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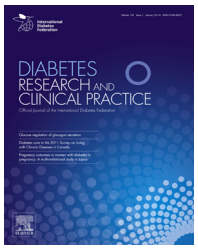

Review

Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes☆

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ABSTRACT

Chronic hyperglycemia is the main risk factor for the development of diabetes-related complications in both type 1 and type 2 diabetes, but it is thought that frequent or large glucose fluctuations may contribute independently to diabetes-related complications.

A systematic literature review was performed using the PubMed, EMBASE and Cochrane Library databases with searches limited to studies published from June 2002 to March 2014, in English and including ≥50 patients. Twenty eight articles were included in the final review.

Eighteen studies reported the association between glucose variability and diabetes-related complications exclusively in type 2 diabetes. A positive association between increased variability and microvascular complications and coronary artery disease was consistently reported. Associations between glucose variability and other macrovascular complications were inconsistent in type 2 diabetes.

Seven studies examined the association between glucose variability and complications exclusively in type 1 diabetes. Increased glucose variability appears to play a minimal role in the development of micro- and macrovascular complications in type 1 diabetes.

Consistent findings suggest that in type 2 diabetes glucose variability is associated with development of microvascular complications. The role of increased glucose variability in terms of microvascular and macrovascular complications in type 1 diabetes is less clear; more data in are needed.

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1. Introduction

Diabetes guidelines state that optimal glycemic control, defined by glycated hemoglobin (HbA1c), is a fundamental treatment goal [1]. A wealth of studies, in type 1 and type 2 diabetes, including the landmark Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have shown that chronic hyperglycemia is the main risk factor for the development of diabetes-related complications. However, a key caveat of HbA1c is that it does not capture information relating to short-term fluctuations in glucose levels, which have been postulated to have an independent role in the etiology of diabetes-related complications [2]. The development of continuous glucose monitoring (CGM) systems has paved the way for accurate measurement of short-term glucose variability and the investigation of the role of glucose fluctuations in the development of diabetes-related complications [3,4]. A number of early studies used 7- or 8-point self-monitoring of blood glucose (SMBG) profiles to assess glucose variability; however, a disadvantage of this was that SMBG-based studies typically yield little information on nocturnal glycemic patterns.

Glycemic fluctuations are manifest principally as post-prandial glycemic spikes and minor (or asymptomatic) hypoglycemia. However, the term glycemic variability may refer to within day variability, variability between daily means, or within series variability. Several methods have been proposed for the measurement of glucose variability including standard deviation or coefficient of variation, the mean amplitude of glycemic excursions (MAGE) for intra-day variability, the mean of daily differences (MODD) for inter-day variability, high blood glucose index (HBGI), low blood glucose index (LBGI), glycemic risk assessment diabetes equation (GRADE), or continuous overlapping net glycemic action (CONGA) (more details on the methodology for each of the methods mentioned are provided in a 2013 review by Service) [5]. However, at present there is little consensus regarding which method offers the most meaningful assessment of glucose variability.

It has also been suggested that indicators of variability may provide a better indication than HbA1c of overall long-term problems with glycemic control [6]. In short-term (<1 month), retrospective, general population studies of critically ill patients, glucose variability has been implicated in increased mortality rates, as such there is increasing interest in the possible role of glucose variability in the development and underlying pathology of diabetes-related complications [7,8]. In vitro studies have shown that glucose fluctuations are linked to pathologic processes including the production of reactive oxygen species with some studies suggesting that large fluctuations in glucose levels may be a greater trigger of oxidative stress processes than chronic sustained levels of hyperglycemia [9].

To more fully elucidate the role of short-term glucose variability in the development of long-term complications in type 1 and type 2 diabetes, a systematic literature review was performed. The aim of the current review was to establish whether the current evidence base suggests if, and the extent to which, short-term glucose variability is involved in the development of chronic diabetes-related complications.

2. Methods

A systematic literature review was performed to identify studies investigating the relationship between short-term glucose variability and the incidence/prevalence of chronic complications in type 1 or type 2 diabetes. Searches were performed using the PubMed, EMBASE and Cochrane library databases. The search strategy was designed based on high level Medical Subject Heading (MeSH) terms (full details are provided in Appendix A). The search strategy was designed to capture articles where the main focus was on the association between chronic complications of diabetes and short-term measures of glucose variability rather than acute complications such as hypoglycemic events and diabetic ketoacidosis. Studies that captured measures of short-term (typically intra- or inter-day) glucose variability (including, but not limited to, SD, MAGE, and CONGA) assessed using either SMBG or CGM were included in the review (studies focusing on long-term variability of HbA1c were excluded from the present review). The time horizon was initially limited to articles published in the last 10 years (2002–2012) but an update of searches was performed in 2014 to ensure that the most recent data were captured in the review. Literature searches identified published congress abstracts in addition to full publications, which were included in the present review. Where abstracts were identified supplementary hand searches of the congress websites were performed to attempt to identify the full poster/presentation where possible. In instances where only the abstract was available, data available in the abstract were used, but no conclusions were drawn beyond methods, results, and conclusions presented by the authors in the abstract.

Following exclusion of duplicates, a total of 1718 unique hits remained in the initial literature searches, the titles and