Is avoidance of hypoglycaemia a better target than HbA1C in older people with diabetes?

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In this commentary, the authors put forward a case for greater use of continuous glucose monitoring (CGM) in older people with diabetes to aid deprescribing and avoidance of hypoglycaemia rather than using HbA1c targets.

Diabetes mellitus is a complex chronic illness often accompanied by multiple co-morbidities and polypharmacy in the older person . Worldwide, there are about 425 million people living with diabetes, of whom approximately 123 million are aged between 65 to 99 years.

The aim of diabetes management is to achieve optimum glycaemic control, in order to prevent long-term microvascular, macrovascular and neurological complications. Glycated haemoglobin (HbA1C) is currently the key surrogate marker for long-term diabetes control and complications. However, HbA1C is depicts only a single estimate of average glucose over the last 2–3 months, and fails to give information on glucose fluctuations or variability in the patient's daily life. An established method of capturing glucose levels on a day to day basis is via finger-prick testing (self-monitoring of blood glucose (SMBG)). However, a Cochrane review reported that SMBG did not provide consistent long-term improvements in glycaemic control for non-insulin users with Type 2 diabetes(1).

The challenge regarding the evidence-based management of diabetes in older people is that the bulk of the underlying data comes from randomized controlled trials in younger participants. Lipska et al have pointed out that older people may not benefit from tight glycaemic control in the same way that younger adults do, and that older people are prone to serious adverse effects of hypoglycaemia from intensive therapy targeted at lowering HbA1C (2). Various guidelines for the management of diabetes in older people have been developed, which contain recurring themes such as adopting a more personalised approach taking into account each person's co-morbidities, frailty, polypharmacy and life expectancy (3).

Despite these guidelines, recent studies have found that older people with type 2 diabetes are still at risk of being overtreated with diabetes drugs. Hambling et al found that nearly a third of older people with type 2 diabetes living in Norfolk, England, were on potentially hazardous agents such as sulfonylureas and/or insulin, despite presence of comorbidities such as chronic kidney disease or dementia that substantially increase the risk of serious adverse effects (4).

There are well-recognized hazards from use of sulfonylureas and insulin in older people, who are at particular risk of hypoglycaemia. Symptoms of hypoglycaemia are person-specific and can change with advancing age, due to changes in the hormonal response to hypoglycaemia(5). This is a particular problem in those with cognitive decline who may not be able to recognize symptoms of hypoglycaemia, or to take action in monitoring blood glucose and self-treating the hypoglycaemia. Feinkohl et al in the Edinburgh Type 2 Diabetes Study found that those with cognitive impairment had a twofold higher incidence of severe hypoglycaemia over 4 years. In addition, severe hypoglycaemia was associated with a steeper decline in cognitive function(6).

Insulin has been shown to be the second most common medication associated with accident and emergency visits or hospitalisation(7). We have identified major consequences such as falls and fractures, mortality and cardiovascular events in older people who have suffered severe hypoglycaemia (8).

Here, the major challenge is difficulty in detecting and recording hypoglycaemia. The disadvantage of widely-used finger prick SMBG is that it will only provide a snapshot of an individual's glucose levels as and when that person makes a conscious decision to test. This is problematic in an older person who may not recognise symptoms of hypoglycaemia and/or has cognitive problems. In addition, neither finger-prick or HbA1c testing provide any insight into trends and variability throughout an entire 24 hour period, as there are no continuous measurements**.** In order to illustrate the weakness of HbA1C as a marker, we have come up with simulated examples in Figure 1 (based on models presented by Vigersky et al.), where three people with completely contrasting daily glucose variation could turn out to have similar measured HbA1c (9).

Figure 1 Simulated examples of blood glucose variability throughout the day in three patients who may have similar HbA1C readings (9)

Whilst HbA1c is currently still recognised as the key surrogate marker to gauge average treatment efficacy, we argue that the inability to measure hypoglycaemia or capture day to

day variability, renders it completely uninformative when addressing hypoglycaemia risk and optimizing benefit-harm balance of drug therapy in older people with diabetes.

More importantly, the advent of continuous glucose monitoring (CGM) is a major step forward in enabling round the clock capture of hypoglycaemic episodes (especially at night where the patient may be asleep) and assessment of variability in glucose readings throughout the 10-14 day lifespan of a sensor. Current day CGM systems comprise of a sensor sitting just under a patient's skin that measures interstitial glucose levels Results can either be accessed by the patient through swiping a reader over the sensor or can be transmitted remotely via Bluetooth. Alarms can be set to indicate if glucose levels go too high or low. Newer CGM devices allow real-time sharing of data with either a carer (in older people with cognitive difficulties) or parents (in children with type 1 diabetes).

A systematic review of studies using CGM in older people found that hypoglycaemic episodes were occurring in 28-65% of participants with most of those episodes (80%) being asymptomatic (and thus likely to have gone undetected if the patients were not fitted with the CGM device) (10). Despite the technological challenges and concerns about user-friendliness, recent studies using CGM in older people have shown that older people and their carers find the devices acceptable and helpful in the management of their diabetes (11).

The wealth of data captured by CGM has led to a rethink of how the findings should be interpreted to guide prescribing of diabetes medications. CGM measurements provide information on the percentage of readings and time spent per day within target, below target or above target. An international panel of experts has produced recommendations for clinical targets for CGM data(12). Importantly, for older adults the recommendation is to have less than 15 minutes per day exposed to hypoglycaemia (below 3.9 mmol/L), whilst having more than twelve hours per day between in the optimal range of 3.9-10 mmol/L.

Instead of focusing on HbA1C, clinicians should, with the aid of CGM, interpret "time in range" to inform and tailor an individual's diabetes medication. Indeed, CGM can be considered as a particularly sophisticated form of therapeutic drug monitoring where the body's response to the drug can constantly be evaluated to guide accurate medication regimens. In older people with diabetes who are at high risk of adverse effects, CGM enables fine and regular adjustments to the drug regimen to achieve an acceptable balance between

benefit and harm, without the pain and inconvenience of frequent finger-prick testing. Clinicians and patients may be more confident and motivated to proceed with de-prescribing of sulfonylureas and insulin if CGM reveals hypoglycaemic episodes that they were completely unaware of.

There are a number of important issues with regards to further research and implementation of CGM:

- How often should CGM be used in older people with diabetes who are at high risk of hypoglycaemia, and is intermittent use a valid approach?
- Can interpretation of the CGM findings and changes to medication (such as de-prescribing of insulin and sulfonylureas) be safely conducted in primary care?
- Can deployment CGM ultimately lead to reduction in serious hypoglycaemia episodes and hospital admission in older people with diabetes?

At present, the availability of CGM for older people with diabetes has not been a priority in publicly-funded health services. For instance, in England, the National Health Service has prioritized CGM for patients with type 1 diabetes. There is no explicit mention of the role of CGM in older people with type 2 diabetes on medications which carry a high risk of hypoglycaemia (insulin, sulfonylureas), and who may need carer support (for example due to underlying dementia) with the management of their diabetes. The availability and costs of CGM for medical practice in developing and/or middle income countries is a challenge. If CGM were to be used intermittently in older people with diabetes, research will need to be carried out to prove that its costs can be offset by rationalising diabetes medications and reduction in adverse events (eg emergency attendances, hospitalisations, falls and fractures).

The healthcare community has to seriously think about older people with diabetes (especially those on insulin or sulfonylureas, as well as memory problems) and how best to manage diabetes in later life.

The focus should be on minimisation of hypoglycaemia through careful CGM-guided adjustment of drug therapy, rather than the relentless pursuit of HbA1c targets. This will require an enormous shift in mindset by healthcare professionals and policy makers. Is it

really appropriate in a 90-year old patient with diabetes to pursue an HbA1c target whose main benefit is reduction of long-term complications in the next 10 or 20 years?
We have to realise that avoiding immediate harm from hypoglycaemia in older people with diabetes is far more pertinent than using HbA1c targets. It is time to rethink.

Competing Interests: The authors have no competing interests to declare.

List of Figures
Figure 1 Simulated examples of blood glucose variability throughout the day in three patients who may have similar HbA1C readings

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