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EDITORIAL

Understanding the pathogenesis of hip fracture in the elderly, osteoporotic theory is not reflected in the outcome of prevention programmes

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Abstract

Hip fractures are an acute and worsening public health problem. They mainly affect elderly people, a population group that is highly vulnerable to disease and accidents, and to falls in particular. Although it has been suggested that osteoporosis is the cause of hip fractures, they mainly occur after a fall has been suffered. The underlying causes of a fall are not related to osteoporosis, although pharmaceutical companies have coined the term "osteoporotic fracture" for hip fractures in the elderly. Drug treatments for osteoporosis have not diminished the frequency of these injuries, nor have they prevented the occurrence of a subsequent fracture. Since pharmaceutical interests require osteoporosis to be considered a disease, rather than a normal condition of senescence, they go further by assuming that treatment for osteoporosis is essential, and that this policy will diminish the incidence of hip fractures. On the other hand, the origin and treatment of conditions that may be conducive to provoking falls are very difficult to elucidate. In this paper, we consider some of the medical and social problems that arise in this area, as well as conflicts of interest regarding the aetiopathogenesis and prevention of hip fracture, and propose a new paradigm for the prevention of falls.

Key words: Hip fracture; Osteoporosis; Overtreatment; Social medicine; Political economy; Political actions; Conflict of interest; Genome; Transcriptome; Metabolome

Core tip: This paper rejects the role of osteoporosis in the pathogenesis of hip fracture and proposes medically-based political action to support new omics technologies to detect the risk of falls by elderly people, by detracting resources from those currently employed

in the treatment of osteoporosis.

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INTRODUCTION

In developed countries, hip fracture is a major public health problem. Increased life expectancy, in conjunction with social changes, has made many elderly persons vulnerable to loneliness and to disability. This population group tends to suffer more frequently from hip fracture because they have a higher propensity to falls, as a result of sensorial and neurological deterioration, together with muscular atrophy. Any elderly person, irrespective of concurrent osteoporosis, may suffer a hip fracture because, apart from the unusual case of pathological fracture, a traumatism is a necessary cause[1]. In other words, in the absence of a fall, hip fracture is very unlikely to occur.

Nevertheless, world-wide programmes to address the question have not been undertaken in accordance with this pathogenic outlook. On the one hand, new and more expensive drugs are continuously being marketed for the treatment of osteoporosis, holding this disease primarily responsible for the occurrence of hip fracture, although such drugs have never been shown to diminish its prevalence or to avoid secondary effects[2]. On the other hand, financial support for these treatments is becoming even more restricted as national health services are forced to cut budgets. Thus, expensive pharmacologic treatment for osteoporosis adds an extra burden to the cost of providing for the needs of elderly patients. The treatment is purported to reduce the incidence of hip fracture, but the practical outcome is a significant reduction in the options open to the public welfare system, with particular regard to pensions, and in consequence many elderly people lack the means to cope with this situation.

Therefore the problem of hip fracture is twofold: Medical and social. Any approach to this pathology must take into account both aspects, if health policies for hip fracture prevention are to be successful.

THE MEDICAL PROBLEM

Falls are known to be the main cause of hip fracture. However, this pathology is commonly held to be closely related to osteoporosis. The pharmaceutics industry has coined the term "osteoporotic fracture" for any fracture suffered by an elderly person. Although all elderly people do indeed present osteoporosis, among other aspects of their health status, they may also be affected by heart disease, stroke or ocular or inner-ear balance problems, any one of which may provoke a fall. However, the fracture is never called an "ophthalmic fracture" or a "labyrinth fracture".

Since osteoporosis alone never provokes a fall, and as a fall is the main antecedent of a hip fracture, there must be some mismatch in the assumption of causality between osteoporosis and hip fracture, *i.e.*, in the pathogenesis of this condition. Osteoporosis only helps to fracture a bone with less energy than non-osteoporotic bone. It has been established that although all elderly people present osteoporosis, only some will suffer a fall, and that less than half of those having a fall will suffer any injury as a result of it[3]. Moreover of the persons aged 65 years or older who do suffer a fall, over half will experience a repeat of this event within a year[4]. Although these persons may or may not suffer a hip fracture, pharmaceutical companies cite this circumstance to argue that persons who have had an "osteoporotic fracture" need treatment to prevent the occurrence of a second one. It has been claimed that in order to prevent hip fractures, the supposed bone metabolism disorder that diminishes "bone strength" should be treated. Nevertheless, the available evidence does not show that, as discussed below.

The oral intake of vitamin D, with or without calcium, is the classical treatment for osteoporosis. Nonetheless, low plasma 25-hydroxy vitamin D concentration is associated with high arterial blood pressure and the risk of hypertension[5], and therefore a constant therapy of vitamin D, either alone or combined with calcium, for the prevention and treatment of osteoporosis, in the absence of explicit risk factors for vitamin D deficiency, appears to be inappropriate[6,7]. Indeed, this therapy may provoke a significant rise in gastrointestinal symptoms and renal diseases[6]. Yet despite the dangers, nearly half of all over-50s continue to use these supplements[8]. The effect of vitamin D on the mortality of the elderly is in fact very odd: Whereas vitamin D3 seems to decrease mortality, vitamin D2, alfacalcidol and calcitriol apparently have no beneficial effects at all[6], and may even provoke hypercalcaemia; moreover, if vitamin D3 is administered together with calcium supplementation, the risk of nephrolithiasis is increased[7]. However, the current use of vitamin D by elderly people as a strategy for the prevention of hip fracture could be promoted just for its effects on muscular atrophy. This would reinforce the hypothesis that hip fracture is provoked by a fall, not by osteoporosis.

Mineralisation deficit has also been proposed as a cause of "bone weakness" making elderly persons liable to suffer an "osteoporotic" hip fracture. But according to recent studies, the problem of mineralisation in elderly people is not one of a regular decrease of calcium in the bone, but rather the irregular distribution of its mineralisation. Tissue mineral density is significantly

higher in the periosteal, and decreases from there to the endostium; it diminishes from the distal to the proximal part of the femur neck, and thus varies in a radial fashion. In addition, tissue variations in the axial direction of the femoral neck are responsible for important alterations in bone elasticity. Therefore, this spatial heterogeneity of elastic coefficients of bone tissue has consequences for bone as an organ[9,10]. In a similar fashion, mineral crystals at the external cortical bone surfaces of the femoral neck of patients with a fractured hip are larger than in a non-fracture control group. Moreover, the mineral content is higher, with cortical porosity values being almost 35% higher than in control groups, while the osteocyte lacunar number density is significantly lower than in controls[11]. Consequently, the cortical bone of the superolateral femoral neck of hip fracture patients presents distinct signs of fragility at various levels of its structure[12]. These findings could be very important to understanding the pathogenesis of bone weakness in hip fractures. Hence, merely providing "remineralising" drugs to prevent the occurrence of hip fracture appears too simple a notion. Recent research findings have further reinforced the hypothesis that hypermineralisation and the heterogeneity of mineralisation patterns are at the root of bone fragility[9-12].

An increased mineral content of bone tissue, in addition to heightened porosity, has also been observed in femur bone obtained from autopsies[13], with the consequent deleterious effects on bone strength and the risk of fracture.

The calcium-phosphorus ratio does not vary between hypermineralised osteocyte lacunae and bone matrix, according to studies of osteoporotic patients and an osteoarthritic control group. The role of hypermineralised osteocyte lacunae in the biomechanical properties of bone is not totally clear, but investigating the relation between hypermineralisation and femoral neck fracture susceptibility would constitute a very interesting line of research to obtain a better knowledge of the bone stiffness-flexibility relation. Previous studies have found that bone fragility may be greatly increased in the presence of bone tissue heterogeneity in osteons and interstitial tissue[12], and other researchers have reported that the degree of bone tissue mineralisation is significantly lower in the osteons than in the interstitial tissue both in hip fracture patients and in controls, whereas the presence of osteons and interstitial tissue is significantly greater in hip fracture patients. These data further support the view that bone fragility may be related to a higher degree of tissue mineralisation[14].

We performed similar studies, but retrieving the bone samples from the base of the femoral neck, as in osteoarthritis the femoral head becomes very dense, and obtaining the samples from this area might provoke a bias, in comparison with samples from osteoporosis patients. We determined microcrystalline salt standards in order to quantify Ca and P, in accordance with the methods reported in previous publications by our group[15]. All results were calculated as the weight fraction percentage of Ca and P[16]. Cancellous bone in hip osteoarthritis was found to be stoichiometrically similar to normal bone; that is to say, it is characterised by a Ca/P molar ratio corresponding to hydroxyapatite. However, the cancellous bone in hip fracture patients had an increased Ca/P ratio, associated with higher concentrations of Ca and P. We believe this further refutes the idea that calcium intake should be increased or drugs administered to "improve mineralisation" in osteoporotic patients and thus prevent hip fracture (unpublished data). The determination of Ca and P fractions in bone mineral density (BMD) in order to enhance fracture risk assessment and thus enable more targeted therapies to be devised has also been recommended[17].

Other therapies intended to diminish the risk of hip fracture, such as the combination of anabolic agents with bisphosphonates, have had little success. Similarly, the combination of teriparatide and denosumab, although increasing the bone matrix density more than is achieved by either agent alone[18], not only does not reduce the risk of fracture but may also produce long-term collateral effects. These new therapies, targeted at inhibiting bone resorption and enhancing bone formation, through a better understanding of the signalling network for osteoblast-osteoclast coupling, will allow novel therapeutic targets to be established for osteoporosis treatment but they have nothing to do with decreasing the risk of hip fracture. Denosumab, a monoclonal antibody for the receptor activator of the NF-κB ligand, a key osteoclast cytokine; odanacatib, a specific inhibitor of the osteoclast protease cathepsin K; and antibodies against the proteins sclerostin and dickkopf-1, two endogenous inhibitors of bone formation, have all achieved promising results in the treatment of osteoporosis[19].

Therefore, if osteoporosis were the cause of hip fracture, then by treating osteoporosis many fractures could be prevented. However, as the real causal framework is different, the following questions (and answers) arise. What actually provokes a fracture? In many cases, a fall and what provokes a fall? In many cases, a sensory deficit and which sensory deficits are capable of provoking a fall? Apparently, ophthalmic and/or auditory disorders, brain disease or reduced mobility. In consequence, taking action to prevent falls caused by these circumstances will reduce the prevalence of hip fracture. Unfortunately, comparison between races (Caucasian *vs* Asian, and particularly to black race) is very difficult as social situation are different.

THE SOCIAL PROBLEM

Funding

Undoubtedly, if pharmacological treatment for osteoporosis were the solution for "osteoporotic" hip fractures, financial support for this purpose would be

needed. Funding would have to be obtained either directly, from the patient, or indirectly, *via* a public welfare system. Since the end of World War 2, European welfare systems, based on principles of solidarity, have been the linchpins of funding for disease prevention and treatment programmes. However, following the onset of the economic crisis in 2007, governments have declared that such systems are no longer sustainable. National health service budgets have been slashed throughout Europe[20], but in many countries pharmaceutical expenses are either still rising or are falling at a slower rate than other items in health system budgets, thus forming a recurrent financial problem that presents a major challenge to society.

In Europe, national health services spent typically accounts for 6%-12% of Gross Domestic Product (GDP), but elsewhere the situation may be very different. Thus, in the United States, where a more market-oriented system exists, health spending represents nearly 18% of GDP. Nevertheless, a large sector of the population remains without access to a good quality health service. Private medical insurance can be cripplingly expensive, and many are forced to do without in order to meet day-to-day living costs. The Health Alliance International of the Washington University School of Public Health has reported that for this reason millions of persons in the first world are condemned to suffer avoidable disease and early death[21].

The austerity policies currently being applied throughout Europe slow economic growth and hamper the repayment of external debt[22-24]. Paul Krugman, the Nobel Prize-winning economist, has advocated raising government budgets for public welfare policies, including health programmes[25,26]. Similar conclusions were drawn by Greek authors in a recent paper published in the *Lancet*[27].

National policies to prevent hip fracture need generous budgets, but since spending cannot rise indefinitely, national budgets for healthcare policies must be focused on efficiency and effectiveness. Thus, current spending on ineffective medicaments should be readdressed toward effective medical actions, and as the medical treatment of osteoporosis does not reduce the prevalence of hip fracture[2,8,28,29], the national health services budgets for such treatments should be reassigned toward social support, particularly fall prevention. The question remains: Will national governments do so?

The power of pharmaceutical companies

There is much current debate concerning the real need for medicaments. An increasing number of doctors are convinced that a significant proportion of the drugs currently prescribed are ineffectual if not actually harmful[28-44]. Obviously, many drugs are necessary and valuable, but pharmaceutical and medical device companies often trial their products among the most favourable population and comparison groups in order to obtain the most positive outcomes for their interests. Company staff controls the data and perform the analyses in-house, while academic researchers are often paid to be listed among the authors when in fact they have contributed little and cannot vouch for the data presented; although difficultly, current rules, and regulations try to avoid that. Many "opinion leaders" work for pharmaceutical companies as advisers, and most doctors on the committees of scientific societies have links to companies that are an important source of funds to these societies[28]. In many cases, too, trials with negative results are suppressed and remain unpublished[29-31]. In the nineteenth century, Quetelet[30] observed, "society prepares the crime and the guilty person is only the instrument by which it is executed", and this proposition is still applicable today.

Drug companies are very powerful and have often been accused of making illicit payments to individuals or institutions to further their ends. In addition, many have been convicted of marketing harmful - often fatal - drugs, of committing fraud, of manipulating prices and of concealing evidence[31]. The fines levied against drug companies for these offences are insignificant in comparison to the enormous profits obtained, and are often regarded as merely the cost of doing business[31]. In 2012, a major United States pharmaceutical company agreed to pay a fine of $60.2 million in order to forestall an investigation into the corruption of foreign doctors, hospital managers and pharmaceutical controllers in Europe and Asia[32].

Both in the United States and elsewhere, the large pharmaceutical concerns head the ranking of the most unlawful companies[31,33]. In the United States, the drug market is regulated by politicians, who have come to be a prime target for industry lobbying[31]. At one point, indeed, the United States Secretary of Defense was at the same time the Chief Executive Officer of an important pharmaceutical company, while the budget director of the White House later became Vice-President of a top drug company, and the President himself was a member of the board of this company before coming into power[28].

The same conflict of interest issue has occurred in the United Kingdom. Thus, in 2005 the House of Commons Health Committee highlighted the enormous and uncontrolled power of the pharmaceutical industry, and accused it of exerting pressure on doctors, Non-governmental organizations, patients' associations, journalists and politicians[34-37]. Nevertheless, after receiving this report, the British Government did nothing to change the situation - an outcome influenced by the fact that the pharmaceutical industry, after tourism and finance, is the most profitable business activity in the country[31,35].

Several books have analysed this problem in detail, including a recent very well documented one by the director of the Nordic Cochrane Centre[31], two by past editors of the *New England Journal of Medicine*[28,38] and

one by an editor of the *British Medical Journal*[39]. Other publications have reported on abuses in specific medical fields[40-42] and on the scourge of overdiagnosis[29,43,44].

Are osteoporosis patients victims of this conflict of interests?

The treatment of osteoporosis is also affected by the above-described conflict of interests. In 2005, a major drug company agreed to pay $36 million to settle criminal and civil charges related to the illegal marketing of raloxifene, a drug used in the treatment of osteoporosis. The company had claimed this medicament prevented breast cancer and cardiovascular diseases, but failed to reveal that it also increased the risk of ovary cancer[31].

The problem in this context begins with the very definition of osteoporosis. The pharmaceutical industry, among others, sponsors the definition of diseases[45,46]. Although osteoporosis is defined as a metabolic disorder characterised by decreased bone mass and deteriorated bone structure, resulting in an increased susceptibility to fractures[47], osteoporosis - the visual image of osteopaenia - is actually a normal skeletal situation among elderly people. The World Health Organization (WHO) definition of osteoporosis is based on bone density data presented by young women[48], which has nothing to do with the situation of elderly persons, among whom bone deterioration is just a part of body decline in general. No objective reason was presented by the WHO group on osteoporosis when it was decided that anyone with a BMD that lies 2.5 standard deviations or more below the average value for young healthy women would be considered as having osteoporosis[48]. However, so far, no an alternative standard has been published.

On the basis of the WHO definition, densitometry is considered by patients' associations to be the gold standard for the diagnosis of osteoporosis. However, according to technological evaluation agencies, the truth is quite the opposite[31]. Both the defining body and many patients' associations are funded by pharmaceutical companies[31], which have an evident interest in ensuring that all persons presenting osteoporosis, under the WHO densitometry definition, should receive pharmaceutical treatment[48]. It has been shown that all post-menopausal women will present osteoporosis. In consequence, according to the drug companies' approach, from a given age, at least half of the entire population should be pharmacologically treated for this disease. In fact, the evidence base has been systematically distorted, and evidence-based medicine and guidelines have been hijacked by pharmaceutical companies[49,50].

Health technology agencies have published data obtained from five independent evaluations of the predictive performance of bone density measurements. Depending on the threshold values used and the assumed lifetime incidence of hip fracture, these studies have reported predictive values for positive results in BMD tests ranging from 8% to 36%[51]. Similarly, recent systematic reviews have concluded that there is insufficient evidence to inform the choice of which bone turnover marker to use in routine clinical practice to monitor the response to osteoporosis treatment. Consequently, the research priority should be to identify the most promising treatment-test combinations for evaluation in subsequent, methodologically sound, randomised controlled trials (RCTs), in order to determine whether or not bone turnover marker monitoring actually improves treatment management decisions, and ultimately impacts on patient outcomes in terms of reduced incidence of fracture. Given the large number of potential patient population-treatment test combinations, the most promising combinations would initially need to be identified in order to ensure that the RCTs focus on evaluating those strategies[52]. Such projects should also focus on the multifactorial etiology (co-morbidity, type and circumstances of trauma, polypharmacy, previous fractures, hereditary, menopause, *etc.*) of broken bones. International registries are a major step forward to this approach.

BMD studies do not predict hip fracture and long-term pharmacological treatment for osteoporosis does not reduce the incidence of hip fracture cases[53]. Furthermore since the new drug-induced bone formed has not a normal structure, iatrogenic fractures can appear. The majority of women of menopausal age are at low risk of "osteoporotic" fracture in the short-medium term. If BMD testing leads to unnecessary treatment and anxiety (typical effects of disease mongering), it may do more harm than good[45].

Moynihan *et al*[45] suggest that preventive medicine is threatening the viability of publicly funded healthcare systems, and that osteoporosis has been effectively sponsored by the pharmaceutical industry. Too many people who fall and develop a fracture are considered for treatment of osteoporosis[45]. Conversely, systematic reviews of randomised trials have shown that the decline in BMD is attenuated with exercise[54,55], and one such review found that some forms of supervised exercise increase muscle mass and reduce the incidence of falls[56]. Observational studies have shown there is a protective association between regular exercise and hip fracture[57].

The field of osteoporosis is an obscure one, particularly when conflicts of interest arise in addressing the relationship between osteoporosis and hip fracture. There are three main reasons why a patient with osteoporosis or any disease may experience symptomatic improvement: Medicament effect, placebo effect and the natural course of the disease. Most published reports of patient improvement are strongly affected by bias[31]. In the field of orthopaedics, unfounded research claims have been made by companies manufacturing joint implants[58,59]. Apart from medical researchers and physicians, scientific journals also seem to have been affected by dishonest reporting[60]. Osteoporosis associations reject comments on their funding[61], but the

fact is that while some osteoporosis associations receive funding from government agencies, lists of commercial sponsors also appear on their websites[28,31,45].

A PROPOSED NEW PARADIGM FOR THE AETIOPATHOGENESIS OF HIP FRACTURE IN THE ELDERLY: THE BASIS OF PREVENTION

Since hip fracture is usually caused by a fall, by identifying the population with a propensity to suffer a fall, *i.e.*, those with a sensory or cognitive problem aggravating the risk of a fall, and then providing proper treatment for such problems, both falls and hip fractures could be prevented.

Each year, approximately 30% of non-institutionalised persons aged over 65 years suffer a fall. Group and home-based exercise programmes and home safety interventions can reduce the risk and hence the rate of falls[54,55]. Multifactorial assessment and public health intervention programmes, on the other hand, reduce the rate of falls but not the risk of falling; certain specific forms of exercise, such as Tai Chi, also reduce the risk of falling. Vitamin D supplementation does not appear to reduce the risk or rate of falls but may be effective in people who have low levels of vitamin D before treatment[56].

Hip protectors probably reduce the risk of hip fractures when provided to older people in nursing care or residential care settings, without increasing the frequency of falls. However, since they are very uncomfortable, patients keep them in the wardrobe. They also may slightly increase the risk of pelvic fractures. Poor acceptance and adherence by older people offered hip protectors is a barrier to their use[62].

Together with these physical actions to prevent falls, some basic lines of scientific research must be undertaken to establish a new paradigm. In this respect, genetic research has been employed to address the question of osteoporosis. It has been reported that two gene variants of key biological proteins can increase the risk of osteoporosis and osteoporotic fracture. The combined effect of these risk alleles on fractures is similar to that of most well-replicated environmental risk factors, and they are present in more than one in five white people, suggesting a potential role in screening[63]. Although the authors of this paper studied the risk of osteoporosis they did not consider the risk of fracture or of falls. Another study, in an *in vivo* analysis of zebrafish, examined the bone regulatory properties of plastin 3 (PLS3), a protein involved in the formation of filamentous actin (F-actin) bundles, and found it to be related to osteogenesis imperfecta type I, with a rare variant (rs140121121) in PLS3. The association of this variant with the risk of fracture among elderly heterozygous women indicates that genetic variation in PLS3 is a novel aetiological factor that is involved in common, multi-factorial osteoporosis[64]. The question then arises: How many elderly persons present this complex mechanism, which, according to theory, can account for the risk of hip fracture?

One thing is to alleviate osteoporosis but quite another to imagine that, even if this were achieved, it would prevent or reduce the incidence of hip fracture. New research into "omics" is enhancing our understanding of the pathogenesis of osteoporosis, but this does not mean that a new paradigm for the aetiopathogenesis of hip fractures is being created. Again, in accordance with the real causality framework that has been established, research should be focused, not on osteoporosis, but on preventing falls by vulnerable persons. New findings in the fields of the human genome, transcriptome and metabolomics, if appropriately addressed, would reveal the susceptibility of elderly people to falls and thus open the way to preventing many hip fractures.

Genome

The completion of the Human Genome Project[65], followed by the development of a more manageable understanding of the human genome in the Hap Map Project[66] and the launch of Genome-Wide Association Studies (GWAS)[67], marked a great accomplishment and initiated a burst in scientific discovery of the genetic underpinnings of common diseases. Therefore it is expected that our knowledge of the factors provoking falls will also benefit from genome studies.

GWAS have located most of the very common gene variants in the human genome and have identified over 500 independent strong single nucleotide polymorphism associations. The 1000 Genomes Project[68] and the UK10K Project[69] are population-level sequencing projects that have led to an explosive growth of individual whole genome sequencing (WGS) data.

In the post-genomic era, next-generation sequencing (NGS) technologies have become more accessible in terms of cost, analytic validity and rapidity. Whole-exome sequencing (WES) using NGS has the capacity to determine in a single assay an individual's exomic variation profile, limited to about 85% of the protein coding sequence of an individual, composed of some 20000 genes, 180000 exons, and constituting approximately 1% of the whole genome. A sensitivity of 98.3% for detecting previously identified mutations, as well as benign variants, has been reported by WES[70]. Furthermore, WES allows the phenotype expansion and identification of new candidate disease genes that would have been impossible to diagnose by other targeted testing methods[70]. Proof-of-concept examples of the identification of rare, disease-causing variants are now available for WGS and WES strategies[71-73]. A major indication for their use is the molecular diagnosis of patients with suspected genetic disorders or that of patients with known genetic disorders with substantial genetic heterogeneity involving significant gene complexity. Particular limitations in WES are the gaps in coverage of the exome, the difficulty of finding

the causal mutation among the enormous background of individual variability in a small number of samples, and the difficulty interpreting variants. It is in this field of work where new bioinformatic tools are currently of great assistance to researchers. A large database would be of great benefit in producing a profile of elderly people predisposed to suffer falls.

Transcriptome

The transcriptome is the complete set of transcripts in a cell, and their quantity, for a specific developmental stage or physiological condition. Understanding the transcriptome is essential for interpreting the functional elements of the genome and revealing the molecular constituents of cells and tissues, and also for understanding development and disease. The key aims of transcriptomics are: (1) to catalogue all species of transcript, including mRNAs, non-coding RNAs and small RNAs; (2) to determine the transcriptional structure of genes, in terms of their start sites, 5′ and 3′ ends, splicing patterns and other post-transcriptional modifications; and (3) to quantify the changing expression levels of each transcript during development and under different conditions[74]. The human transcriptome is comprised of over 80000 protein-encoding transcripts and the estimated number of proteins synthesised from these transcripts is in the range of 250000 to 1000000. These transcripts and proteins are encoded by fewer than 20000 genes, suggesting a wide regulation of transcription, at the post-transcriptional and translational levels. RNA sequencing (RNA-seq) technologies have increased our understanding of the mechanisms that give rise to alternative transcripts and translations[75]. Next-generation sequencing technologies are evolving rapidly and it is likely that RNA-seq will become routine for many laboratories in coming years. Sequencers are becoming smaller and more personal and are beginning to equip individual departments and laboratories. Library preparation protocols are also becoming shorter and more efficient. Single molecule sequencing will afford insights into the precise orientation of transcription. Advances in methods to acquire sequences are likely to be accompanied by equally rapid advances in computation and data analysis[76].

The study of transcriptome allows us a deeper understanding of the pathogenesis of various diseases and makes it possible to select biomarkers to facilitate the early detection and therapeutic monitoring of these diseases. Recently published studies have compared healthy bone tissue with that of patients diagnosed with osteosarcoma (OS). Differences in the expression of certain genes were found between these experimental groups. These genes appear to be involved in the development of OS or other cancers, and could be used as biomarkers or as new drug targets[77]. Other studies have shown how multiple transcription factors and multiple signal transduction pathways are coordinated and temporally regulated during endochondral bone formation. Modelling these pathways and the interactions of groups of strain-specific genes will allow us to infer the interactions between transcription factors and signal transduction pathways that coordinate the training of vascular and skeletal tissues[78].

The study of bone transcriptome can enhance our understanding of the pathogenesis of hip fracture, enabling us to select biomarkers and thus facilitate early detection of elderly persons' susceptibility to falling. Nevertheless costs of these projects, and, if possible, therapy for these patients are unknown.

Metabolomics

Metabolomics is an emerging multidisciplinary science that requires cooperation between chemists, biologists and computer scientists. The metabolome refers to the complete inventory of small molecules, non-protein compounds, such as metabolic intermediates (ATP, fatty acids, glucose, cholesterol, hormones and other signalling molecules), and secondary metabolites found in a biological sample[79,80].

The metabolome changes continuously, depending on the activation and interaction of the various metabolic pathways within the cell. It also reflects the phenotype that can be used to interfere with gene function. Although genomics and proteomics can provide important information on the expected function, metabolomics provides an immediate snapshot of all biological functions that reflect current events at an exact moment[81,82]. By measuring the population of biomarkers (metabolites), it may be possible to distinguish the profiles or signatures of healthy individuals from those of persons with specific diseases[83]. Moreover, metabolomics may provide evidence of a metabolic disorder or injury with a high degree of precision and at less cost than by means of genomics, transcriptomics or proteomics. Therefore, it is a very suitable technique for generalised research in life sciences[84,85]. In the last decade of development of spectrometry, metabolic profiling using high-resolution magic-angle-spinning nuclear magnetic resonance (HR-MAS NMR) has made it possible to analyse intact tissue.

This technique has been applied to the study of specific tissue toxicity, to characterise the composition and structure of tissues, and to analyse human samples (such as biopsies, cells or tumours)[86,87]. In recent years, the number of papers published in this field has grown appreciably, and many of these describe the characterisation of the metabolic profile of different types of human tumours, including brain tumours[88,89], breast cancer[90-92], colorectal cancer[93] and prostate cancer[94,95]. The fact that no sample processing takes place provides the added advantage that the tissue can be recovered and analysed histologically a posteriori, thus providing the possibility of establishing direct correlations between the metabolic profiles and the histological[96] or even genomic results[97].

CONCLUSION

Precision medicine (PM) has the potential to produce

a fundamental change in how health care is practiced, but it does require health care personnel to understand the complexities present in this field. An important component of PM is the use of an individual's genomic information to offer targeted treatment, tailored to the individual. Whether or not the "omic" technologies eventually provide a practical contribution to our understanding of causality, offering significant advances in the real aetiopathogenesis of hip fracture, in any case, they will not appear to be subject to any conflict of interest, although new industries for "omic" technologies are emerging. If this advance comes to pass, will over-diagnosis cease to be a problem caused by scientific misjudgement or by conflicts of interest[98-100]. The respond will be in the future.

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