Self monitoring of blood glucose in type 2 diabetes

May not be clinically beneficial or cost effective and may reduce quality of life

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In the accompanying papers, O'Kane and colleagues report a randomised controlled trial of blood glucose self monitoring in people with newly diagnosed diabetes (ESMON trial) and Simon and colleagues report a cost effectiveness analysis that ran alongside the previously published blood glucose self monitoring in type 2 diabetes (DiGEM) trial.[1-3]

The question of whether people with type 2 diabetes who do not use insulin should monitor their own blood glucose has been the subject of some lively exchanges in the *BMJ* for more than 10 years. In 1997, Marilyn Gallichan wrote, "The inappropriate use of self monitoring of glucose is wasteful of NHS resources and can cause psychological harm. There is no convincing evidence that self monitoring improves glycaemic control, nor that blood testing is necessarily better than urine testing."[4] These challenging observations were disputed by correspondents who suggested that self monitoring might help people with diabetes improve blood glucose control, avoid hypoglycaemia, improve quality of life, and enhance long term prognosis.[5]

The NHS Health Technology Assessment programme responded by commissioning a systematic review and a clinical trial.[3 6 7] In the systematic review, a meta-analysis of four randomised trials showed that in subjects with type 2 diabetes who were not treated with insulin, self monitoring of blood or urine glucose gave an estimated mean difference in glycated haemoglobin (HbA1c) of –0.25% (95% confidence interval –0.61% to 0.10%) when compared with people who did not self monitor.[6] A meta-analysis of three randomised controlled trials showed that, when compared with urine testing, blood glucose self monitoring did not improve glycated haemoglobin.[6] In a second meta-analysis published in 2005, the estimated difference in HbA1c between blood glucose self monitoring groups and no monitoring groups was –0.39% (–0.56% to –0.21%),[8] but two of the studies included in this meta-analysis had recognised methodological problems.[9] Despite apparently minimal clinical benefit, the use of blood glucose self monitoring has increased.[10]

In 2007, the *BMJ* published the results of the DiGEM trial of blood glucose self monitoring in type 2 diabetes.[3] The investigators responded to criticisms of earlier trials by including clearly structured advice to participants on how to use the results of self monitoring to adjust their diet, level of physical activity, and drug adherence. The difference in HbA1c associated with more intensive self monitoring compared with no monitoring was –0.17% (–0.37% to 0.03%) over 12 months. This result is consistent with the initial meta-analysis,[6] and it suggests that blood glucose self monitoring has little or no effect on medium term blood glucose control in type 2 diabetes not treated by insulin. Mild hypoglycaemic symptoms were uncommon and were more often recorded in the self monitoring groups. Only one patient in the control group had a serious hypoglycaemic episode.

The *BMJ* published 33 rapid responses to the DiGEM trial, and nearly all criticised the trial's conclusions. Some respondents argued that self monitoring would be especially beneficial in people with newly diagnosed diabetes. Another concern was that increased detection of hypoglycaemia in the self monitoring groups might represent a true clinical benefit. People with diabetes expressed concerns that restriction of self monitoring would limit their freedom to manage their own illness and deprive them of perceived benefits.

O'Kane and colleagues' ESMON trial found no significant difference in HbA1c between people with newly diagnosed diabetes allocated to blood glucose self monitoring and controls managed according to the same well defined algorithm without self monitoring at 12 months' follow-up.[1] The two groups showed no significant difference in hypoglycaemia. Patients who were allocated to self monitoring reported greater self rated depression than controls.

Simon and colleagues' cost effectiveness analysis of the DiGEM trial confirms that subjects in the self monitoring group had reduced self rated quality of life, perhaps as a result of increased anxiety and depression associated with blood glucose self monitoring.[2] It also shows that the additional healthcare costs associated with blood glucose self monitoring amount to about £90 (€114; $180) for each patient each year. This is mostly attributable to the costs of monitoring materials.

These results put the debate concerning self monitoring into a new ethical perspective. The DiGEM economic evaluation and the ESMON study draw attention to potential harms from self monitoring. Self monitoring is associated with reduced quality of life and increased depression for people with type 2 diabetes. The healthcare costs of self monitoring have been estimated comprehensively and, with diabetes now affecting some 3-4% of the population of the United Kingdom, the total healthcare cost of self monitoring may now exceed £100m each year in the UK.[11] This represents a substantial opportunity cost in terms of alternative interventions that might have improved the health of people with diabetes. For patients, self monitoring carries an opportunity cost in terms of the attention that they might have given

to more effective disease control measures aimed not just at blood glucose but also at blood pressure, cholesterol, smoking, body weight, and physical activity.

The statistician Austin Bradford Hill held as an ethical principle that health interventions must be evaluated before they are introduced into practice (WW Holland, personal communication, 2008). Self monitoring of blood glucose in type 2 diabetes provides an example of the difficulties that arise if this principle is not followed.

It is 25 years since the cardiologist, John Hampton, pronounced the end of clinical freedom, observing, "if we do not have resources to do all that is technically possible, then medical care must be limited to what is of proved value and the medical profession will have to set opinion aside."[12]

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Screening for and prevention of type 2 diabetes

Intervention should be sooner rather than later, even though exact costs and benefits are uncertain

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Cost effectiveness models are widely used to help policy makers and clinicians make decisions about alternative interventions. Models have limitations that are well understood—a model is only as reliable, or generalisable, as the assumptions and data that inform it. Moreover, a cost effectiveness model will not deal with questions about feasibility, acceptability, or affordability that may be crucial to decisions about implementation. However, decision analysis models often help to clarify the key factors likely to influence cost effectiveness, so that decision makers can better understand the importance of remaining uncertainties and make more logical decisions in the face of uncertainty.[1 2]

In the accompanying paper, Gillies and colleagues report a cost effectiveness analysis for screening and prevention of type 2 diabetes.[3] They compare four strategies—screening for diabetes; screening for diabetes and impaired glucose tolerance, followed by either lifestyle interventions or drugs; and no screening. Their findings are consistent with the intuitively logical view that, given the strong evidence base for prevention of diabetes in people with impaired glucose tolerance, it is more cost effective to intervene early, rather than to screen but then ignore impaired glucose regulation until it is severe enough for a diagnosis of diabetes.

This evidence for early preventive interventions comes from the results of trials of interventions for diabetes prevention that have proved highly effective[4] despite data that show how difficult it is to change behaviour,[5] particularly in an obesogenic environment.[6] Prevention is cost effective in part because we do not yet have effective interventions to prevent complications in screen detected or clinically diagnosed diabetes. This is highlighted by models that make more optimistic assumptions about progression and complication rates in screen detected diabetes, which then make preventive interventions seem less cost effective.[7]

A new Department of Health policy initiative for England is the promotion of systematic assessment of cardiovascular risk from the age of 40 to 75, including testing for diabetes and impaired glucose tolerance in high risk groups.[8] Given this new policy and the substantial evidence base, why are clinicians not more enthusiastic about primary care screening programmes for impaired glucose tolerance and diabetes?

The reasons include remaining uncertainties about the real costs and benefits of screening and practical considerations about feasibility and affordability. The potential to do more harm than good through screening is still real, even when the screening test is relatively risk free. Most important is the potential risk of false reassurance for people with risk factors for diabetes but a negative test result, most of whom still have a high risk of diabetes and cardiovascular disease and would benefit from lifestyle changes.

Uncertainty also exists about key model parameters. Although we have effective drugs for coexisting cardiovascular risk factors (particularly hypertension

and hyperlipidaemia), the effect of earlier treatment of hyperglycaemia on long term outcomes is still unclear. Similarly, the biggest uncertainty in relation to drug treatment for impaired glucose tolerance is whether the reduction in blood glucose will translate into benefits that matter to patients. This is still a powerful argument for remaining sceptical about the benefits of drug treatment for impaired glucose tolerance.[9]

There are also at least two major practical barriers to screening. Firstly, access to oral glucose tolerance tests is limited. To achieve the high sensitivity values used in Gillies and colleagues' model, a high proportion of people at risk will need an oral glucose tolerance test. In many countries, including the United Kingdom, and even in well resourced screening pilots, access to these tests is often limited.[10] Organising appointments for tests, performing tests, and getting valid results from fasting blood tests and oral glucose tolerance tests may require additional training for staff and improvements in arrangements for collection and analysis of samples.

Secondly, effective and affordable lifestyle interventions are still lacking. Most of the intensive interventions used in diabetes prevention trials are unavailable or unaffordable in everyday practice. Several major research programmes to develop and evaluate feasible and affordable interventions in different settings are under way, but most of these are still to report, and the long term effects will take years to evaluate.

So what should we do in the meantime? Given current trends in the prevalence of diabetes, inaction is not an option.[11] Instead, we can try to ensure that all patients with risk factors for diabetes receive advice and encouragement to reduce their risk through dietary change and increased physical activity. If oral glucose tolerance tests are used as a screening or diagnostic test for diabetes, we should be proactive when impaired glucose tolerance is detected. Advice and support should be offered, and the patient should be referred for supported lifestyle change, if available. Such a policy will probably be more effective and more cost effective than waiting to intervene further down the line.

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Emergency treatment of anaphylaxis

Revised UK guidelines are a concise evidence based resource

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The Resuscitation Council of the United Kingdom recently updated its guidelines on the emergency treatment of anaphylactic reactions.[1] The guidelines stress the importance of an early call for help from a resuscitation team or an ambulance. They introduce the ABCDE approach (airway, breathing, circulation, disability (level of consciousness), and exposure (of the skin)). They emphasise that prompt intramuscular injection of adrenaline (epinephrine) is the initial treatment of choice, along with other measures as indicated. These may include placing the patient in a comfortable position, providing airway management, giving high flow oxygen, and rapidly administering a large volume of intravenous fluid. They also advise subsequent referral to an allergy specialist for risk assessment and institution of long term measures to reduce risk.

No new drugs are available for the acute treatment of anaphylaxis. Currently used agents such as adrenaline, glucocorticoids, H_1 antihistamines, and H_2 antihistamines were introduced before the era of randomised controlled trials and evidence based medicine. Systematic reviews of these drugs are being conducted to document the existing evidence base.[2-4] This consists of clinical experience and expert opinion, observational studies, epidemiological studies, fatality studies, in vitro studies, and randomised, placebo controlled investigations in animal models and in people who have had anaphylaxis previously but are not experiencing it at the time of the study.[5-7]

Few published national guidelines are available on the treatment of anaphylaxis, but they all agree that adrenaline is fundamental to acute management.[1 8] Interestingly, no agreement exists on the initial dose of intramuscular adrenaline, which—for patients age 12 years or more—is 0.5 mg in the UK guidelines and 0.3-0.5 mg in most others.[1 8]

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Adrenaline prevents and relieves laryngeal oedema and circulatory collapse through its α_1 adrenergic effects. It provides bronchodilation and reduces the release of histamine and other mediators through its β_2 adrenergic effects. A brief window of opportunity seems to exist, during which even a relatively low intramuscular dose—such as 0.3 mg—is efficacious. Failure to inject adrenaline promptly increases the risk of a biphasic anaphylactic reaction, and death. Although adrenaline is sometimes blamed for causing myocardial ischaemia and cardiac dysrhythmias, anaphylaxis itself can cause these problems before adrenaline is given.[6 7] Transient palpitations, tremor, and pallor after injection of adrenaline reflect the anticipated pharmacological effects of the drug.

In healthcare settings, the risk of harmful effects is lower with intramuscular adrenaline than with intravenous adrenaline. As pointed out in the revised UK guidelines, continuous monitoring and dose titration by an appropriately trained specialist are mandatory if adrenaline is given intravenously.[1] Error and delay in adrenaline dosing have been attributed to the common practice of using ratios—such as 1:1000—to express drug concentrations, so mass concentrations such as milligrams per millilitre are preferred.[9]

In community settings, although adrenaline autoinjectors might be overprescribed in some countries, they are either not available or not affordable in many others,[10] and even when they are readily available and affordable they are underused during anaphylactic reactions. Limitations of currently available adrenaline autoinjectors include a restricted range of premeasured doses and needle lengths.[6 7]

In contrast to universal recommendations for injecting adrenaline in anaphylaxis, national guidelines do not agree on the role of other commonly used drugs such as glucocorticoids, H_1 antihistamines, and H_2 antihistamines; indeed, H_2 antihistamines are not even mentioned in the UK guidelines.[1 8] It might therefore be possible to study these other drugs prospectively in rigorously designed, randomised, placebo controlled multicentre trials in which they are tested individually, with appropriate precautions, in addition to standard of care treatment which includes adrenaline, positioning the patient comfortably, airway management, supplemental oxygen, and intravenous fluid, as indicated.

Placebo controlled trials of adrenaline would clearly be unethical[1 4-7]—indeed, the underuse of adrenaline for treating anaphylaxis in healthcare settings is also a concern.[11] However, it might be possible to conduct randomised trials comparing two different doses of adrenaline—for example, the two commonly recommended initial intramuscular doses of 0.3 mg and 0.5 mg.

Randomised controlled trials of any intervention would be difficult to conduct in people who present to accident and emergency departments with anaphylaxis, because no baseline measurements are available, and symptoms and signs of anaphylaxis might be resolving as a result of first aid treatment or endogenous production of adrenaline, angiotensin II, endothelin, and other substances.

Such studies might be possible, however, in well equipped healthcare settings in which anaphylaxis sometimes occurs—for example, in selected patients undergoing a physician supervised controlled challenge with a food or an insect sting as part of their anaphylaxis risk assessment, or in those receiving allergen specific immunotherapy. In these settings, staffed by professionals with appropriate training and experience in the prevention, recognition, and management of anaphylaxis, it would be possible to obtain informed consent and baseline measurements would be available. Moreover, if anaphylaxis inadvertently occurs, standard of care treatment with adrenaline, positioning the patient comfortably, airway management, supplemental oxygen, and intravenous fluid would be instituted promptly, as indicated. Continuous cardiac and blood pressure monitoring and pulse oximetry could be performed. Improved ability to confirm the clinical diagnosis of anaphylaxis with a laboratory test, and validation of anaphylaxis severity scores and other clinical outcome measures, would help to facilitate such studies.[12]

In summary, the revised UK Guidelines on Emergency Treatment of Anaphylactic Reactions are an important resource and a model for other national and international anaphylaxis guidelines being developed. The possibility of conducting randomised controlled trials in anaphylaxis should be considered.

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Quality improvement in the NHS

Refinement of current reforms is needed through a new national strategy

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Although not always recognised by clinicians and the public, the principal aim of most of the reforms of the NHS in England over the past decade has been not only to increase efficiency and productivity but also to improve the quality of care—that is, its effectiveness, humanity, and equity. For example, establishing the National Institute for Health and Clinical Excellence and national service frameworks was meant to enhance effectiveness; introducing competition and choice was partly intended to improve the patient's experience of care; and adjusting resource allocation to commissioners sought to achieve greater equity.

The multiplicity of changes to the governance, organisation, and financing of services has made it difficult to judge the effects of any single reform on the quality of health care. Despite this, there has been no shortage of people ready to express opinions, from members of the public and patients' organisations, through royal colleges and trades unions, to the private sector and parliamentarians. Inevitably, such views tend to be partial and to reflect particular interests. An attempt to provide a more independent dispassionate view, based on objective evidence, is therefore to be welcomed and valued.[1]

The Quest for Quality, an ambitious and unique report from the Nuffield Trust, brings together quantitative data from diverse sources to answer three questions. Are the improvements in quality over the past decade as good as could have reasonably been expected? How much of the improvement can be attributed to deliberate reforms? Has a reliable capacity for improvement been embedded in the NHS? Answering such questions was a formidable challenge, given the well recognised shortcomings of routine data in the NHS (lack of data on outcomes, limited ability to adjust for case mix, missing and inaccurate data, and lack of connection between primary and secondary care). In addition, when evaluating any complex diffuse change, it is difficult to establish causal links between specific interventions and outcomes.

Despite the restricted opportunities for quantitative analysis, the report provides a clear and extensive account of the quality reform agenda since 1998, alongside the available data on changes in the health of the population, healthcare activity, and health outcomes. It considered six aspects of quality and concluded that effectiveness had improved (greater adherence to evidence based clinical guidelines, reduced mortality for the major disease groups), access to care was better (shorter waiting times for many services), facilities and capacity had improved, and progress had been made on reducing hospital acquired infections. In contrast, it recognised some shortcomings, such as little change in patients' experience of care and a widening gap in life expectancy between socioeconomic groups.

Reflecting on these successes and failures, and on the confusion of organisations and activities that have been introduced to improve quality, the report suggests that "what is needed now is refinement, not rejection, of the reforms through the development of a comprehensive English national quality programme." A coordinated approach led by a national quality steering group is advocated, which would ensure that the responsibilty for quality is diffused throughout central and local organisations. A national quality programme should articulate national goals for quality, agree on NHS-wide quality indicators, strengthen national clinical audits, and develop policies for all aspects of public reporting of indicators, including an annual report to parliament.

Few people will disagree with the need for a more coordinated approach that gives a higher priority to consideration of quality. Indeed, members of the public would probably be surprised (and perhaps alarmed) to discover that quality of care is rarely, if ever, discussed by the boards of NHS trusts. They might also question Department of Health funding priorities that allocate a 100 times more money to research than to clinical audit. Concern about the current situation is shared by the Department of Health, which has recently established the National Clinical Audit Advisory Group to help develop policy and strategy with the aim of reinvigorating clinical audit both nationally and locally. Although the report identifies several challenges, there are grounds for optimism given the current confluence of several initiatives—world class commissioning, revalidation of healthcare professionals, risk management of provider organisations, public choice, competition between providers, and marketing—each of which needs better information on outcomes and can help catalyse quality improvement.

Achieving the improvements in quality will depend on meeting several challenges. Firstly, a better accommodation between the centre—trying to direct and control—and the periphery—pursuing local priorities and wanting ownership—will require understanding and compromise from both areas. Secondly, a more holistic approach to considerations of quality will need stronger links between those currently responsible for assessing effectiveness (such as national clinical audits) and those assessing the humanity of care (such as the Healthcare Commission). This is connected to the third challenge—the need for a better balance between, on the one hand, the predominant biomedical perspective that seeks technological solutions to poor quality, such as better drugs, and on the other hand, recognition of organisational and cultural change as key factors to improving quality. And fourthly, regardless of the appropriate solution to any given problem regarding quality, the need for more rigorous approaches that are based on scientific evidence of the cost effectiveness of interventions.

By tackling these and other underlying problems, quality improvement can gain prestige and take its rightful place alongside more highly respected activities such as research and education. The recent report should help in the pursuit of such ambitions.

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Food additives and hyperactivity

Evidence supports a trial period of eliminating colourings and preservatives from the diet

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Whether preservatives and colourings cause or exacerbate hyperactive behaviours is an important question for many paediatricians and parents. A recent randomised placebo controlled trial in 297 children aged 3-9 years provides evidence of increased hyperactive behaviour after they ate a mixture of food colourings and a preservative (sodium benzoate).[1] In contrast to many previous studies, the children were from the general population and did not have attention-deficit/hyperactivity disorder. The trial found an adverse effect of the mixture on behaviour as measured by a global hyperactivity aggregate score. The daily dose approximated that found in two 56 g bags of sweets.

In view of the potential importance of these findings, the European Food Safety Authority (EFSA) recently provided an opinion that takes other evidence into account.[2] The release of the EFSA findings was reported in a news article in the *BMJ* under the headline "Agency rejects research on food additives" and the EFSA opinion was characterised as a "highly critical assessment."[3] The news article stated that the EFSA has "rejected suggestions . . . of a link between hyperactivity in children and two mixtures of food colours and the preservative sodium benzoate."

Closer analysis of the EFSA report, however, does not support this negative interpretation. The EFSA panel reanalysed the data and found that their analysis with a recalculated global hyperactivity score "led to broadly similar conclusions" to the original paper. The panel concluded that, "the study provides limited evidence that the two different mixtures . . . had a small and statistically significant effect on activity and attention." Importantly, the trial examined a cohort of normal (not hyperactive) children, but the findings have obvious implications for children with hyperactivity.

The EFSA panel reviewed the evidence linking preservatives and colourings with hyperactive behaviours. The panel reviewed 22 studies from 1975 to 1994 and two meta-analyses. Of the 22 studies, 16 reported positive effects in at least some children. In positive studies, only a subgroup of those with hyperactive behaviours were affected by the additives. The most recent meta-analysis found that artificial food colours had an overall effect size of 0.283 (95% confidence interval 0.079 to 0.488) on the hyperactivity score, and this fell to 0.210 (0.007 to 0.414) after excluding the smallest and lowest quality trials.[4]

The panel rightly pointed out that attention-deficit/hyperactivity disorder has multifactorial causes, and exclusively focusing on food additives may "detract from the provision of adequate treatment" for children with the disorder. However, it could be said that neglecting the substantial body of evidence on dietary factors may also do this.

Three main treatments are available for hyperactivity in children—drugs, behavioural therapy, and dietary modification. Interestingly, the use of drugs and dietary modification is supported by several trials,[4-6] whereas behavioural therapy—which is presumably thought necessary for "adequate treatment"—has little or no scientifically based support.[6 7] A recent review of treatment by the American Academy of Paediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder said that, "the evidence strongly supports the use of stimulant medications," whereas "behaviour therapy alone has only limited effect on symptoms."[7] For unknown reasons, the subcommittee did not review dietary modification.

Eliminating colourings and preservatives is regarded by some as an "alternative" treatment rather than a "standard" treatment (stimulant drugs) for attention deficit disorder.[8] "Alternative" medicine is popular with the public—40-50% of children attending tertiary children's hospitals in the UK and Australia have used it in the past year[9]—but it is rightly regarded with suspicion by many medical practitioners because of lack of evidence. However, meta-analysis shows that dietary elimination of colourings and preservatives provides a statistically significant benefit. In view of the relatively harmless intervention of eliminating colourings and preservatives, and the large numbers of children taking drugs for hyperactivity (2.4% of children in the state of Western Australia receive stimulant drugs for attention deficit disorder[10]), it might be proposed that an appropriately supervised and evaluated trial of eliminating colourings and preservatives should be part of standard treatment for individual children.

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