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## REVIEW

**How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes?**

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## **Abstract**

In 2010, the James Lind Alliance published a “top 10” list of priorities for type 1 diabetes research. Whether reducing fluctuations in blood glucose can prevent long-term microvascular and macrovascular complications was one of these. In this narrative review, we have assessed the updated evidence for the assertion that increased glucose variability plays an independent and clinically important role in the complications of type 1 diabetes, over and above mean blood glucose and the effects of hypoglycaemia: the “glucose variability hypothesis.” While studies in cultured cells and *ex vivo* vessels have been suggestive, most studies in type 1 diabetes have been small and/or cross-sectional and based on “fingerprick” glucose measurements that capture glucose variability only in waking hours and are affected by missing data. A recent analysis of the Diabetes Control and Complications Trial that formally imputed missing data found no independent effect of short-term glucose variability on long-term complications. Few other high quality longitudinal studies have directly addressed the glucose variability hypothesis in type 1 diabetes. We conclude that there is little substantial evidence to date to support this hypothesis in type 1 diabetes, although increasing use of continuous glucose monitoring (CGM) provides an opportunity to test it more definitively. In the meantime, we recommend that control of glycaemia in type 1 diabetes should continue to focus on sustained achievement of target HbA1c and avoidance of hypoglycaemia.

*(231 words)*

## **Introduction**

Unexplained minute-to-minute, hour-to-hour and day-to-day fluctuations in blood glucose are an important cause of frustration for people living with type 1 diabetes, causing anxiety and affecting quality of life. Greater than average variability of blood glucose is accompanied by more frequent episodes of hypoglycaemia (1), resulting in well-known adverse effects ranging from stress and inconvenience, through problems with driving and employment, to accidents, cardiovascular morbidity and mortality (2–4).

But do the adverse effects of glucose variability (GV) go further than those mediated by mean blood glucose and hypoglycaemia? One of the top ten research questions emerging from the 2010 James Lind Type 1 Diabetes Priority Setting Process was *“How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes?”*(5). A considerable amount has been written attributing a role of glycaemic variability in the pathogenesis of microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (cardiovascular) complications of type 1 diabetes, but it is unclear to what extent people with the condition should strive to minimise it.

In this non-systematic review, we therefore evaluate the evidence that fluctuations in blood glucose contribute independently to the development of long-term complications of type 1 diabetes (6), over and above the effects of mean blood glucose [as reflected by glycated haemoglobin (HbA1c)] and the frequency of hypoglycaemia (Figure 1).

### **Glucose, HbA1c and glucose variability**

The Diabetes Control and Complications Trial (DCCT) and its post-randomisation follow-up study Epidemiology of Diabetes Interventions and Complications (EDIC) have made a unique contribution to the field of type 1 diabetes. Together, they have demonstrated over 30 years of follow-up that: (i)

hyperglycaemia is the most important modifiable risk factor for both microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (cardiovascular) complications of type 1 diabetes; and (ii) intensive control of blood glucose can substantially prevent and delay these (7–9). Glycated haemoglobin (HbA1c) was central to the design of the DCCT: it can be conceptualised as reflecting time-averaged glucose values over the 8-12 weeks prior to blood sampling (10).

Largely because of the benefits of intensive glucose control in DCCT-EDIC, HbA1c has become widely available as a real-time measurement in diabetes clinics as the principal basis for making treatment decisions aimed at achieving and maintaining optimal glycaemic control. It has also been adopted as the primary endpoint of most clinical trials assessing the glucose-lowering efficacy of new therapies, including insulins. Although HbA1c principally reflects “average” glucose values, the relative contribution of post-prandial vs fasting glucose to the measured HbA1c value increases as ambient glucose levels move closer to the target range i.e. it is not independent of glucose variability (11). Nevertheless, it is well-recognised that two individuals with the same HbA1c value can have very different levels of glucose variability.

The notion that glycaemic variability contributes additional risk over and above the risk conferred captured by HbA1c can be termed the “glucose variability hypothesis (12).” Two types of short-term glucose variability are recognised:

- (i) “Within-day” glucose variability : greater than expected oscillations in blood glucose in excess of normal physiological variation within a 24 hour period. Thus, an individual whose blood glucose in a typical day is usually 6-10 mmol/L for twelve hours of the day but 4-6 mmol/L for 6 hours and 10-12 mmol/L for the remaining six hours is hypothesised to have a higher risk of long term complications than Person B whose blood glucose is usually around 6-10 mmol/L throughout the 24 hour period, even though both have a mean glucose of 8 mmol/L (and the same HbA1c).

- (ii) “Between-day” Glucose Variability : glucose levels are close to target on some days but far from target on others (11,13), or exhibit greater “spread” at specific times of the day.

It has further been suggested (on the basis of cross-sectional data) that “spikes” of hyperglycaemia are associated with atherosclerosis, even in healthy individuals (14).

In practice, both forms of short-term glucose variability are frequently seen in the same individual: this form of glucose variability is more relevant to the James Lind question than long-term glycaemic variability, which is derived from serial assessments of HbA1c, rather than from blood glucose *per se*.

### **Causes of glucose variability in type 1 diabetes**

Glucose variability is a physiological phenomenon that is almost by definition exaggerated in type 1 diabetes as minute-to-minute homeostatic changes in rates of  $\beta$ -cell insulin secretion in response to changes in blood glucose cannot occur. Its existence to a greater extent in some individuals may arise for a number of reasons (15):

- (i) Insulin supply: e.g. problems with obtaining or storing insulin, lack of mixing (e.g. for isophane preparations), or low adherence (e.g. missed injections).
- (ii) Injection technique: e.g. overuse and/or lipohypertrophy of injection sites; not changing needles between injections.
- (iii) Inaccurate blood glucose meter readings: e.g. device failure, use of wrong calibration fluid, lack of hand-washing.
- (iv) Meal-related factors: e.g. errors in estimation of carbohydrate according to portion size, inaccurate estimation of insulin dose required per unit carbohydrate intake, missed meals, inappropriate corrective doses [see (iii)], sporadic ingestion of unpredictable quantities of refined CHO.

- (v) Physiological factors: e.g. impaired gastric emptying (autonomic neuropathy), individual differences in hormonal counter-regulation, variation in the degree to which fasting hepatic glucose production is suppressed.
- (vi) Lifestyle factors e.g. unpredictable bouts of physical exertion.

This list is not exhaustive. From our clinical experience, increased glycaemic variability is rarely caused by a single factor, and often a specific cause cannot be identified.

### **How might glucose variability cause complications?**

Hyperglycaemia causes micro- and macrovascular complications by a number of mechanisms. Oxidative stress, and in particular increased superoxide production at a mitochondrial level, is widely considered the key link (16,17). Overproduction of superoxide by the mitochondrial electron transfer chain activates a cascade of deleterious metabolic events including the polyol pathway, formation of advanced glycation end products, and activation of both protein kinase C and nuclear factor  $\kappa$ B (16).

The origins of the glucose variability hypothesis lie in experiments performed two decades ago in which investigators exposed cultured vascular cells and *ex vivo* tissue preparations to oscillating glucose levels and reported deleterious effects additional to those seen with constant high glucose (17–20). For example, in rat thoracic aorta, Azuma et al demonstrated that repetitive fluctuating high glucose induced a greater degree of monocyte-endothelial activation, a marker of endothelial inflammation, than constant high glucose (21). Similarly, this group demonstrated that atherosclerosis-prone mice exhibited accelerated formation of fibrotic arteriosclerotic lesions when subjected to GV, and that reducing these glycaemic excursions reduced vascular inflammation (22–24).

It has further been proposed that short-term glucose variability can cause coronary plaque instability (25,26), prolongation of the QT interval (27), and that it is associated with subclinical atherosclerosis (28). However, all of these studies were cross-sectional (although one describes itself as prospective) (25), one was very small (n=46) (25), and the largest (n=595) (28) concerned long-term glucose

variability as measured by HbA1c. All were conducted in people with either type 2 diabetes (27,28) or without diabetes (25). For people with type 1 diabetes, they can therefore at best be described as “hypothesis-generating.”

As mentioned above, increased glycaemic variability in type 1 diabetes is associated with increased rates of hypoglycaemia (1,29). This provides a further complication in testing whether glucose variability is independently associated with complications as hypoglycaemia can also trigger an inflammatory response by stimulating inflammatory cytokines (including C-reactive protein, Interleukin-6 and Tumour necrosis factor- $\alpha$ ), as well as neutrophil and platelet activation (2,30).

Another outcome that has been investigated in relation to glucose variability is length of hospital stay and increased mortality in hospitalised people with diabetes. In a retrospective cohort study of over 4000 patients admitted to non-ICU medicine and surgery over a two year period, Mendez et al reported a longer hospital stay by 4.4% and an increased 90 day relative risk of death of 8% for every 10 mg/dL increase in SD (31). Although these findings were adjusted for age, race, BMI, diagnosis of diabetes, treatment regimen, mean glucose, and rates of hypoglycaemia, a prospective trial of an intervention that reduced glucose variability in this context would clearly be required to impact clinical practice (31). **Measures of glucose variability**

It is often stated that there is no consensus on how best to assess glucose variability and that this lack of standardisation makes comparison between studies difficult and unreliable. A simple method is to calculate the standard deviation (SD) of multiple self-monitoring of blood glucose (SMBG) fingerprick measurements within a specific time period e.g. “seven point profiles” (32). The SD can be a suitable parameter even in datasets in which glucose values do not follow a Gaussian distribution, as it has a near linear relationship with the interquartile range (33).

It is important to appreciate that glucose variability is influenced by mean blood glucose i.e. a biological dataset containing higher glucose levels will almost certainly exhibit higher glucose variability. For example, if blood glucose varies by 10% around a mean of 10 mmol/L, the range will

be 2 mmol (i.e. 9 to 11 mmol/L), whereas if it varies by the same percentage around a mean of 5 mmol/L the range will be 1 mmol/L (i.e. 4.5 to 5.5 mmol/L). This problem can be avoided by using the Coefficient of Variation (CV) (the SD divided the mean blood glucose values x 100%). There is an emerging consensus for using CV as the preferred parameter to describe within-day glucose variability (34), not least because it is necessary to correct other measures statistically for differences in mean glucose when making comparisons between groups (although this is not always done) (13).

Another simple parameter of within-day glucose variability is the mean of the differences between the peaks and nadirs of a glucose profile, namely the Mean Amplitude of Glycaemic Excursions (MAGE) (19), while Continuous Overall Net Glycaemic Action (CONGA) is more complex. Short-term *between-day* variability can be described using the Mean of Daily Differences (MODD) (26).

A key difficulty when calculating any parameter of GV from real world “seven point” glucose profiles is how to handle missing data. If preprandial values are missing, within-day SD is overestimated, while if postprandial values are missing, the SD is underestimated. Differences in approach can lead to a degree of operator-dependence. Equally important, overnight readings are rarely available.

### **Biomarkers of glucose variability**

Urinary excretion rate of 8-iso-PGF<sub>2α</sub> has been proposed as a biomarker of oxidative stress (35); it is synthesised *in vivo* through non-enzymatic free radical peroxidation of arachidonic acid. In a small cross-sectional study in type 2 diabetes, Monnier and Colette demonstrated a correlation between urine concentrations of 8-iso-PGF<sub>2α</sub> and MAGE (36). On the basis of a regression line between mean urinary excretion rate of 8-iso-PGF<sub>2α</sub> and MAGE in 21 healthy individuals, they extrapolated a suggested “target MAGE level” of glucose variability [40mg/dl (2.2 mmol/L)] (18). However, in a case-control study by other authors in which 8-iso-PGF<sub>2α</sub> was on average higher in individuals with type 1 diabetes, there was no correlation between glucose variability and 8-iso-PGF<sub>2α</sub> (37).

Other biomarkers including glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG) have been shown to correlate with glucose variability parameters. Glycated albumin is a fructosamine and reflects short time glycaemia due to the half-life of albumin which is approximately 3 weeks (38,39). It has been suggested as a method of monitoring short term glycaemic control in type 2 diabetes, especially in those with fluctuating glycaemia (11), and the glycated albumin/HbA1c ratio has been proposed as a method of identifying people with larger glycaemic excursions on the basis of a cross-sectional study in 600 people with types 1 and 2 diabetes (40).

Another potential biomarker of glucose variability is the monosaccharide 1,5-anhydroglucitol (41). Structurally similar to glucose, its usual filtration and reabsorption in the renal tubules is inhibited when serum glucose levels are high. As plasma levels therefore decrease during hyperglycaemia and normalise during sustained euglycaemia, low levels indicate increased glucose variability over a period of days to weeks (42). However, in the largest observational study to date in type 1 diabetes (n=136), BMI and adiposity were stronger predictors of glucose variability (43).

At the time of writing, the clinical utility of these glucose variability biomarkers remains unclear.

### **Clinical trials and cohort studies**

DCCT-EDIC is the only large (n= 1441) longitudinal dataset to date containing both robust measures of glucose variability (seven-point profiles every three months) and long-term high-fidelity data on complications (Table). The first analysis on this topic (by Service et al) was conducted on n=565 DCCT participants without missing data: this showed a weak relationship between MAGE and the risk of retinopathy (45). In an analysis of a larger dataset, Kilpatrick et al subsequently found no evidence that either intra-day or between-day variability (SD) of blood glucose influenced the risk of nephropathy or retinopathy (44). More recently, a further analysis has been conducted in the whole dataset using multiple imputation to estimate missing blood glucose profiles from other

measurements (46). This reached a similar conclusion i.e. a lack of association between within-day glycaemic variability derived from three-monthly seven-point glucose profiles and the future risk of developing microvascular complications in type 1 diabetes, following adjustment for mean blood glucose. However, as a *caveat* it was acknowledged (as mentioned above) that seven point glucose profiles may be insufficient to fully capture the extent of glucose variability.

Most other studies in type 1 diabetes have been cross-sectional (47) or have lacked the long term follow-up required to address this question. A near exception was a Swedish prospective cohort study over eleven years in 100 people with type 1 diabetes, in which glucose variability at baseline (SD of blood glucose levels over four weeks) had an association with incident peripheral neuropathy of borderline statistical significance (48). However, no associations were detected between glucose variability and either nephropathy or retinopathy: despite an ambitious duration of follow-up, this study may ultimately have been underpowered for detailed examination of these associations. .

### **Insights from type 2 diabetes**

Glucose variability can be just as troubling for people with type 2 diabetes (T2D) who require insulin treatment as it is for those with type 1 diabetes. There is observational evidence that post-prandial and/or post-load blood glucose is associated with all-cause mortality (49), and more limited evidence that it is associated with cardiovascular events (22). On this basis, it has been suggested that glucose variability may play a role in the pathogenesis of cardiovascular complications in type 2 diabetes: for example, in a cross-sectional study, SD of glucose variability derived from continuous glucose monitoring (CGM) (see below) was associated with the presence of microalbuminuria (although this finding was no longer significant after adjustment for mean glucose) (50).

The glucose variability hypothesis was recently tested more comprehensively in type 2 diabetes in a *post hoc* analysis of the DEVOTE cardiovascular outcome trial, in which 7637 people with T2D were

randomised to long-acting insulin degludec or insulin glargine U100 for 24 months (51). Between-day glucose variability was derived from the variance of three pre-breakfast self-measured blood glucose readings per month. Glucose variability by this measure was associated, as would be expected, with episodes of severe hypoglycaemia, and also with all-cause mortality. However, the association with cardiovascular complications was no longer statistically significant following adjustment for baseline HbA1c, or indeed the most recent value. This may suggest that a proportion of the deaths in the study associated with glucose variability were attributable to hypoglycaemia rather than to cardiovascular disease. It was not possible to derive a measure of within-day glucose variability+ from this dataset.

### **Continuous glucose monitoring**

As summarised above, the majority of the evidence available to date addressing the relationship between glucose variability and future diabetes complications has been based on fingerprick SMBG profiles. Non-invasive continuous glucose monitoring (CGM) devices using a sensor to measure interstitial glucose concentrations every five minutes have been available for more than 15 years, but only at the time of writing are becoming widely reimbursed by healthcare providers and therefore more widely used (52). Many of the measures of glucose variability summarised above can readily be calculated from glucose profiles captured from these devices, providing an amount of information that is an order of magnitude more comprehensive than SMBG. As a starting point, Monnier et al have suggested that a coefficient of variation (CV) of < 36% should be targeted, as a higher degree of variability is associated with an increased rate of hypoglycaemia (53). However, CGM data are not as yet available from any type 1 diabetes cohorts that have been followed up with high fidelity in the long term. It will therefore take several more years before sufficient evidence is available to assess whether parameters of glucose variability derived from frequent measures of interstitial glucose concentration are independently predictive of rates of complications. An exciting and challenging prospect in the meantime is use of big data methods and cloud computing to capture, securely store

and analyse CGM data for this purpose, while respecting the privacy of users. Such studies will only be definitive if conducted in populations with sufficiently robust contemporaneous information on complications available.

### **How can glucose variability be reduced in type 1 diabetes?**

It is accepted by advocates of the glucose variability hypothesis that long-term intervention studies are necessary to provide definitive evidence that reducing short-term glucose variability can reduce rates of long-term micro- and/or macrovascular complications (23). One potential method for reducing glucose variability in type 1 diabetes is training in hypoglycaemia avoidance (54): this has already been shown to reduce glucose variability in those with impaired awareness of hypoglycaemia but would require validation before use in a more general population with type 1 diabetes. Another is switching to more recently-introduced long-acting basal insulins that have been shown to reduce glucose variability in people with type 2 diabetes (51) (although in one small study in type 1 diabetes (n=36) there was no difference in glucose variability between insulin degludec and standard of care comparator insulin glargine U100) (55). A third potential method is to use CGM as an intervention (56): studies to test the effectiveness of this strategy will require participants in the intervention arm to wear two CGM devices, one open to the user and one blinded for outcome assessments (56). Finally, continuous subcutaneous insulin infusion (CSII) can reduce intra-day and between-day glucose variability by providing quantities of insulin that are more closely matched to physiological insulin requirements (50–52); this also applies to sensor augmented pumps (55).

It should be noted that all of the above interventions are already used to target mean blood glucose as assessed by HbA1c.

In a recent review article, Ceriello et al argued that studies aimed at testing the glucose variability hypothesis should avoid use of insulin therapy as it could potentially mask an effect of glucose

variability on complications by reducing inflammation, thrombosis, and oxidative stress (26). This stipulation, which clearly cannot be applied in type 1 diabetes, argues against the potential clinical importance of any effect of glucose variability on complications, as all individuals with type 1 diabetes rely in any case on insulin for survival.

### **HbA1c Variability**

Not directly relevant to the James Lind question, but worth mentioning in the interests of clarity, is that *long term* glycaemic variability (as assessed by the SD of HbA1c measured every three months) added predictive value to mean HbA1c in predicting retinopathy and nephropathy in the DCCT (57). While glucose variability as discussed above indicates within- or between-day (short-term) variability in blood glucose, HbA1c variability reflects periods of weeks or months during which glycaemic control is close to target interspersed with equivalent periods of time when it is not. Analysis of publicly-available DCCT data by Kilpatrick et al demonstrated that HbA1c variability contributes independently to mean HbA1c in predicting microvascular complications in diabetes: for every 1% increase in HbA1c SD there was an approximate twofold increase in risk of development or progression of both retinopathy (hazard ratio 2.26 [95% CI 1.63-3.14]  $P < 0.0001$ ) and nephropathy (1.80 [1.37-2.42]  $P < 0.0001$ ) (8). More recently, a systematic review and meta-analyses of seven type 1 diabetes studies by Gorst et al demonstrated a positive relationship between HbA1c variability and renal disease (risk ratio 1.56 [95% CI 1.08-2.25]) and cardiovascular disease 1.98 [95% CI 1.54-2.89], with similar findings in type 2 diabetes studies (58). While this review suggested that longer term glycaemic variability is independently linked with complications when calculated by several different HbA1c-based methods, Lachin et al did not find a similar effect in DCCT when it was calculated from six monthly periods of glucose data; such measures were not available in the studies used for the systematic review (46).

Kilpatrick et al have convincingly argued that an effect of long term glycaemic variability on complications may be mediated by “normoglycaemic re-entry” (8). Although the mechanism for this

is not fully understood, early worsening of complications when a rapid improvement in glycaemic control is achieved is clinically recognised and was described in the DCCT (??) (59). It most often occurs in women with type 1 during pregnancy but can also be seen in type 2 diabetes when a substantial improvement in glycaemic control is achieved (e.g. worsening of proliferative retinopathy with semaglutide in SUSTAIN-6) (60). As it does not seem biologically plausible for “re-entry” to mediate an effect of within- or between-day (short-term) glucose variability on complications, we consider short- and longer-term glucose variability to be distinct phenomena.

## **Summary**

Biologically plausible mechanisms exist by which glucose variability may contribute independently beyond HbA1c and hypoglycaemia to the risk of long term complications associated with type 1 diabetes, and there are some limited data linking glucose variability and complications in type 2 diabetes. However, there are few robust data of an observational nature, and no direct clinical trial evidence, to support the glucose variability hypothesis in type 1 diabetes. Methods are already available that help people with type 1 diabetes avoid excessive glucose variability, reduce the risk of hypoglycaemia and increase quality of life. On the basis of the evidence reviewed, we do not recommend targeting a specific level of glucose variability for the purpose of reducing T1D diabetes complications pending a full prospective assessment of the associated risks and benefits. Fortunately, more widespread contemporary use of CGM devices provides considerable opportunities for the appropriate research to be conducted.

There is therefore currently insufficient evidence to answer the James Lind research question ‘How tightly controlled do fluctuations in blood glucose need to be to reduce complications?’ Current efforts to reduce complications by improving glycaemic control should continue to focus on sustained achievement of target HbA1c and avoidance of hypoglycaemia.

*(3757 words)*

**Novelty statement:**

**“What is already known?”**

- Hyperglycaemia is the most important modifiable risk factor for both microvascular and macrovascular complications of type 1 diabetes
- Intensive control of blood glucose can substantially prevent and delay these complications

**“What does this review add?”**

- There is currently insufficient evidence to answer the James Lind research question ‘How tightly controlled do fluctuations in blood glucose need to be to reduce complications?’

**“What are the clinical implications of the review?”**

- Efforts to reduce complications by improving glycaemic control in type 1 diabetes should continue to focus on sustained achievement of target HbA1c and avoidance of hypoglycaemia
- More widespread use of continuous and flash glucose monitoring devices offers opportunities for more definitive research on this topic (both cohort and intervention studies)

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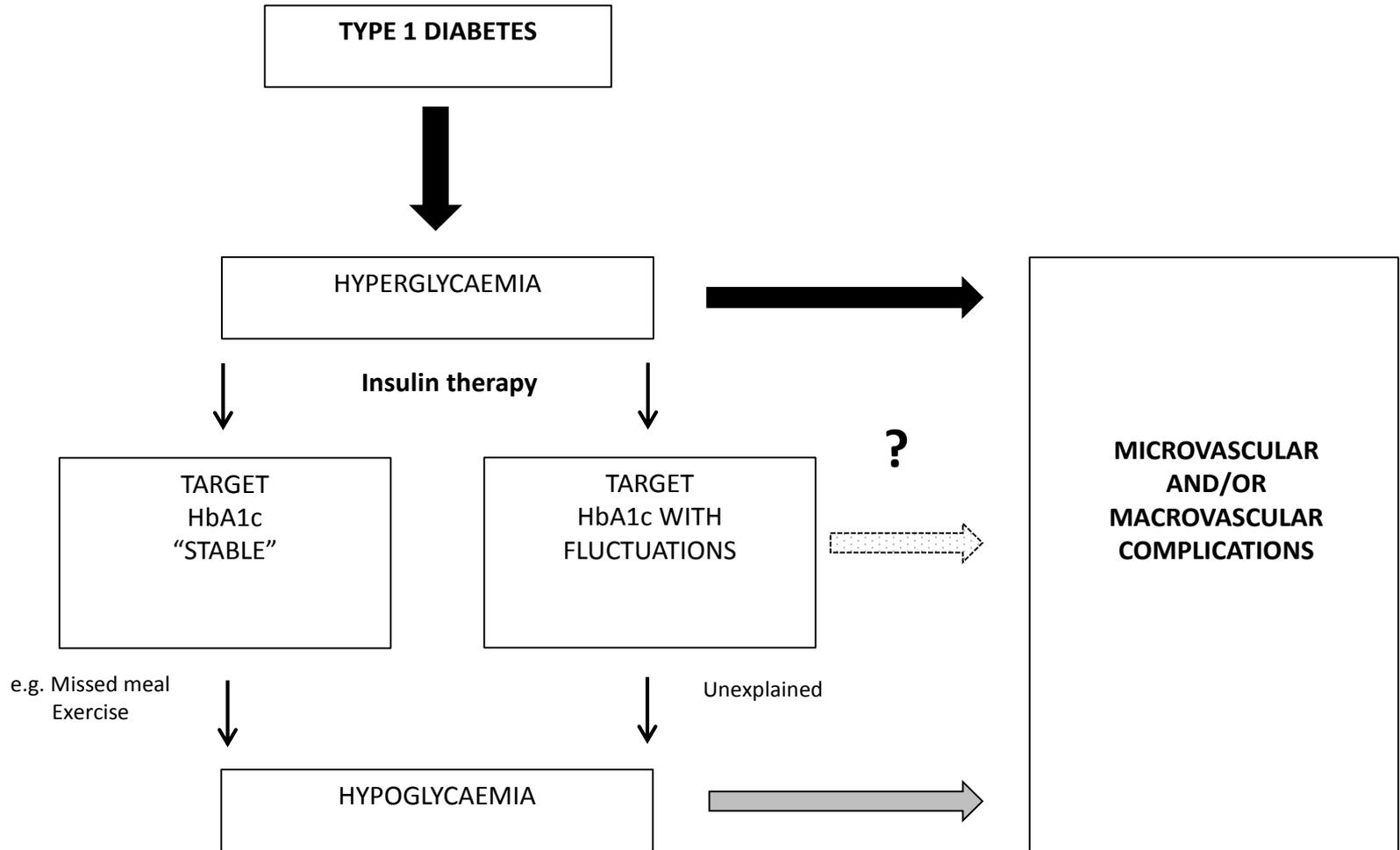
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## Figure legend

**The glucose variability hypothesis.** Fluctuations in blood glucose contribute independently to the development of long-term complications of type 1 diabetes, over and above the effects of mean blood glucose [as reflected by glycated haemoglobin (HbA1c)] and the frequency of hypoglycaemia. Dark lines indicate proven causality; grey or shaded lines indicate probable or possible causality. The question mark (“?”) denotes the specific pathway glucose variability discussed in the text.



**Table. Summary of analyses of DCCT (and EDIC) data relating glucose variability measures to complications**

Year	First author	Cited as reference	Pubmed ID	Number included in analysis	Handling of missing data	Short term glycaemic variability measure assessed*	Long term glycaemic variability measure assessed	Complications assessed at end of DCCT (or later)	Independent effect of glucose variability on complications?
2001	Service	45	11692169	n=565	Participants selected were in DCCT > 4 years and had 80% of measurements available	SD, MAGE	-	Retinopathy	Short-term: weak association with MAGE Long-term: not analysed
2006	Kilpatrick <sup>#</sup>	44	16801566	Up to n=1441 (not specified)	Minimised by selecting earlier follow-up time point	Within and between-day SD; MAGE	-	Retinopathy, nephropathy	Short-term: no Long-term: not analysed
2008	Kilpatrick <sup>#</sup>	57	18650371	Up to n=1441 (not specified)	Not stated but few were missing	-	HbA1c (SD)	Retinopathy, nephropathy	Short-term: not analysed Long-term: yes
2009	Kilpatrick <sup>#</sup>	8	19549736	n=1208	Only those with data at EDIC Year 4 included	SD, MAGE	-	Retinopathy, nephropathy at EDIC year 4	Short-term: no Long-term: not analysed
2017	Lachin	46	28404658	n=1441	Multiple imputation (for 16.3% of missing values)	Within and between-day SD; MAGE	Longitudinal MAGE	Retinopathy, nephropathy, neuropathy	Short term: no Long term: possible (p=0.06) association with microalbuminuria only

<sup>#</sup>authors accessed publicly-accessible data from NIH (NIDDK) repository; \*calculated from quarterly 7-point blood glucose profiles during DCCT  
**Abbreviations:** DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; MAGE, Mean Averaged Glucose Excursion; SD, Standard Deviation