Osteoporosis and the new absolute fracture risk algorithm

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Dr Stuart Silverman was born in Chicago (IL, USA) and graduated from Princeton University (NJ, USA) cum laude in biology with an interest in art history. He received his MD from Johns Hopkins (MD, USA) in 1973. He was an intern and resident in the Boston University Hospital System (MA, USA) and was a rheumatology fellow at Boston University under Dr Alan Cohen. Following his rheumatology fellowship he was a Thorndike research fellow. He is board-certified in internal medicine, rheumatology and allergy-immunology, and has served as a lecturer in rheumatology at Tufts University, assistant professor at University of Pennsylvania (PA, USA) and is currently Clinical Professor of Medicine at University of California, Los Angeles (UCLA, CA, USA). He has served as acting chief of rheumatology at Greater Los Angeles VA Medical Center where he currently holds a research appointment. His clinical practice is based at Cedars-Sinai (CA, USA). Dr Silverman is medical director of the OMC Clinical Research Center, a nonprofit public benefit corporation, with the mission of bringing cutting edge research and education to the community. The OMC is currently running over 20 clinical trials for patients with fibromyalgia, osteoporosis, women's health, osteoarthritis and rheumatoid arthritis. The OMC has been the recipient of both federal (NIH) and state grants. Dr Silverman has a special interest in fibromyalgia, chronic fatigue, myofascial pain syndromes and osteoporosis, and is the author of over 60 original articles, 100 abstracts and ten book chapters. Here, he talks to Head of Commissioning, Laura Dormer, about his current work on the WHO absolute fracture risk algorithm task force.

After completing your internship and residency at Boston University Hospital you became a rheumatology fellow – what led you to pursue a career in this area?

There were two factors that led to my interest in rheumatology. When I was in medical school I had the good fortune to spend some time in London (UK) – I was a medical student at Johns Hopkins (MD, USA) and I chose an elective at Guy's Hospital. By luck I ended up working with Rodney Grahame, a rheumatologist at Guy's, and conducted a research project with him on hypermobility (double-jointedness) in London school children. This involved going out into schools in London, and we found that children who were interested in dance were also often hypermobile. We found that it was useful to have the motivation to be a ballet dancer, but that it was also good to have the right genetic background of hypermobility.

Later on, I went to Boston University (MA, USA) and the Chief of Medicine was Dr Alan Cohen, who was a rheumatologist. He asked me if I would come and join his section. When asked by the Chief of Medicine to join as a fellow in his section, most people would not turn him down! But by that point I had already fallen in love with rheumatology, through the work I had done in the UK.

Are there any particular scientists you have worked with who have had an impact on the path your research has taken?

During the beginning of my research career, Alan Cohen was certainly a big influence on me, as he got me into rheumatology. I also spent many years at Boston University working with Edgar Cathcart and exploring cellular immunology.

From Boston I moved to Philadelphia and eventually to the Cedars-Sinai Medical Center/UCLA (CA, USA), where I began to conduct clinical research. My first interest was the development of a questionnaire to measure quality of life in patients with osteoporosis. I developed the Osteoporosis Assessment Questionnaire (OPAQ), which became the first international quality-of-life assessment in osteoporosis. I had a wonderful mentor in Ron Hays at RAND, who developed the SF-36, which is probably the most widely used quality-of-life instrument around the world for assessing burden of disease. Ron taught me how to develop a quality-of-life questionnaire.

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Another important mentor to me is my wife, who is an occupational therapist. When I began devising OPAQ, I spent hours working with her, because as an allied health professional, she was more aware of the impact of osteoporosis on patients than a physician such as myself. She guided me in drafting the preliminary questions, and, of course, the patients then helped; we interviewed 100 patients with osteoporosis to try and find out what their concerns were regarding their quality of life. OPAQ is now used throughout North America, Australia and New Zealand (and a similar questionnaire, QUALEFFO, is used in Europe). That was an exciting project that still continues and I am still working on now, validating a modified questionnaire in males.

Another person who had a major influence on my work was a colleague in California. I had realized that the data we had regarding osteoporosis epidemiology was based on data from Rochester (MN, USA); this was wonderful work, but was based on a largely Caucasian community. I was living in California where Caucasians are actually going to be in a minority very soon, and I wanted to understand the impact of disease on minority populations. So I reached out to a local professor, Roberta Madison at Cal State Northridge (CA, USA), and she helped me begin to understand how to use observational databases. We used a large database of hospitalizations in California and found some very interesting data on the incidence of hip fractures in Caucasians versus Asians versus African–Americans; we found that Hispanic–Americans had the same incidence as African–Americans, which had never been reported before. This was a landmark study published in the *American Journal of Public Health*. We followed that up with studies of secular trend analysis showing that the incidence of hip fracture has doubled in the last 10 years in Hispanic–Americans in California.

When we switched from daily to weekly bisphosphonates a couple of years ago, I again became involved with Prof. Madison and another physician at Yale, Joyce Cramer, in looking at compliance and persistence in multiple databases, confirming that compliance and persistence were suboptimal with oral bisphosphonates. We are currently looking at not only ethnic trends in hip fracture, but also nonvertebral fracture across the different Hispanic–American populations in the US (Cuban American in Florida, Mexican–American in California and Puerto Rican in New York). My work with databases led me to also use databases to compare the nonvertebral fracture efficacy of two oral bisphosphonates, confirming data from post-hoc analysis of randomized, controlled trials.

The final person to mention who has influenced me is John Kanis, who made me much more aware of the need to think globally. I was fortunate enough to have been picked 3 years ago to be on the WHO task force for the new absolute fracture risk algorithm, which has developed a global fracture risk platform. I am also currently spearheading the US effort for a global project called ICUROS, which is looking at the costs and utilities related to loss of quality of life following osteoporotic fracture around the world (seven or eight countries are involved). The US effort will focus on claims data from healthcare databases.

What would you say have been the most important milestones during your time in the field?

A lot of things have happened within my lifetime. Certainly the advent of the biological agent, the TNF inhibitors, brought about a dramatic change, first in rheumatoid arthritis, but then laterally, to psoriatic arthritis and ankylosing spondylitis.

There has been a very dramatic change in spondyloarthritis (ankylosing spondylitis). When I was still reading with Alan Cohen, ankylosing spondylitis was still being discussed and thought of as a form of rheumatoid arthritis.

One of the two areas that my work is focused on is osteoporosis. When I started working in this field in Los Angeles there were no US FDA-approved therapies. The milestone is that we now have a whole range of therapies. Previously we had agents such as fluoride that improved bone density, but at that time we did not know they did not reduce fracture. The milestone was the development of agents such as alendronate and calcitonin that were proven to reduce fracture risk. We have also moved from oral to nasal to intravenous agents. So there has been exciting progress in osteoporosis research, in that we now have effective agents; however, we obviously have a long way to go, as this is still an under-diagnosed and undertreated disease, and compliance is suboptimal.

The other area of research that I am involved with is fibromyalgia. This is a disease that had no respect, and even now does not command a lot of respect. A landmark milestone for me in this area was in 1990, when the American College of Rheumatology developed criteria that

gave the disease some reputability. Probably the most important milestone occurred just a few weeks ago, when the FDA approved the first drug for fibromyalgia, pregabalin. By having an approved drug, fibromyalgia is starting to gain legitimacy. However, very recently there was an article in the *New York Times* asking whether fibromyalgia is real. So we are still fighting a battle, but a battle that I think can be won very shortly.

You are a member of the WHO task force working on the new absolute fracture risk algorithm. Briefly, could you describe the aims of the task force?

It is recognized that we cannot afford to treat everybody in the world for osteoporosis, and that there is a need to be selective. Ideally, we need to treat those people who most need therapy. But how do we achieve that? Unfortunately, bone density assessment alone is not sufficient to find those patients who are at risk. BMD measurement is specific but not that sensitive, in that approximately half the people in the community who fracture do not have osteoporosis. Furthermore, global access to dual-energy x-ray absorptiometry (DXA) scanners is limited. The USA has a population of 300 million people and 20,000 DXA scanners, China has 1.3 billion people and 300 DXA scanners, and India has 1.1 billion people and less than 50 DXA scanners, so obtaining bone density measurements in many parts of the world is not realistic. The aim of the WHO task force was to think about how to help the primary care physician in deciding who is most at risk, and therefore best to treat using clinical risk factors with or without BMD measurement.

What methods have been used in the past to predict fracture risk, and hence decide treatments?

In fact, in the past the risk of developing osteoporosis was talked about, rather than risk of fracture. So we are now changing the language; previously, advertising and textbooks talked about the known causes of osteoporosis; we are now talking about the risks of fracture, which is a big shift that has yet to be fully exploited. Talking about fracture, rather than osteoporosis becomes important, as fracture is a signal event. Around the world, fracture is probably the most important indicator for osteoporosis, but it is generally ignored. The USA uses a performance criteria for managed care plans called HEDIS, and it has been found that less than one in five women aged 67 years or older within 6 months of having a fracture of their hip are ever diagnosed or treated. I have been involved with quality performance measures that may eventually identify if a hospital that has a patient with a wrist fracture from a fall is not diagnosed or treated. This will involve coordination of care and electronic medical records, and the fracture will become the key pivotal event.

How will the new WHO algorithm achieve its aims?

The WHO algorithm does include bone density, but for places in the world where this is not available, it uses BMI, which tracks with BMD except for when the BMD is very low, in which case BMI imparts increased fracture risk. BMD is used, with clinical risk factors, to determine the patient's 10-year risk of hip fracture and 10-year risk of clinical fracture. The decision to treat is then based on intervention threshold. For example, in the UK and Sweden, a 4% 10-year risk of hip fracture is considered cost effective, while in the USA it would be at approximately 3%, as the USA spends more money on healthcare (the UK spends 8% of its budget on healthcare, compared with 16–20% in the USA). In emerging socialist market economies, such as Bulgaria and Romania, it will be a higher risk to be cost effective to treat that patient. Therefore the algorithm allows the determination of fracture risk globally, with the intervention threshold determined by the willingness of a particular country to pay. This is a fascinating new concept for the globalization of medical practice, and may be applied in the future to all chronic diseases. There will be a risk of an event based on data from global cohorts, and then an intervention threshold based on regional willingness to pay, so regardless of where you are in the world, you can use the same common algorithm, just by being aware of what that part of the world is willing to pay.

In what ways will the new algorithm aim to improve treatment of osteoporosis?

The total number of people being treated will remain the same or grow, but there will be a shift in those who are treated. A 50-year-old woman who may have been worried and had a low bone mass without clinical risk factors would now be recognized as having a low risk of fracture and neither she nor her practicing

physician would want to treat her. If a 50-year-old woman had a 10-year risk of hip fracture of 2% and treatment would reduce the risk to 1%, it is not likely that either the patient or the physician would want to start therapy. Previously we mostly relied on bone density, and were talking about osteoporosis rather than fracture; therefore, a T score of less than -2.5 was thought to be osteoporosis, so if a patient had a score that was close to that, there was a temptation to treat them. But with the new algorithm you may not receive treatment in your 50s, but hopefully people who are older, in their 70s and 80s, who might have only mildly low bone density but are recognized as having a very high fracture risk (i.e., they may have a T score of -1.5 but also already have had a fragility fracture), will receive treatment.

There is one caveat; one of the medicines that we use to prevent bone loss in women, raloxifene, has just received approval for reduction of the risk of invasive breast cancer. Therefore, this may lead to an era in which it may not be cost effective to treat a woman due to her bone density to prevent fracture, but if her risk of breast cancer is added, it may become cost effective. Therefore, osteoporosis doctors will need to think about breast cancer as well, which is an exciting new chapter.

The algorithm is expected to be published in 2008. We then anticipate that all the bone density software in the world will be upgraded to include the information subsequently. Bone density technologists will then have the opportunity to ask the WHO questions. Eventually, physicians will see BMD, T score and absolute fracture risk on their bone density print out.

Would you say that the current amount of research into new diagnostics and treatments in rheumatology is sufficient to meet current and future demands?

The present political climate in the USA has not been as supportive as it needs to be. Osteoporosis is an epidemic, and the cost of hip fractures alone in another two or three decades will be the equivalent of the whole Medicare budget several years ago. We do not have a way to measure bone quality in clinical practice and further work is needed.

In my other field of interest, fibromyalgia, we have a good start with the first FDA-approved medication, pregabelin, but not all patients respond to this medication and of those who do it helps manage the pain but not cure it. In terms of therapy for pain disorders, we are only part of the way there. In addition, there is currently no easy way for physicians to diagnose fibromyalgia, short of a good history and tender point examination. Overall, there is a clear-cut need for more diagnostics and more therapeutics in the field of rheumatology.

Finally, where do you think your research efforts will be focused over the next 5 years?

A big issue will be the ability to learn more from databases, firstly at a national level to understand cost and loss of quality of life due to fracture, using administrative databases throughout the USA and combining that with self-report data from Europe. I am also currently involved in observational studies such as the Global Longitudinal Registry of Osteoporosis in Women, looking at risk factors for osteoporosis in a large cohort of postmenopausal women.

There is a need to go beyond claims databases and use information in charts, which can be obtained when there are electronic medical records. For example, I am working with Joanne Lafleur at the University of Utah (UT, USA), and we have just finished a study using GE Centricity, which is a large electronic medical-records system. We were able to go back a step and look at what happened from when a doctor wrote a prescription on a chart. This was then correlated with what happened later. We followed several thousand people, and, worryingly, we discovered that if people were prescribed a bisphosphonate for osteoporosis, in actuality fracture reduction from the time of writing the prescription was almost zero. This was because many prescriptions never get filed, which would be missed in a regular database, some people stop taking the medication due to GI intolerance, and of those people who do take the medication, many do not take them correctly. So in actuality the fracture reduction was minimal.

One of the key things we need to think about as physicians is that we have very powerful, positive data from randomized controlled trials, but what is really happening in the community? That is the challenge for us; from the time a doctor writes a prescription, what is the likelihood that it is going to be filled and then have any effect on the patient? A lot of the current data are from pharmacy claims databases, but it is necessary to go back to administrative claims databases to obtain information on the patient's age, secondary illnesses, comorbidities, socio-economic data

and so on, in order to understand the whole process. We need to understand that we may be doing less for our patients than we think we are, and try and improve this. It is therefore important to look at other issues, such as decision making and patient communication. I am currently working on a project to develop a module on how to talk to patients in all CME presentations. In addition, early last year I conducted presentations in Prague on the concept of shared decision making and what information needs to be given to patients in order to make sure they understand why they are taking an osteoporosis medication and how to take it to ensure that the medicines are more effective. My goal is to help patients help themselves get better.

Financial & competing interests disclosure

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