Abstracts

Vitamin D supplements, calcium supplements and cardiovascular risk

The authors of this study investigate the effects of personal calcium supplement use on cardiovascular risk in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk.

The design was a re-analysis of the WHI CaD Study limited access dataset and incorporation in meta-analysis with 8 other studies. The WHI CaD Study, a 7-year, randomised, placebo-controlled trial of calcium and vitamin D (1 g calcium and 400 IU vitamin D daily) in 36 282 community-dwelling postmenopausal women, was analysed.

The main outcome measures were the incidence of 4 cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data.

In the WHI CaD Study there was an interaction between personal use of calcium supplements and allocated calcium and vitamin D for cardiovascular events. In the 16 718 women (46%) who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (p=0.05 for clinical myocardial infarction or stroke, p=0.04 for clinical myocardial infarction or revascularisation), whereas in the women taking personal calcium supplements cardiovascular risk did not alter with allocation to calcium and vitamin D. In meta-analyses of 3 placebo-controlled trials, calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% confidence interval 1.01 - 1.44), p=0.04), stroke (1.20 (1.00 - 1.43), p=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 - 1.32), p=0.02). In meta-analyses of placebo-controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from 8 trials of calcium supplements and the WHI CaD participants not taking personal calcium supplements. In total 1 384 individuals had an incident of myocardial infarction or stroke. Calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 - 1.45), p=0.004) and the composite of myocardial infarction or stroke (1.15 (1.03 - 1.27), p=0.009).

The conclusions were that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction, a finding obscured in the WHI CaD Study by the widespread use of personal calcium supplements. A reassessment of the role of calcium supplements in osteoporosis management is warranted.

Bolland MJ, et al. BMJ 2011;342:d2040.

Detecting multidrug-resistant tuberculosis

The Xpert MTB/RIF test (Cepheid, Sunnyvale, CA, USA) can detect tuberculosis and its multidrug-resistant form with very high sensitivity and specificity in controlled studies, but no performance data exist from district and subdistrict health facilities in tuberculosis-endemic countries. The authors aimed to assess operational feasibility, accuracy, and effectiveness of implementation in such settings.

They assessed adults (≥18 years) with suspected tuberculosis or multidrug-resistant tuberculosis consecutively presenting with cough lasting at least 2 weeks to urban health centres in South Africa, Peru, and India, drug-resistance screening facilities in Azerbaijan and the Philippines, and an emergency room in Uganda. Patients were excluded from the main analyses if their second sputum sample was collected more than 1 week after the first sample, or if no valid reference standard or MTB/RIF test was available. We compared one-off direct MTB/RIF testing in 9 microscopy laboratories adjacent to study sites with 2 - 3 sputum smears and 1 - 3 cultures, dependent on site, and drug-susceptibility testing. They assessed indicators of robustness, including indeterminate rate and between-site performance, and compared time with detection, reporting, and treatment, and patient drop-outs for the techniques used.

They enrolled 6 648 participants between 11 August 2009 and 26 June 2010. One-off MTB/RIF testing detected 933 (90.3%) of 1 033 culture-confirmed cases of tuberculosis, compared with 699 (67.1%) of 1 041 for microscopy. MTB/RIF test sensitivity was 76.9% in smear-negative, culture-positive patients (296 of 385 samples), and 99.0% specific (2 846 of 2 876 non-tuberculosis samples). MTB/RIF test sensitivity for rifampicin resistance was 94.4% (236 of 250) and specificity was 98.3% (796 of 810). Unlike microscopy, MTB/RIF test sensitivity was not significantly lower in patients with HIV co-infection. Median time to detection of tuberculosis for the MTB/RIF test was 0 days (IQR 0 - 1), compared with 1 day (0 - 1) for microscopy, 30 days (23 - 43) for solid culture, and 16 days (13 - 21) for liquid culture. Median time to detection of resistance was 20 days (10 - 26) for line-probe assay and 106 days (30 - 124) for conventional drug-susceptibility testing. Use of the MTB/RIF test reduced median time to treatment for smear-negative tuberculosis from 56 days (39 - 81) to 5 days (2 - 8). The indeterminate rate of MTB/RIF testing was 2.4% (126 of 5 321 samples) compared with 4.6% (441 of 9 690) for cultures.

The MTB/RIF test can effectively be used in low-resource settings to simplify patients' access to early and accurate diagnosis, thereby potentially decreasing morbidity associated with diagnostic delay, drop-out and mistreatment.

Boehme CC, et al. Lancet 2011;377:1495-1505.

Screening for prostate cancer – yes or no

In this study the authors assess whether screening for prostate cancer reduces prostate cancer-specific mortality. They used a population-based randomised controlled trial. The setting was the Department of Urology, Norrköping, and the South-East Region Prostate Cancer Register.

The participants were all aged between 50 and 69 and from the city of Norrköping, Sweden, identified in 1987 in the National Population Register (N=9 026). From the study population, 1 494 men were randomly allocated to be screened by including every 6th man from a list of dates of birth. These men were invited to be screened every 3rd year from 1987 to 1996. On the first two occasions screening was done by digital rectal examination only. From 1993, this was combined with prostate-specific antigen testing, with 4 µg/l as cut-off. On the 4th occasion (1996), only men aged 69 or younger at the time of the investigation were invited.

Data on tumour stage, grade, and treatment from the South East Region Prostate Cancer Register were used as the main outcome

measure, as was prostate cancer-specific mortality up to 31 December 2008.

In the four screenings from 1987 to 1996 attendance was 1 161/1 492 (78%), 957/1 363 (70%), 895/1 210 (74%), and 446/606 (74%), respectively. There were 85 cases (5.7%) of prostate cancer diagnosed in the screened group and 292 (3.9%) in the control group. The risk ratio for death from prostate cancer in the screening group was 1.16 (95% confidence interval 0.78 - 1.73). In a Cox proportional hazard analysis comparing prostate cancer-specific survival in the control group with that in the screened group, the hazard ratio for death from prostate cancer was 1.23 (0.94 - 1.62; p=0.13). After adjustment for age at start of the study, the hazard ratio was 1.58 (1.06 - 2.36; p=0.024).

After 20 years of follow-up the rate of death from prostate cancer did not differ significantly between men in the screening group and those in the control group.

Sandblom G, et al. BMJ 2011;342:d1539.

Multidrug pills may be better than single drugs for tuberculosis

Fixed-dose drug regimens for the treatment of tuberculosis have been advocated to prevent antibiotic resistance. Such regimens could also improve adherence because fewer pills need to be taken than with separate drug regimens. An open-label trial with 1 585 participants from Asia, Latin America, and Africa, all with newly diagnosed tuberculosis of the lungs, tested the non-inferiority of a 4-drug fixed regimen (rifampicin, isoniazid, pyrazinamide, and ethambutol) against separate administration of these drugs in the first 2, most intensive, months of treatment. Thereafter all participants took a fixed-dose combination of rifampicin and isoniazid 3 times each week for 18 weeks.

The non-inferiority of the fixed-dose regimen was shown in the per protocol analysis and a *post hoc* modified intention to treat analysis, but not in the prespecified modified intention to treat analysis, where 83.3% (570/684) of patients had a favourable outcome (negative culture result at 18 months) in the fixed-dose group compared with 84.8% (563/664) in the separate drugs group (risk difference −1.5%, 90% CI: 4.7 - 1.8%). The analysis of efficacy used complex definitions, which complied with the latest regulators' recommendations for assessment of antituberculosis drugs. Adverse events were similar across the study groups.

Despite incompletely demonstrated non-inferiority the authors endorse the push of fixed-dose regimens but stress that direct observation of patients' use of drugs remains essential for tuberculosis control.

Lienhardt C, et al. JAMA 2011;305:1415-1423.

BRIDGET FARHAM

SINGLE SUTURE

Smoking banned … again

China, the world's largest consumer of cigarettes, is having another crack at kicking the habit. The Chinese government has announced that it will ban smoking in enclosed public venues from May.

Businesses will have to put no-smoking signs on prominent display and carry out promotional activities warning people of the dangers of smoking.

But China's past record on anti-smoking measures is patchy at best. In January it missed a deadline to restrict indoor smoking. And a survey of over 12 000 Chinese citizens, published last year, found that 41.1% of smokers admitted to lighting up at work despite smoke-free policies.

Researchers say that raising the price of cigarettes would be a better strategy. Despite government plans to increase tobacco taxes, Chinese cigarettes remain among the cheapest in the world.

New Scientist, 2 April 2011, p. 7.

SINGLE SUTURE

Diet pill concern

Pressure is being put on the US Food and Drug Administration to ban the weight-loss drug orlistat, following new evidence linking it to liver and kidney problems.

Orlistat works by preventing the absorption of fat in the intestine. It is currently the only weight-loss drug approved by the FDA. Matthew Weir and colleagues at the University of Western Ontario in London, Canada, observed the rate of acute kidney injury in 953 orlistat users. In the year before orlistat use, 0.5% of the group experienced kidney problems, but this leapt to 2% in the year when they were taking the drug.

Previous research has shown a link between orlistat use and liver damage, prompting the adoption of a revised drug label warning of this side-effect. Consumer group Public Citizen information obtained from FDA files on adverse reactions links orlistat to 47 cases of acute pancreatitis and 73 cases of kidney stones. The drug should be removed from sale, it says.

New Scientist, 23 April 2011, p. 4.