Original Research Article

Use of drugs against osteoporosis in the Baltic countries during 2010–2014

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\textbf{A B S T R A C T}

Background and objective: Osteoporosis is a major health threat nowadays. Aging of the population and changes in peoples’ lifestyle result in a constant increase in the number of fractures all over the world. Our study aimed at describing the drug utilization pattern and choice of active substances of antioesteroporic medicines in the Baltic countries.

Materials and methods: Sales data of the antioesteroporic medicines was obtained from the internet. These are available on the website of medicines regulatory agencies. The World Health Organization (WHO) methodology of Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) was used to compare the data among countries.

Results: During the study period the consumption of antioesteroporic medicines was rather stable in all the countries. The overall choice of active substances used to treat osteoporosis is similar in all the Baltic countries but the market shares of substances were different. Estonia stands out with high use of combination product of alendronic acid and colecalciferol. In Latvia the highest consumption was of risedronic acid. In Lithuania the most used active substance in 2014 was ibandronic acid and second was denosumab with 0.8 daily doses per 1000 inhabitants per day (DID) and 25% of the total share.

Conclusions: The differences in consumption of drugs against osteoporosis in the Baltic countries are not very big. The consumption of antioesteroporic drugs is not to be regarded as sufficient though. The generally low consumption of osteoporotic medicines in the Baltic countries can be attributed to the overall less than EU average wealth of the countries and less than optimal expenditure on healthcare out of the GDP.

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1. **Introduction**

Osteoporosis is a major health threat nowadays [1-3]. It alters bone architecture leaving them more fragile and more susceptible to fractures [4]. The number of osteoporosis induced fractures is estimated to be 3.5 million annually in the European Union [5]. The main negative health outcome of fractures is loss of quality of life due to pain and disability caused by them [6,7]. Loss of bone mass itself is asymptomatic until a fracture occurs [8] and osteoporosis has clinical and public health relevance only cause of the fractures [9]. Aging of population and changes in people's lifestyle result in a constant increase in the number of fractures all over the world [9,10].

Effective pharmacological treatment options are available (e.g., bisphosphonate and combination with the latter, denosumab, strontium ranelate) [11] that have all been shown to reduce the risk of vertebral fracture, some have also been shown to reduce the risk of non-vertebral fractures and fracture risk at the hip [11,12]. With no single agent demonstrating superiority over another in preventing fractures [13].

Osteoporosis pharmacotherapy needs to be used for a longer period of time and patients need to adhere to treatment to be effective and cost-effective [14,15]. The number of patients who receive treatment within a year after a fragility fracture is less than 20% [16]. Half (50%) of the patients receiving the treatment adherence to it sufficiently and only 35% continue the treatment for at least a year [17,18]. The International Osteoporosis Foundation has declared an increasing need for management strategies to be placed in an appropriate health economic perspective for guideline development and for reimbursement [10,19]. Osteoporosis as a growing chronic health state in the Western world is putting a significant load on both the individual and the society [20].

Our study aimed to describe the drug utilization pattern and choice of active substances of antosteoporotic medicines in the Baltic countries. Such studies have been carried out before to describe consumption change of drugs against osteoporosis within country [21,22], but none has compared consumption in the Baltic region.

2. **Materials and methods**

Drug utilization data was analyzed using the Anatomical Therapeutic Chemical (ATC) classification and defined daily dose (DDD) methodology that is developed and maintained by the World Health Organization (WHO) (www.whocc.no). The methodology is used in most of the European countries to serve as the tool for drug utilization research. The national statistics of medicine consumption gathered by governmental bodies is usually based on this to keep track of changes in drug utilization.

An ATC code classifies active substances according to their main indication of use and chemical characteristics. The classification consists of 5 levels with therapeutic areas as the first level and specific active substances as the fifth level. Active substances that affect bone structure and mineralization are mainly included in the group M05B, which is further divided into groups of plain bisphosphonates, bisphosphate combinations and other drugs affecting bone structure and mineralization (e.g., strontium ranelate and denosumab).

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is described as a unit of measurement and not always reflecting the recommended dose or the actual prescribed daily dose. In case of drugs against osteoporosis this is not the case as the doses used do not differ much and the DDD applied by the WHO depict very well the actual doses used. This allows us to evaluate the number of patients receiving the treatment in a period of time rather accurately.

The number of DDDs is reported as per 1000 inhabitants per day (DDD/1000 inhabitants/day or DID). This enables to compare the consumption of medicines in different countries and in different years.

We used the 2015 version of the ATC/DDD classification in the study.

Our study included consumption data from the years 2010 to 2014. Data included in the study was obtained from the internet, published by the authorities gathering medicines consumption data. All the study countries collect the data from wholesalers and it represents medicine sales to pharmacies [23]. Sales data from all the countries cover 100% of consumption of antosteoporotic medicines in the countries [24-26].

We used comparison of regression lines with STATGRAPHICS Centurion XVII Version 17.1.12 in order to establish differences in trends of medication consumption between the study countries.

3. **Results**

During the study period the consumption of antosteoporotic medicines was rather stable in all the countries (Fig. 1).

In Lithuania there was a slight decrease in consumption while in 2010 the consumption was 3.4 DID and in 2014 it was 3.3 DID. In Estonia, the consumption of antosteoporotic medicines was exactly on the same level in 2014 as it was in 2010, i.e., 4.6 DID. In 2013, the consumption increased to 5.0 DID but an 8% decrease in consumption the following year put it back on 2010 level. In Latvia we can see the only increase in consumption of antosteoporotic medicines in the Baltic countries during the study period. In 2010 the consumption in Latvia was 4.2 DID and in 2014 it was 5.2 DID which is an overall increase of almost 24%. The consumption was even higher in Latvia in 2012 when 5.6 DID of antosteoporotic medicines were used (33% more than in 2010). There was a drop in consumption in all the countries during the last year of the study compared to the year before. The decrease was on average 6% with 4.7% in Latvia, 6.2% in Lithuania and 7.8% in Estonia. The annual average change of consumption was +0.3% in Estonia, +5.9% in Latvia, and −0.8% in Lithuania. The trends were not statistically significantly different with a P value of 0.41 between Estonia and Latvia; 0.46, between Estonia and Lithuania; and 0.24, between Latvia and Lithuania.

The choice of active substances used within the country changed little during the study period (Fig. 2), with the only
exception of denosumab, the consumption of which and share of total consumption of the antosteoporotic medicines increased in all the countries. Most noticeably in Lithuania where in 2010 denosumab was not used at all and in 2014 its consumption was 0.8 DID. In Estonia and Latvia, the increase was slower with 0.4 DID and 0.2 DID, respectively, during the 5 year period but it still brought denosumab to a share of 5%–10% of the total of medicines against osteoporosis. While consumption of bisphosphonates was stable in all the countries and the consumption of denosumab increased then the consumption of strontium ranelate decreased in Lithuania and in Estonia following the restriction of its use by the European Medicines Agency in April 2013, in Latvia the consumption stayed on the same level. As its former share was biggest in Lithuania, the decrease was also steepest – from 0.6 DID in 2013 to 0.2 DID in 2014.

The overall choice of active substances used to treat osteoporosis is similar in all the Baltic countries but the market shares of substances were a bit different amongst the study countries (Fig. 3). Estonia stands out with high use of combination product of alendronic acid and colecalciferol that formed almost 60% of the drug class’s total consumption in 2014. Other more used active substances were ibandronic acid and plain alendronic acid with 14% and 10% market share, respectively of the total consumption in 2014. In Latvia the highest consumption was of risedronic acid – 2.1 DID (40% of total). The combination of alendronic acid and colecalciferol and ibandronic acid were also used more than 1 DID, 1.3 and 1.1, respectively. Plain alendronic acid which is the oldest bisphosphonate was used less than 0.01 DID in Latvia in 2014. In Lithuania the most used active substance in 2014 was ibandronic acid with 0.9 DID (26% of the total share). Close
second was denosumab with 0.8 DID and 25% of the total share. High consumption of denosumab differentiates Lithuania from the other Baltic countries where all the most used antiosteoporotic preparations are plain or combinations of bisphosphonates. The consumption is more equally divided between active substances in Lithuania as three most used active substances made up 68% of the total consumption compared to 84% in Estonia and 86% in Latvia.

4. Discussion

Studies on osteoporosis medication consumption carried out in Europe before have showed continues increase in consumption [21,27]. On the other hand, the trend in the United States seems to be decreasing [22]. Our study shows a rather stable consumption in all the Baltic countries, although changes in peoples lifestyles and the aging of population would suggest an overall increase in the consumption of medicines [28]. The possible reason for the stability in consumption might be that our study period follows the economic recession and as one of the key elements to influence drug use is affordability [29] downturn in peoples income probably influenced the consumption of osteoporosis medication.

The differences in consumption of drugs against osteoporosis in the Baltic countries are not very big, though utilization in Lithuania is somewhat smaller than in Estonia and Latvia. The trends in consumption are not statistically significantly different, but if we had a longer study period the results would be more reliable. There are some differences in the choice of active substances used in the different countries. In all the countries the consumption of antosteoporotic drugs remained rather stable during the 5 year study period, with only Latvia showing an increase in consumption. Utilization decreased compared to the previous year in all the countries in the last year of the study – 2014.

In 2014 alendronic acid combined with colecalciferol constituted to 59% of total antiosteoporotic medicines consumption in Estonia. In Latvia the most used active substance was plain risedronic acid with 40% of the total. Lithuania stood out of the rest of the countries with high 25% of the total M05B consumption of denosumab. In the other countries denosumab comprised 7.6% in Estonia and 3.7% in Latvia of the total in 2014. While in Estonia and Latvia the top 3 most used active substances (or combination of substances) remained the same all through the study, in Lithuania denosumab was not used at all at the beginning of the study in 2010 and it rose to be the second most used active substance by the end of the study in 2014.

The most used active substance in 2014 in Estonia was the combination of alendronic acid and colecalciferol. The cheapest out of oral products was ibandronic acid with 0.25€ per DDD but its market share was still only 14% in 2014. The most expensive in 2014 of oral bisphosphonates or combinations of the latter was the combination of alendronic acid and colecalciferol with 0.51€ per DDD which is twice as much as the cheapest plain bisphosphonate. This can be explained by the fact that for the patient the combination preparation is reimbursed and the plain colecalciferol product is not. This makes the combination product still cheaper to use for the patient and explains the high proportion of combination product use out of the total of the drugs against osteoporosis.

After the increase of antiosteoporotic medicines consumption of 25% in Latvia in 2011 compared to 2010 the differences of total consumption has stayed relatively the same with Latvia using around 0.6 DID more than Estonia and 1.9 DID more than Lithuania. In 2010 Estonia lead the consumption with 4.6 DID.

In the Baltic countries the population at risk of osteoporosis is similar with estimated prevalence of 5.3% in Lithuania and 5.8% in Estonia and Latvia of total population [10]. The consumption of antiosteoporotic drugs is not to be regarded as sufficient though as the estimated number of women and men with osteoporosis is assessed to be around 80,000 in Estonia, 130,000 in Latvia and 175,000 in Lithuania [19] and according to our study daily treatment was received by

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Fig. 3 – The consumption of drugs against osteoporosis (ATC group M05B) in the Baltic countries in 2014 expressed as the number of defined daily doses per 1000 inhabitants per day (DDD/1000 inhabitants/day) and dived by the active substances.
approximately 6000 patients in Estonia, 11,000 in Latvia and 10,000 in Lithuania in 2014. This is <10% of patients with osteoporosis risk. The same conclusions are stated also in EU osteoporosis report that use of pharmacological prevention of osteoporosis is significantly less than optimal in the Baltic countries, suggesting that a change in healthcare policy concerning the disease is warranted [19]. Though several factors influence drug utilization the key drivers for not sufficient use seem to be availability and price of medicines.

The generally low consumption of osteoporotic medicines in the Baltic countries can be attributed to the overall less than EU average wealth of the countries and less than optimal expenditure on healthcare out of the GDP. This results in general as higher co-payment for patients in the Baltic countries which the patients cannot afford.

The dynamics of consumption in the study countries is peculiar as one would expect an increase in consumption while bisphosphonates are getting cheaper and the number of people at risk of osteoporosis is rising. Instead for the five year study we saw a 25% increase in Latvia during one year, stable consumption for 3 years with a drop in consumption in the last year and stable consumption throughout the study for Estonia and Lithuania. It can be related to the fact that for instance in Estonia reimbursement system for the drugs against osteoporosis is not changed and there are still only limited group of patients (fragility fracture + DXA T-score < –2.5SD) who get medications reimbursed at 75% or 90% (patients over 63) rate.

The interpretation of results from our study is limited to the extent of overall consumption and preference of active substances in different countries and assessment of prescribing quality or real treatment recommendations for patients cannot be monitored as the study is based on wholesale data. Also the data derives from wholesales and there is a gap between delivering the medication to the pharmacy and when a patient actually takes them. All the medicines might never reach the patient in fact. As the wholesalers and pharmacies are private entrepreneurs they work toward minimizing loss of product and storing them for longer periods of time. Taking this into account we can assume wholesale data correlates with real consumption rather well. When interpreting DID data it always has to be considered whether the DDD applied by the WHO depicts actual doses so we can assess the number of patients taking the drugs. In case of antiosteoporotic medicines this is not an issue as for every active substance always the same daily doses are used and combination therapy is not used. The strength of the study is that we have robust data covering all of national consumption from all the countries and a solid methodology that is used similarly in all countries.

Whether a stable consumption while less than 10% of people with estimated osteoporosis receive treatment need regulatory or informative action or both in the study countries and also the question of prescribing quality remain to be answered by more explicit studies.

5. Conclusions

The opportunities for osteoporosis treatment are similar in the Baltic countries. Our study shows a stable consumption of antiosteoporotic medicines in the Baltic countries, but also highlights some differences in choices of active substances used to treat osteoporosis in the Baltic countries as the most used preparation in Estonia is the combination product of alendronic acid and colecalciferol, in Latvia risedronic acid and in Lithuania ibandronic acid but closely followed by denosumab which consumption is more than 2-fold of that in Estonia and more than 4-fold of that in Latvia.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors’ contributions

O.L. and K.M. conceived the study, participated in its design and drafted the initial manuscript. O.L. collected the data. S.K. and A.M. participated in the design of the study, coordinated data interpretation and helped to draft the manuscript.

All authors read and approved the final manuscript.

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REFERENCES