Reduced serum vitamin B-12 in patients taking metformin

Until the clinical importance is clear, simple dietary advice could solve the problem

PETER TITMUSS/ALAMY

RESEARCH, p 1177

Josep Vidal-Alaball honorary research fellow
vidal-alaballj@cf.ac.uk
Christopher C Butler professor of primary care medicine, Department of Primary Care and Public Health, Heath Park, Cardiff CF14 4YS

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work."

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2010;340:c2198
doi: 10.1136/bmj.c2198

As many as 22% of people with type 2 diabetes could have vitamin B-12 deficiency.[1] The cause of vitamin B-12 deficiency in these patients remains controversial,[2] but it can have important consequences and should be considered in the differential diagnosis of diabetic neuropathy. In small short term studies, treatment with metformin has been associated with reduced vitamin B-12 concentrations and an increased risk of vitamin B-12 deficiency.[3 4]

Kooy and colleagues conducted a trial of the long term effects of metformin treatment on metabolic and microvascular and macrovascular complications in patients with type 2 diabetes who were already taking insulin.[5] Three hundred and ninety patients were randomised to receive insulin plus metformin or insulin plus placebo. After a follow-up of 4.3 years, the study found fewer macrovascular events in the metformin group, which was largely accounted for by the beneficial effect of metformin on weight.

In the linked study this same group of authors, but with de Jager as first author, perform a further analysis of their earlier study and report important differences in serum vitamin B-12 in participants. In the placebo group, vitamin B-12 increased by 0.2 pmol/l (0%, 95% confidence interval −3% to 4%), whereas in the group with the addition of metformin vitamin B-12 was reduced by 89.8 pmol/l (−19%, −22% to −15%). At baseline, three participants in the metformin group and four in the placebo group had vitamin B-12 concentrations below 150 pmol/l. At follow-up after 4.3 years this had increased to 19 and five participants, respectively. The reduction in concentrations of vitamin B-12 in the metformin group persisted and become more apparent over time. The number needed to harm per 4.3 years was 13.8.[6]

Although the absolute number of affected participants was small the differences in vitamin B-12 concentrations are convincing. A strength of this study is the long period of follow-up.

The authors recommend that regular measurement of vitamin B-12 concentrations during long term metformin treatment should be considered. Sadly, though, they do not report on quality of life, neurological status, or measures of fatigue. Neither do they report whether participants received any dietary advice regarding vitamin B-12. As their introduction makes clear, we have no robust research underpinning the assumption that people with vitamin B-12 concentrations of 150 pmol/l or less are indeed vitamin B-12 deficient. Although they may be at higher risk for vitamin B-12 deficiency related effects, these risks are not clearly quantified or always directly related to vitamin B-12 concentrations. An opportunity may have been missed to elucidate whether reduced vitamin B-12 concentrations resulted in meaningful symptoms. Were the participants with lower concentrations of vitamin B-12 more likely to feel worse and have adverse effects?

Other uncertainties include whether or not these findings apply to most patients managed in primary care, who are not usually treated with insulin—should these patients also be monitored for vitamin B-12 concentrations? The conversion of patients with type 2 diabetes to insulin treatment is controversial,[7] and it is the minority of patients whose diabetes is hardest to control who typically start insulin treatment. If patients are monitored, how should serum vitamin B-12 be measured?[8] Furthermore, it is not clear what form the intervention should take. The options include dietary advice; increase intake of foods rich in calcium and vitamin B-12; and vitamin B-12 supplements, which could be taken orally or injected[9 10]—most patients will not have problems absorbing vitamin B-12 from the gut because this form of vitamin B-12 deficiency is unlikely to be related to intrinsic factor or bowel disease.

There are several other questions related to vitamin B-12 replacement. Given the long time it takes to deplete vitamin B-12 stores, how often—if at all—would intramuscular injections need to be repeated? Should concentrations be monitored once treatment is started? Can treatment be stopped after dietary improvement? Would we miss important morbidity by proceeding on the basis of symptoms and heightened clinical suspicion rather than on systematic screening in all patients taking metformin?

The case that de Jager and colleagues make for routine assessment of serum vitamin B-12 concentrations is based on findings from patients taking insulin and with no evidence that monitoring will benefit patients. The mechanisms are unclear, but it could be something as simple as the dietary change associated with metformin. We first need to determine whether simple dietary counselling when metformin is started and at medication/annual reviews will solve the problem. If it does not, a trial of screening for vitamin B-12 deficiency in patients taking metformin would be needed. Patients taking metformin (not just those also treated with insulin) should be randomised to systematic serum vitamin B-12 screening or routine care, with patient oriented outcomes and costs included in the outcomes. Otherwise, we risk increasing the burden on patients and the costs of care by treating biochemical outcomes rather than outcomes that matter to patients.

1 Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Topolski R. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes: a cross-sectional study. *J Am Board Fam Med* 2009;22:528-34.
2 Andres E, Noel E, Goichot B. Metformin-associated vitamin B12 deficiency. *Arch Intern Med* 2002;162:2251-2.
3 Ting RZ-W, Szeto CC, Chan MH-M, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. *Arch Intern Med* 2006;166:1975-9.
4 Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, Burg B, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med* 2003;254:455-63.
5 Kooy A, de Jager J, Lehert P, Wulffele MG, Bets D, Donker AJM, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med* 2009;169:616-25.
6 De Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010;340:c2181.
7 Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010;375:481-9.
8 Goringe A, Ellis R, McDowell I, Vidal-Alaball J, Jenkins C, Butler CC, et al. The limited value of methylmalonic acid, homocysteine and holotranscobalamin in the diagnosis of early B12 deficiency. *Haematologica* 2006;91:231-4.
9 Vidal-Alaball J, Butler CC, Potter CC. Comparing costs of intramuscular and oral vitamin B12 administration in primary care: a cost-minimization analysis. *Eur J Gen Pract* 2006;12:169-73.
10 Vidal-Alaball J, Butler C, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev* 2005;(3):CD004655.

Diagnosing diabetes using glycated haemoglobin A1c

Could have several advantages over traditional diagnostic methods

RESEARCH, p 1178

Wenying Yang head of endocrinology department, China-Japan Friendship Hospital, Beijing, 100029, China
ywy_1010@yahoo.com.cn

Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: (1) No financial support for the submitted work from anyone other than his employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouse, partner, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2010;340:c2262
doi: 10.1136/bmj.c2262

Diabetes is one of the three most prevalent chronic diseases that pose serious threats to health. A recent study of 46 239 Chinese people aged 20 years or more indicated a prevalence of diabetes and prediabetes (blood glucose between normal and diabetic values) of 9.7% and 15.5%, respectively.[1] These figures translate into a total of 92.4 million people in China with diabetes. In the linked study, Bao and colleagues assess the value of glycated haemoglobin A1c (HbA_{1c}) in diagnosing diabetes and identify the optimal HbA_{1c} cut-off value to be used in Chinese adults.[2]

Currently, fasting plasma glucose values and the oral glucose tolerance test are most commonly used for the screening and diagnosis of diabetes. However, both require a fast of at least eight hours, and the oral glucose tolerance test also requires multiple blood collections, aspects that reduce patient compliance and limit their clinical application.

Recently HbA_{1c}, a measure of long term glycaemic control, has been suggested as an alternative tool for diagnosing diabetes. Because HbA_{1c} values are proportional to the mean blood glucose concentration over the previous two to three months, patients do not need to fast, making these tests convenient and easy to perform.

In June 2009, an international expert committee consisting of members from the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation published a report recommending the use of an HbA_{1c} value of 6.5% or more as a diagnostic criterion for diabetes.[3] In the latest 2010 version of *Standards of Medical Care in Diabetes* released by the American Diabetes Association,[4] HbA_{1c} values of 6.5% or more and of 5.7% or more are recommended as diagnostic and screening criteria for diabetes, respectively. Similarly, a recent community based study assessing the validity of HbA_{1c} for the diagnosis of diabetes in Asian Indians proposed that HbA_{1c} thresholds of 6.1% and 6.5% could be used as screening and diagnostic tests for diabetes, respectively.[5] Previous studies have shown, however, that the optimal cut-off point of HbA_{1c} for detecting diabetes may vary by racial or ethnic group.[6 7]

Little information regarding the usefulness of HbA_{1c} tests in the diagnosis of diabetes is available for Chinese populations. In the linked cross sectional survey Bao and colleagues assess the usefulness of HbA_{1c} as a screening and diagnostic tool for diabetes compared with fasting plasma glucose concentrations and the oral glucose tolerance test in 4900 Chinese adults with no history of diabetes.[2] Their results suggest that for those at high risk for diabetes, an HbA_{1c} cut-off value of 6.3% or more had a significantly higher sensitivity than fasting plasma glucose at 7.0 mmol/l or more and of the generally suggested HbA_{1c} threshold of 6.5% or more. HbA_{1c} therefore provides an alternative method for screening and diagnosing diabetes in the clinical setting. Furthermore, HbA_{1c} can be sampled at any time, improving patient compliance and enabling timely diagnosis of people who do not meet the criteria for fasting and those who are unwilling to take the oral glucose tolerance test.

Currently, most general hospitals in China can carry out HbA_{1c} tests. In addition, the Chinese Ministry of Health is implementing a quality control system for HbA_{1c} tests. The study by Bao and colleagues established an optimal HbA_{1c} cut-off value of 6.3% or more as a diagnostic criterion for diabetes in Chinese adults. Nevertheless, further epidemiological and clinical studies on a larger scale, particularly prospective ones, are needed to validate the efficacy of HbA_{1c} for diagnosing diabetes, and to tackle the association of HbA_{1c} diagnostic cut-off points with chronic complications of diabetes, such as retinopathy.

1 Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362:1090-101.
2 Bao Y, Ma X, Li H, Zhou M, Hu C, Wu H, et al. Glycated haemoglobin A1c for diagnosing diabetes in Chinese population: cross-sectional epidemiological survey. *BMJ* 2010;340:c2249.
3 International Expert Committee. International expert committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327-34.
4 American Diabetes Association. Standards of medical care in diabetes-2010. *Diabetes Care* 2010;33(suppl 1):S11-61.
5 Kumar PR, Bhansali A, Ravikiran M, Bhansali S, Dutta P, Thakur JS, et al. Utility of glycated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study. *J Clin Endocrinol Metab* 2010 Published online 6 April.
6 Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, et al. Use of GHb (HbA_{1c}) in screening for undiagnosed diabetes in the U.S. population. *Diabetes Care* 2000;23:187-91.
7 Nakagami T, Tominaga M, Nishimura R, Yoshiike N, Daimon M, Oizumi T, et al. Is the measurement of glycated hemoglobin A1c alone an efficient screening test for undiagnosed diabetes? Japan national diabetes survey. *Diabetes Res Clin Pract* 2007;76:251-6.

HIV transmission in serodiscordant heterosexual couples

Risk is not zero but is low if the infected partner takes antiretrovirals

DAVID HOFFMAN/ALAMY

RESEARCH, p 1179

Marie-Claude Boily senior lecturer in infectious disease ecology, Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, London W2 1PG
mc.boily@imperial.ac.uk
Anne Buvé professor, Department of Microbiology, Institute of Tropical Medicine, Antwerp, B-2000, Belgium
Rebecca F Baggaley research fellow, Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, London W2 1PG

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2010;340:c2449
doi: 10.1136/bmj.c2449

bmj.com podcasts

Listen to a podcast about HIV transmission in serodiscordant couples with Anne Buvé
http://podcasts.bmj.com/bmj/

Antiretroviral treatment inhibits HIV viral replication and reduces plasma viral load. Low plasma viral load is associated with a lower probability of HIV transmission, which opens the possibility of treatment to reduce HIV transmission.[1 2] The feasibility, potential effectiveness, and risks of such treatment are unclear, and a key uncertainty is the extent to which successful antiretroviral treatment reduces HIV infectivity. In the linked observational study, Del Romero and colleagues estimate the risk of heterosexual transmission of HIV-1 from infected people taking combined antiretroviral treatment.[3]

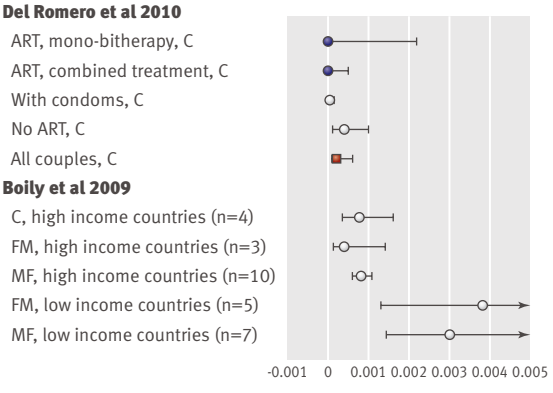
Only randomised controlled trials comparing transmission in HIV serodiscordant couples, where the infected (index) partner receives or does not receive antiretroviral drugs, can accurately estimate the effect of such treatment on infectivity. The HPTN-052 trial is the only ongoing trial of this type. In this trial, partners infected with HIV are assigned to immediate antiretroviral treatment or deferred treatment when their CD4 count drops below 250 cells/μl. This trial will hopefully provide a good estimate of the effect of antiretroviral treatment in patients with more than 250 CD4 cells/μl, but it will obviously not obtain an estimate in patients with fewer than 250 CD4 cells/μl.

Evidence that antiretroviral treatment reduces sexual transmission of HIV comes from observational studies of serodiscordant couples and ecological studies,[2 4 5] but transmission from patients on antiretroviral treatment has also been documented.[6] Del Romero and colleagues' study is a welcome addition to the observational studies that estimate infectivity in serodiscordant couples. In partners of patients with HIV not receiving treatment, the incidence of HIV was 0.6 per 100 couple years, whereas none of the partners of patients on antiretroviral treatment seroconverted. The authors also computed the probability of transmission per unprotected sex act (figure). The infectivity estimates were low and imprecise, with no significant difference between treated and untreated patients (figs 1 and 2, see bmj.com). The authors therefore conclude that transmission of HIV from successfully treated patients cannot be excluded, because it is biologically possible and because the data are consistent with one infection per 91 couple years (compared with one per 71 couple years in untreated couples). Moreover, because this is an observational study, the treated and non-treated groups are most probably not comparable. Patients receiving treatment are necessarily different because of their poorer clinical history. Some differences were also seen in risk behaviour and characteristics of the index partners at baseline and during follow-up, which may have increased transmission in couples with an untreated index partner.[3]

How do the results of Del Romero's study compare with other studies? Apart from four studies from high income countries conducted before the era of antiretroviral treatment that also reported no seroconversion, the infectivity estimates in the non-treated group were generally lower in Del Romero's study than in previous studies.[4 7 8] A recent systematic review of observational studies in heterosexual serodiscordant couples found five studies reporting HIV infectivity estimates according to treatment. In two of these studies with information on viral load, no seroconversions were seen when treated index patients had viral loads of fewer than 400 copies/ml. One study from Uganda reported no seroconversions in partners of treated cases despite only 79% having achieved a viral load fewer than 400 copies/ml six months after the start of treatment. A more recent study (not in the systematic review[4]) in seven African countries observed one seroconversion in 256 person years of follow-up in partners of index cases.[9]

Together, these seven studies of patients receiving antiretroviral treatment independently of viral load will help to provide a more precise overall estimate of the seroconversion rate.[3 4 9] Although the probability of transmission during antiretroviral treatment seems to be greater than zero, these studies support the idea that treatment reduces infectivity, which could translate into benefits at the population level, as long as risk behaviour does not increase. To date, some studies,[5] but not all,[10] suggest a beneficial effect of antiretroviral treatment at the community level.

What effect do these data have on counselling serodiscordant couples? In 2008, the Swiss Federal AIDS Commission released a controversial statement to the effect that HIV infected people with undetectable concentrations of the virus (<40 copies/ml) for at least six months, who adhered to a strict antiretroviral drug programme and had no other sexually transmitted infections, were not infectious to their regular heterosexual partners.[11] The challenge for counsellors is to ensure that people understand the exact set of conditions and time period when it seems to be safe to have unprotected sex. Del



Per sex act heterosexual transmission probability estimates with and without antiretroviral treatment (ART)[3] compared with pooled estimates before the ART era.[7] n=number of studies included in pooled estimates; FM=female to male, MF=male to female; C=MF and FM combined

Romero and colleagues are more cautious and continue to promote the use of condoms regardless of viral load; in their study condom use reduced HIV transmission by 93%.

On the basis of current evidence, we conclude that although taking antiretroviral treatment reduces the risks of vaginal intercourse with an HIV positive partner, intercourse is not totally risk free. Despite their limitations, additional studies in discordant couples are needed to estimate the infection risk more precisely, especially for homosexual and heterosexual anal intercourse.[7 12] It is unclear how these results for heterosexual populations will translate to homosexuals.

1 Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000;342:921-9.
2 Cohen MS, Gay C, Kashuba ADM, Blower S, Paxton L. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. *Ann Intern Med* 2007;146:591-601.
3 Del Romero J, Castilla J, Hernando V, Rodríguez C, García S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ* 2010;340:c2205.
4 Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009;23:1397-404.
5 Montaner J, Wood E, Kerr T, Yip B, Lima V, Shannon K, et al. Association of expanded HAART coverage with a decrease in new HIV diagnoses, particularly among injection drug users in British Columbia, Canada [abstract]. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, 2010:88LB.
6 Sturmer M, Doerr HW, Berger A, Gute P. Is transmission of HIV-1 in non-viraemic serodiscordant couples possible? *Antiviral Ther* 2008;13:641-2.
7 Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis* 2009;9:118-29.
8 Baggaley RF, White RG, Boily MC. Heterosexual HIV infectivity estimates from prospective discordant couples studies by gender and setting: a systematic review and meta-analysis [abstract]. Seventeenth International AIDS Conference, Mexico City. 2008:MOPE0321.
9 Donnell D, Kiarie J, Thomas K, Beaten J, Lingappa J, Cohen C, et al. ART and risk of heterosexual HIV-1 transmission in HIV-1 serodiscordant African couples: a multinational prospective study [abstract]. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, 2010:136.
10 Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Prins M, et al. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. *AIDS* 2008;22:1071-7.
11 Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitement antirétroviral efficace ne transmettent pas le VIH par voie sexuelle. *Bulletin des Médecins Suisses* 2008;89(5). www.saez.ch/html_f/2008/2008-05.html.
12 Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. *Int J Epidemiol* 2010; published online April 20.

Wellbeing in the workplace

Lack of precise measurement or recommendations should not deter employers from taking action

Michael F Roizen chief wellness officer and chair, Cleveland Clinic Wellness Institute, 9500 Euclid Ave, Cleveland, OH, 44195, USA
roizenm@ccf.org
Keith W Roach associate professor of clinical medicine, associate professor of public health and epidemiology, Weill Medical College of Cornell University, 505 East 70th, New York, NY, 10021, USA

Cite this as: *BMJ* 2010;340:c1743
doi: 10.1136/bmj.c1743

In November 2009, the National Institute for Health and Clinical Excellence (NICE) published guidance for employers on promoting mental wellbeing through productive and healthy working conditions.[1] Excess work related stress harms employees' physical and mental health. From an economic perspective, impaired efficiency at work associated with mental health problems costs the United Kingdom £15.1bn (€16.9bn; $22.5bn) a year.[2] From a health perspective, stress at work is consistently associated with increased total mortality and acute myocardial infarction.[3 4]

Ideally, the guidelines should outline discrete steps that could easily be implemented, improve the efficiency and satisfaction of workers, and ultimately be shown in a randomised controlled trial to improve morbidity and mortality. Although the guidance falls short of this ideal, business managers and human resources departments may still benefit from the advice.

Unfortunately, some of the advice is so general that it is almost useless. For example, the first recommendation in the guidance is to: "Adopt an organisation-wide approach to promoting the mental wellbeing of all employees, working in partnership with them. This approach should integrate the promotion of mental wellbeing into all policies and practices concerned with managing people, including those related to employment rights and working conditions." This reads more like a mission statement than a discrete step that a responsible business manager could implement. Other recommendations are more practical, however; examples of how to monitor mental wellbeing

INSADCO/ALAMY

(such as attitude or satisfaction surveys, and data on absence rates and employee turnover) are reasonable and appropriate for different sized businesses. Other advice, such as allowing workers flexible hours, and that managers "respond with sensitivity to employees' emotional concerns" may seem to lag behind policies already in place in many human resource departments.

Perhaps the lack of concrete guidance comes from the diverse and changing nature of stress. Stress is not easy to measure—after all, it is subjective. The NICE guidance defines stress as "the adverse reaction people have to excessive pressure or other types of demand placed on them," meaning that, by definition, workplace stress is excessive. Other major causes of chronic disease—physical inactivity,

smoking, poor nutrition, and excessive alcohol use—are at least quantifiable, so it is easier to study the effects of specific interventions.[5]

Physical inactivity can be measured using a pedometer, which can be provided to each employee with encouragement to walk for 30 minutes every day. Smoking can be measured by cotinine concentrations and banned on premises, and there could be a ban on hiring smokers (allowable in 39 US states). Unhealthy eating and obesity can be monitored through body mass index, waist size, and portion sizes. People can be advised to eat five servings of fruits and vegetables a day, and the organisation can help them do this by making healthy food available and unhealthy food less so. Alcohol intake can be quantified.

Evidence shows that programmes to manage stress in the workplace have beneficial effects. Much of the best work in this field comes from Japan, where workplace stress is high—more than 60% of Japanese workers report high levels of anxiety and stress.[6] Two recent randomised controlled trials showed that single session educational programmes for supervisors, compared with no programme, can significantly improve knowledge,[7] reduce psychological distress in workers, and improve job performance.[6 8] One programme that taught stress management in hospitals decreased the frequency of malpractice claims (arguably a proxy in the United States for preventable medical errors) in 22 hospitals by 71% compared with a 3% decrease in hospitals without a stress management programme.[9] Such a programme also decreased physician (and nurse) burnout and improved physician (and nurse) satisfaction with work.[10 11]

The NICE guidance implies that the difficulty in measuring stress should not deter organisations from trying to reduce it. Organisations will be more successful if employers help their workers to manage stress.[9]

The science of reducing stress in the workplace is in its infancy, and completing the circle from business policies to improved clinical outcomes is far away. In the meantime, the NICE guidelines can provide some basic advice for businesses wishing to make an impact on productivity and their employees' health.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: (1) MFR has received no financial support for the submitted work; KWR has support from Cornell University and RealAge for the submitted work; (2) MFR has received a salary from and is employed by the Cleveland Clinic, which may have an interest in the work, and founded and sold his shares in RealAge to Hearst in December 2007; MFR serves on the scientific advisory board of RealAge, which might have an interest in the submitted work; KWR has no relationships with companies that might have an interest in the submitted work; (3) their spouses, partners, and children have no financial relationships that may be relevant to the submitted work, except they had ownership interests in RealAge, which were sold in December 2007; and (4) MFR writes books that deal with this subject and leads the Wellness Institute of the Cleveland Clinic and thus has non-financial interests that may be relevant to the submitted work. KWR has no non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 National Institute for Health and Clinical Excellence. Promoting mental wellbeing through productive and healthy working conditions: guidance for employers. 2009. www.nice.org.uk/nicemedia/pdf/PH22Guidance.pdf.
2 Sainsbury Centre for Mental Health. Mental health at work: developing the business case. Policy paper 8. 2007. www.scmh.org.uk/pdfs/mental_health_at_work.pdf.
3 Matthews KA, Gump BB. Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the multiple risk factor intervention trial. *Arch Intern Med* 2002;162:309-15.
4 Rosengren A, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:953-62.
5 US Centers for Disease Control. Chronic diseases and health promotion. www.cdc.gov/chronicdisease/overview/index.htm.
6 Nishiuchi K, Tsutsumi A, Takao S, Mineyama S, Kawakami N. Effects of an education program for stress reduction on supervisor knowledge, attitudes, and behavior in the workplace: a randomized controlled trial. *J Occup Health* 2007;49:190-8.
7 Anderson R. Stress at work, the current perspective. *J R Soc Promot Health* 2003;123:81-7.
8 Takao S, Tsutsumi A, Nishiuchi K, Mineyama S, Kawakami N. Effects of the job stress education for supervisors on psychological distress and job performance among their immediate subordinates: a supervisor-based randomized controlled trial. *J Occup Health* 2006;48:494-503.
9 Jones JW, Barge BN, Steffy BD, Fay LM, Kunz LK, Wuebker JL. Stress and medical malpractice: organizational risk assessment and intervention. *J Appl Psychol* 1988;73:727-35.
10 Krasner MS, Epstein RM, Beckman H, Suchman AL, Chapman B, Mooney CJ, et al. Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. *JAMA* 2009;302:1284-93.
11 Pipe TB, Bortz JJ, Dueck A, Pendergast D, Buchda V, Summers J. Nurse leader mindfulness meditation program for stress management: a randomized controlled trial. *J Nurs Adm* 2009;39:130-7.

Acupuncture transmitted infections

Are underdiagnosed, so clinicians should have a high index of suspicion

Patrick C Y Woo professor
pcywoo@hkucc.hku.hk
Ada W C Lin specialist
Susanna K P Lau associate professor
Kwok-Yung Yuen chair of infectious diseases, Department of Microbiology, University of Hong Kong, Hong Kong

Cite this as: *BMJ* 2010;340:c1268
doi: 10.1136/bmj.c1268

Acupuncture, which is based on the theory that inserting and manipulating fine needles at specific acupuncture points located in a network of meridians will promote the harmonious flow of "Qi," is one of the most widely practised modalities of alternative medicine. Because needles are inserted up to several centimetres beneath the skin, acupuncture may pose risks to patients. One of the most important complications is transmission of pathogenic micro-organisms, from environment to patient or from one patient to another.

In the 1970s and 1980s most infections associated with acupuncture were sporadic cases involving pyogenic bacteria.[1] So far, more than 50 cases have been described globally. In most cases, pyogenic bacteria were transmitted from the patient's skin flora or the environment because of inadequate skin disinfection before acupuncture. In localised infections, meridian specific and acupuncture point specific lesions were typical. About 70% of patients had musculoskeletal or skin infections, usually in the form of abscesses or septic arthritis, corresponding to the site of insertion of the acupuncture needles.[1 2] A minority had infective endocarditis, meningitis, endophthalmitis, cervical spondylitis, retroperitoneal abscess, intra-abdominal abscess, or thoracic empyema.[3 4]

As in other musculoskeletal or skin infections, *Staphylococcus aureus* was the most common bacterium responsible, accounting for more than half of the reported cases.[1 2] Although most patients recovered, 5-10% died

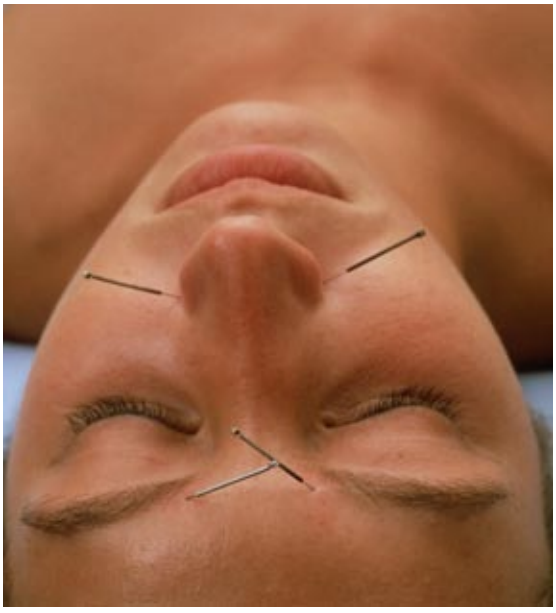
Response on bmj.com **"This kind of article could easily create an unhealthy scare in the public against acupuncture when there is minimal evidence here that current practices are actually problematic. The authors mostly talk about spread of infection in a setting that no longer exists. Every acupuncturist in the United States is bound by clean needle standards to single use, sterile needles."** Steven Mavros, president, Association for Professional Acupuncture, PA, USA
To submit a rapid response, go to any article on bmj.com and click "Respond to this article"

of the infections and at least another 10% had serious consequences such as joint destruction, paraplegia, necrotising fasciitis, and multiorgan failure.[1 2]

Apart from pyogenic bacterial infections, five outbreaks of hepatitis B virus infection associated with acupuncture, which affected more than 80 patients, have been described globally since the 1970s.[5 6] In most outbreaks the sources were infected patients, and the virus was transmitted from one patient to another through improperly sterilised or unsterilised reusable acupuncture needles, but in one outbreak an acupuncturist who was positive for hepatitis B surface antigen and hepatitis B e antigen was thought to be the source.[5 6]

The other two major bloodborne viruses, hepatitis C virus and HIV, could hypothetically be transmitted by acupuncture. Most evidence for the association of hepatitis C virus infection with acupuncture came from epidemiological and case-control studies, where acupuncture was found to be an independent risk factor for hepatitis C virus infections.[7] Although no clear evidence exists to support a link between acupuncture and HIV infection, there are reports of patients with HIV who had no risk factors other than acupuncture.[8]

A new clinical syndrome has emerged in the 21st century—acupuncture mycobacteriosis—which is mainly caused by rapidly growing mycobacteria.[9] These mycobacteria are thought to be transmitted from the environment to patients via contaminated equipment used in acupuncture, such as cottonwool swabs, towels, hot pack covers, and boiling tanks. All mycobacterial infections associated with acupuncture so far have been characterised by localised meridian specific and acupuncture point specific lesions without dissemination.[9 10] The lesions usually first appear as erythematous papules and nodules that subsequently develop into large pustules, abscesses, and ulcerative lesions after several weeks to months. Patients tended to delay seeking medical advice because of the slowly developing and relatively mild symptoms. Owing to the relatively hardy nature of mycobacteria,[10] the long incubation period of the infection, and the difficulty in making a diagnosis, mycobacteria have caused two large outbreaks associated with acupuncture, which affected more than 70 patients.[11 12]



TIM MALYON AND PAUL BIDDLE/SPL

The case reports and outbreaks of acupuncture transmitted infections may be the tip of the iceberg. The first reports of meticillin resistant *S aureus* (MRSA) transmitted by acupuncture appeared in 2009.[2] The emergence of community associated MRSA infections may aggravate the problem. To prevent infections transmitted by acupuncture, infection control measures should be implemented, such as use of disposable needles, skin disinfection procedures, and aseptic techniques. Stricter regulation and accreditation requirements are also needed.

Clinicians should also have a high index of suspicion, particularly for viral and mycobacterial infections transmitted by acupuncture because of their prolonged incubation periods, and they should alert health authorities about clusters of cases.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that all authors had: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Izatt E, Fairman M. Staphylococcal septicaemia with disseminated intravascular coagulation associated with acupuncture. *Postgrad Med J* 1977;53:285-6.
2 Woo PC, Lau SK, Yuen KY. First report of methicillin-resistant Staphylococcus aureus septic arthritis complicating acupuncture: simple procedure resulting in most devastating outcome. *Diagn Microbiol Infect Dis* 2009;63:92-5.
3 Lee RJ, McIlwain JC. Subacute bacterial endocarditis following ear acupuncture. *Int J Cardiol* 1985;7:62-3.
4 Vucicevic Z, Sharma M, Miklic S, Ferencic Z. Multiloculated pleural empyema following acupuncture. *N Engl J Med* 2004;350:1763.
5 Boxall EH. Acupuncture hepatitis in the west Midlands, 1977. *J Med Virol* 1978;2:377-9.
6 Kent GP, Brondum J, Keenlyside RA, LaFazia LM, Scott HD. A large outbreak of acupuncture-associated hepatitis B. *Am J Epidemiol* 1988;127:591-8.
7 Kweon SS, Shin MH, Song HJ, Jeon DY, Choi JS. Seroprevalence and risk factors for hepatitis C virus infection among female commercial sex workers in South Korea who are not intravenous drug users. *Am J Trop Med Hyg* 2006;74:1117-21.
8 Vittecoq D, Mettetal JF, Rouzioux C, Bach JF, Bouchen JP. Acute HIV infection after acupuncture treatments. *N Engl J Med* 1989;320:250-1.
9 Woo PC, Li JH, Tang W, Yuen K. Acupuncture mycobacteriosis. *N Engl J Med* 2001;345:842-3.
10 Woo PC, Leung KW, Wong SS, Chong KT, Cheung EY, Yuen KY. Relatively alcohol-resistant mycobacteria are emerging pathogens in patients receiving acupuncture treatment. *J Clin Microbiol* 2002;40:1219-24.
11 Song JY, Sohn JW, Jeong HW, Cheong HJ, Kim WJ, Kim MJ. An outbreak of post-acupuncture cutaneous infection due to Mycobacterium abscessus. *BMC Infect Dis* 2006;6:6.
12 Tang P, Walsh S, Murray C, Alterman C, Varia M, Broukhanski G, et al. Outbreak of acupuncture-associated cutaneous Mycobacterium abscessus infections. *J Cutan Med Surg* 2006;10:166-9.