion was made that a patient with AS may have recurrent bone fractures that have not been

described until now in this syndrome. In the etiology of these fractures the following should be considered: possible negative effect of the chronic anti-seizure treatment, genetic defect being the cause of AS, and also movement and somatoform disorders. The practical aspect of the presented elaboration is the recommendation to perform a comprehensive assessment of mineral balance, bone metabolism and calcium and phosphorous balance indicators in a child with the diagnosed Angelman syndrome.

SUMMARY

Main exploratory conclusions

1. Molecules such as IL-6, IL-1, IGF-I and elements of the system OPG/RANK/RANKL seem to be important factors involved in etiopathogenesis of idiopathic bone mineral density disorders in children (**publication 1,2,3**).
2. Nutritional status and body composition as well as vitamin D supply are important modifiers of skeletal bone mineral density and its susceptibility to fractures, and the negative effect of body mass deficiency on bone status increases with age and is more important in older children than in the younger ones (**publication 4,5,8**).
3. Important differences within Z-scores in Total body and Spine projection between patients with vertebral fractures and without fractures support the use of these parameters for the assessment of vertebral fracture risk in children (**publication 6**)
4. High correlation coefficients between DXA and QUS tests results confirm diagnostic usefulness of the quantitative ultrasound in the initial, screening, non-invasive assessment of skeletal calcification status (**publication 6**)
5. Environmental factors are an important element which has to be taken into consideration when estimating the risk of fracture in a patient, irrespectively of bone mineral density (**publication 7**)
6. Lowering of mineral density is the most frequent (because stated in 2/3 of patients) factor that predisposes children to recurrent bone fractures (**publication 8**)
7. Bone metabolism disorders expressed as increased bone turnover and abnormalities within the scope of calcium and phosphorous balance indicators are factors that promote recurrent bone fractures (**publication 8**)
8. Increased blood expression of acute phase proteins such as haptoglobin and alpha-1-

acid glycoprotein in children with severe osteogenesis imperfecta suggests a participation of inflammatory component in the course of this disease. However, it was not present in children with recurrent fractures of unknown etiology. Further studies and follow-up of patients with increased transthyretin and apolipoprotein A-I expression are necessary in order to explain its causes and a possible relation of these proteins with recurrent bone fractures (**publication 9**)

9. Recurrent fractures may occur as one of bone symptoms in patients with Angelman syndrome (**publication 10**)
10. Bone fractures may also occur in children with no disorders stated in the available diagnostic tests of skeletal calcification status and mineral balance, further follow-up of these patients and searching for other casual factors is thus recommended (**publication 6, 8, 9, 10**)

Practical conclusions

1. In patients with bone mineral density disorders and/or recurrent fractures chronic latent inflammatory state needs to be excluded (**publication 1, 9**)
2. Perhaps in the future, the use of molecules interfering in osteoprotegerin/RANK/RANKL system or GH/IGF-1 axis, or other agents with positive effect on bone metabolism, for treatment of severe forms of osteoporosis will be justified (**publication 2, 3**)
3. In the process of treatment of bone mineral density disorders in the developmental age as well as in prophylaxis of recurrent fractures, the most fundamental factor is body mass normalization, especially in patients with body mass deficiency, as well as vitamin D supply (**publication 4, 5**)
4. Patients with lowered Z-score Spine values <= -2.0 should have lateral X-rays of the Th/L spine in order to detect vertebral fractures that are frequently asymptomatic, and to implement appropriate treatment (**publication 6**)
5. Quantitative ultrasound (QUS) is a useful diagnostic tool in the initial, screening, non-invasive assessment of skeletal quality (**publication 6**)
6. Teaching principles of healthy lifestyle and eating habits should be the basis for the prevention of bone fractures in children and adolescents. The knowledge of child's physical activity and eating needs in the period of the intensive growth should be

practically used to determine recommendations concerning prophylaxis of the recurrent fractures in this period of life (**publication 7**)

7. Repeating bone fractures in the developmental age are an indication for quantitative assessment of bone mass and calcium and phosphorous balance indicators as well as for bone turnover markers in order to exclude disorders within this scope, and to determine further treatment (**publication 8**)
8. Angelman syndrome diagnosis should be an indication for comprehensive assessment of mineral balance, bone metabolism and calcium and phosphorous balance indicators (**publication 10**)

5. Discussion of other research and scientific/artistic achievements

a) Short bibliometric analysis of academic achievement

Total number of full-version publications is **50**, including:

- **45** original and casuistic papers (10 works published with IF, including 4 in reviewed supplements)
- **5** review works

Total number of **impact factor (IF)** points for the works without supplements is **16,257** (by year of publication **13,965**), of which **12,030** (by year of publication 10,962) falls to first-author original and casuistic works.

Total number of **MNiSW** points for the works is **356** (by year of publication 279), of which **140** (by year of publication 127) falls to first-author original and casuistic works.

Additionally 4 original papers in reviewed supplements with **IF 2,400** (by year of publication 2,022), **60** MNiSW points (by year of publication 40).

Total IF 18,657 (by year of publication 15,987), MNiSW 416 (by year of publication 319).

Additionally participation in multicenter work published with **IF 4,319** (participant listed in appendix).

Additionally co-author of **3** monographs and **1** textbook chapter and **108** scientific meeting communications, including **37** international conference summaries and **71** national conference summaries.

A total of 15 citations, h-index of 2 (source: ISI Web of Science Core Collection)

A total of 33 citations, h-index of 4 (source: ISI Web of Science All Databases)

A total of 53 citations, h-index of 4 (source: Scopus)

A total of 64 citations (source: Google Scholar)

A full list o publications and bibliometric analysis prepared by the Main Library of the Medical University of Lodz are attached separately (Appendix No. 4 and 8).

b) Other directions of conducted studies

1. **Studies on genetic causes of recurrent bone fractures**. They are the follow-up of studies presented in the series of publications reported at present as an achievement. They were conducted mainly within the scope of MNSiW/NCN own grant "Znaczenie wybranych składowych szlaku WNT/β-katenina oraz zmienności genu kolagenu typu I w etiologii nawracających złamań kości u dzieci" ["Significance of selected elements of WNT/β-catenin pathway and variability of type I collagen gene in etiology of recurrent bone fractures in children"] that I was the manager of. In this project *COL1A1, LRP5, DKK1* genes were studied in children with recurrent fractures in idiopathic osteoporosis and osteogenesis imperfecta. A relationship between the detected abnormalities within these genes and mineral balance indicators, bone metabolism as well as selected elements of WNT/β-catenin pathway was studied. The results of these studies have been presented at national and international conferences, full-version papers were sent for publication. Until now have been published as abstracts, including: **Rusińska A.**, Borowiec M., Młynarski W., Antosik K., Michałus I., Chlebna-Sokół D. Novel LRP5 mutation in a 14-year-old boy with recurrent fractures and low bone mass. *European Congress on Osteoporosis and Osteoarthritis (ESCEO13-IOF) Rome, Italy, 17-20 April 2013. Osteoporosis International 2013, 24 (Supplement 1), s295;* **Rusińska A.**, Borowiec M., Młynarski W., Antosik K., Michałus I., Golec J., Chlebna-Sokół D. LRP5 mutation in two children with recurrent fractures and low bone mass. *10th Baltic Bone Conference, Poznań, 6-8 czerwca 2013. Abstract Book, s.6;* **Rusińska A.**, Borowiec M., Młynarski W., Antosik K., Michałus I., Golec J., Chlebna-Sokół D. Recurrent fractures and low bone mass in a patient with new mutation of LRP5 gene. *6th International Conference on Children's Bone Health and European Calcified Tissue Society, Rotterdam, The Nederland, 22-25 June 2013, Abstract Book, s.10;* **Rusińska A.**, Borowiec M., Młynarski W., Antosik K., Michałus I., Golec J., Chlebna-Sokół D. Nawracające złamania u dwojga dzieci z mutacją

genu LRP5 [Recurrent fractures in two children with LRP5 mutation]. *5th Central European Congress on Osteoporosis and Osteoarthritis, Kraków 20-21 września 2013. Ortopedia Traumatologia Rehabilitacja 2013, 15 (Supplement 2), 127-128*

- **Studies on genetic causes and molecular diagnostics of osteogenesis imperfecta**. They were reflected in the invitation to the meeting of the European Molecular Quality Genetics Network (EMQN) working group for cooperation in terms of setting guidelines for the molecular diagnostics of osteogenesis imperfecta, later published as "EMQN Best Practice Guidelines for the Laboratory Diagnosis of Osteogenesis Imperfecta" in *European Journal of Human Genetics 2012, 20, 11-19;* active participation in Best Practice Meeting on 28-29 June 2010 in Amsterdam, the Netherlands. In the next year, international cooperation to create guidelines referring to genetic study performance and their clinical utility in patients with osteogenesis imperfecta, and then publishing of work results: van Dijk F.S., Dalgleish R., Malfait F., Magueri A., **Rusinska A.,** Semler O., Symoens S., Pals G.: Clinical utility gene card for: osteogenesis imperfecta. *European Journal of Human Genetics 2012, e1-e4; doi: 10.1038/ejhg.2012.210.* These recommendations were then partially presented, among others, in the form of an oral presentation at the Congress in Krakow: **Rusińska A**. Najnowsze osiągnięcia w diagnostyce molekularnej i leczeniu wrodzonej łamliwości kości u dzieci [Recent advances in the molecular diagnostics and treatment of osteogenesis imperfecta in children]. *5th Central European Congress on Osteoporosis and Osteoarthritis, Kraków 20-21 września 2013. Ortopedia Traumatologia Rehabilitacja 2013, 15 (Supplement 2), 90-91*
- **Studies on phenotypic variability and heterogeneity of osteogenesis imperfecta symptoms.** Studies are conducted based on the comparison of symptoms and clinical description of about 100 patients with this rare disease, who remain under the supervision of our Clinic. The results of these studies that have been partly published are papers of: Michałus I., Jakubowska-Pietkiewicz E., **Rusińska A.**, Chlebna-Sokół D.: Wrodzona łamliwość kości jako stan zagrożenia życia noworodka [Osteogenesis imperfecta as a life-threatening condition of a newborn]. *Postępy Neonatologii, 2012, 2 (18), 52-56;* Jakubowska-Pietkiewicz E., **Rusińska A.,** Michałus I., Chlebna-Sokół D.: Wrodzona łamliwość kości typu III u noworodków – obserwacje własne [Osteogenesis

imperfecta type III in newborns – own experience]. *Przegląd Lekarski, 2012, 69 (3), 1-4;* **Rusińska A.**, Jakubowska-Pietkiewicz E., Michałus I., Kurnatowska O., Rychłowska E., Chlebna-Sokół D.: Heterogenność objawów klinicznych wrodzonej łamliwości kości – trudności diagnostyczne na podstawie doświadczeń własnych [Clinical heterogeneity of osteogenesis imperfecta: diagnostic difficulties on the basis of our own experience]. *Ortopedia Traumatologia Rehabilitacja 2013, 15 (Supplement 2), 126-127;* Jakubowska-Pietkiewicz E, Michałus I., **Rusińska A.**, Chlebna-Sokół D. Osteogenesis imperfecta type II and III – problem of early diagnosis and perinatology care. *Archives of Perinatal Medicine 2014, 2(3), 124-128*

- **Evaluation of effectiveness and safety of osteoporosis and osteogenesis imperfecta treatment in children**. The object of these studies was to assess pharmacological preparations of calcium and vitamin D, as well as biophosphonates used in the most severe cases. Results of these analyses were published in papers of: Loba-Jakubowska E., Chlebna-Sokół D., **Rusińska A.**: Zastosowanie alendronianu sodu w leczeniu osteoporozy u dzieci - doświadczenia własne [The use of alendronate sodium in treatment of osteoporosis in children – own experience]. *Postępy Osteoartrologii 2003,14 (2), 45-51;* Chlebna-Sokół D., Błaszczyk A., **Rusińska A.**, Loba-Jakubowska E.: Leczenie osteoporozy i osteopenii u dzieci – doświadczenia własne [Treatment of osteoporosis and osteopenia in children-own experience]. *Przegląd Lekarski 2003, 1, 5-11;* Chlebna-Sokół D., Jakubowska-Pietkiewicz E., **Rusińska A.**, Kiliańska A., Michałus I., Frasunkiewicz J., Kulińska-Szukalska K., Romanowska-Pietrasiak B.: Analiza skuteczności, tolerancji i bezpieczeństwa leczenia laktoglukonianem wapnia osteopenii i osteoporozy w wieku rozwojowym. Część 1. Ocena kliniczna i densytometryczna [Efficacy, tolerance and safety analysis of calcium lactate gluconate in treatmemt of osteopenia and osteoporisis in the developmental age. Part 1. Clinical and densitrometric assessment]. *Przegląd Pediatryczny 2007, 37, 2: 188-194;* Jakubowska-Pietkiewicz E., Chlebna-Sokół D., **Rusińska A.**, Kiliańska A., Michałus I., Frasunkiewicz J., Kulińska-Szukalska K., Romanowska-Pietrasiak B.: Analiza skuteczności, tolerancji i bezpieczeństwa leczenia laktoglukonianem wapnia osteopenii i osteoporozy w wieku rozwojowym. Część 2. Ocena gospodarki wapniowo-fosforanowej i markerów obrotu kostnego [Efficacy, tolerance and safety analysis of calcium lactate gluconate in treatmemt of osteopenia and osteoporisis in the developmental age. Part 2. Calcium and phosphorous balance and bone turnover

markers assessment]. *Przegląd Pediatryczny 2007, 37, 3: 273-278;* **Rusińska A.,** Chlebna-Sokół D., Karalus J.: Idiopathic osteoporosis in children – an example of severe course of the disease, diagnostic difficulties and effective treatment. *Endokrynologia Pediatryczna 2009, 8, 4(29), 95-100;* **Rusińska A.,** Jakubowska-Pietkiewicz E., Chlebna-Sokół D.: Evaluation of the effects of sodium pamidronate therapy in children with osteogenesis imperfecta. *11th International Conference on Osteogenesis Imperfecta, Dubrovnik, Croatia 2-5 October 2011. Abstract Book, p. 113.*

- **Evaluation of mineral balance and bone metabolism disorders in children with rare diseases.** These studies involve patients with different rare diseases, such as fibrous dysplasia, neurofibromatosis, artrogriposis, hypophosphatemic rickets, vitamin D-resistant rickets, cleidocranial dysplasia, spondylometaphyseal dysplasia, achondroplasia, hypochondroplasia, Marfan syndrome. Results of these studies were published among others in the following papers: **Rusińska A.**, Chlebna-Sokół D., Loba-Jakubowska E.: Wielokrotne złamania kości u chorego na dysplazję włóknistą typu Jaffego i Lichtensteina – opis przypadku [Multiple bone fractures in a patient with Jaffe and Lichtenstein fibrous dysplasia – case study]. *Postępy Osteoartrologii 2005, 16 (1-4): 27-32;* Jakubowska-Pietkiewicz E., **Rusińska A.**, Kulińska-Szukalska K., Chlebna-Sokół D.: Analiza zaburzeń mineralizacji szkieletu u dzieci w przebiegu wybranych chorób kości o podłożu genetycznym – obserwacje własne [Skeletal mineralization disorders in children in the course of selected bone diseases with genetic background]. *Przegląd Pediatryczny 2009, 39, 3, 168-171;* Fijałkowski B., **Rusińska A.**, Chlebna-Sokół D.: Powikłania ze strony układu kostnego u dwojga dzieci z neurofibromatozą [Bone system complications in two children with neurofibromatosis]. Standardy Medyczne Pediatria 2014, 11, 778-781; **Rusińska A.,** Golec J., Michałus I., Chlebna-Sokół D.: Artrogrypoza u trojga noworodków – opis przypadku [Arthrogryposis in three newborns – case study]. *Ortopedia Traumatologia Rehabilitacja 2011, vol.13, Supplement 1, 140-141.*
- **Population studies in healthy children evaluating the effect of calcium and vitamin D intake on skeletal mineralization status in the developmental age.** They refer to the subject of an achievement presented in the series of presentations, i.e. causes of fractures and mineral density disorders in children. However, they were not included in the discussed series of papers as they did not refer to sick patients with diagnosed disorders but to the healthy population. These studies were conducted in a group of 643

schoolchildren form primary schools in Łódź within the scope of the grant of the President of Łódź entitled: "Ocena czynników ryzyka osteoporozy u dzieci łódzkich w wieku 9-13 lat" ["Assessment of osteoporosis risk factors in children from Łódź between 9 and 13 years of age"]. A diet was assessed by writing down a 3-day eating programme and quantitaive utrasound scan of calcaneus was performed to assess mineralization status and bone structure. Results of studies conducted within this scope were published in the paper of the following authors: **Rusińska A.,** Michałus I., Karalus J., Golec J., Chlebna-Sokół D. Spożycie witaminy D i wapnia a jakość kości dzieci łódzkich w wieku 9-13 lat [Vitamin D and calcium intake and bone quality in children from Łódź between 9 and 13 years of age]. *Pediatric Endocrinology, Diabetes and Metabolism 2011, 17, 2, 82-87.* Results of other studies conducted within this project as well as prophylactic recommendations were published in the monograph: Chlebna-Sokół D., Kiliańska A., Kulińska-Szukalska K., Frasunkiewicz J., Michałus J., **Rusińska A.:** Zdrowe kości. Uwarunkowania rozwoju masy kostnej u dzieci łódzkich w wieku szkolnym [Healthy bone. Causation of bone mass development in school children from Łódź]. Monograph – collective work edited by Danuta Chlebna-Sokół. *Wyd. PPH exall. sp. o.o., Łódź 2007, p.1-79*

- **Population studies evaluating health status and somatic development of nursery-age children from Łódź.** The study involved a group of 896 children at the age between 6 months and 5 years. Results of this analysis were published in the paper of the following authors: Chlebna-Sokół D., Loba-Jakubowska E., **Rusińska A.**: Rozwój somatyczny dzieci łódzkich uczęszczających do żłobków [Somatic development of nursery children from Łódź]. *Zdrowie Publiczne 2003, 113 (1/2), 48-52* and in monograph: Chlebna-Sokół D., Haładaj K., Ligenza I., Loba-Jakubowska E., **Rusińska A.,** Rychłowska E., Wlazłowski J.: Dziecko Łódzkie. Stan zdrowia i rozwój fizyczny dzieci uczęszczających do żłobków [Children of Łódź. Health status and physical development of nursery children]. Scientific editor of the monograph: Danuta Chlebna-Sokół. *Wyd. Ankal, Łódź 2001, p. 1-103*
- **Bone mineralization disturbances diagnosis in the developmental age:** bone densitometry and quantitative ultrasound assessments in children, and their interpretation, problems with mineral density assessment in small children, bone turnover markers in the diagnosis of bone metabolism disorders in children. Results of these studies were published among others in the following papers: Chlebna-Sokół D.,

Rusińska A., Błaszczyk A., Lewiński A., Loba-Jakubowska E.: Ocena porównawcza ilościowych badań kości u dzieci metodą DEXA i ultradźwiękową [Comparative evaluation of quantitative bone test using DEXA and ultrasound methods]. *Przegląd Pediatryczny 2003, 33, 1, 54-59;* **Rusińska A.**, Chlebna-Sokół D., Jakubowska-Pietkiewicz E., Golec J. The usefulness of quantitative ultrasound method in the assessment of bone mineralization disturbances in children. *Clinical Experimental Medical Letters 2009, 50(4), 215-219;* Jakubowska-Pietkiewicz E., **Rusińska A.**, Michałus I., Chlebna-Sokół D.: Problemy z oceną gęstości mineralnej kości u małych dzieci – doświadczenia zespołu kliniki [Problems with bone mineral density assessment in children under 5 years of age - experience of our department]. *Przegląd Pediatryczny 2012, 42, 4, 183-187*

- **Studies on secondary disorders of bone mineralization in children** in the course of i.a. nephrotic syndrome, kidney stones, lymphoproliferative diseases, inflammatory diseases of the digestive tract and absorption disorders. Results of these studies were published among others in the following papers: Chlebna-Sokół D., Kozłowski J., Loba-Jakubowska E., Spadło A., **Rusińska A.**, Bodalski J.: Ocena stanu mineralizacji kośćca i gospodarki wapniowo-fosforanowej u dzieci z zespołem nerczycowym [Evaluation of bone mineralization status and calcium and phosphorous balance in children with nephrotic syndrome]. *Polski Merkuriusz Lekarski, 2000, 46, 228-30;* Chlebna-Sokół D., Loba-Jakubowska E., **Rusińska A.**, Lorenc R.S., Lewiński A., Bodalski J.: Abnormalities in bone metabolism in children with long-term glucocorticoid treatment. *Endokrynologia Polska - Polish Journal of Endocrinology 2002, 53, 159-170;* **Rusińska A.**, Chlebna-Sokół D., Loba-Jakubowska E., Olszowiec-Chlebna M.: Rozwój somatyczny oraz gęstość mineralna kości u dzieci leczonych glikokortykosteroidami wziewnymi z powodu astmy oskrzelowej [Somatic development and bone mineral density in children treated with inhaled glicocorticosteroids because of asthma]. *Acta Pneumonologica et Allergologica Pediatrica 2005, 9, 1: 16-20*
- **Generalized infections**. Studies on etiology, clinical course and treatment of generalized infections, including sepsis and meningitis in children. Results of these studies were published among others in the following papers: Chlebna-Sokół D., Sikora J.P., Sabanty W., Loba-Jakubowska E., Bujnowski T., **Rusińska A.**: Etiologia i przebieg kliniczny posocznicy u dzieci przedwcześnie urodzonych [Etiology and clinical course of sepsis in premature children]. *Pediatria Polska, 2000, 1, 57-62;* Chlebna-Sokół D., Sikora J.P.,

Bujnowski T., Sabanty W., **Rusińska A.**, Loba-Jakubowska E.: Przebieg kliniczny i czynniki etiologiczne posocznicy u dzieci w różnych grupach wieku [Clinical course and etilogical factors in children from different age groups]. *Przegląd Epidemiologiczny 2000, 54, 351-6;* Chlebna-Sokół D., Loba-Jakubowska E., Sabanty W., **Rusińska A.**, Sikora J.P.: Posocznice u dzieci wywołane przez bakterie Gram–ujemne – obserwacje własne [Sepsis in children caused by Gram-negative bacteria – own observation]. *Wiadomości Lekarskie 2001, 54, 5-6;* **Rusińska A.**, Fijałkowski B., Chlebna-Sokół D.: Wewnątrzczaszkowe powikłania zapalne i zakrzepowe jako następstwo zapalenia ucha środkowego o etiologii Streptococcus pneumoniae – opis przypadku [Intracranial inflammatory and thrombotic complications as a consequence of otitis media caused by Streptococcus pneumoniae – case study]. *Przegląd Pediatryczny 2011, 41 (3), 128-132*

c) Participation in research projects

- **2010 - 2013** MNiSW/NCN own grant No. N407 060938 „Znaczenie wybranych składowych szlaku WNT/β-katenina oraz zmienności genu kolagenu typu I w etiologii nawracających złamań kości u dzieci" ["Significance of selected elements of WNT/β-catenin pathway and variability of type I collagen gene in etiology of recurrent bone fractures in children"], **principle investigator and manager of the project**
- **2007 - 2010** MNiSW own grant No. N407 063 32/2713 "Badania dotyczące czynników ryzyka oraz wskaźników biochemicznych i densytometrycznych metabolizmu kostnego u dzieci ze złamaniami kości" [„Studies on risk factors and biochemical and densitometric indicators of bone metabolism in children with fractures"], **principle investigator**
- **2007 – 2009** own research financed by the Medical University of Lodz from the funds granted by MNiSW, No. of project 502 11 599 "Analiza jakościowa białek osocza u dzieci z wielokrotnymi złamaniami kości – badania pilotażowe" ["Qualitative analysis of serum proteins in children with multiple fractures – pilot study"], **principle investigator and manager of the project**
- **2004 - 2006** grant of the President of Łódź No. G-24/2005 "Ocena czynników ryzyka osteoporozy u dzieci łódzkich w wieku 9-13 lat" ["Assessment of risk factors for osteoporosis in children aged 9-13 years in Lodz"], **investigator**

- **2004 - 2006** own research project financed by the Medical University of Lodz from the funds granted by MNiSW, No. of project 502-11-211 „Uwarunkowania i przebieg kliniczny złamań kości u dzieci" ["Causes and clinical course of bone fractures in children"], **investigator**
- **2004 - 2006** Research project in cooperation with Polfa-Łódź „Analiza skuteczności, tolerancji i bezpieczeństwa leczenia laktoglukonianem wapnia osteopenii i osteoporozy w wieku rozwojowym" ["Efficacy, tolerance and safety analysis of calcium lactate gluconate in treatmemt of osteopenia and osteoporisis in the developmental age"], **investigator**
- **2003 - 2006** KBN own grant No. 3 P05E 05624 „Badania nad etiopatogenezą samoistnej osteopenii i osteoporozy w wieku rozwojowym" ["Study on etiopathogenesis of idiopathic osteopenia and osteoporosis in the developmental age"], **principle investigator**
- **1999 - 2001** own research project financed by the Medical University of Lodz from the funds granted by MNiSW, No. of project 502-11-578 "Ocena udziału wybranych cytokin w etioatogenezie samoistnej osteoporozy i osteopenii u dzieci i młodzieży" ["Assessment of selected cytokines' participation in etiopathogenesis of idiopathic osteoporosis and osteopenia in children and adolescents"], **investigator**
- **1999 – 2001** KBN own grant No. 4 P05E 03816 „Diagnostyka i leczenie osteoporozy w wieku rozwojowym" [„Diagnosis and treatment of osteoporosis in the developmental age"], **investigator**

d) Awards and distinctions

- **2014** – 1st grade scientific award of the Rector of the Medical University of Lodz for the series of publications entitled: "Badania nad uwarunkowaniami nawracających złamań kości u dzieci" ["Studies on causation of recurrent bone fractures in children"] with the total IF of 10,057
- **2013** – distinction for the paper entitled: „*LRP5* mutation in two children with recurrent fractures and low bone mass"; authors: **Rusińska A.**, Borowiec M., Młynarski W., Antosik K., Michałus I., Golec J., Chlebna-Sokół D. presented at 10th Baltic Bone and Cartilage Conference in Poznań
- **2013** – nomination for Professor Zbigniew Religa memorial competition title of "Wyjątkowy Lekarz" [„Exceptional Doctor"] organized by the foundation: Fundacja Dzieciom „Zdążyć z Pomocą" [Foundation for Children "Help on Time"] in Warsaw

- **2010** – distinction for the paper entitled: „Zastosowanie pamidronianu w leczeniu wrodzonej łamliwości kości u dzieci" ["Use of pamidronate in treatment of osteogenesis imperfecta in children"]; authors: Jakubowska-Pietkiewicz E., **Rusińska A.,** Michałus I., Golec J., Chlebna-Sokół D. presented at the 21st Multidisciplinary Osteoporotic Forum in Warsaw.
- **2008** – distinction in the competition "Paper of the year" – Edition 2008 of the journal Ortopedia, Traumatologia, Rehabilitacja for co-authoring the paper entitled: "Ocena gęstości mineralnej i metabolizmu kostnego u dzieci z wielokrotnymi złamaniami kości" ["Evaluation of bone mineral density and bone metabolism in children with multiple bone fractures"]; authors: Michałus I., Chlebna-Sokół D., **Rusińska A.,** Jakubowska-Pietkiewicz E., Kulińska-Szukalska K.
- **2008** – distinction in the competition for the best poster in terms of content at the 19th Multidisciplinary Osteoporotic Forum in Warsaw for the work entitled: „Ocena kliniczna i densytometryczna dzieci z niską masą kostną leczonych laktoglukonianem wapnia i witaminą D_3 – część I" ["Clinical and densitometric assessment of children with low bone mass treated with calcium lactate gluconate and vitamin D_3 – part I"]; authors: Chlebna-Sokół D., Jakubowska-Pietkiewicz E., **Rusińska A.**, Michałus I., Frasunkiewicz J., Kulińska-Szukalska K., Prochowska A.M.
- **2004** – 1st grade team scientific award of the Rector of the Medical University of Lodz for a series of publications referring to tests from the scope of bone metabolic diseases and a monograph entitled: "Diagnostyka i leczenie osteoporozy i osteopenii w wieku rozwojowym" ["Diagnosis and treatment of osteoporosis and osteopenia in the developmental age"]
- **2005** – award for a series of works presented at the 4th Scientific Symposium under the cycle Dziecko Łódzkie [Children of Łódź] „Problemy Dzieci Niepełnosprawnych" ["Problems of Children with Disabilities"] in Łódź.
- **2005** – distinction in the competition of poster presentations at I Central European Congress on Osteoporosis and Osteoarthritis in Kraków for the work entitled: „Obraz kliniczny zaburzeń mineralizacji szkieletu u dzieci w przebiegu chorób uwarunkowanych genetycznie" ["Clinical course of skeletal mineralization disturbances in children with genetic bone diseases"]; autorzy: Loba-Jakubowska E., Błaszczyk A., **Rusińska A.**, Kulińska K., Chlebna-Sokół D.

- **2002** – outgoing scholarship beneficiary of Foundation for Polish Science – participation in the World Congress on Osteoporosis in Lisbon, Portugal
- **2002** – doctoral thesis defense with distinction – paper subject: "Ocena udziału wybranych cytokin w etiopatogenezie samoistnej osteoporozy i osteopenii w wieku rozwojowym" ["Assessment of selected cytokines' participation in etiopathogenesis of idiopathic osteoporosis and osteopenia in the developmental age"]
- **2001** – award for content and form of the presented work in poster session at the 2nd Symposium under the cycle Dziecko Łódzkie „Problemy zdrowotne i psychospołeczne populacji wieku rozwojowego" [Children of Łódź "Health and psychosocial problems in developmental age population"] in Łódź
- **1999** – distinction in the competition for the best poster in terms of content at the 10th Multidisciplinary Osteoporotic Forum in Warsaw for the paper entitled: „Osteopenia w wieku rozwojowym – obniżenie mineralizacji kośćca czy zaburzenie ogólnoustrojowe?" ["Developmental osteopenia: decrease of bone mineral density or systemic impairment?"]; authors: Chlebna-Sokół D., **Rusińska A.**, Szkudlarek J., Szkudlarek E.
- **1997** - 1st prize of Student Scientific Society for the scientific work presented at the 35th National Conference of the Student Scientific Society at the Medical University of Lodz

e) Participation in the most important international and national scientific conferences - summary

- IOF World Congress on Osteoporosis (IOF-WCO):
  - Lisbon, Portugal, 2002
  - Rio de Janeiro, Brazil, 2004
  - Toronto, Canada, 2006
  - Florence, Italy, 2010
- European Congress on Osteoporosis and Osteoarthritis (ESCEO-IOF):
  - Roma, Italy, 2013
- International Conference on Children's Bone Health (ICCBH):
  - Sorrento, Italy, 2005
  - Montreal, Canada, 2007
  - Cambridge, UK, 2009
  - Rotterdam, The Netherlands, 2013

- International Conference on Osteogenesis Imperfecta:
    - Dubrovnik, Croatia, 2011
- Central European Congress of Osteoporosis and Osteoarthritis, Cracov, Poland:
    - 2005;
    - 2007;
    - 2009;
    - 2011;
    - 2013
- Baltic Bone Conference (BBC):
    - Poznan, Poland 2013
- Multidisciplinary Osteoporotic Forum, Warsaw, Poland
    - annual participation between 1999 and 2010

A full list of publications and papers presented at international and national conferences was included in a separate document (Appendix No. 4)

Information on achievements in teaching, organization, cooperation with research institutions, and other scientific achievements and activity promoting science, was included in a separate document (Appendix No. 5)

Agnieszka Rusińska