Continuation of metformin after introduction of insulin in type 2 diabetes

Can prevent weight gain in non-obese patients and potentially improve cardiovascular outcomes

Metformin is the cornerstone of treatment early in the course of type 2 diabetes. Recent studies also provide evidence for the benefits of metformin when given late in the course of the disease, after the introduction of insulin. However, because metformin targets insulin resistance in overweight patients, can it be as beneficial in non-obese patients?

In the linked randomised controlled trial, Lund and colleagues compare the effects of metformin versus repaglinide in non-obese patients with type 2 diabetes treated with insulin. They randomised 102 patients (body mass index ≤27 and glycated haemoglobin ≥6.5), after a run-in period with combined repaglinide and metformin, to receive either repaglinide 6 mg plus insulin or metformin 2000 mg plus insulin. Patients had been known to have diabetes for about 10 years. After 12 months, they found no significant difference between the groups in the primary outcome of glycemic control—glycated haemoglobin decreased from 8.15 to 6.71 in the metformin plus insulin group and from 8.07 to 6.90 in the repaglinide plus insulin group (P=0.125). However, after excluding patients (n=7) with a positive glutamic acid decarboxylase-65 antibody status (a sign of autoimmunity), they found a small but significant difference in mean glycated haemoglobin in favour of the metformin plus insulin group (−0.29, 95% confidence interval −0.56 to −0.02; P=0.034). The daily dose of insulin was similar in both groups, as well as the overall risk of hypoglycaemia. However, metformin (versus repaglinide) significantly prevented weight gain (a secondary outcome) during insulin therapy (weight difference of −2.51 kg, −4.10 to −0.95; P=0.002). This finding is particularly important because repaglinide, the comparator in this study, is a short acting insulin secretagogue associated with a favourable metabolic profile and a slight to moderate weight gain during monotherapy (compared with other sulphonylureas), as shown in a Cochrane review.

Both regimens seemed to achieve tight glycaemic control in non-obese patients, but what about cardiovascular outcomes? No placebo controlled intervention trials exist with (conclusive) data on the long term effects of repaglinide on cardiovascular outcomes in patients with type 2 diabetes. Prevention of weight gain by metformin in overweight patients with type 2 diabetes who are taking insulin may reduce the risk of cardiovascular disease. In a long term placebo controlled trial, about 40% of the favourable effects of metformin on macrovascular disease was explained by reduction in weight, and about 35% was probably caused by an intrinsic effect of metformin on endothelial functions, partly independent of glycaemic control. Other studies support this last mechanism of action.

In overweight patients with type 2 diabetes and insulin resistance, metformin affects glucose metabolism by improving the responsiveness of the liver to insulin. Interestingly, in non-obese patients with type 2 diabetes, in whom insulin resistance is not pronounced, metformin lowers glucose as effectively as insulin secretagogues. Could metformin affect glycaemic control independently of the extent of insulin resistance? New evidence shows that metformin might act as a secretagogue of glucagon-like peptide type 1 (GLP-1), a gut hormone that acts on insulin release from the β cell and on glucagon release from the α cell to normalise blood glucose, in a glucose dependent manner. This additional effect of metformin may contribute to better glycaemic control in non-obese patients with type 2 diabetes, but this needs further investigation.

What are the implications of these findings for general practice? The prevention of weight gain by metformin (versus repaglinide) in non-obese patients with type 2 diabetes who are taking insulin is promising because an increase in body mass index from 25 to 27 is known to increase the risk of cardiovascular disease in the presence of type 2 diabetes. Continuation of metformin after the introduction of insulin in non-obese patients with type 2 diabetes may therefore not only reduce weight but have beneficial cardiovascular effects in the longer term. If metformin is contraindicated, repaglinide might be a reasonable alternative, at least for one year.

Food incentives and completion of tuberculosis treatment

A free lunch—not to be missed, but not effective as an incentive to complete treatment

In the linked randomised controlled trial, Martins and colleagues assess the effectiveness of a food incentive to enhance completion of treatment for tuberculosis in Timor-Leste. The meal, or “feijuada,” was provided at health centres and comprised meat, beans, and vegetables with rice. It seems unlikely that anyone could describe the free lunch as anything but beneficial. Or could they? We need to know if the intervention is effective in achieving its desired purpose and what the opportunity costs may be before deciding if it is beneficial.

Although the success of treatment depends on treatment adherence, many patients do not follow their prescriptions and treatment recommendations. In the case of chronic communicable diseases such as tuberculosis and HIV infection, maximising adherence is crucial to optimising the outcomes of treatment not only for the individual but also for the community, through decreased transmission and risk of generation of drug-resistant strains.

Experience across a variety of diseases shows that adherence is determined by a complex array of factors, including socioeconomic ones and those related to the health system, disease, treatment, and patient. Not surprisingly, no “magic bullet” can ensure adherence. Various measures have been promoted—for example, for adherence to tuberculosis treatment (box), which must be adapted to local circumstances (feijudas in Timor-Leste, fajitas in Mexico). Multidisciplinary research on the problem of adherence to tuberculosis treatment is needed as urgently today as it was in 1957, when a World Health Organization study group recommended that “research employing the disciplines of both the medical sciences and the social sciences is urgently needed.”

Incentives are aimed at increasing the patient’s motivation and reinforcing the behaviour necessary to complete treatment. Their effectiveness has been accepted for some time in developed countries—for example, financial incentives in the United States—but has not been evaluated rigorously in developing countries.

Martins and colleagues’ randomised controlled trial using food as an incentive to adhere to treatment is welcome for several reasons. It has shown the feasibility of conducting a high quality randomised controlled trial of such an intervention in a developing country. It evaluated whole food as a nutritional intervention for patients with tuberculosis rather than the vitamin and micronutrient supplements evaluated in other trials in developing countries (which found no convincing evidence of a beneficial effect on clinical outcomes). It investigated adherence to tuberculosis treatment, which is vital to the success of global efforts at tuberculosis control, and needs rigorous evaluation in developing countries and less attention paid to the controversy regarding the value of directly observed treatment.

Although the aim of the trial was to evaluate the effectiveness of a whole meal as an incentive to improve completion of tuberculosis treatment, provision of a meal may affect adherence via factors other than the patient’s motivation and behaviour. These factors include socioeconomic factors (by helping to mitigate the effect of poverty), health system factors (by making attendance at the health centre more attractive), factors related to the disease (if food makes a difference to...
treatment response), and factors related to the treatment (by removing hunger as a barrier to ingestion of drugs that increase appetite).

The study found that the food intervention had no significant effect on completion of treatment (76% v 78% completion, P=0.7) or adherence (93% for both groups, P=0.7). However, it did lead to improved weight gain at the end of treatment (10.1% v 7.5% improvement, P=0.04). The importance of the slightly greater weight gain in the intervention group by the end of treatment is doubtful—longer follow-up would show whether this simply reflects the earlier restoration of pre-illness weight expected in patients receiving more food.

Food supplements are popular with patients with tuberculosis and are increasingly made available in national tuberculosis control programmes, often with the support of food agencies such as the World Food Programme. In Martins and colleagues’ study, providing a free lunch that cost $2-3 (£1.2-1.9; €1.4-2.0) resulted in a doubling of the cost of treatment per patient. Because of the large number of malnourished people in the world and the limited supply of food supplements, how do we decide who should receive them? The argument for giving food supplements to patients with tuberculosis because they are often malnourished is a good one, but the argument based on improved completion of treatment and clinical outcomes is not supported by the study in Timor-Leste. Similarly rigorous studies are needed in different settings on food interventions aimed at improving treatment completion and outcomes, not just for tuberculosis but for other chronic communicable diseases, such as HIV infection.

There is no such thing as a free feijuada—there is a strong ethical imperative to ensure that resources are directed towards interventions with known value, especially where resources are particularly constrained. In view of the uncertain benefit of food supplements for HIV treatment, the time is ripe for updated guidance that is based on rigorous evaluation.


Clashes between the government and its expert advisers
Advisers need clearer rules on how to express contrary views

In the United Kingdom, experts advise and government ministers make policy with no obligation to accept their experts’ advice. For example, ministers have often declined to accept expert advice to raise alcohol taxes as a way of reducing problem drinking. The recent sacking of Professor David Nutt from the chairmanship of the Advisory Council on the Misuse of Drugs (ACMD) occurred because a minister rejected the recommendations of an expert adviser who continued publicly to express a view that was contrary to government policy.

The question of how science should be used to formulate government policy has been a problem on many occasions, in the UK and elsewhere. Disagreements between government and experts on the risks of bovine spongiform encephalopathy (BSE) from eating beef in the late 1990s prompted the reformulation of rules on the use of scientific evidence in developing policy. In the BSE affair, ministers discounted expert advice that the disease in cows might spread to humans, and the official BSE Inquiry subsequently recommended that the advice and the reasoning of expert advisory committees should be open and transparent.

The circumstances leading up to the sacking of Professor Nutt can be traced back to the request in 2007 by the home secretary for the ACMD to reassess the risks of cannabis use and its classification. The council’s response to the home secretary’s request was contained in its 2008 report. After a detailed review of the evidence, the ACMD advised against changing the classification of cannabis from a class C drug to a class B one (equivalent in its harms to amphetamines). This advice was rejected by the previous home secretary and the current one, Alan Johnson, as conflicting with what the government regarded as widely held public concerns about the risks of using cannabis and ecstasy. In January 2009, the government moved cannabis back into class B to avoid “sending mixed messages.” What has caused the trouble is that the ACMD chair subsequently continued to express views on the comparative harms of cannabis, alcohol, and other illicit drugs, even though his views reflect those of many other experts in the addictions field. Alan Johnson sacked Professor Nutt because he had “lost confidence” in him. The immediate cause was the publication of a lecture given by him to the centre for crime and justice studies at King’s College London. In this paper, Professor Nutt argued that ecstasy and
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Competing interests: MG was a specialist adviser on drugs to the  
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(2004) that looked at drug classification; he is also a member of  
of the Ministry of Justice Criminal Services Accreditation Panel. WH advised the Advisory Council on the Misuse of Drugs (ACMD) on drug-related deaths in 1999. He made a submission to the ACMD in 2008 about the proposed reclassification of cannabis and in 2008 he worked with Professor Nutt as part of a team of six ethicists and addiction researchers preparing a report for the European Monitoring Centre on Drugs and Drug Addiction on the ethical implications of neuroscience research on addiction.

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Panton-Valentine leucocidin associated  
Staphylococcus aureus infections

Early diagnosis and treatment, and screening of close contacts are essential

Panton-Valentine leucocidin (PVL) is a cytotoxin produced by  
Staphylococcus aureus that lyses leucocytes by creating pores on the cell surface. PVL was first detected in meticillin susceptible  
S aureus (MSSA) and then later in meticillin resistant  
S aureus (MRSA). Awareness of diseases related to PVL has increased since the worldwide emergence of these community acquired MRSA strains. In the United States, PVL positive MRSA has been associated with outbreaks of skin and soft tissue infection and sporadic life threatening diseases.  
In contrast, in Europe, especially in the United Kingdom, PVL positive  
S aureus strains are more commonly meticillin susceptible.  
Therefore, in the US, Switzerland, and Canada national guidelines for managing PVL positive  
S aureus disease are recommended for MRSA infections and in the UK for both MRSA and MSSA infections.

Regardless of meticillin resistance, PVL positive  
S aureus cause either recurrent spontaneous skin infections

or rare severe illnesses, such as necrotising pneumonia and rapidly progressive musculoskeletal infections.  
The common presence of PVL genes in these isolates belonging to different genetic backgrounds means that PVL is a major determinant of virulence. To understand the role of PVL in the pathogenesis of human infections, studies in animals have used PVL isogenic strains. Rabbits, rather than mice, seem to be a more relevant model for investigating PVL related diseases.

In humans, PVL seems to invade healthy skin—PVL positive strains are isolated mainly from primary abscesses that develop on previously normal skin without trauma, surgery, injected drug use, or underlying skin disease. In contrast, PVL negative  
S aureus are often isolated from secondary abscesses. This suggests that PVL may have no specific role in the development of secondary abscesses; it also explains why current animal models, which only explore secondary cutaneous infections, do
not always reflect the pathogenesis of PVL.\(^6\)

Management of uncomplicated skin and soft tissue infections caused by PVL positive \textit{S. aureus} consists mainly of incision and drainage of abscesses. When lesions are suspected in deep tissues, surgical management should be guided by repeated imaging. Magnetic resonance imaging seems to be the best modality to detect and assess the full extent of musculoskeletal involvement.\(^5\) Antibiotics have a moderate effect on clinical outcome, and it is proposed that their use is limited to patients who have a suboptimal response to surgery.\(^7\)

In Europe, empirical treatment of PVL positive \textit{S. aureus} infections does not require coverage for MRSA. Recently published UK guidelines for the treatment of PVL induced skin and soft tissue infections recommend the use of fluclxacillin, clindamycin, rifampicin, and co-trimoxazole.\(^6\) Nevertheless, PVL associated skin infections often reoccur after initial healing. Interestingly, treatment of community acquired MRSA skin abscesses with co-trimoxazole, after incision and drainage, reduced recurrence at 10 days follow-up.\(^7\)

Although much less frequent than skin and soft tissue infections, severe necrotising pneumonia linked to PVL positive \textit{S. aureus} can occur after influenza (or other respiratory) virus infection, and associated mortality is high.\(^8\) In light of a potential flu pandemic, health professionals need to be aware of PVL induced necrotising pneumonia, because flu patients have a higher risk of PVL positive \textit{S. aureus} superinfection. Leucopenia below 3 × 10\(^9\)/l and haemoptysis seem to predict mortality in community acquired pneumonia caused by PVL positive \textit{S. aureus} in children and young adults,\(^6\) and death occurs in 56-75\% of patients within four days.\(^5,9\) Prompt administration of drugs that block toxin production or its side effects is therefore essential. Because PVL is released during the early stages of the disease, the effects of the toxin should be reduced by using antibiotics that inhibit PVL production in vitro (clindamycin, rifampicin, or linezolid)\(^10\) and administering neutralising polyclonal human immunoglobulins.\(^11\) An increase in the leucocyte count indicates improvement. Bacterial clearance is necessary for full recovery, so the bacterial load can be reduced by combining bactericidal antibiotics with repeated surgical drainage of pleural empyema or pulmonary abscesses.

Hygiene and decolonisation can control household outbreaks of community acquired MRSA. The same measures might also reduce the burden of PVL positive \textit{S. aureus} in the community and prevent the spread of highly virulent strains. Topical decolonisation with nasal mupirocin and antiseptic solutions should be used for patients who have recurrent skin infections or severe PVL diseases (necrotising pneumonia or musculoskeletal involvement). Nasal carriage of PVL positive \textit{S. aureus} is rare except in infected patients—in healthy people it is more commonly carried in the throat. Therefore, screening of close contacts (household, family, partner) including swabbing of the throat is necessary.11 Similar decolonisation and hygiene measures should be observed by any contacts found to be positive on screening.

7. Dumong M, Markwell S, Peter J, Barenkamp S, Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. \textit{Ann Emerg Med 2009; Published online Apr 29.}

Economic progress and health improvement

Performance indicators should reflect both

The economic performance of countries is generally compared using the concept of gross domestic product (GDP). This is a measure of economic activity developed in 1940 by two British Nobel prize winning economists, James Meade and Richard Stone.\(^1\) The concept and the associated data framework—national accounts—were designed to manage the economy in wartime. The extent to which it has gained much wider currency is perhaps surprising.

Even with a very restricted notion of welfare, the link between GDP and welfare is not straightforward,\(^2\) and it has been recognised for many years that there is more to welfare than consumption.\(^3\) In 2008 President Sarkozy was concerned that France’s opinion of itself suffered because it compared badly with some other advanced countries on the basis of GDP per capita. A part of the reason for this “underperformance” is that France’s per capita labour supply is lower because the typical working
The National Institute for Health and Clinical Excellence (NICE) requires strong reasons for supporting an intervention that costs more than £30 000 (£33 300; $49 200) to deliver a year of good quality life.\textsuperscript{7} The Department of Transport generally puts a much higher value on life when deciding on measures to reduce the risk of road and rail deaths. This implies that lives could be saved with no extra overall expenditure by diverting resources from spending on road and rail safety to spending on medical interventions.\textsuperscript{8} More controversially still, some economists have argued that the value of life depends on what people can afford,\textsuperscript{9} with the inference being that life is worth more to the rich than to the poor, an approach that, despite the logic behind it, is unlikely to find widespread popular support. But a general point emerges that, even with a relatively modest value put on life, such as that proposed by NICE, the value of the increase in longevity over the 20th century is very substantial compared with the increased value of economic output.

If producing a measure of the value of life is controversial, at least survival rates can be measured clearly. A more complete measure of welfare would take into account not only how long people live but also their state of health. Measures of quality adjusted life years (QALYs) or disability adjusted life years (DALYs) of course exist. To produce these, people's state of health needs to be measured in a coherent way, and—if a single indicator is produced—a means of comparing the different health states is needed, which once again requires some kind of valuation.

Aside from the production of aggregate indicators, the report stresses a separate question about how far social and economic inequalities should be taken into account—also a longstanding problem faced by economists.\textsuperscript{10} Again, it is hard to foresee a satisfactory answer. Overall, the report regards itself as opening rather than closing a discussion. If it helps policy makers and commentators to see that there is more to life than GDP it will have made a valuable contribution.

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