

Knowledge gap among general practitioners, endocrinologists and orthopedic surgeons regarding atypical lesions and fractures of the femur due to long-term use of bisphosphonates

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Summary

Introduction. Bisphosphonates prevent osteoporotic fractures in women younger than 80 years of age with documented osteoporosis. However adverse events related to these agents may affect the patients. There is a strong association between long-term use of bisphosphonates and occurrence of atypical femoral lesions and fractures. Our study investigates the awareness level of community physicians for early recognition and prevention of atypical femoral hip fractures in osteoporotic patients treated with bisphosphonates in three groups of physicians: General physicians, orthopedic surgeons and endocrinologists. **Aim.** The aim of this study is to examine the awareness level in these three groups and to suggest acts for early recognition and prevention of atypical hip fractures in patients using bisphosphonates.

Methods. General physicians, orthopedic surgeons and endocrinologists were asked to anonymously fill a questionnaire checking their common knowledge regarding adverse effects associated with long-term use of bisphosphonates, optimal duration of treatment with bisphosphonates, recognition of atypical lesions or fractures, and prevention of further fractures.

Results. The study involved 229 participants. The highest level of awareness was demonstrated by endocrinologists. On the other hand, lowest rates of awareness to clinical aspects, treatment options as well as ways of prevention of atypical fractures were found in the group of general physicians. In the orthopedic surgeons group some aspects of long-term use of bisphosphonates and atypical

fractures were found to be poor. In summary, among all participants combined, a substantial knowledge gap was found in all aspect studied: 41.5% knowledge gap in questions regarding treatment, 39.5% in diagnosis issues, and 38% in regard to general familiarity with atypical lesions and fractures derived by bisphosphonate treatment.

Conclusions. There is an obvious need to raise the awareness about the possibility of atypical hip lesions and fractures in patients treated with bisphosphonates which could contribute to early diagnosis of atypical femoral lesions and prevention of subsequent fractures.

KEY WORDS: atypical fractures; osteoporosis; bisphosphonates; knowledge gap.

Introduction

Bisphosphonates are the first line of treatment of osteoporosis caused by various etiologies, e.g. the post menopause or steroid treatment (1, 2).

Bisphosphonate group agents' mechanism of action is a specific depression of bone osteoclast cells activity and decreasing their number, among others, by induction of apoptosis (3, 4). This group of drugs is a major pharmacological tool of osteoporosis treatment, due to its efficiency in reducing the risk for fractures of spinal vertebrae, hip neck and other sites. The efficiency, proved by controlled prospective trials, differs slightly between the various products and fracture sites, and averages around 50% (4, 5).

In the past few years we have witnessed the phenomenon of atypical hip fractures among patients treated with bisphosphonate agents for a prolonged period. Many reports of these atypical fractures are available in the literature (6-8). Major and minor characteristics of these atypical fractures were specified (Table 1) (8).

A patient who suffers from an atypical fracture is at risk for a similar lesion or fracture in the contralateral limb. Figure 1 exhibits the typical characteristics of atypical femoral fracture, after internal fixation using a cephalomedullary nail, in our institute. Awareness is needed to recognize the underlying cause of the fracture and to exclude a bilateral lesion in order to prevent a subsequent fracture in the same patient. For example a bilateral imaging in the patient just described reveals a similar lesion in the contra-lateral side, and bisphosphonates use was terminated.

Numerous published works demonstrated increased risk of femoral subtrochanteric fractures following prolonged treatment (over 5 years) with bisphosphonates. These researches were based on a wide database. Among the patients with atypical fractures there is a 4 fold increased incidence of bisphosphonates use, compared to patients with typical fractures (9, 10).

Table 1 - Atypical Subtrochanteric Fractures Criteria (8).

| Major Criteria | Minor Criteria |
|---|--|
| Proximal fracture line under the lesser trochanter and distal fracture line above the femoral condyles | Periosteal reaction along the lateral cortex |
| No trauma or low-energy trauma | Increased cortical thickness |
| Transverse or only slightly oblique fracture line (angle < 30°) | Prodrome pain in the groin or thigh |
| Non comminuted fracture | Bilateral fracture or symptoms |
| Complete fracture crossing from one cortex to the other, with or without a medial cortical beak or incomplete fracture (or fissure) involving only the outer cortex | Delayed healing |
| | Co-morbidities: rheumatoid arthritis, vitamin D deficiency, hypophosphatasia; Concomitant treatments: bisphosphonates, glucocorticoids, proton pump inhibitors |



Figure 1 - A patient treated with bisphosphonate for a prolonged period. On the right a mildly oblique fracture line, with cortical thickening (arrow) is demonstrated; on the left a lateral cortical subtrochanteric thickening is noticed (double arrow). These findings are compatible with atypical fracture and lesion, respectively.

Current guidelines for the treatment of an atypical fracture or a characteristic prodrome of pain in the proximal femur region mandates the termination of bisphosphonates treatment, evaluation of the calcium balance, treatment with calcium and vitamin D supplements and consideration of an anabolic treatment, with teriparatide (11-13).

It is obvious that an awareness of hospital and community physicians to the extent of the problem, the risks, the special meaning of atypical fractures, the importance of the typical prodromal pain in the proximal thigh, the diagnosis of atypical fractures and the alternative means of treatment for osteoporosis, is lacking. Consecutively, a mild rise of the incidence of these fractures in the past few years was observed (8, 14, 15). The extent of the use of bisphosphonates drugs, nowadays, may very well raise this incidence even further.

Treatment gap is defined as the gap between the numbers of patients with a specific medical problem, which has an established treatment, to the actual number of patients being treated accordingly. The treatment gap for osteoporosis, reflected by the percentage of patients diagnosed with an os-

teoporotic fracture, and is not adequately treated, is up to 80% (16). In accordance, knowledge gap can be defined as the gap between accumulated knowledge in the literature, and the actual acquired and applied knowledge by physicians, within their expertise. Since only recent evidence is available regarding the adverse effect of osteoporosis prolonged treatment, manifested by atypical lesions and fractures, the literature still hasn't examined the knowledge gap in this field, in regard to the general knowledge on the prevention and treatment of osteoporotic fractures. Since atypical lesions eventually become atypical fracture, to our opinion raising the physicians awareness to the unique characteristic of these lesions, is critical in order to lower the rate of these fractures, and change mode of treatment.

In this work we have tested the knowledge level of physicians regularly treating patients diagnosed with osteoporosis, concerning atypical lesions and fractures of the femur under prolonged bisphosphonates treatment, their ability to recognize prodromal signs preceding the atypical fracture, the alternatives for treatment and the prevention of additional fractures.

Establishing the knowledge gap existence may lead to methods of decreasing the gap, and the rate of atypical lesion and fracture in the population of osteoporotic patients.

Methods

The data was collected during the years 2015-2016, using a short questionnaire, consists of 11 questions (Appendix 1), regarding general knowledge and awareness of the subject, atypical fractures causes, clinical features, means of diagnosis and appropriate treatment. The questionnaire was distributed in professional medical conventions in Israel during the years 2015-2016. It was matched to three fields – community physicians (general practitioners - residents and seniors), orthopedic surgeons (residents and seniors) and endocrinologists. Statistical analysis was executed using Microsoft Excel program.

Results

A total number of 229 physicians participated in the survey. 58 orthopedic surgeons who work in the community, 69 residents of orthopedic surgery, 38 general practitioners, 34 residents of family medicine and 30 endocrinologists.

Analysis of the data reveals that even though most responders (88.7%) were familiar with the term of atypical fracture derived by prolonged bisphosphonate treatment, only 58.5% recommend their patients to terminate this treatment after prolonged treatment. Only a minority (32.3%) terminates this treatment after any osteoporotic fracture.

In addition, only 50.7 and 58.5% are aware of the prodrome preceding an atypical fracture, and the radiologic characteristics of atypical lesions, respectively. This knowledge gap reflects a concern regarding the capability of the treating physicians to prevent developing atypical lesions and fractures.

Only 59.4% is customary of ordering a contra-lateral side imaging when suspecting an atypical lesion. A similar rate of the orthopedic surgeons (66.1%) would order a contra-lateral side imaging, when an atypical fracture is suspected.

63.3% and 68.1% would stop bisphosphonate treatment once an atypical lesion or fracture is discovered, respectively. However, 31% of the responders is not familiar with any treatment alternatives.

The results were analyzed in reference to the different physician' populations, concerning several issues.

Knowledge of the phenomenon

100% of the endocrinologists were familiar with the term of atypical fractures, followed by residents in orthopedic surgery (95.7%), surgeons (88.9%), residents in family medicine (85.3%) and lastly general practitioners (73.7%). Given that general practitioners are exposed to most patients treated with bisphosphonate agents, a higher level of awareness to the phenomenon of atypical fractures derived by it could be expected from this group. A prodrome of several months of pain prior to a fracture in the femoral subtrochanteric region was described. Awareness to this term has a direct association to early diagnosis and prevention capability. Except the high level of knowledge in the endocrinologists group (79.3%), a substantial knowledge gap was found among orthopedic surgeons and general practitioners. 52.2 and 65.5%

of the residents of orthopedic surgery and surgeons, respectively, were familiar with this term, as only 20.6 and 31.6% of the residents in family medicine and general practitioners, respectively. Similarly, most endocrinologists (79.3%) reported of experience in treating atypical fractures, followed by orthopedic surgeons (62.1%), residents in orthopedic surgery (60.9%), residents in family medicine (14.7%) and general practitioners (7.9%).

When computing the results of all the questions concerning the familiarity and awareness to atypical lesions and fractures by these three groups of physicians treating these patients, a knowledge gap of 38% was found. Hence, 38% of the physicians are lacking basic knowledge of the subject of atypical lesions and fractures.

Diagnosis

80% of endocrinologists was familiar with the radiologic characteristics of atypical lesions (however only 13.8% specified at least one when asked to), as 76.7% would order X-ray of the contra-lateral hip upon diagnosis of an atypical lesion. Among orthopedic surgeons, 74% of the senior surgeons and 73.9% of the residents were familiar with the radiologic characteristics of atypical lesions (but only 48.3 and 44.9% specified at least one), as 67.2 and 72.5% would order contra-lateral imaging, respectively. However, among general practitioners, the knowledge level of the radiologic characteristics of atypical lesions was found to be much lower. Only 29% of the practitioners stated knowing these characteristics, as 34.2% would image the contra-lateral hip. The residents' in family medicine level of awareness was even lower. Only 14.7% of them stated of knowing these characteristics, as 32.5% would image the contra-lateral hip.

When suspecting an atypical fracture, 63.8% of orthopedic surgeons would order contra-lateral imaging, as 68.1% of the residents. This question was addressed to orthopedics only since hip fractures are usually diagnosed in the emergency department rather than the community.

When computing the results of all the questions concerning diagnosis of atypical lesions and fractures, a knowledge gap of 39.5% was found.

Management and treatment

All endocrinologists except one (96.7%) reported stopping bisphosphonate treatment after prolonged treatment and the diagnosis of atypical lesion or fracture (only 1/3 was specific regarding duration limit, average 7.6 ± 1.6 years). Similarly, 86.7% of them terminated the treatment following a diagnosis of either osteoporotic fracture. Moreover, all endocrinologists surveyed (except one) were able to specify alternatives for osteoporosis treatment.

65.8% of the general practitioners would recommend termination of bisphosphonate treatment after a prolonged treatment (only half was specific, average 6.8 ± 1.9 years), but only 50 and 55.3% would do so once diagnosing an atypical lesion or fracture, respectively. A minority of 42.1% of them would recommend the same once diagnosing an osteoporotic fracture. In spite of that, 84.2% of them was familiar with treatment alternatives (although only 42.1% actually specified at least one alternative excluding vitamin D or calcium supplements when asked to). 76.5% of residents in family medicine stated to stop bisphosphonate treatment following prolonged treatment (only 1/3 was specific, average 7 ± 1.8 years), and 41.2 and 47.1% once diagnosing an atypical lesion of fracture, respectively. A total of 8.8% terminate treat-

ment once diagnosing an osteoporotic fracture. 76.5% of residents was familiar with alternative options for bisphosphonates (but only 38.2% actually specified at least one).

Half of the orthopedic surgeons would recommend stopping treatment of bisphosphonate after prolonged period (only about a quarter of them were specific, average 4.8 ± 2.2 years), as 40.6% of residents in orthopedic surgery would (only 21% was specific, average 4.3 ± 1.3 years). 67.2% and 72.5% of surgeons and residents respectively, would terminate treatment once diagnosing an atypical lesion, and a similar rate (63.8% and 68.1%) once diagnosing an atypical fracture. A minority of 24.1% of surgeons and 21.7% of residents would recommend ending of bisphosphonate treatment following the diagnosis of either osteoporotic fracture. 69% of surgeons and 46.4% of orthopedic residents stated knowing treatment alternatives (but only 41.4 and 36.2% specified at least one, excluding vitamin D or calcium supplement).

When combining the results of all the questions concerning management and treatment of atypical lesions and fractures, a knowledge gap of 41.5% was found.

In summary, except the endocrinologists group, the surveyed population demonstrated a substantial knowledge gap on this important subject (Figure 2). Most noted is the knowledge gap in treatment (41.5%), followed by diagnosis (39.5%) and general familiarity with atypical lesions and fractures derived by bisphosphonate treatment (38%).

Discussion

Bisphosphonates are widely prescribed to treat osteoporosis due to its proven efficacy in preventing osteoporotic fractures in the spine, hip and other common osteoporotic sites.

In the past few years a possible relationship between this treatment and the incidence of atypical lesions and subsequent fractures was suggested. Many studies were recently

published in the literature, and the U.S. Food and Drug Administration (FDA) published in October 2010 a statement which is the conclusion of a task force for the matter. The FDA had expressed a concern that suggests these fractures as a side effect of long term bisphosphonate treatment, thus decided to add a warning to each drug from this group administered in the USA as a treatment for osteoporosis. In addition, despite the fact that bisphosphonate treatment reduced significantly the risk of osteoporotic fractures, the American FDA recommends to consider termination of this treatment after 5 years.

This study was conducted to test the familiarity of physicians treating osteoporotic population on a regular basis with the adverse effects of long-term use of bisphosphonates, and common recommendations to lower morbidity associated with this treatment.

Taking all responders as a group, a substantial knowledge gap was found regarding all aspects reviewed - the phenomenon, its characteristics, diagnosis and current recommended treatment.

Among endocrinologists, we have found a high level of awareness to all aspects. On the other hand however among general practitioners and orthopedic surgeons the knowledge gap was found to be unacceptable, especially with regard to the fact that these two professions encounter osteoporotic patients during every day routine much often than endocrinologists.

A lack of awareness among general practitioners and orthopedic surgeons was found in regard to the FDA's recommendation of stopping bisphosphonate treatment after prolonged treatment, maybe the most cost effective step in preventing atypical lesions and fractures. These findings stand in contrast with the fact that the majority of participants in the survey did report a familiarity with the subject (average of 89% of the responders). This could be explained by the unwillingness to admit non knowledge. However, the knowledge gap was revealed when detailed questions were conducted.

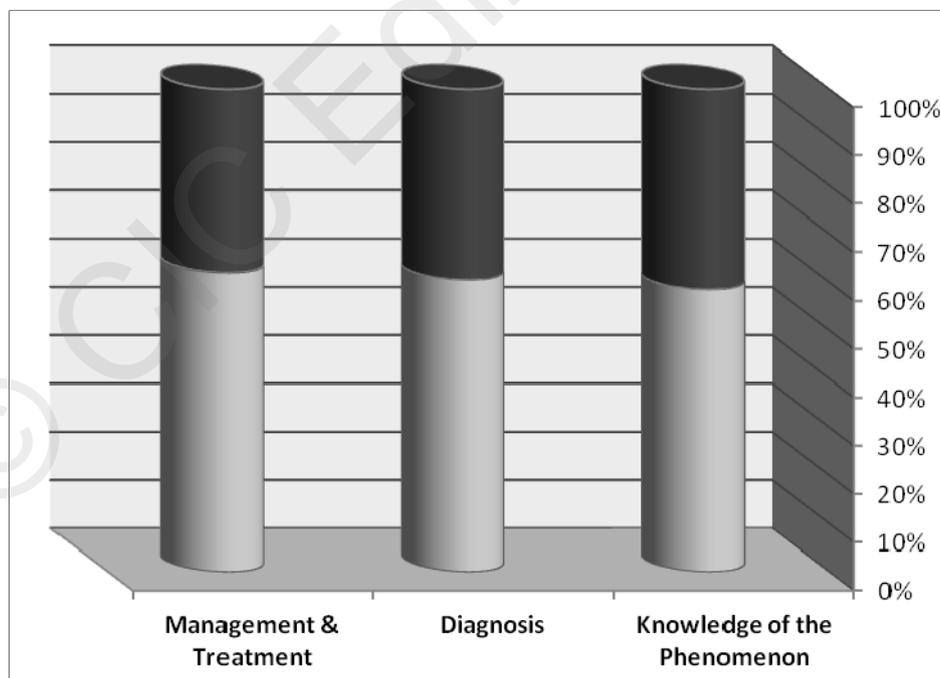


Figure 2 - Knowledge gaps (dark gray) of the survey's population, summarized according to categories.

The possibility of bi-lateral lesions is realistic, and diagnosing an atypical lesion or fracture is a red flag requiring additional work out to exclude a bilateral disease, hence reducing morbidity. It is unacceptable to have a patient suffer another atypical fracture just because of lack of knowledge of his or her treating physician or surgeon.

In this regard, general practitioners were found to have the lowest level of awareness. Given that they are exposed to the highest number of osteoporotic patients in the community, the need to improve knowledge and awareness is crucial. Moreover, it is disturbing to find that only 63.8% of the orthopedic surgeon and 68.1% of the residents in orthopedic surgery would request a contra-lateral side imaging when discovering an atypical femoral fracture. Insufficient awareness to this matter may lead to late diagnosis and inability to prevent an additional fracture.

There are some limitations in this study. The investigated population is concentrated in a relatively small country with unified residency programs. The situation might prove different elsewhere. However, to the best of our knowledge, no such study was performed on the subject before.

Another limitation might be the compliance bias of this type of research. However, it might illustrate further the need to improve the knowledge gaps illustrated.

Conclusion

In summary, this survey points out that, with the exception of endocrinologists, a substantial knowledge gap exists among general practitioners and orthopedic surgeons regarding the phenomenon of atypical lesions and fractures. Reducing this gap may lead to improved treatment and, of course, the prevention of future fractures. In light of the high awareness of the endocrinologists to the subject, the cooperation with endocrinologists in the form of fracture liaison programs should be increased in the community and hospitals.

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Appendix 1

The survey questionnaire

Questions 1, 2, 4: Knowledge of the phenomenon

Questions 5-7: Diagnosis

Questions 3, 8-11: Treatment and management

A survey on the subject of atypical fractures of the femur under prolonged treatment of bisphosphonate agents

Please mark your field of practice:

A. Orthopedic surgery

B. General practitioner/Family medicine/Internal medicine in the community

C. Endocrinology

Please mark: Specialist/Resident

1. Is the term "atypical femoral fracture" familiar to you?
2. Have you treated patients with atypical femur fractures with the possible etiology of bisphosphonate use? If so, how many?
3. Do you terminate treatment of bisphosphonate agents after a prolonged treatment? If so, please specify the time (in years).
4. Are you familiar with the pain prodrome of atypical femur fracture?
5. Do you know the imaging characteristics of atypical femur lesions? If so, please specify.
6. Do you order a contralateral X-ray when atypical femur lesion is suspected?
7. Do you order a contralateral X-ray when atypical femur fracture is suspected? (Question is referred to orthopedic surgeons/residents only).
8. Do you terminate bisphosphonate treatment once atypical femur lesion is diagnosed?
9. Do you terminate bisphosphonate treatment once atypical femur fracture is diagnosed?
10. Do you terminate bisphosphonate treatment once an osteoporotic fracture (wrist, hip, vertebrae and humerus) is diagnosed?
11. Are you familiar with treatment alternatives to bisphosphonate agents? If so, please specify.