Review

The use of continuous glucose monitoring in people living with obesity, intermediate hyperglycemia or type 2 diabetes

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ABSTRACT

A global trend towards increased obesity, intermediate hyperglycemia (previously termed prediabetes) and type 2 diabetes, has prompted a range of international initiatives to proactively raise awareness and provide action-driven recommendations to prevent and manage these linked disease states. One approach, that has shown success in managing people already diagnosed with type 2 diabetes mellitus, is to use continuous glucose monitoring (CGM) devices to help them manage their chronic condition through understanding and treating their daily glucose fluctuations, in assocation with glucose-lowering medications, including insulin. However, much of the burden of type 2 diabetes mellitus is founded in the delayed detection both of type 2 diabetes mellitus itself, and the intermediate hyperglycemia that precedes it. In this review, we provide evidence that using CGM technology in people at-risk of intermediate hyperglycemia or type 2 diabetes mellitus can significantly improve the rate and timing of detection of dysglycemia. Earlier detection allows intervention, including through continued use of CGM to guide changes to diet and lifestyle, that can delay or prevent harmful progression of early dysglycemia. Although further research is needed to fully understand the cost-effectiveness of this intervention in people at-risk or with early dysglycemia, the proposition for use of CGM technology is clear.

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1. Introduction

Obesity, particularly abdominal obesity, is a significant risk factor for the development of insulin resistance, which is a precursor to both intermediate hyperglycemia and type 2 diabetes [1,2]. The terms pre-diabetes, non-diabetic hyperglycemia and intermediate hyperglycemia have been used interchangeably to indicate a state of increased risk of progressing to type 2 diabetes mellitus. For consistency, we will refer to only intermediate hyperglycemia throughout the rest of this discussion. Excess fat, especially in the abdominal area, leads to an increase in fatty acids and inflammation, which can impair the body's ability to use insulin effectively. Insulin resistance as a consequence of obesity is a common feature of intermediate hyperglycemia, with elevated blood glucose as the body struggles to use insulin effectively, eventually progressing in many individuals to type 2 diabetes mellitus if not managed. A series of major studies in the USA, Finland, and China have shown that interventions to increase dietary weight loss and improve physical activity, can prevent progression to type 2 diabetes mellitus in high-risk persons by 51–58 %, for at least 6 years following the original intervention [3–5], with continued protection of 27–43 % for up to 20 years [5–7]. The efficacy of successful intervention has been attributed to a multiplicity of factors, including: lifestyle coaches; contact with at-risk persons; education, and; networks for feedback and support [8]. The opportunity provided by proactive use of CGM systems to provide aspects of this support at lower resource intensity, for example by using remote versus in-person contacts with healthcare professionals (HCPs) must be considered here.

An important goal in the chain of metabolic dysregulation is to limit the risks associated with type 2 diabetes mellitus as early as possible, through interventions to promote weight loss and mitigate the adverse effects of hyperglycemia. A recent study has shown that modification of lifestyle behavior is important to prevent damage to kidney function among the overweight prediabetic population in men [9]. The attributes of continuous glucose monitoring (CGM) technologies, which are proven to improve glycemic control for adults with type 1 diabetes (T1D) [10–14], are increasingly proposed as an intervention for managing obesity, by enabling behavioral change that drives weight loss, and for glycemic control in intermediate hyperglycemia and type 2 diabetes mellitus. A small number of proof-of-concept studies have shown that adults with type 2 diabetes mellitus using CGM do choose lower glycemic index foods [15], increased physical activity [16], decreased caloric intake, weight loss, and reduced postprandial glucose levels [17]. Among people with intermediate hyperglycemia, there is only one published study addressing the role of CGM in promoting behavior change, and, while it showed greater dietary self-efficacy, neither weight nor glycemic measures were reported [18].

Ultimately, there is a significant unmet need to emphasize with at-risk persons and those with intermediate hyperglycemia that there are a significant number of modifiable factors within their own capabilities to change – and get them to act on them, while bearing in mind other contributing factors such as social deprivation. Through empowerment of these groups of people, the burden of type 2 diabetes mellitus can be restricted or delayed. Lifestyle and dietary interventions managed in primary care can restore normoglycemia for people with intermediate hyperglycemia [19]. Significantly, despite concerns about the negative connotations of being 'labelled' with intermediate hyperglycemia, at least one study has indicated that intermediate hyperglycemia was not considered as negative but an opportunity to engage with primary-care supported dietary interventions [20]. Equally, although people with lower social determinants of health (SDoH) are known to have reduced access to healthcare services, education has been shown to support improved glycemic performance and encourage healthy lifestyle changes in people with intermediate hyperglycemia from communities with lower socioeconomic status [21]. In each of these situations, there is a need to emphasize that the application of CGM can be part of continuous glucose education.

As CGM devices are becoming available without medical prescription in the USA, increasing random use is anticipated with likely additional burden to the primary care level physicians and teams, with no available guidance on how to instruct this populations.

2. The evidence for using CGM in normoglycemic persons living with obesity

The rationale for using CGM in obese persons without intermediate hyperglycemia or type 2 diabetes mellitus is to support lifestyle changes to diet and physical activity, by providing real-time biofeedback on postprandial glucose spikes and glycemic variability (GV), that have been proposed to drive hyperinsulinemia and increased fat storage [22,23]. However, research in this aspect of obesity management is a significant unmet need. One study using CGM in normoglycemic adults has shown that glucometric data measuring glycemic variability was not different between obese (BMI > 30 kg/m^2) and non-obese persons [24]. A separate study on normoglycemic but severely (Class 3) obese people (BMI $\geq$ 40 kg/m^2) did find significantly increased metrics of GV, compared to normoglycemic non-obese persons [25], similar to severely obese people diagnosed as having intermediate hyperglycemia. This suggests that the goal of influencing behavior using biofeedback from CGM devices may be more realistic in severely obese people, but no studies have examined this proposition.

2.1. Targeting and modifying behavior using CGM in persons living with obesity

Studies using CGM have confirmed that overweight and obesity in men without diabetes and with a 2-hour plasma glucose during oral glucose tolerance test (OGTT) < 200 mg/dL (11.1 mmol/L), is associated with eating and snacking behaviors that increase CGM-detected indices of hyperglycemia, including maximal glucose, time above range (TAR) between 140 mg/dL (7.8 mmol/L), and 200 mg/dL (11.1 mmol/L), as well as the frequency of postprandial hyperglycemia [26,27]. A low physical activity profile has also contributed to impaired glycemic control in this group. Notably, these associations were found to be independent of measured pancreatic β-cell function.

In this context, a qualitative study has concluded that successful weight-loss interventions for adults living with obesity but without a diagnosis of diabetes are dependent on regular monitoring and feedback to encourage ownership, accountability and self-efficacy, to develop behaviors adapted to long-term adherence with weight-loss goals [28]. Periodic use of CGM can be argued to support these aspects of behavior change, providing daily feedback to the user on healthy versus unhealthy activities, along with objective data on glycemic patterns that can be reviewed with their HCP. A small-scale pilot study using CGM to support people with intermediate hyperglycemia or type 2 diabetes mellitus has shown that using CGM to provide biofeedback was effective at promoting attendance at planned exercise sessions and registration for future exercise activities, compared to participants not using CGM [29]. Looking at dietary interventions, CGM has been used to monitor and support adult males (n = 15, mean age 55 yrs) taking part in a study on time-restricted eating (TRE) over one week [30]. The outcomes of this study showed a limited benefit on mean fasting glucose during TRE phase. Use of CGM in adolescents living with obesity has also provided some evidence that adherence with TRE strategies may be supported when participants wear CGM to monitor adherence with TRE activities [31]. Overall, the available studies support the proposition that, rather than simply being tools that help users to 'react' to hypoglycemia or hyperglycemia, CGM devices can help people with prediabetes or diabetes to proactively make preventive lifestyle behavior changes [32]. However, larger-scale studies are necessary to fully-explore these

associations.

Consensus statements. People living with obesity and at-risk of progression to type 2 diabetes mellitus.

- The goal of addressing modifiable risk factors in people living with obesity is realistic, such that progression to intermediate hyperglycemia and type 2 diabetes mellitus may be reduced.
- Benefits at a global population level will only be realised if access to CGM technology is improved to enable widespread adoption, especially in developing countries where burden and impact from diabetes remains highest.
- Periodic use of CGM should be considered in people living with obesity and at-risk of developing type 2 diabetes mellitus based on established risk factors [33], to assess glycemic risks and support early intervention.
- Measures of CGM-defined glycemic risk amongst people living with obesity centered on time above tight range (TATR) > 140 mg/dL (7.8 mmol/L) and glycemic variability may be used to identify persons at-risk of intermediate hyperglycemia.
- The application of CGM should be considered during proactive efforts to modify diet and physical activity in people living with obesity, in order to provide immediate feedback on the glycemic impact of dietary choices, as well as the glycemic benefits of physical activity and exercise.
- Any at-risk individual living with obesity and with normoglycemia, as assessed by FPG, plasma glucose during OGTT or standard HbA1c testing, should have periodic use of CGM to assess glycemic control patterns under free-living conditions.
- There is an unmet need for prospective studies to understand the value of CGM use in people living with obesity and at-risk of type 2 diabetes mellitus. This should include studies to investigate the real-time glycemic patterns that characterize these at-risk persons and also investigate the value of CGM to support dietary and lifestyle interventions.
- Further developments and integration of CGM data and providing artificial intelligence (AI) enabling Clinical Decision Support Systems (CDSS) is required to simplify interpretation for those with lower digital and health literacy.

3. The evidence for using CGM in intermediate hyperglycemia

Intermediate hyperglycemia is defined by either: HbA1c 5.7–6.4 % (39–47 mmol/mol), impaired glucose tolerance (IGT) with fasting plasma glucose (FPG) 100–125 mg/dL (5.6–6.9 mmol/L) or IGT with 2-hour plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L) or a 1-hour plasma glucose ≥ 155 mg/dL (8.6 mmol/L) following a 75 g OGTT [34,35]. Each of these criteria provides a single measurement at a single timepoint, and are impractical to repeat serially. In contrast, the use of a single CGM sensor for a 10–15-day period can provide a wealth of glycemic data under real-world conditions, including at home and work, that can provide a definitive diagnosis of intermediate hyperglycemia, along with additional insights into day-to-day glycemia and how it is affected by meal planning and lifestyle. All of this can be managed with remote monitoring, such that a clinic visit may not be required in many cases.

People living with intermediate hyperglycemia have an 83 % increased risk of CVD [36], although non-glycemic health status indicators also contribute to this risk. A *meta*-analysis of 71 studies assessing the impact of GV on cardiometabolic risk factors in people without diabetes found that elevated GV in intermediate hyperglycemia is associated with risk of developing coronary atherosclerosis, independently of obesity or traditional risk factors [37]. Intermediate hyperglycemia is also associated with increased incidence of microvascular complications [38–42]. In progression to type 2 diabetes mellitus, the prediabetic period has been separated into stage 1 (early) and stage 2 (late) [43,44], and CGM can be an effective tool to identify the presence and severity of dysglycemia for persons living with intermediate hyperglycemia [44]. For example, GV [45,46] and time above tight range (TATR) > 140 mg/dL (7.8 mmol/L) [47] can be used separately or together to distinguish between people with or without type 2 diabetes mellitus. Using CGM in people without a diagnosis of type 2 diabetes indicates that TATR > 140 mg/dL (7.8 mmol/L) is uncommon [48,49], suggesting that %TATR > 140 mg/dL (7.8 mmol/L) may be clinically meaningful in assessing the risk of developing type 2 diabetes mellitus amongst people living with intermediate hyperglycemia [50]. This is further supported by a retrospective comparative analysis of CGM

data from 836 adults across 5 separate studies, including normoglycemic persons, those with intermediate hyperglycemia, people with type 2 diabetes mellitus and HbA1c < 6.5 % (<48 mmol/mol), <7.0 % (<53 mmol/mol) or ≥ 7.0 % (≥53 mmol/mol) [51]. The outcomes showed a progressive deterioration in GV and %TATR > 140 mg/dL (7.8 mmol/L) from normoglycemia to dysglycemia, through to type 2 diabetes mellitus with HbA1c < 6.5 % (<48 mmol/mol) and thereafter to type 2 diabetes mellitus with HbA1c ≥ 7.0 % (≥53 mmol/mol). Established CGM metrics also show a progression of dysglycemia from at-risk persons to those with intermediate hyperglycemia and those with type 2 diabetes mellitus [52], who demonstrated increased TATR 140–180 mg/dL (7.8 – 10.0 mmol/L), during the day and overnight. Stratifying CGM readings by time of day and the range 140–180 mg/dL (7.8 – 10.0 mmol/L), provides additional metrics to differentiate between the groups.

In people considered to be nondiabetic using the established criteria (i.e., HbA1c < 6.5 % [<48 mmol/mol] or 2-hour 75 g OGTT > 200 mg/dL), application of CGM has identified an additional 15 % of people with intermediate hyperglycemia [53], with significantly increased metrics of GV, which can differentiate between people with normal glucose tolerance and those with intermediate hyperglycemia, who are matched for HbA1c [54–56], indicating that CGM metrics of GV may be a more-sensitive indicator of intermediate hyperglycemia. The use of CGM metrics together with isolated abnormalities in OGTT testing has also been proposed as a way to identify persons at high-risk of intermediate hyperglycemia or type 2 diabetes mellitus, despite HbA1c < 5.7 % (<39 mmol/mol) [57]. It seems clear that, compared to HbA1c or OGTT testing, the key benefit of CGM is the stratification of intermediate hyperglycemia according to GV metrics, as this may provide stronger information of β-cell function and insulin sensitivity [58], and potentially to identify glucotypes [53,59] that may guide better personalized prevention strategies earlier in the disease process. Recently, the International Diabetes Federation has issued a position statement supporting the value of 1-hour glycemia ≥ 155 mg/dL (8.6 mmol/L) during a 75 g OGTT as a stronger tool for the early diagnosis of intermediate hyperglycemia, with a 1-hour plasma glucose of ≥ 209 mg/dL (11.6 mmol/L) indicating type 2 diabetes mellitus [35]. In this context, it is also important to note that 1-hour glycemia has been associated with a high risk for both macro- and microvascular complications [60]. Studies in this setting, involving CGM, are not yet available.

Although CGM-derived metrics of remission of intermediate hyperglycemia to normoglycemia have not been investigated formally, the evidence, as discussed above, suggests that optimizing TITR 70–140 mg/dL (3.9–7.8 mmol/L) and reducing TATR > 140 mg/dL (>7.8 mmol/L) should be targeted. Although studies vary, individuals with intermediate hyperglycemia may have < 77 % TITR 70–140 mg/dL (3.9–7.8 mmol/L), compared to > 87 % for normoglycemic individuals, with up to 17 % TATR > 140 mg/dL (>7.8 mmol/L) compared to 12 % [61]. Given the increased risks for macrovascular and microvascular disease for people with intermediate hypeglycemia, this is an important goal. Studies have shown that TITR 70–140 mg/dL (3.9–7.8 mmol/mol) is inversely correlated with the occurrence of cerebrovascular accidents (CVAs) after adjustment for HbA1c [84]. Regression analysis concluded that for every 10 % increase in TITR 70–140 mg/dL (3.9–7.8 mmol/mol) the risk of a CVA event was reduced by 45 % (p < 0.01). Similarly, each 10 % increase in TITR 70–140 mg/dL (3.9–7.8 mmol/mol) has been associated with a 12 % rate reduction in the incidence of peripheral neuropathy [45] and a 56 % lower rate of diabetic retinopathy [72]. These data refer to study cohorts with a diagnosis of diabetes, and additional studies are required specifically in individuals with intermediate hyperglycaemia.

With the availability of numerous CGM-derived metrics that allow detection and monitoring of intermediate hyperglycemia, it has been proposed that this is an opportunity to avoid therapeutic inertia in the progression to confirmed type 2 diabetes mellitus [62], since these glycemic changes will indicate ongoing cellular dysfunction that can generate insulin deficiency, insulin resistance or both. Given that changes in meal-planning and physical activity are more-effective than

pharmacotherapy in preventing progression from intermediate hyperglycemia to type 2 diabetes mellitus in adults [3], the use of CGM as a motivational tool for making lifestyle changes is of considerable importance. Only limited data is available from a small number of studies, but the data does support the proposition that using CGM can lead to improved PA, dietary choices and weight loss in people with intermediate hyperglycemia. Daily consumption of carbohydrate and refined grains have been found to be associated with higher GV, whereas whole grains and daily protein intake have been related to lower GV in people with IGT. These results can offer further insights into designing a more efficacious dietary intervention in people with intermediate hyperglycemia [63]. One small pilot study (n = 13) on exercise, including participants with intermediate hyperglycemia and diabetes, reported positive changes in body composition and increased fitness when using CGM, as well as improved goal setting and self-monitoring behavior [29]. A larger study (n = 168) in adults living with intermediate hyperglycemia [64] showed that a 12-week intervention with a smartphone app and CGM increased TITR 70–140 mg/dL (3.9–7.8 mmol/L), accompanied by reduced carbohydrate intake and weight loss. A single-arm prospective study of CGM use in 32 people with intermediate hyperglycemia [65], reported satisfaction with CGM use was largely positive, and the majority agreed (60 %) or strongly agreed (22 %) that wearing a CGM sensor reminded them to stay healthy every day. Another study assessed the satisfaction and feasibility of using CGM in 15 adults with intermediate hyperglycemia in combination with a low-carbohydrate diet [66]. In addition to a high rate of satisfaction (93 %) among participants, investigators observed significant reductions in HbA1c and body weight.

3.1. Remission of type 2 diabetes mellitus to intermediate hyperglycemia

It is widely accepted that type 2 diabetes mellitus is a chronic disease, which can be controlled through lifestyle adaptations and drug treatment or metabolic surgery, but which is progressive and inevitable. Consequently, remission of type 2 diabetes mellitus is rarely addressed as a treatment goal. However, remission of type 2 diabetes mellitus to glucose levels in the range of intermediate hyperglycemia, or even normoglycemia, is now considered an achievable goal for certain persons [67,68]. A 2022 consensus has proposed that, from a glycemic standpoint, remission in type 2 diabetes mellitus can be defined as a return to an HbA1c < 6.5 % (48 mol/mol), measured at least 3 months following the cessation of active glucose-lowering pharmacotherapy [69]. Although FPG < 126 mg/dL (7.0 mmol/L) in the absence of pharmacotherapy can be considered in some settings as an alternative criterion for remission of type 2 diabetes mellitus [70], the need for overnight fasting and the significant variation between repeated FPG measurements is a critical disadvantage. HbA1c itself is affected by a number of non-glycemic factors and repeated HbA1c testing is meaningful only every 3 months, which limits its value for the timely detection of a recurrence of hyperglycemia. Thus, use of CGM to monitor maintained euglycemia in remission of type 2 diabetes mellitus is of interest.

Remission of type 2 diabetes mellitus has become a realistic goal largely as a result of research showing the metabolic benefits of sustained weight loss, typically as a result of dietary restrictions, when insulin secretion and insulin sensitivity are not significantly impaired. The primary-care DiRECT trial in the UK showed remission of type 2 diabetes mellitus in 46 % of participants after 1 year following an intensive dietary replacement intervention [71]. After 2 years, and 12 months after the end of the intervention, remission was still evident in 36 % of participants, with loss of remission being associated with weight gain [67]. Notably, restoration of β-cell function was also evident, associated with reduced ectopic fat in the liver and pancreas. Similar outcomes using the DiRECT protocol have been observed in a primary-care study in Australia [72]. These outcomes were confirmed in the DIADEM-I RCT [73], showing remission of type 2 diabetes mellitus in

60 % of participants after a 12-month dietary intervention, including a return to normoglycemia in 30 % of participants. The long-term follow-up of the DiRECT trial also indicates that the metabolic signature associated with development of type 2 diabetes mellitus can be modified and reversed by weight-loss interventions [74].

The Look AHEAD study, which used a lifestyle intervention based on frequent counselling to reduce calorific intake and increase physical activity, reported a type 2 diabetes mellitus remission rate of 11.5 % among participants at 12 months, falling to 7 % at 2 years [75]. However, an important outcome for participants who showed evidence of remission of type 2 diabetes mellitus was a 33 % reduced risk of chronic kidney disease (CKD) and a 40 % reduced risk of CVD after 8 years of follow-up, compared to participants who did not exhibit remission [76].

Pharmacotherapy to support intensive weight-loss programs in obesity and type 2 diabetes mellitus has been proposed as a way to reduce the hunger associated with caloric restriction and to increase adherence with low-energy diets [77]. This has been evaluated in pilot studies on dulaglutide [78], a once-weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA), which has an appetite-suppressant action [79,80]. A 12-week intervention showed that use of dulaglutide alongside a low-calorie diet promoted a mean 9.5 kg loss of weight and a reduction in HbA1c of –1.4 % (–15.8 mmol/mol). Although these reductions in weight and HbA1c are significant over a 3 month period, no comparator arm was included in this pilot investigation.

TIR does not appear to be helpful for assessing diabetes remission to the intermediate hyperglycemic state, in contrast to TITR which is a more beneficial CGM metric for confirming normoglycemia, as has been recently suggested [81]. Discussion of CGM metrics of remission in cases of previously diagnosed type 2 diabetes mellitus are largely focused on glycemic changes following either dietary intervention or bariatric surgery in people with type 2 diabetes mellitus [82–85]. Although the 14–18 % TATR > 140 mg/dL (7.8 mmol/L) values identified in these remission studies [82,84,85] are aligned with the investigations on intermediate hyperglycemia described earlier in this paper, the achievement of only 70 % TITR is not consistent with restored normoglycemia [84,85]. The limited evidence does imply that a target of < 20 % TATR > 140 mg/dL (7.8 mmol/L), for at least a 12-month duration in the absence of pharmacological therapy, may support maintenance of remission from overt type 2 diabetes mellitus but still indicate intermediate hyperglycemia. Additional studies are needed to better understand how CGM may be used in this group of people with dysglycemia. It is also important to identify a wider selection of CGM measures of glycemia in people with type 2 diabetes mellitus during periods of confirmed remission to intermediate hyperglycemia, with sustained HbA1c 6.5 % (<48 mmol/mol), including the correlation between the CGM-derived glucose management indicator (GMI), derived from mean glucose levels, and HbA1c during remission.

The potential value and suitability of using CGM systems, both to assess and manage intermediate hyperglycemia, is clearly indicated by these few studies, and underscores the need for further prospective studies on the application of CGM in persons living with intermediate hyperglycemia.

Consensus statements. People living with intermediate hyperglycemia and at-risk of progression to type 2 diabetes mellitus.

- The goal of reversing dysglycemia in people living with intermediate hyperglycemia is realistic, as is delaying progression to type 2 diabetes mellitus.
- Benefits at a global population level will only be realised if access to CGM technology is improved to enable widespread adoption, especially in developing countries where burden and impact from diabetes remains highest.
- Periodic use of CGM should be considered in people living with intermediate hyperglycemia, based on established risk factors for type 2 diabetes mellitus [33], to assess glycemic risks and support early intervention when needed.
- For persons with prior intermediate hyperglycemia and a recent diagnosis of type 2 diabetes mellitus and able to meet CGM targets for > 70 % TIR, setting targets for TITR can be considered to aim for near-normal glycemia or remission.
- Remission criteria for people being treated for type 2 diabetes mellitus should mirror diagnostic criteria, and include: FPG < 126 mg/dL (7.0 mmol/L), mean

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Consensus statements. People living with intermediate hyperglycemia and at-risk of progression to type 2 diabetes mellitus.
glucose levels < 100 mg/dL (5.6 mmol/L), GMI < 6.5 % (<48 mmol/mol), sustained over 3 months in the absence of pharmacotherapy.
• Use of CGM should be considered as part of proactive efforts to modify diet and physical activity in people living with intermediate hyperglycemia, in order to provide immediate feedback on the glycemic impact of dietary choices and physical activity or exercise.
• There is an unmet need for prospective studies to understand the value of CGM use in people living with intermediate hyperglycemia and at-risk of progression to type 2 diabetes mellitus. This should include studies to investigate the real-time glycemic patterns that characterize intermediate hyperglycemia and to investigate the value of CGM to support dietary and lifestyle interventions in intermediate hyperglycemia.
• Further developments and integration of CGM data is required to simplify interpretation for those with lower digital and health literacy.

4. The evidence for using CGM in people with type 2 diabetes mellitus

Compared to the very limited data on the use of CGM in at-risk, normoglycemic obese adults and those with a dysglycemic profile characteristic of intermediate hyperglycemia, the data on outcomes following initiation of CGM in people with diagnosed type 2 diabetes mellitus are substantial, including those on non-insulin therapies. Besides the glycemic benefits summarized below, there are several studies that have demonstrated the benefits of CGM for supporting behavioral change, including weight loss, lower carbohydrate intake and improved physical activity [15–17,86–89]. One of the more important goals of using CGM in type 2 diabetes mellitus is to combat therapeutic inertia, in which escalation of drug therapy is delayed well beyond recommended guidelines. Although therapeutic inertia is a consequence of several intersecting factors [90–93], fear of hypoglycemia is a key problem [94,95], because of its association with adverse outcomes [96,97]. Use of CGM can make this a modifiable factor and several studies have shown that using CGM in T1D is associated with reduced fear of hypoglycemia [98,99]. More significantly, retrospective analysis of large healthcare claims datasets indicate that application of CGM in type 2 diabetes mellitus is associated with more-timely treatment intensification, compared with self-monitored blood glucose (SMBG) testing [100].

4.1. Persons with type 2 diabetes mellitus on intensive insulin therapy

There is considerable evidence that people with type 2 diabetes mellitus on intensive insulin therapy (either multiple daily injections [MDI] with insulin or continuous subcutaneous insulin infusion [CSII]) can benefit from CGM devices in the same way as has been demonstrated for people with T1D. This includes lower HbA1c [101,102] and reduced hypoglycemia [102,103], as well as fewer hospital admissions for acute diabetes events (ADEs), such as diabetic ketoacidosis (DKA) or severe hypoglycemia [104–106], or for long-term microvascular and macrovascular complications [107]. Consequently, guidelines recommend CGM in type 2 diabetes mellitus on intensive insulin therapy [108,109], given the clinical benefits and cost effectiveness [110,111].

4.2. Persons with type 2 diabetes mellitus on basal insulin therapy

Initiation and titration of basal insulin therapy can be associated with episodes of problematic hypoglycemia, particularly in older people [112], and application of CGM can help to reduce such episodes following the start of basal insulin, by allowing the persons with type 2 diabetes mellitus to see their glucose levels in real time, as well as whether they are falling and how fast, using the trend arrows. Similarly, persistent TAR can be recognized using CGM and addressed by adjusting basal insulin doses upwards.

The MOBILE RCT has shown that use of CGM can significantly reduce HbA1c, time in hyperglycemia and the rate of hypoglycemia events over an 8-month period, compared to a control group using SMBG testing alone [113]. These data are consistent with results of other randomized controlled trials (RCTs) [114,115] and retrospective studies [116,117] demonstrating significant reduction in HbA1c for people with type 2 diabetes mellitus on basal insulin therapy. Equally, use of CGM in type 2 diabetes mellitus treated with basal insulin is associated with reduced hospital admissions, both for ADEs [118] and for cardiovascular complications [107]. Overall, use of CGM in type 2 diabetes mellitus treated with basal insulin has been shown to be cost effective, compared to routine SMBG testing [119].

4.3. Persons with type 2 diabetes mellitus on non-insulin therapies

A number of RCTs and real-world studies have shown that the use of CGM in non-insulin treated type 2 diabetes mellitus can significantly reduce HbA1c [120–124], particularly for those with higher HbA1c levels [125]. Glycemic variability, which is associated with adverse clinical outcomes [126–129], is also reduced in people with type 2 diabetes mellitus on non-insulin therapy using CGM [121]. Similarly, use of CGM in type 2 diabetes mellitus on non-insulin therapy is associated with reduced ADEs requiring hospital attendance or admission [125]. Notably, CGM has been shown to act as a motivational tool for helping people with inadequately controlled type 2 diabetes mellitus on non-insulin therapy to establish and adhere to lifestyle changes, and thereby reduce glycemia [130,131].

The use of CGM on a periodic basis can be a viable option at regular intervals or during treatment intensification or deintensification, particularly if oral insulin-secretagogue drugs (such as sulphonylureas) have been prescribed and where a risk of hypoglycemia is evident [132]. Blinded CGM has revealed that approximately 50 % of people with type 2 diabetes mellitus, including those on non-insulin therapy, experience frequent mild or clinically significant hypoglycemia [133], which is typically asymptomatic.

Together, these studies show that intermittent use of CGM systems provides glycemic information of value both to the person with type 2 diabetes mellitus and to their healthcare professional, which can facilitate improved glycemic control through changes to lifestyle and periodic medication adjustments. An important goal for this group of people with type 2 diabetes mellitus is to delay progression to insulin therapy. Since obesity is a major factor in metabolic decompensation leading to insulin treatment, it can be proposed that CGM can be used to monitor hyperglycemia for people with type 2 diabetes mellitus on weight-loss medications [134,135], during this period.

4.4. The newly diagnosed person with type 2 diabetes mellitus

The heterogeneity of disease for people diagnosed with type 2 diabetes mellitus is significant and can be mapped to a number of glucometric profiles, including for people newly diagnosed with type 2 diabetes mellitus [53,59,136]. The UKPDS study population consisted of 5,102 people with newly diagnosed type 2 diabetes mellitus, and demonstrated the importance of early and proactive glucose control for reducing long-term diabetes complications [137–139]. Therefore, CGM can be an effective option during the period following diagnosis of type 2 diabetes mellitus, to establish baseline glycemic profiles for each individual, against which subsequent treatment decisions may be compared and disease progression monitored.

4.5. Targeting and modifying behavior using CGM in people living with type 2 diabetes mellitus

The goal of addressing unhealthy dietary and lifestyle factors that may contribute to a diagnosis of type 2 diabetes mellitus may be productively addressed in people newly diagnosed, when motivation may be high to make positive changes to self-management behaviors related

to diet and exercise. Dietary interventions have been shown to be successful in adults with newly diagnosed type 2 diabetes mellitus, as measured by blinded CGM that is not used as a motivational tool [140]. A 2022 pilot study [82] specifically used CGM as a part of a 3-month intervention, focused on minimizing postprandial excursions in 17 adults with recently-diagnosed type 2 diabetes mellitus and mean HbA1c 8.0 % (64 mmol/mol), through educated use of CGM to understand the glycemic impact of food choices and exercise on PPE. After 3 months, 67 % of the participants exhibited remission of type 2 diabetes mellitus, with HbA1c < 6.5 % (<48 mmol/mol), TATR > 140 mg/dL (7.8 mmol/L) was significantly reduced, and consumption of carbohydrates and BMI were significantly lower. Although the study conclusions are limited by the small study size, similar outcomes for remission of type 2 diabetes mellitus were achieved as in the 12-month DiRECT study (see above), but over a 3-month period and without whole-scale dietary replacement. The CGM-directed intervention also involved regular motivational text messaging, thus leveraging multiple technologies, but participants reported that CGM use was the most significant element of the intervention. This pilot study did not have a control arm but the outcomes were improved compared to similar studies using education to minimize PPE and using standard SMBG to monitor glucose fluctuations [141,142]. Use of CGM actively to support behavior change through education aimed at reducing PPE has also shown significant reductions in HbA1c in adults with a type 2 diabetes mellitus duration of up to 11 years, compared to a control group using SMBG [123]. Significantly reduced glycemia > 180 mg/dL (>10.0 mmol/L), lowered mean HbA1c (−1.0 % [-11 mmol/mol) and weight loss (≥4 lbs) has also been demonstrated among 72 people with type 2 diabetes mellitus not on insulin using CGM, with or without a food-logging app, over 90 days [143].

Consensus statements. People living with type 2 diabetes mellitus.

- The goal of reversing dysglycemia in people newly diagnosed with type 2 diabetes mellitus is achievable in many cases.
- Benefits at a global population level will only be realised if access to CGM technology is improved to enable widespread adoption, especially in developing countries where burden and impact from diabetes remains highest.
- For people with newly diagnosed type 2 diabetes mellitus, CGM should be applied to establish their baseline glycemic profile and deciding and monitoring their initial treatment approach. Where restoration of normoglycemia is assessed as achievable, use of CGM should be used as part of this approach.
- For people with type 2 diabetes mellitus on non-insulin therapy, CGM use should be considered as an educational and motivational tool during diabetes self-management education and support (DSMES) interventions targeted at diet, physical activity and exercise.
- CGM should be applied as standard of care in people living with type 2 diabetes mellitus on non-insulin therapies, at any point where treatment intensification or deintensification is required.
- For people with type 2 diabetes mellitus on insulin therapy, we endorse existing international recommendations on the access and use of CGM technology[144]
- Further developments and integration of CGM data is required to simplify interpretation for those with lower digital and health literacy.

5. The value of CGM for predicting long term complications of type 2 diabetes mellitus

To date, HbA1c is the established reference metric for the assessment of glycemia in people with type 2 diabetes mellitus, based on its correlation with the incidence of microvascular and long-term macrovascular disease [137], although this assumption has been recently questioned [145]. The increasing use of CGM in type 2 diabetes mellitus has prompted a recent systematic review [146] of eleven studies, including a total of 13,987 people with type 2 diabetes mellitus, that evaluated the relationship between CGM measured TIR and diabetes complications. In each of these, the study cohort was not differentiated by treatment type. Four studies examined TIR in diabetic retinopathy and diabetic nephropathy, while seven studies evaluated TIR in diabetic peripheral neuropathy (DPN). A 10 % increase in TIR was associated with significant reductions in albuminuria, severity of retinopathy, and prevalence

of DPN and cardiac autonomic neuropathy (CAN).

Subsequent cross-sectional studies have confirmed that CGM-defined TIR is emerging as a relevant surrogate endpoint for microvascular complications, with increased TIR being associated with decreased rates of retinopathy [147,148], painful diabetic neuropathy [149] and preserved peripheral nerve function [150]. Both intra-day GV and time in hypoglycemia have been associated with retinal nerve-fiber thinning in retinopathy and neuropathy in type 2 diabetes mellitus [38,151], and GV has also been associated with cardiovascular autonomic neuropathy [152].

In terms of macrovascular outcomes, lower TIR is associated with surrogate vascular risk markers [153,154], increased risk of all-cause and CVD mortality [155], as well as peripheral artery disease [156] and diabetic foot ulcers [157]. Overall, in type 2 diabetes mellitus there is a consistent association between higher TIR and fewer macro- and microvascular complications [150,153,158–162]. Since the use of CGM is a driver for increased TIR in type 2 diabetes mellitus, the goal of reducing complications in type 2 diabetes mellitus can be associated with wider application of CGM systems, although further prospective longitudinal studies are necessary to validate these metrics for comprehensive risk profiling.

6. Primary care is a critical resource for management of obesity, intermediate hyperglycemia and type 2 diabetes mellitus

The majority of people living with obesity or intermediate hyperglycemia, who are at-risk of developing type 2 diabetes mellitus, and people with type 2 diabetes mellitus who are not on insulin therapy, are typically managed within primary care. The key goal for primary care teams must be the health promotion for at-risk populations and prevention of type 2 diabetes mellitus, especially amongst people living with obesity or intermediate hyperglycemia. This is made more-complex by the multitude of different populations of people at risk or with type 2 diabetes mellitus, the task of managing the multiple long-term conditions of associated macro- and microvascular disease, as well as their diverse ethnic and SDoH profiles. It is important that the landscape of digital health application evolves to meet this challenge. A 2018 survey reported that 89 % of primary care physicians (PCPs) across the EU did not use telemedicine with their patients and 81 % did not use it with other HCPs [163]. However, from 2020 onwards, the COVID-19 pandemic significantly changed the delivery of diabetes care to emphasize telemedicine in diabetes consultations [164], with evidence that this was not inferior to in-clinic consultations [164,165]. A small number of studies have also indicated that primary care teams and patients have embraced telemedicine as a consequence of the pandemic [166,167].

This trend is accompanied by evidence that use of CGM is increasing rapidly in adults with type 2 diabetes mellitus, with most growth in primary care. A review of e-health records from 30,585 adults with type 2 diabetes mellitus in Tennessee in the US [168] revealed a prevalence of 13 % of CGM use among this cohort, of whom 12 % were not on insulin. Twenty three percent of CGM users reported to only have visited their PCP during the previous year. Between 2020 and 2021, this study reported an overall monthly increase in new prescription rates for CGM of 36 % across all services, whereas the growth rate in primary care prescriptions was 125 % in the same period. New CGM users in primary care were mostly on intensive insulin regimen (49 %), whereas, 28 % were not using insulin.

The acknowledged efficacy of using CGM in people with dysglycemia should give primary care teams a significant tool to manage these populations, if access can be provided. However, experience with using and interpreting CGM systems, and the glucometric data that they provide, is a significant unmet need within primary care. Limited resources, with multiple competing priorities, are a barrier to uptake in primary care. A systematic review of the few studies available indicates that using CGM in the primary care setting for the management of adults

with type 2 diabetes mellitus is more effective than relying on SMBG for reducing HbA1c [169]. Just as important, people with type 2 diabetes mellitus reported that CGM improved treatment satisfaction, with better understanding of self-management needs and how therapy of type 2 diabetes mellitus works. PCPs reported that CGM and the glycemic reports generated assisted in effective communication with their patients and that they were willing to continue using CGM.

Using CGM and CGM-derived glucose data facilitates cooperation between PCPs and people with diabetes for clinically relevant, person-centered, achievable glycemic goal setting [170]. This empowers people with diabetes to manage the challenges of daily self-management and may even lead to healthy lifestyle behavior changes. Small-scale training for PCPs in the application and use of CGM by family-practice teams is well received and may be the best way to meet the needs of people with diabetes in their clinics [171]. Interest in applying CGM in their practices amongst PCPs has been assessed as higher among those with practices located further from endocrinology centers [172]. As with all settings, the management of type 2 diabetes mellitus in primary care services requires that access to CGM technology is improved, including reimbursement, to enable widespread adoption [173].

A further consideration that can support PCPs in using CGM devices and data with people who have intermediate hyperglycemia or are diagnosed with type 2 diabetes mellitus, is the use of AI-CDSS. Such tools are a natural development, since the management of people with dysglycemia and diabetes is laid out in comprehensive guidelines that are driven by clear treatment algorithms [108]. The development of AI-CDSS, that marry the decision paths laid out in guidelines with objective data on short and long-term glycemic performance, will create significant benefits for PCPs and people with intermediate hyperglycemia or type 2 diabetes mellitus in their care. At least one small-scale survey has indicated that PCPs have a generally positive view of AI, dependent on the context in which AI was adopted [174], and the use of AI-CDSS in the context of diabetes care is suited to the primary care setting, leveraging PCP expertise with knowledge-based machine learning.

Consensus statements. Primary-care management of CGM use in people living with obesity, intermediate hyperglycemia or type 2 diabetes mellitus.

- There is an unmet need for prospective studies in the primary-care setting, centered on the application of CGM technology in the management of people living with obesity, intermediate hyperglycemia or type 2 diabetes mellitus.
- Training and education on the effective application of CGM and interpretation of CGM data must be developed and delivered as part of continuing professional development for all primary-care team members.
- Access to support from specialist diabetes teams on the use of CGM and data interpretation is vital to establishing CGM use in the primary care setting.
- Development of and access to AI-enabled Clinical Decission Support Systems (AI-CDSS) for CGM data interpretation is critical for increasing time efficiency and wider adoption of CGM on the primary care level.
- Clear pathways and guidelines on patient eligibility and prescribing in obesity and intermediate hyperglycemia need to be developed.
- Support for proactive identification of eligible persons in the primary care setting will help to avoid worsening health inequalities.

7. Cost effectiveness of implementing CGM in the management of people living with obesity, intermediate hyperglycemia or type 2 diabetes mellitus

Application of CGM in the management of obesity, intermediate hyperglycemia and type 2 diabetes mellitus has the potential to significantly reduce the burden of disease for people living with each of these chronic conditions and the health services tasked with their care. The cost effectiveness of this intervention needs to be carefully analyzed. To date, there has been very limited cost-effectiveness analysis for use of CGM systems in type 2 diabetes mellitus, and less in either obesity or intermediate hyperglycemia. Of note, when looking at diabetes prevention strategies, for example in obesity or intermediate hyperglycemia, strategies that target populations from more-disadvantaged SDoH

groups may be cost-effective at higher input costs and lower efficacy compared to untargeted policies [175].

7.1. Type 2 diabetes mellitus on intensive insulin therapy

Use of CGM for people with type 2 diabetes mellitus on either MDI or CSII therapy has been assessed as cost-effective compared to standard care with SMBG, based on a 40-year horizon [110,111,176]. This includes total intervention costs and direct medical costs, as well as hospital admission costs for ADEs, in two of these analyses [111,176]. Productivity loss was included in the third study [110]. Use of CGM improves quality-adjusted life years (QALYs) for people with type 2 diabetes mellitus on intensive insulin therapy, which supports a favorable incremental cost-effectiveness ratio (ICER) [110,111,176].

7.2. Type 2 diabetes mellitus on basal insulin therapy

Intermittent use of CGM in four cycles over 3 months, followed up to 52 weeks, compared to using SMBG has been shown to be cost effective [119]. Direct medical costs, including treatment for depression and for diabetes complications were included. Improved Life expectancy and quality-adjusted life expectancy (QALE) outcomes for the CGM cohort generated gains for ICER and QALY. Notably, the cost-effectiveness in this model was attributed to users making informed behavioral choices without clinician guidance [119].

7.3. Type 2 diabetes mellitus on any insulin therapy

Using CGM in people with type 2 diabetes mellitus on intensive or basal insulin therapy was associated with increased QALYs and improved ICER over a lifetime horizon, compared with SMBG, based only on direct healthcare costs in the UK. Drivers included HbA1c reduction and reduced SMBG strip-testing [177].

7.4. Type 2 diabetes mellitus in the primary care setting

A randomized, 6-month prospective US trial was conducted using CGM compared to SMBG testing for participants receiving usual care in primary care clinics [178]. Of the 99 participants, 93 had a diagnosis of type 2 diabetes mellitus but were selected without consideration of their current dietary, oral medication or injectable therapeutic regimens. After 6 months, CGM users had reduced costs overall for primary care visits, emergency department attendance and laboratory investigations. Savings were not universal and depended on the health insurance provider.

Consensus statements. Cost-effectiveness of CGM use in people living with obesity, intermediate hyperglycemia or type 2 diabetes mellitus.

- There is an unmet need for cost-effectiveness analysis of using CGM technology as part of intervention strategies to modify diet and physical activity in people living with obesity, intermediate hyperglycemia or type 2 diabetes mellitus.
- Future health-economic models should incorporate measures of SDOH to improve targeting of CGM as an intervention strategy for prevention or delayed progression of type 2 diabetes mellitus.

8. Summary

Based on available evidence, CGM technology can be used to support behavioral change and improved glycemic control for people at-risk of type 2 diabetes mellitus, including people living with obesity or intermediate hyperglycemia, and for people diagnosed with type 2 diabetes mellitus. The perceived and demonstrated benefits include: (1) to actively engage people with their glycemic status, (2) to evaluate treatment responses and achievement of goals; (3) to reinforce education and self-management skills in people with intermediate hyperglycemia or with type 2 diabetes mellitus; (4) adjust therapy as needed for

people with type 2 diabetes mellitus. Significant further research is needed to fully evaluate the value proposition for CGM technology in normoglycemic obese at-risk persons and in those with intermediate hyperglycemia. It is important to state that the benefits of the application of CGM technology will only be fully realized with significant widening of access globally, to avoid regional disparities and inequities, along with further refinements to improve simplicity and interpretation of CGM data to include people with lower levels of digital and health literacy, where AI-CDSS may play a critical role.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TB served on advisory panels of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, Abbott, Indigo Diabetes. TB received honoraria for participating on the speaker's bureau of Eli Lilly, Novo Nordisk, Medtronic, Abbott, Sanofi, Dexcom, Aventis, Astra Zeneca, and Roche. TB's Institution received research grant support from Abbott, Medtronic, Novo Nordisk, Sanofi, Novartis, Sandoz, and Zealand Pharma, Slovenian Research and Innovation Agency, the National Institutes of Health, and the European Union. SH has served on the advisory board for Tandem, Dexcom, Medtronic, Sanofi, Vertex; undertaken non-promotional educational and/ or consultancy work for Abbott UK, Insulet, Dexcom, and Roche; SH's institution has received research grant support from Abbott and Insulet. PT served on advisory boards of Eli Lilly, Boehringer Ingelheim, Novo Nordisk, Lifescan and Astra Zeneca. PT participated in CME's supported by Astra Zeneca, Boehringer Ingelheim, Eli Lilly and Novo Nordisk. PT is the vice chair of PCDE, which has received corporate sponsorship from AstraZeneca, Eli Lilly, Novo Nordisk, and Roche Diagnostics, but the companies had no input in the study protocols. TT has served on advisory panels of Boehringer Ingelheim, Astra Zeneca, NovoNordisk, EliLilly, Medtronic. TT has received honoraria for participating in speaker's bureau of Boehringer Ingelheim, Astra Zeneca, NovoNordisk, Eli Lilly, Merck, Sanofi, MSD, Servier. CM serves or has served on the advisory panel for Dexcom, Roche, Medtronic, Insulet. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from Medtronic. CM serves or has served on the speakers bureau for Medtronic. Financial compensation for these activities has been received by KU Leuven. CM is president of EASD. All external support of EASD is to be found on https://www.easd.org.

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Glossary

ADE: Acute diabetes event
BMI: Artificial intelligence
CAN: Cardiac autonomic neuropathy
CGM: Continuous glucose monitoring
CKD: Chronic kidney disease
DPN: Diabetic peripheral neuropathy
DSMES: Diabetes self-management education and support
FPG: Fasting plasma glucose
GLP-1 RA: Glucagon-like peptide 1 receptor agonists
GMI: Glucose management indicator
GV: Glycemic variability
HCP: Healthcare professional
ICER: Incremental cost-effectiveness ratio
IDF-Eu: International Diabetes Federation Europe
IGT: Impaired glucose tolerance
OGTT: Oral glucose tolerance test
PCDE: Primary Care Diabetes Europe
PCP: Primary care physician
QALE: Quality adjusted life expectancey
QALY: Quality adjusted life year
RCT: Randomized controlled trial
SDoH: Social determinants of health
SMBG: Selfmonitored blood glucose
T1D: Type 1 diabetes
TAR: Time above range
TIR: Time in range
TITR: Time in tight range
TRE: Time restricted eating