Update on lessons learned from glycemia control studies

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Review Article

Abstract

Diabetes is a major health disorder affecting millions of people worldwide. Numerous studies have confirmed that micro and macrovascular complications ensue as a result of hyperglycemia. Initial studies show that while intensive glycemic control has been shown to reduce microvascular complications in both type 1 and 2 diabetics, macrovascular benefits have only been clearly seen in type 1 diabetics. Conflicting results have emerged regarding the benefits and potential adverse effects of tight glycemic control. Recent studies have emerged demonstrating some macrovascular benefits in type 2 diabetics, though this was associated with increased risk of hypoglycemia in some individuals. Thus, glycemic control in individuals with diabetes may need to be individualized in order to maximize benefits while minimizing adverse effects**.**

Keywords Glycemic control· Hyperglycemia· Type 2 diabetes·Glucose

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Mise à jour sur les enseignements tirés de glycémie études de contrôle

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Révision Article

Résumé

Le diabète est un grave trouble de santé affectant des millions de personnes dans le monde entier. De nombreuses études ont confirmé que les micro et complications macrovasculaires découler d' hyperglycémie. Études préliminaires montrent que, bien que intensives de contrôle de la glycémie a été montré à réduire les complications microvasculaires dans le type 1 et 2, les diabétiques macrovasculaires avantages n'ont été clairement perçu dans les diabétiques de type 1. Résultats contradictoires ont vu le jour en ce qui concerne les avantages et les effets indésirables potentiels de serré de contrôle de la glycémie . De récentes études ont émergé démontrant certaines prestations macroangiopathie diabétiques de type 2, même si c'était associé à une augmentation du risque d'hypoglycémie chez certains individus. Ainsi, de contrôle de la glycémie chez les personnes diabétiques peuvent avoir besoin d'être individualisée afin d'en maximiser les avantages tout en minimisant les effets indésirables.

Mots-clés contrôle glycémique Diabète Le diabète de type 2 N·m glucose

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Clinical Trial Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
DCCT	Diabetes Control and Complications Trial
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation and Survival using Glucose Algorithm Regulation
UKPDS	United Kingdom Prospective Diabetes Trial
VADT	Veterans Affairs Diabetes Trial
VISEP	Volume Substitution and Insulin Therapy in Severe Sepsis

Introduction

Diabetes is a chronic disease occurring as a result of insufficient insulin production by the pancreas or ineffective use of the insulin produced by the pancreas (1). A glycated hemoglobin (HbA1C) level of $\geq$ 6.5% is required for diagnosing Diabetes according to the American Diabetes Association (ADA)(2). Regardless of the type of diabetes (type 1 or 2) hyperglycemia is the end result. It has been well documented that adverse macro and microvascular affects ensue from long term hyperglycemia (3). Diabetes doubles the risk of a wide range of vascular diseases and increases the risk of mortality (4). Previous studies have shown that controlling hyperglycemia leads to favorable outcomes, however recent studies have emerged regarding safety issues associated with intense glycemic control in diabetes (5-8). This article discuses findings of major studies involving glycemic control.

What is the rationale for controlling hyperglycemia in diabetic patients?

The Framingham study, published in 1979, established a clear association between hyperglycemia and adverse outcomes in diabetic patients (9). Cardiovascular disease is a major concern in those with diabetes mellitus and remains a leading cause of morbidity and mortality. In 1993 the DCCT provided evidence that microvascular complications can be reduced in type 1 diabetics by maintaining blood glucose at near-normal levels. In this study 1,441 patients were followed for a mean of 6.5 years. Patients were randomly assigned to either receive intensive therapy (an external insulin pump or 3 or more daily insulin injections) or conventional therapy with one or two insulin injections per day. Results revealed that intensive therapy reduced the development and progression of microvascular complications (retinopathy, neuropathy and nephropathy) with hypoglycemia as the main adverse effect. Twelve years later EDIC published an observational follow up to DCCT proving that macrovascular complications were also reduced in patients with type 1 diabetes who received intensive therapy (reduced risk of any cardiovascular disease by 42%, p=0.02) (10). It was inconclusive whether these findings would provide similar benefits in type 2 diabetics. The UKPDS was designed to determine whether intensive glycemic control in type 2 diabetics would reduce the risk of micro and macrovascular complications. The study followed 5,102 newly diagnosed type 2 diabetics for 10 years and found that those receiving intensive therapy (sulfonylureas or insulin) were less likely to develop microvascular complications compared to those receiving conventional therapy (diet alone). However, no macrovascular benefits were noted in the intensive therapy group (11). A subset of 753 overweight patients in the UKPDS were assigned to receive metformin or conventional therapy, with results showing a 36% decrease for all cause mortality in those receiving metformin.

Are there any additional benefits of intensive glycemic control beyond microvascular protection?

Previous studies have been successful in showing clear benefits of intense glycemic therapy in lowering the rate of microvascular complications, but are there any additional benefits? Studies such as the ACCORD, ADVANCE and VADT aimed to determine the answer. In the ACCORD study 10,251 patients with type 2 diabetes were enrolled in a RCT and randomly assigned to either an intensive therapy group with aims of HbA1C < 6% or a standard therapy group with an HbA1C aimed between 7-7.9%. The study ended prematurely after 3.5 years due to a 22% higher mortality rate in the intensive therapy group. No significant reduction in major cardiovascular events was noted. After termination of the study those receiving intensive therapy were switched to standard therapy with a glycated hemoglobin goal of 7-7.9% and followed for another 1.2 years. The trends remained consistent during the follow up period (intensive therapy group showed no significant difference compared to the standard therapy group in primary care outcomes but had more deaths from all cause mortality) (12).

The ADVANCE and VADT studies also randomized patients into intensive therapy or standard therapy. The ADVANCE study enrolled 11,140 type 2 diabetics while the VADT study enrolled 1791. Patients were followed up for 5 and 5.6 years in the ADVANCE and VADT, respectively (5,6). The primary end points were similar in both studies and included development of major cardiovascular outcomes. Both studies failed to show a significant reduction in major cardiovascular events between the intensive therapy group compared to the standard therapy group. Both studies showed a reduction in microvascular complications in the intensive therapy group, consistent with the UKPDS.

The results of the above studies seemed to indicate that intensive glycemic control provides no benefit in type 2 diabetics. However, multiple limitations of these studies may have contributed to such outcomes. With a premature termination at 3.5 years for the ACCORD trial (although patient subsequently followed for an additional 1.2 years showed similar outcomes) and a 5 and 5.6 year follow up of the ADVANCE and VADT respectively, concerns as to whether sufficient follow up time had passed to detect any cardiovascular benefit are raised. This concern may be further strengthened by the UKPDS trial in which no cardiovascular benefit was seen in the intensive control group within the first 10 years, however an additional 10year monitoring (UKPDS 80) revealed a reduction in MI by 15% (P-0.01) and a reduction in all cause mortality by 13% (p-0.007) (13).

Another limitation may be an inadequate sample size. Despite negative results in individual trials meta-analysis showed conflicting results. In 2009 a meta-analyses by Ray et al, which included data from 5 studies (ACCORD, ADVANCE, VADT, UKPDS and PROactive) revealed a 17% reduction in nonfatal MI within the intensive therapy group (14). An additional analysis of the four RCT (ACCORD, ADVANCE, VADT and UKPDS) with over 27,000 participants revealed a 9% reduction in cardiovascular events in the intensive therapy group. These results were primarily due to a 15% decrease in the risk of MIs. Other meta-analysis showed similar results (14,15). These results suggest that the benefits of intensive glycemic control may only be seen after prolonged duration and with a large number of participants.

Additionally, the use of certain drugs may have contributed to the lack of expected cardiovascular benefits. Evidence has been produced that the use of rosiglitazone, a thiazolidinedione, increases the risk of cardiovascular disease (16). In the ACCORD trial 92% of participants in the intensive therapy group received this drug as compared to 58% in the standard therapy. Sulfonylureas were a major drug used in the intensive therapy of the ACCORD, ADVANCE and VADT, however previous studies have raised suspicion regarding the

increase cardiovascular risk associated with this drug (17-19). Lastly, the use of insulin therapy itself may promote weight gain leading to an increase risk of developing cardiovascular disease.

Is there increased risk of harm when intensive glycemic control is the goal?

Indeed there are many benefits of intense glycemic control, most notably a decrease in microvascular events, but adverse effects are also of major concern. One of the greatest concerns regarding intense glycemic control resides in the development of hypoglycemia, particularly with the use of insulin treatment. Hypoglycemia itself can result in sudden death, myocardial ischemia and arrhythmias (20-22). The use of insulin and thiazolidinediones in the intensive therapy in the ACCORD trial may explain the 3.5kg weight gain seen in this group. A meta-analysis of 33,040 found that participants receiving intensive therapy were 2.5 kg heavier than those receiving standard therapy (14).

Should Glycemic Control in Type 2 Diabetic Patients Be Individualized?

Approximately 347 million people are affected by diabetes worldwide (23). Hyperglycemia has been linked to micro and macrovascular complications and should be the aim in treating diabetics. Studies have been successful in showing clear benefits of intensive glycemic control in type 2 diabetics, however these studies have also shown adverse effects. Organizations such as the American Diabetes Association (ADA) recommend an HbA1C level of less than 6.5 (24). Many patients receive multiple drugs, often a mixture of insulin and oral agents to achieve such targets. These organizations however also recognize that targets should be individualized.

One treatment regimen may provide benefit to one patient while harming another. When employing a treatment strategy certain factors within each patient's profile should be taken into consideration.

New recommendations by the Canadian Diabetes Association state that where as an HbA1C <7% should be adequate for most type 1 and 2 diabetics to lower the risk of complications, a greater range of 7.1-8.5% may provide greater benefit for a certain patient profile including those with limited life expectancy, multiple co-morbidities, and a history of recurrent severe hypoglycemia (25) . A study by Reaven et al. (26) used coronary artery calcium (CAC) to assess whether cardiovascular outcomes where influenced by baseline coronary atherosclerosis following intensive glycemic treatment in the VADT study. The study revealed that cardiovascular events were decreased among those receiving intensive therapy with a CAC score $\leq$100 compared to those in the intensive therapy group with a CAC score $\geq$100. Similar findings were seen in a meta-analysis by Turnbull et al (27) in which those with no history of macrovascular disease achieved benefits while receiving intensive therapy as compared to those with a prior history of macrovascular disease in which no benefit was achieved. These studies suggest that individualizing glycemic control may not only be beneficial but crucial in maximizing benefits while minimizing risks and that many other factors should be explored as possible exclusion criteria in those receiving intensive therapy.

What is New in the Management of Hyperglycemia in Acutely ill Patient?

Hyperglycemia is by no means a rare occurrence in the inpatient setting. Most causes of inpatient hyperglycemia can be attributed to diagnosed or undiagnosed diabetes as well as stressed induced hyperglycemia. Both are associated with poor outcomes and should be a major concern to physicians. The balance between controlling glucose while avoiding hypoglycemia can be a challenging task for many physicians. Prior studies have shown improved outcomes associated with the treatment of hyperglycemia in hospitalized patients (28-30). A study by Van den Berghe et al randomized critically ill patients to

receive tight control or usual care and found a 34% reduction in mortality in those receiving tight glycemic control (28). The American Association of Clinical Endocrinologist (AACE), American Diabetes Association (ADA) and the American College of Endocrinology have since established recommendations for treatment of inpatient hyperglycemia (31).

Findings similar to Van den Berghe et al have been described (30,32), however conflicting results have been found in other studies (8,33-35). One of these studies, VISEP, evaluated the effects of intensive insulin therapy in patients with severe sepsis and found the rate of severe hypoglycemia ($\leq$ 40mg per deciliter) to be higher in the intensive therapy group ($P<0.001$) in addition to the rate of serious adverse event ($P=0.01$) (34). A larger study, NICE-SUGAR, randomized 3,054 critically ill patients to receive intensive glucose control (with a blood glucose aim of 81-108mg per deciliter) and 3,050 critically ill patients to receive conventional control (with a target glucose of $\leq$180mg per deciliter). Similar to the VISEP trial, the intensive insulin therapy was associated with a higher rate of hypoglycemia as compared to the conventional therapy group ($P<0.001$). Of the total deaths (829), 27.5% received intensive therapy vs. 24.9% who received conventional therapy ($P=0.02$). A meta-analysis of 26 trials of 13,567 patients including the NICE-SUGAR study suggests a mortality benefit for critically ill surgical patients rather than medical patients.

The most recent updates by the ADA and AACE suggest that insulin infusion should be used to control hyperglycemia in critically ill patients in the ICU, with an initial threshold of $\leq$180mg/dl until the initiation of intravenous insulin. Once IV insulin has commenced blood glucose levels should be maintained in the range of 140-180mg/dl.

Conclusions

Hyperglycemia is a major concern amongst physicians, particularly in regards to diabetics. With this condition affecting millions of individuals worldwide much effort has been put into research regarding the best treatment strategies and target HbA1C. Regardless of the approach used to control blood sugar one thing appears consistent, minimizing adverse effects while maximizing benefits remains a key focus. No two patients are exactly the same and with so many patient profiles treatment should be individualized. Clinicians should determine which therapy, whether intensive or standard, a patient will likely benefit most from.

It is our belief that early detection along with continuous monitoring by concerned physicians will yield the greatest benefits. Treatment strategies such as diet and exercise, blood pressure and lipid control should be instituted. Indeed a better understanding of such an important health issue is needed. Future studies should aim to determine which therapies are beneficial and harmful to certain patient characteristics.

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