Bone health in children

Guidelines for calcium intake should be revised

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Conventional wisdom, public policy on nutrition in many westernised countries, and advertisements for dairy products link increased consumption of calcium to better bone health and prevention of osteoporosis in later life. However, a meta-analysis by Winzenberg and colleagues in this week's *BMJ* shows that calcium supplementation in children is unlikely to result in a clinically relevant decrease in the risk of fracture in childhood or in later life.¹

Previous research has questioned whether increasing calcium intake through diet or supplements benefits children's or young adults' bones. Exercise significantly increased bone density and bone strength, but calcium intake between 500 and 1500 mg had no effect on the same outcomes in adolescent girls studied prospectively for 12 years as they passed into young adulthood.² Of three qualitative reviews of literature published in this decade, two concluded that it is not known whether the modest increments in rate of bone gain after supplementation with calcium or dairy produce will translate into clinically meaningful reductions in the risk of osteoporosis later in life or even persist beyond the treatment period.^{3 4} The third concluded that increases in dairy or total dietary calcium intake did not reliably increase bone mineral density or reduce fracture rate in children or adolescents.⁵

None the less, the recommended intake of calcium in children remains high in the United Kingdom, the European Union, Australia, the United States, and Canada (350-800 mg/day for children and 800-1300 for adolescents).⁶ Consequently, policy guidelines and nutrition programmes promote the intake of two to four servings of dairy products daily. For example, the US government promotes the consumption of three or more servings of cow's milk or other dairy products daily, and it subsidises the distribution of dairy products through the national school lunch programme and the women's, infants', and children's nutrition programme. The justification has been to avert a so called "calcium crisis" (a mismatch between calcium intake and recommendations) thought to be responsible for high rates of osteoporosis later in life.

What if we—researchers, paediatricians, marketers, and policy experts—have been wrong? What if increasing calcium intake in youth has no significant impact on fracture risk in early or later life as Winzenberg and colleagues conclude? Populations that consume the

most cow's milk and other dairy products have among the highest rates of osteoporosis and hip fracture in later life.^{6 7} Given this fact, it is important to ask whether sufficient evidence exists to continue assuming that consumption of these foods is part of the solution.

Furthermore, we need to ask the question of whether we are doing children a disservice by encouraging them to meet recommendations. Childhood obesity is on the rise in westernised countries, and dairy products—the main source of calcium recommended by nutrition guidelines—contribute greatly to the intake of fat and sugar in children.⁸ Nearly three quarters of the world's population are estimated to be lactose intolerant after the age of weaning and therefore do not tolerate the consumption of milk and other dairy products well. In addition, some studies suggest that the consumption of cow's milk increases the risk of some types of cancer.^{9 10}

The meta-analysis by Winzenberg and colleagues strengthens previous evidence that calcium or dairy products do not have a clinically relevant impact on bone health in youth. The focus on calcium recommendations in nutrition policy and research draws attention away from more comprehensive research on how to promote long term bone health among young people. Public health would be better served by researching how other dietary and lifestyle factors affect children's bones. Promising areas include the effect of regular exercise, vitamin D status, increasing fruit and vegetable consumption, limiting salt intake, limiting or avoiding animal protein, and avoiding smoking.

It is time to revise our calcium recommendations for young people and change our assumptions about the role of calcium, milk, and other dairy products in the bone health of children and adolescents. While the policy experts work on revising recommendations, doctors and other health professionals should encourage children to spend time in active play or sports, and to consume a nutritious diet built from whole foods from plant sources to achieve and maintain a healthy weight and provide an environment conducive to building strong bones.

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Prevention of diabetes

Drug trials show promising results, but have limitations

Diabetes affects one in 20 adults worldwide and 333 million cases are projected worldwide by 2025.¹ Treatment can prevent some of the microvascular and macrovascular complications, but diagnosis is often delayed until complications present,² so attention has focused on prevention and early screening. Two strategies currently exist for reducing the onset of diabetes—lifestyle interventions and drugs.

The Diabetes Prevention Program Research Group study found that lifestyle interventions delivered over 2.8 years reduced the incidence of diabetes by 58%.³ A similar reduction in risk was found in a Finnish study of 522 people at risk.⁴ The problem is that these interventions are labour intensive—one study needed 16 one to one sessions delivered by case managers to achieve target weight reduction and exercise levels.³ Although lifestyle interventions produce successful results in research settings, they are difficult to replicate even in well funded healthcare systems.

Considerable interest has focused on the prevention of diabetes with drugs. For instance, the Diabetes Prevention Program Research Group study found a 31% reduction in the incidence of diabetes with metformin at 2.8 years.³ Previously troglitazone was shown to be effective in controlling blood sugar levels but was removed from the market because of serious liver toxicity.⁵ In people with obesity orlistat has been shown to reduce the risk of diabetes by 37% when compared with placebo.⁶

More recently came the publication of the diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial.^{7,8} In this trial, which cost \$25m (£13m; €20m), 5269 people over 30 years with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were randomised to receive either rosiglitazone 8 mg daily or placebo, or ramipril 15 mg daily or placebo. The primary outcome was a composite of incidence of diabetes or death over a three year median follow-up period.

The trial was well executed; randomisation produced equivalent groups via a concealed computer telephone group. Although the drop out rate was high at around 25%, the analysis was on an intention to treat basis. At the end of the study 306 (11.6%) of the patients taking rosiglitazone developed diabetes compared with 686 (26%) of those given placebo (hazard ratio 0.40, 95%

confidence interval 0.35 to 0.46, $P < 0.0001$). Ramipril did not reduce the risk of diabetes.

These results are promising, but they should be interpreted with caution. The mean fasting plasma concentration of glucose in both groups at baseline was 5.8 mmol/l, whereas the two hour impaired glucose tolerance test had a value of 8.7 mmol/l. The study population was therefore composed predominantly of people with impaired glucose tolerance rather than those with abnormal fasting glucose. Fasting glucose concentrations rather than impaired glucose tolerance are usually used to screen for diabetes in the United Kingdom. Secondly, the rationale for using a composite end point of death and diabetes is unclear. Several considerations should be taken into account when using a composite end point.⁹ These include whether the component outcomes carry similar weight of importance to patients; and whether the component outcomes are likely to have similar relative risk reductions. This is not the case for death rates, which were similar in both groups and therefore should be analysed separately. Furthermore, despite the population being at low risk of heart failure (10 year risk 0.33%) a significant increase (0.4%) in heart failure was seen in the rosiglitazone group compared with placebo (7.03, 1.60 to 30.9, number needed to harm at three years 250). The use of thiazolidinediones is increasingly recognised as being associated with fluid retention and heart failure, and this is more common when they are combined with insulin.⁵ Also the drug showed no clear benefit on patient relevant outcomes at three years—the rate of all cardiovascular events was higher in the intervention group (1.37, 0.97 to 1.94, $P = 0.08$).

A key question that remains is whether rosiglitazone prevents the onset of type II diabetes or merely lowers blood sugar concentrations in patients with new onset diabetes. As in the metformin trial in 2002, this can only be resolved by analysis after a washout period, which is promised later in the year.

The finding that rosiglitazone can prevent diabetes in people at risk of getting diabetes needs to be tempered with possible adverse effects of the drug, such as heart failure, and perhaps the risk of medicalising a lifestyle issue. Providing drugs is expensive, even without the additional costs of monitoring their side effects and treating them. Lifestyle interventions seem to work but they are difficult to replicate. What we still

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