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THE IMPACT OF INTENSIVE GLYCAEMIC CONTROL IN DIABETES: TIME FOR A RETHINK?

A LITERATURE REVIEW

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Abstract

Diabetes is rapidly evolving disease worldwide across all age groups. This has been identified by major worldwide organisations such as World Health Organisation (WHO), International Diabetes Federation (IDF) and American Diabetes Association (ADA). Increasing incidence, particularly in the developing world, poses significant threat to morbidity and mortality of local populations and puts a significant strain on healthcare systems. The question of optimum glycaemic control for our patients is one which is at the center of clinical care, but more recently, the focus has shifted to patient safety and meaningful clinical outcomes. Practice variations across healthcare systems combined with clinical inertia does negatively impact patient outcomes. To address this, a review was conducted pertaining to tight glycaemic control in

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patients living with diabetes. The UKPDS trial established the legacy effect of early glycaemic control in the disease trajectory, however, follow on trials, such as ACCORD, suggested a negative impact of tight glycaemic control with an increase in mortality in patients living with the condition for a longer period of time. Certainly, the heterogeneity of the patient population participating in the trials could explain the differences in outcomes but there were significant differences between macrovascular/ microvascular outcomes as well. There is growing clinical evidence for the role of individualisation of glycaemic targets for every patient to improve clinical outcomes. As clinicians, it is essential that we review our current clinical practice and facilitate patient empowerment to enable a healthcare system where patients are at the centre of chronic disease management.

Keywords: Diabetes, glycaemic control, American Diabetes Association, individualisation, Primary Healthcare Corporation

نبذة مختصرة

تتطور حالياً خطورة مرض السكري في جميعِ أنحاء العالم مع زيادة في سرعة إنتشارهِ وقوة تأثيره على جميع الفئات العمرية ومنظمة ،(WHO) وقد تم تحديد هذا التغير والإنتشار كأولوية من قِبل المنظمات العالمية الكبرى، مثل منظمة الإتحاد الدولي للسكري . (IDF) والجمعية الأمريكية للسكري ،(ADA) الصحة العالمية.

حالياً تُشكل هذه الزيادة السريعة في الحالات، ولا سيما في دول العالم النامي تهديداً كبيراً للصحة العامة وزيادة في نسبةِ المرضِ وأعداد الوفيات للسكان المحليين، فضلاً عن أنها تُشكل ضغطاً كبيراً على أنظمةِ الرعايةِ الصحيةِ.

إنَ التَحَكُم الأمثل في نسبةِ السُكر في الدم للمرضى كانت دائماً مسألةُ أساسية ورئيسية عند إتخاذِ قرارات الرعايةَ الطبية، ولكن في الآونةِ الأخيرةِ تحولَ التركيزُ إلى إستعمالِ مُعطيات طبية تأخذُ في عَين الإعتبار السلامةَ السريريةَ وجَودَةَ الحياةَ الشخصيةَ للمريض. هذه التغيراتُ الإيجابيةُ تواجِهُها تَحدياتُ منها الإختلافات بين أنظمة الرعاية الصحية المختلفة والمقاومة للتغييرِ في بعض المنظومات الطبية، وكل هذا قد يكون له تأثير سلبي على نتائجِ المرضى.

ولإبراز أهميةَ هذا التغيير في الأسلوب، أجرينا مراجعةً للتجاربِ السريريةِ البارزة بالإضافةِ إلى الإستناد إلى أحدثِ الأدلةِ الطبية لمساعدتِنا على فَهمِ تأثير التحكُم في نسبةِ السكرِ على مرضانا الذينَ ينتمونَ للفئاتِ العُمرية المختلفة.

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ويُعد فَهم أحدث الأدلة والتأثير الذي يُحدِثُه ذلك على ممارساتنا السريريةِ اليوميةِ أمرًا أساسيًا لتحسين جودةِ الرعاية للمرضى. هناك أدلة متزايدة على التأثير الرئيسي الذي يحتَلُهُ دور إضفاء الطابع الفردي على نسبة السكر في الدم لكلِ مريضٍ باستخدام الأدويةَ الحديثةَ التي تستهدف تقليل الأحداث القلبية الوعائية الرئيسية. كأطباء من الضروري أن نراجع ممارستنا السريرية لصالح مرضانا وتمكينهم من إستخدام نظام الرعاية الصحية بشكل فاعل حيث يكون المريض هو المركز والركن الأساسي في تحديد أي قرارات صحية تُتَخذ لصالحه

الكلمات المفتاحية:

مرض السكري ، التحكم في نسبة السكر في الدم ، جمعية السكري الأمريكية ،الأهداف المتفردة ، مؤسسة الرعاية الصحية الأولية

Introduction

"Diabetes is one of the largest global public health concerns, imposing a heavy global burden on public health as well as socio-economic development." (1) It is well established that patients living with diabetes have a reduced quality of life and a 2–3 folds risk of all-cause mortality. (2) Glycaemic control plays an important role in to the prevention of microvascular and macrovascular complications with endorsements from multiple leading professional organisations.

Atherosclerotic cardiovascular disease (ASCVD) is most common cause of morbidity and mortality in diabetes. Diabetes is association with excess mortality in all ages with young patients with type 1 diabetes being the worst affected. (3) ASCVD risk increases exponentially in patients with diabetes compounded by the presence of metabolic syndrome. Diabetes increases

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the risk of rates of incident hospitalization for heart failure by two-fold (4). Therefore, cardiovascular risk reduction is crucial in trying to reduce the excess mortality in patients.

The ADA sets clear targets for glycaemic control:

1. An HbA1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia.
2. Less stringent A1C goals (such as <8% [64 mmol/mol]) for patients with limited life expectancy, or where the harms of treatment are greater than the benefits. (5)

Discussion:

Several important studies have examined the effect of tight glycaemic control on both microvascular and macrovascular complications with mixed results.

The landmark Diabetes Control and Complications Trial (DCCT) trial assessed the role of intensive glycaemic control (mean HbA1c about 7%) in type 1 diabetes versus convention control(mean HbA1c of 9%).Intensive control led to 50-76% reductions in the development of microvascular complications and a trend towards lower risk of cardiovascular events.(5) Long follow up of this cohort in the Epidemiology of Diabetes Interventions and Complications study (EDIC) showed that the beneficial effects of intensive glycaemic control on microvascular complications persisted over two decades. (5) 17 years follow up of the DCCT/EDIC cohort revealed that intensive control led to a 42% risk reduction in any cardiovascular event (p=0.02)(6).Furthermore,30 year follow up data suggested a 32% reduction in the risk of major cardiovascular events which was statistically significant.(7) Hence intensive control in type 1 diabetes has an enduring benefit on the risk of macrovascular complications.

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For type 2 diabetes, benefits of intensive glycaemic control on the incidence of microvascular complications was confirmed by both the Kumamoto Study (8) and the UKPDS trial (9).

The UKPDS, another landmark study, assessed the role of intensive glycaemic control in patients who were newly diagnosed with type 2 diabetes. The results published in 1998 have been influential to diabetes guidelines. They revealed that every 1% reduction in HbA1c led to a 25% risk reduction in the development of microvascular complications, a nonsignificant reduction in the risk of myocardial infarction and no improvement in overall mortality. (9) However, approximately 85% of the effect on microvascular complications was related to retinal photocoagulation. This benefit was sustained during the posttrial follow up despite the convergence of HbA1c levels during the two groups of patients. 10 year follow up data revealed that intensive treatment led to significant relative risk reductions in microvascular complications (24%), myocardial infarction (15%) and all-cause mortality (13%). (10)

The UKPDS gave evidence for the legacy effect of glycaemic control in newly diagnosed patients suggesting that the risk of complications is directly related to glycaemia over time. Glycaemic control is central to the development and progression of microvascular complications, however for macrovascular complications, the impact of intensive glycaemic control takes time to show effect. UKPDS data also suggests that the reduction in macrovascular complications may not be as impressive as that for microvascular complications.

Multiple large clinical trials have assessed the impact of glycaemic control on macrovascular complications in type 2 diabetes with quite mixed results. The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial and the Veterans Affairs Diabetes Trial (VADT) assessed the impact of intensive glycaemic control on patients with a long history of type 2 diabetes. The participants of all 3 studies were closely matched in term of age, age and duration

of diabetes. However, it must be noted that the participants in ACCORD and VADT had higher BMI as compared to their counterparts in ADVANCE. The results were extremely insightful.

The ACCORD study randomised patients to either intensive (HbA1c of less than 6%) vs conventional treatment (HbA1c 7-7.9%).35% of patients had known cardiovascular disease. Aggressive reductions in HbA1c in the intensive arm led to a 22% mortality and the trial was suspended after 3 years.

The ADVANCE trial (target HbA1c of <6.5% in the intensive arm) suggested no significant impact on macrovascular outcomes during the median follow up of 5 years. (5) Results showed a significant 14% reduction in microvascular outcomes. It must be pointed out that this was mainly in the development of macroalbuminuria.(11) Intensification of glycaemic control did not lead to an increase in overall cardiovascular mortality.(11)Long term follow up has been neutral in terms of effect on cardiovascular outcomes.(12)

Similarly, results from the VADT trial((target HbA1c reduction of 1.5% as compared to controls) failed to show a reduction in the incidence of cardiovascular events following a median follow up of 5.6 years.(13)Analysis suggested that patients with diabetes for less than 12 years appeared to have some cardiovascular benefit from intensive control. However, intensification in those with a longer duration of diabetes resulted in neutral or (in some cases) adverse outcomes. The trial gave evidence for poor control driving the risk of cardiovascular complications in the context of the natural history of the condition.10-year follow up revealed some benefit in the risk of cardiovascular events, however, this benefit was not maintained at 15 years. (14)

Meta-analysis of the four trials (UKPDS, ACCORD, ADVANCE and VADT) suggests a modest decrease of 9% in cardiovascular events. (15) Despite heterogeneity of the results from the trials, the analysis concluded that patients without previous history of cardiovascular disease benefitted

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from a significant 16% reduction in CVD, however, patients with a known history of CVD did not benefit from this risk reduction. (15)

The legacy effect phenomenon was tested in the real world setting in The Diabetes and Ageing Study. This observational cohort study revealed that in newly diagnosed patients with type 2 diabetes and an estimated survival of more than 10 years of survival, "Compared with an HbA1c <6.5% (<48 mmol/mol) for the 1st year after diagnosis, higher HbA1c levels were associated with a higher risk for microvascular and macrovascular events, and HbA1c levels ≥7.0% (≥58 mmol/mol) were associated with a higher risk for mortality."(16) This study reinforces evidence from UKPDS for early glycaemic control and the impact of this on the patient's morbidity and mortality.

The effect of intensive glycaemic control on microvascular complications is well established. However, for macrovascular complications, the evidence suggests probable reduction over a long period of observation. Hence, older patients with a reduced life expectancy and multiple comorbidities are likely to experience diminished benefits. Meta-analysis data suggests "glycaemia is a substantially weaker risk factor for CHD than cholesterol or blood pressure, and very much weaker than blood pressure when it comes to stroke." (18)

Conclusion:

Microvascular and macrovascular complications affect the patient's quality of life and length of life respectively. Intensification comes at a cost to the patient as well as the healthcare system. The risks associated with hypoglycaemia, medication side effects and reduced quality of life from treatment burden is substantial hence must be considered. Hence, efforts and resources

should be directed to individualising targets for our patients and to act as a catalyst to help them achieve a safe compromise between glycaemic control and associated risks.

Evidence suggests that individualised glycaemic targets lead to improvement in patients' quality of life and a reduction in healthcare costs. (6) Certainly, evidence from future studies assessing the impact of individualised glycaemic targets on complications and patient outcomes may help us to understand this subject better.

After individualising the target HbA1c for our patient, the clinician-patient discussion is the most crucial part of the assessment. Understanding our patient profile enables us to start the discussion around lifestyle intervention, treatment targets and determine the need for additional pharmacotherapy. Knowledge of patient's health beliefs, preferences, patients' cognitive status, health literacy and social determinants of health is important for patient engagement and delivery of personalised care. .

Behind every statistic lies a patient's journey. Hence, glycaemic control needs to be tailored to the individual to ensure optimum health outcomes

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