EDITORIALS

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Calcium supplements do not prevent fractures

Revisit recommendations to increase intake beyond a normal balanced diet

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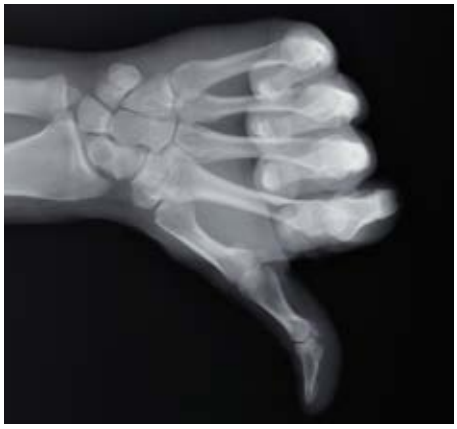
Calcium's serum concentration is tightly regulated. Net calcium excretion must be replaced, but the amount of calcium needed has been debated for decades. Twenty five years ago in this journal, Kanis and Passmore concluded that calcium supplements to prevent fractures were not justified by the available evidence,[1] though this view was challenged by determined opponents. According to two linked articles,[2 3] the conclusions of Kanis and Passmore still hold true. Furthermore, there seems little to be gained from an increased consumption of calcium rich foods.

In the first paper, Tai and colleagues report a systematic review and meta-analysis of randomised controlled trials of extra dietary or supplemental calcium in women and men aged over 50.[2] They found a meagre increase in bone mineral density, with no further gains beyond the first year. Importantly, this limited improvement was no greater when calcium was combined with vitamin D at any dose, even among participants with low serum concentration of 25-hydroxyvitamin D (25-OH-D), a high calcium dose, or baseline dietary calcium intake <800 mg/day.

In the second paper, Bolland and colleagues explored whether increased calcium intake could reduce the risk of fractures.[3] Most of the trials in this review tested supplements, and the authors identified evidence of publication bias in small or moderate sized trials. Meta-analyses confined to trials at lowest risk of bias found that calcium supplements had no effect on risk of fractures at any site. A clear exception was the classic French study by Chapuy and colleagues, performed in women living in nursing homes with a mean age of 84 who had the combination of a habitual low calcium intake (500 mg/day), very low serum concentrations of vitamin D (20 nmol/L), and low serum concentrations of calcium.[3 4]

Evidence on dietary calcium came mostly from heterogeneous cohort studies.[3] The studies differed in size, the quality of dietary assessments, range of exposures, adjustments for energy intake, selection of covariates, and ascertainment of fractures. Nonetheless, Bolland and colleagues found little evidence to support the theory that higher intake of dietary calcium could reduce risk of fractures.[3]



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The verdict on supplements

A very low calcium intake might lead to rickets and osteomalacia when serum vitamin D concentrations are only moderately low, while very low vitamin D concentrations will not necessarily lead to these conditions if calcium intake is adequate.[5] This interplay between vitamin D status and calcium intake is probably just as important in the prevention of fractures. Identifying the optimum interdependent thresholds for both would be a substantial clinical advance that could help to target interventions.

> The emphasis on ever increasing intakes of calcium and vitamin D is puzzling

A large scale meta-analysis of individual patient data from high quality trials could be one way to quantify the effects of extra calcium from diet or supplements at different thresholds of vitamin D concentration, baseline dietary calcium intake, or serum calcium concentration. We should also evaluate possible effects of different dairy products[6] and the potential impact of other nutrients and foods on risk of fracture.[7] The evidence currently available, however, gives us a strong signal that calcium supplements with or without vitamin D do not protect older people in general from fractures. This view is shared by the United States Preventive Services Task Force after their recent meta-analysis.[8] Calcium supplementation alone might even increase the risk of hip fracture.[3 9]

The official recommendations in the UK and Nordic countries of 700-800 mg/day of dietary calcium for adults seem at present to be enough. This intake can be achieved with a normal varied diet. Other guidelines such as from the US National Osteoporosis Foundation (NOF; http://nof.org/calcium) promote at least 1200 mg calcium and 800-1000 IU vitamin D daily as a goal for women aged 50 or older. Few women can achieve these intakes through dietary means alone.[10 11] As a result, most middle aged and older women in the US now take calcium and vitamin D supplements. As there is currently little, if any, firm evidence that higher intakes prevent bone loss, falls, or fractures in middle aged and older women and men living in the community,[2 3 10-13] the continued emphasis by several organisations (such as NOF) on ever increasing intakes of calcium and vitamin D is puzzling.

Follow the money

The profitability of the global supplements industry probably plays its part, encouraged by key opinion leaders from the academic and research communities.[14] Manufacturers have deep pockets, and there is a tendency for research efforts to follow the money (with accompanying academic prestige), rather than a path defined only by the needs of patients and the public. The research agenda and recommendations can also be influenced by the conflicts of interest that arise when leading academics have shares or management positions in companies making supplements.

While the study by Chapuy and colleagues has been influential,[9] calcium and vitamin D supplements have been marketed well beyond that trial's target population. Following guidelines, such as those of the NOF and the International Osteoporosis Foundation, would turn virtually the entire population aged over 50 into patients.[10 11] Most will not benefit from increasing their intakes[2 3 10-13] and will be exposed instead to a higher risk of adverse events such as constipation, cardiovascular events, kidney stones, or admission for acute gastrointestinal symptoms.[3] The weight of evidence against such mass medication of older people is now compelling, and it is surely time to reconsider these controversial recommendations.

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RESEARCH, pp 11, 12

Recipients of company gifts were much more likely to prescribe and use the company's products

Leadership by example: saying no to health industry board membership

Prohibition is the best way to safeguard scientific and clinical integrity

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Although medicine came late to managing conflict of interest and promoting transparency, well after law, finance, and government, it now confronts many of the critical issues. Part of the impetus to change was externally driven, with state and federal legislation playing a key role in the United States. For example, US senator Charles Grassley led the initiative to compel drug and device companies to disclose all payments over $10 to physicians and teaching hospitals, with the data accessible, name by name, on a public website.[1] But part of the impetus also came from within medicine. Several medical school deans believed that cosy ties between industry and faculty violated professional standards.[2] At the same time, medical researchers documented the extent and impact of these relations. In a linked paper a study of this problem by Anderson and colleagues is an excellent case in point.[3]

The research into physician-industry ties helped alter attitudes and practices. Dozens of well designed articles refuted some physicians' self serving claims that "you can't buy me for a steak dinner," or for stays in lavish resorts, or sizeable payments to promote a new drug or device. As the researchers found, recipients of company gifts were much more likely to prescribe and use the company's products. Indeed, the company expended its funds to gain market share.[4 5]

Investigators also illuminated institutional conflicts of interest that had remained obscure. One study found that 60% of medical department chairs had financial relations with industry.[6] A commentary on these and other findings noted that academic health centres and industry have different missions. Academic medical institutions seek to expand knowledge through research and to deliver effective patient care; industry looks to enlarge markets and profits to benefit shareholders. Boston's not for profit health system, Partners, did limit the sums its administrators could receive from serving on a healthcare company board of directors, to $5000 a day. Even so, much more needs to be done to curb industry influence over academic institutions.[7]

The study by Anderson and colleague strengthens the case for more stringent policies, by documenting the extent of these ties. In total, 279 academically affiliated directors, including chief executive officers, presidents, trustees, provosts, deans, and department chairs from 85 non-profit academic institutions received on aggregate $55m in compensation for serving on for profit health industry boards; on average they received annual payments of $193 000 and, in addition, stock options. The sums are unsettling—hardly a steak dinner—but effective institutional guidelines have yet to be agreed upon or widely implemented.

The authors provide only limited guidance by way of solutions. Accusations from a small cadre of disgruntled physicians notwithstanding, no one seeks to demonise industry. Academy-company cooperation is necessary for medical progress. But how do we safeguard scientific and clinical integrity, ensuring that it is knowledge and not market share that shapes research and clinical practice? How do we keep the playing field level when industry dispenses hundreds of thousands of dollars to academic leaders?

MALCOLM WILLETT

You *can* buy me for a steak dinner

Anderson and colleagues outline a range of policy choices: compel leaders to disclose and make public the sums they receive, have institutions review disclosures case by case, limit the payments leaders can receive, have leaders consult to companies without compensation, and prohibit the relationship itself. The authors do not advocate a specific solution, so how should we proceed?

Some policies are too weak to warrant much discussion. Disclosure, given the data presented here, already exists; company annual reports and filings provide the information, but this does not inhibit relationships. Institutional case by case determinations are possible But what should be the operating standards and how can institutional leaders be prevented from putting pressure on their subordinates? Payments could be limited, but to how much? And why is $5000 a day acceptable but not $50 000? Even if leaders served on boards without taking payment, there are other more indirect ways that both companies and institutions could find to do each other favours.

The only credible policy

Although it may seem radical, excluding leaders from directorships is the only credible policy. Critics insist directorships promote cooperation and progress; but obviously many ways exist for sharing knowledge without joining a board. By analogy, it is often claimed that Food and Drug Administration advisory committees must be allowed to appoint members with conflicts of interest because they are the most knowledgeable. But surely their insights could be obtained without appointing them to a committee—for example, letting them testify without giving them committee status or votes.

The gains, however, are clear. For one, education by example: medical students, fellows, and assistant professors would have a powerful example to emulate. Yes, share information with industry as appropriate, but do not take payment, travel, and the rest. For another, independence would make apparent that academic medical institutions stand apart, guided by professional principles, autonomous in theory and practice. In this domain as in many others, integrity must take precedence over individuals' compensation.

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RESEARCH, p 14

thebmj.com
- Clinical review: Pharmacogenetics (*BMJ* 2000;320:987)
- Fitting the drug to the patient (*BMJ* 2007;334:452)
- Editorial: Pharmacogenetics (*BMJ* 2001;322:1007)

Studies such as this one make adverse reactions—once classified as type B or idiosyncratic and bizarre—more predictable and avoidable

Pharmacogenetics begins to deliver on its promises

Those promises include safer and smarter use of drugs

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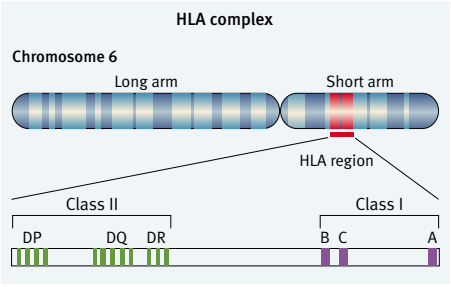
Pharmacogenetics promises the safer use of drugs through personalised prescribing that is informed by the genetic make-up of the individual, cancer tumour, or invading micro-organism. Although the first inherited molecular marker for a severe drug induced toxic effect was identified over half a century ago, until recently, few such markers were routinely used by prescribers. Even pharmacogenetics pioneers were beginning to wonder whether it was all hype. However, rapid progress is being made, and an increasing number of drugs have been licensed for use with a companion genetic test, both to improve the chances of success and to reduce the risk of severe side effects. This progress is typified in a linked article reporting that genetic testing helped to reduce patients' risk of a rare but serious adverse reaction to allopurinol.[1]

Abnormal reactions to foods and chemicals have been recorded since antiquity. Pythagoras, better known for his geometry, commented on hypersensitivity to the broad bean (favism); a reaction now known to be associated with hereditary deficiency in glucose-6-phosphate dehydrogenase (G6PD). Over 2000 years later, Charles Darwin observed that hair and skin colour was "correlated . . . with a complete immunity from the action of certain vegetable poisons, and from the attacks of certain parasites," and that this immunity seemed "to be partly inherent."[2]

With the introduction of synthetic drugs, this interplay between nature, nurture, and variability in drug response became apparent. Some individuals given the antimalarial primaquine developed haemolytic anaemia while most did not. Similar observations in the 1950s led to the birth of pharmacogenetics; the study of hereditary influences on drug response with Mendel's laws of inheritance and Garrod's "inborn errors of metabolism" providing the theory.

Subsequent studies showed that wide variability in dose requirement was often attributable to genetic variation (for example, warfarin). Others discovered that some cancer drug responses depended on specific genetic variations, and ethnic variability in response could sometimes be explained by differences in the prevalence of the variants. Pharmacogenetic targeting is now at the core of drug discovery research, and many highly successful, molecularly targeted agents have emerged within a widening therapeutic spectrum. Prescribed with companion tests, many have become so called "blockbuster" drugs, such as imatinib and trastuzumab.



Revealing its secrets

Explaining idiosyncracy

Pharmacogenetics advanced still further with improved understanding of adverse drug reactions, once termed "idiosyncratic" and generally thought to be immunologically based. In 1980, Baruj Benacerraf, Jean Dausset, and George Snell were awarded the Nobel prize for identifying the genetic locus later shown to be the source of much of this idiosyncracy: the major histocompability complex or the human leucocyte antigen (HLA).

An illustration of the participation of HLA in drug reactions is the strong association between hypersensitivity to abacavir and the HLA-B*57:01 allele.[4,5] Another example is the association of the HLA-B*15:02 allele with carbamazepine induced severe cutaneous adverse reactions (SCARs), including the potentially lethal Stevens-Johnson syndrome and toxic epidermal necrosis.[6]

In this week's issue of *The BMJ*, Ko and colleagues report a prospective evaluation of HLA-B*58:01 genotyping for preventing allopurinol associated SCARs.[1] The researchers genotyped 2910 patients eligible for allopurinol treatment but not previously exposed to the drug, and prescribed alternative or existing treatments for the 571 patients with the target allele. Using historical incidence as a comparator, the researchers expected to see seven cases of SCARs but found none; a highly significant difference.

Are these results generalisable enough to prompt routine genetic testing for patients needing allopurinol? Not yet. Participants were all Han Chinese from Taiwan, a population with a high prevalence of the HLA-B*58:01 allele (about 10%). While the association has been reported in other populations, there are several reasons for caution.[7-10] The risk allele frequency is low in white populations (<1%). More importantly, even in other Asian populations, the strength of association between allele and reaction is weaker. Almost all carriers of HLA-B*58:01 (about 98%) do not develop SCARs, and in some ethnic groups (including white populations), many patients with the adverse effect do not carry the risk allele.[11]

Even when genetic prediction of risk is robust, there are important trade-offs when considering routine testing before treatment. Ko and colleagues chose benzbromarone as the main alternative to allopurinol, a drug with a well defined efficacy and safety profile. Although no major adverse effects were observed, benzbromarone has been withdrawn from the market in many countries because of its potential for hepatotoxicity. The other alternative, febuxostat, is a new and expensive drug with a poorly defined, long term safety profile that includes reports of potentially lethal liver failure and cardiovascular events.[12] If genotyping is not available, prescribers could be tempted to substitute allopurinol for less safe or effective alternatives.

Pharmacogenetic studies have made important contributions to the safer use of drugs. Studies such as the present analysis by Ko and colleagues make adverse reactions—once classified as type B or idiosyncratic and bizarre—more predictable and avoidable.

Fifty years ago, a *BMJ* editorial commented: "To prevent attacks persons deficient in G6PD must avoid all potentially harmful drugs and foods. There is a case to be made for the use of routine screening tests, such as the spot-test, on all males of Mediterranean, Asian, or African extraction before treatment with sulphonamides, aspirin, phenacetin, and other drugs."[13] Such routine testing was never adopted because implementation of pharmacogenetic testing requires careful consideration of the benefits and harms involved, especially if the distribution of a risk allele among different ethnic populations is highly variable.

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RESEARCH, p 13

thebmj.com

- Europe's refugee crisis: an urgent call for moral leadership (*BMJ* 2015;350:h4833)
- Islamic State creates jihadi health service (*BMJ* 2015;350:h3487)

These findings should give pause to anyone who thinks there can be a safe hiding place for women and children when high explosives are being used in populated areas

Recording casualties of war

Why better data are important

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The impulse to create a permanent record of a war, including those who died in it, is far from new. The Louvre's curators believe that the museum contains the remains of the oldest known historical document, and certainly its oldest war memorial, the Stèle des Vatours, so named because of its representations of vultures feasting on the corpses.[1] Dating from around 2450 BC the Sumerian memorial "commemorates not the glorious dead of the victors but their victory and the sorry fate of the vanquished, who are shown on the stele lying piled one upon the other."[2]

Herodotus records 192 Athenians killed in the Battle of Marathon in 490 BC, an exact number that could be verified as much as 600 years later by the ancient Greek geographer Pausanias, who saw the stele inscribed with their names at their burial mound. Tellingly, the rounded number of 6400 Persians killed, estimated by the Greek victors, remains a matter of historical debate[3]—even today any record of casualties that is unable to name the dead faces this risk to its credibility.

Such customary records either exult in the scale of victory or pay tribute to the common sacrifice of soldiers, or both. Contemporary equivalents would include military successes measured in enemy deaths (still prevalent despite the occasional denial[4]) or the many respectful and often beautiful war memorials listing soldiers by name (but generally limited to one side in the conflict).

Move to include details of civilians

Another way of recording casualties has developed, however, that is based largely in civil society and is represented in conflict regions across the globe.[5] It is both more universalist in its values and more reflective of the information age in which we live. And its starting point is concern with the impact of war on people. These projects always include civilians, whom they also try to name, as is only fitting for a record of human losses. Using readily available databases, they systematically store, organise, and classify as much accompanying detail as they can about each victim and their manner of death. The key variables are name, demographic details, cause of injury, and time and location of death. The end result of this sometimes dangerous[6] and always painstaking work is structured data that can be studied. In a linked article Debarati Guha-Sapir and colleagues analyse such data on the Syrian conflict to reveal particular vulnerabilities and patterns of harm among population groups.[7]

FOTOGRAFICZNA CARO/ALAMY

No hiding place

The database for their study was compiled by the Syria based Violations Documentation Center (VDC), a human rights monitoring group that, like several other civil society organisations in the country, has been publishing a continuously updated list of documented and reported casualties in the civil war that broke out in 2011. All such projects (and their counterparts in other countries) have their limitations—and there remains much room for improvement in this fast evolving field. Crucial to Guha-Sapir and colleagues' study is that VDC's project takes pains to distinguish between combatants and civilians.

War and armed violence may be the result of human actions, but that doesn't mean we fully understand its effects (or, for that matter, its causes). One major gap in our knowledge is the large scale effects that various weapons have on civilian men, women, and children. Conventional weapons of war might be designed to kill or wound enemy combatants, as those who design, manufacture, and sell them will be ready to explain. But what effect do they have on civilian populations when used where they live? How much more likely are children to be killed by certain classes of weapons than others?

These are among the questions that Guha-Sapir and colleagues set out to investigate through careful statistical analysis of VDC's dataset. Their findings should give pause to anyone who thinks there can be a safe hiding place for women and children when high explosives are being used in populated areas, or who imagines that Syria's many bombed-out apartment blocks must have first been emptied of civilians. Their analysis also underlines the urgency of growing moves to ban the use of such indiscriminate weapons in populated areas.[8]

A movement for more detailed, consistent, reliable, and useful recording of casualties is gaining momentum and high level support, including from the secretary general of the United Nations[9] and various of its agencies. This is partly because of growing recognition that recording casualties can provide critical and timely information for humanitarian relief work and have an indispensable role in post-conflict truth and accountability processes. The range of good practices in casualty recording is becoming increasingly well understood,[10] and steps are well under way to establish globally recognised standards so that casualty datasets improve.[11]

We may wish that it were no longer true, but recording deaths in war remains a necessity in the 21st century. If treated seriously, the knowledge we gain from doing so may help us prevent further deaths.

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