2011 Guideline for Management of PostMeal Glucose in Diabetes

International Diabetes Federation

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Website

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Methodology

This update builds on the original IDF Guideline for the Management of PostMeal Glucose published in 2007. The methodology used in the development of this guideline is not described in detail here, as it broadly follows the principles described in the IDF Guide for Guidelines (www.idf.org).

In summary:

• The update was overseen by a Guideline Development Group of clinicians and researchers with expertise in the topic and guideline development (see Members of the Guideline Development Group).

• Geographical representation included various IDF regions and countries in different states of economic development.

• The evidence used in developing this guideline included reports from key meta-analyses, evidence-based reviews, clinical trials, cohort studies, epidemiological studies, animal and basic science studies, position statements and guidelines (English language only). Evidence relating to both postmeal and postchallenge plasma glucose was considered and cited as appropriate. Members of the Guideline Development Group were asked to identify any relevant reports or publications.

• The evidence was graded according to criteria presented in Table 1.

• The Guideline Development Group met at a 2-day workshop held in May 2011 to review the evidence and to update or revise the evidence statements and recommendations. A recommendation was made according to the level of scientific substantiation based on evidence ratings whenever possible. However, when there was a lack of supporting studies, the Guideline Development Group formulated a consensus recommendation.

• The final guideline is being made available in paper form and on the IDF website.

• IDF will consider the need to review and update this guideline within three to five years.

Members of the Guideline Development Group

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Duality of interest

Members of the Guideline Development Group have declared relevant dualities of interest in the topic and in relationships with commercial enterprises, governments and non-governmental organizations. No fees were paid to the Guideline Development Group members in connection with the current activity. Members of the Guideline Development Group (except for Antonio Ceriello and Stephen Colagiuri) were not aware of the identity of the sponsors during the entire development of this guideline.

Acknowledgements

This update of the 2007 IDF Guideline for the Management of PostMeal Glucose was supported by unrestricted educational grants from:

Bristol-Myers Squibb
Lilly Diabetes
Novo Nordisk A/S
Nutricia
Roche Diabetes Care

These companies did not take part in any aspect of the development of this guideline.

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Table 1

Evidence-Grading Criteria

From the Scottish Intercollegiate Guidelines Network. SIGN 50. A guideline developer's handbook. January, 2008.

level	Type of Evidence
1++	• High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	• Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	• Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	• High-quality systematic reviews of case-control or cohort studies • High-quality case control or cohort studies with a very low risk of confounding bias and a high probability that the relationship is causal
2+	• Well-conducted case-control or cohort studies with a low risk of confounding bias or chance and a moderate probability that the relationship is causal • Well-conducted basic science with low risk of bias
2-	• Case-control or cohort studies with a high risk of confounding bias or chance and a significant risk that the relationship is not causal
3	• Non-analytic studies (for example case reports, case series)
4	• Expert opinion

INTRODUCTION

An estimated 366 million people worldwide had diabetes in 2011 and this number is projected to reach 552 million in 2030.[1] Diabetes is a leading cause of death in most developed countries, and there is substantial evidence that it is reaching epidemic proportions in many developing and newly industrialized nations.

Poorly controlled diabetes is associated with the development of macrovascular disease, vision loss, renal failure, neuropathy and amputations. [2-6] Macrovascular complications are the major cause of death in people with diabetes.[7]

Large controlled clinical trials have demonstrated that intensive treatment of diabetes can significantly decrease the development and/or progression of micro-vascular complications of diabetes.[2-5] Furthermore, intensive glycaemic control in people with type 1 diabetes or impaired glucose tolerance (IGT) lowers the risk for cardiovascular disease. [8;9]

There appears to be no glycaemic threshold for either microvascular or macrovascular complications; the lower the glycated haemoglobin (HbA_{1c}), the lower the risk. [10-13]

Many epidemiologic studies have demonstrated an association between glycaemia and cardiovascular risk. [14;15] However, the beneficial effect of lowering glucose on cardiovascular disease in type 2 diabetes is still a matter of debate. While the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated significant reductions in microvascular complication risk, there was a non-statistically significant reductions in macrovascular disease. [4-5]

In 2008, the results of several large randomized controlled trials (ACCORD, ADVANCE, VADT, UKPDS-PTM) [16-19] were published. The results of these trials have been reviewed elsewhere. [20] Briefly, the ACCORD, ADVANCE, and VADT trials were all large, randomized controlled prospective studies to answer the question whether intensive glucose lowering would be associated with greater cardiovascular benefit relative to standard therapy in people with type 2 diabetes. In contrast to the UKPDS in which the subjects had newly diagnosed diabetes, the subjects included in these studies had their diabetes for a mean duration of 8-11.5 years and 32-40% of them had a prior history of macrovascular disease. In each of these studies, the primary macrovascular endpoint was reduced (by 6-12%), but in none of the studies was it reduced significantly.

Several subsequent meta-analyses of these major trials have been conducted.[21-23] The meta-analysis by Turnbull et al[21] incorporated the ACCORD, ADVANCE, VADT, and UKPDS trials and demonstrated significant reductions in major cardiovascular events (HR 0.91; 95% CI 0.76-0.94) and myocardial infarctions (OR 0.85; 95% CI 0.75-0.93). There was no overall increase or decrease in all-cause mortality (HR 1.04; CI 0.90-1.20). There were significantly more major hypoglycaemic episodes (HR 2.48; 95% CI 1.91-3.21). Significant heterogeneity for cardiovascular events was observed based on history of macrovascular disease. A significant 16% reduction was observed in those in whom it was absent (HR 0.84; CI 0.75-0.94) while no effect (HR 1.00; CI 0.89-1.13) was observed in those in whom it was present. Other subgroup analyses including age, baseline HbA_{1c} and duration of diabetes did not show any heterogeneity.

Of note is the fact that the ACCORD glycaemic control study was stopped prematurely after a mean follow-up of 3.5 years because of a 22% (95% CI 1.01-1.46; p=0.04) increased mortality in the intensive group. After multiple analyses, no definitive explanation has yet been identified to explain this surprising mortality finding. Achieving a lower HbA_{1c} was not associated with increased mortality. In fact, the mortality was higher in those subjects in the intensive group who did not achieve a lower HbA_{1c}.[24]

The results of the UKPDS 10-year post-trial monitoring (UKPDS-PTM) study are also noteworthy.[19] Whereas the difference in macrovascular complications between the two groups did not achieve statistical significance in the original UKPDS trial, with longer follow-up myocardial infarction risk reduction became significant with a HR of 0.85 (P=0.01) and a number needed to treat (NNT) of 36 over 17 years. All cause mortality risk reduction also became significant with a HR of 0.87 (p=0.007) and a NNT of 29, also over 17 years. Therefore, the results of the 10-year post-trial monitoring have demonstrated significant microvascular and macrovascular risk reduction with early intensive glycaemic control in newly diagnosed type 2 diabetes. There appears to be a "legacy effect" in that early risk reductions persist over time and, in the case of macrovascular risk reduction, may take many years to manifest.

Thus, the preponderance of data support the view that glycaemic control plays a role in reducing cardiovascular complications, but it needs to be instituted early in the disease course and the benefit may take many years to manifest. These benefits are in addition to the reduced risk of microvascular complications.

The relationship between hyperglycaemia and cardiovascular disease is complex with evidence suggesting that an acute increase of glycaemia, particularly after a meal, may have a direct detrimental effect on cardiovascular disease.[25] Moreover, until recently, the predominant focus of therapy has been on lowering HbA_{1c} levels, with a strong emphasis on fasting plasma glucose.[26] Although control of fasting hyperglycaemia is necessary, it is usually insufficient to obtain optimal glycaemic control. A growing body of evidence suggests that reducing postmeal plasma glucose excursions is as important, or perhaps more important for achieving HbA_{1c} goals.[27]

Objective

The purpose of this guideline is to consider the evidence on the relationship between postmeal glucose and glycaemic control (HbA_{1c}), and with diabetes outcomes. Based on this information, recommendations for the appropriate management and monitoring of postmeal glucose in type 1 and type 2 diabetes have been developed. Management of postmeal glucose in pregnancy has not been addressed in this guideline.

The recommendations are intended to assist clinicians and organizations in developing strategies to consider and effectively manage postmeal glucose in people with type 1 and type 2 diabetes, taking into consideration locally available therapies and resources. Although the literature provides valuable information and evidence regarding this area of diabetes management, uncertainties remain about a causal association between postmeal plasma glucose and complications and additional research is needed to clarify our understanding in this area. Logic and clinical judgment remain critical components of diabetes care and implementation of any guideline recommendations.

SUMMARY OF RECOMMENDATIONS

As a basis for developing the recommendations, the Guideline Development Group addressed four questions relevant to the role and importance of postmeal hyperglycaemia in diabetes management. The evidence supporting the recommendations is shown as evidence statements (with the level of evidence indicated at the end of the statement).

Question 1

Is postmeal hyperglycaemia harmful?

EVIDENCE STATEMENTS

Postmeal and postchallenge hyperglycaemia are independently associated with the following in people with diabetes:

- macrovascular disease [Level 1+]
- retinopathy [Level 2+]
- cancer [Level 2+]
- impaired cognitive function in elderly people with type 2 diabetes [Level 2+]
- increased carotid intima-media thickness [Level 2+]
- decreased myocardial blood volume and myocardial blood flow [Level 2+]
- oxidative stress, inflammation and endothelial dysfunction [Level 2+]

RECOMMENDATION

Postmeal hyperglycaemia is harmful and should be addressed.

Question 2

Is the treatment of postmeal hyperglycaemia beneficial in improving clinical outcomes and glycaemic control (HbA_{1c})

EVIDENCE STATEMENTS

• There is currently a lack of direct randomised clinical trial evidence that correcting postmeal hyperglycaemia improves clinical outcomes [Level 1-]

• Treatment with agents which target postmeal plasma glucose reduces vascular events in primary prevention. [Level 1-]

• Targeting both postmeal plasma glucose and fasting plasma glucose is an important strategy for achieving optimal glycaemic control [Level 1+]

RECOMMENDATION

Implement treatment strategies to lower postmeal plasma glucose in people with postmeal hyperglycaemia.

Question 3

Which therapies are effective in controlling postmeal plasma glucose?

EVIDENCE STATEMENTS

• Diets with a low glycaemic load are beneficial in improving glycaemic control [Level 1+]

• Several classes of pharmacologic agents preferentially lower postmeal plasma glucose [Level 1+]

RECOMMENDATION

A variety of both non-pharmacologic and pharmacologic therapies should be considered to target postmeal plasma glucose.

Question 4

What are the targets for postmeal glycaemic control and how should they be assessed?

EVIDENCE STATEMENTS

• Postmeal plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) after food ingestion in healthy non-pregnant people [Level 2++]

• Self-monitoring of blood glucose (SMBG) is currently the optimal method for assessing plasma glucose levels [Level 2++]

RECOMMENDATIONS

• *Postmeal plasma glucose should be measured 1-2 hours after a meal*

• *The target for postmeal glucose is 9.0 mmol/l (160 mg/dl) as long as hypoglycaemia is avoided.*

• *Self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring postmeal glycaemia.*

BACKGROUND

Definition of postprandial glucose and contribution to overall hyperglycaemia.

In people with diabetes, the total exposure to glucose is the sum of two components[28]:

(i) The normal physiological glucose exposure as observed in healthy individuals

(ii) The additional glucose exposure observed in hyperglycaemic individuals which has been defined as all plasma glucose values above 5.5 mmol/l (99 mg/dl). This additional glucose exposure can be further divided into its two subcomponents - basal/preprandial and postprandial hyperglycaemia.

Calculating the absolute and relative contributions of the different components of glucose exposure is best determined using methods based on data provided by continuous glucose monitoring. The overall glucose exposure in a given individual can be estimated by calculating the total area under the 24-h glycaemic profile above zero i.e. PGAUCtotal. Postprandial glucose (PPG) is measured by calculating the AUC above the preprandial values over a 4-h period after the start of the meal i.e. PGAUCpp. The choice of the 4-hour value is dictated by the mean duration of the hydrolysis and absorption of dietary carbohydrates (the so called postprandial state) which equals 4 hours both in normal individuals and in people with diabetes.[29] It should be noted that the postprandial state corresponds to a physiological definition although the postprandial excursions can be shorter or usually longer in type 2 diabetes.[30;31] The contribution of postprandial glucose excursions to HbA_{1c} can be defined according to the following equation[28]:

HbA_{1c} x [PGAUCpp/PGAUCtotal]%.

Using this mathematical approach, it has been demonstrated[32;33] that the absolute impact of PPG excursions on HbA_{1c} was constant at approximately 1% in people with non-insulin-treated type 2 diabetes with an HbA_{1c} ≥6.5%. This calculation provides a simple and generalizable description of the absolute contribution by the PPG excursions to the overall glucose exposure.

In people with non-insulin-treated type 2 diabetes, the contribution of PPG relative to fasting glycaemia is predominant when the HbA_{1c} levels are approximately below 7.5% and the contribution decreases progressively with increasing HbA_{1c} levels.[34]

Postmeal plasma glucose in people with normal glucose tolerance

In people with normal glucose tolerance, plasma glucose generally rises no higher than 7.8 mmol/l (140 mg/dl) in response to meals and typically returns to premeal levels within two to three hours. [35-37]

In this guideline, postmeal hyperglycaemia is defined as a plasma glucose level ›7.8 mmol/l (140 mg/dl) 1-2 hours after ingestion of food. [31]

Postmeal hyperglycaemia begins prior to type 2 diabetes

The development of type 2 diabetes is characterized by a progressive decline in insulin action and relentless deterioration of ß-cell function and hence insulin secretion. [38;39] Prior to clinical diabetes, these metabolic abnormalities are first evident as elevations in postmeal plasma glucose, due to the loss of first-phase insulin secretion, decreased insulin sensitivity in peripheral tissues and consequent decreased suppression of hepatic glucose output after meals due to insulin deficiency. [38-40] Elevated postmeal plasma glucose levels can be associated with deficiencies in glucagon-like peptide-1 (GLP-1) and glucose-dependent gastric inhibitory peptide (GIP), incretin hormones secreted by the gut. [41;42] There is evidence that the gradual loss in daytime postmeal glycaemic control precedes a stepwise deterioration in nocturnal fasting periods with worsening diabetes. [31]

Postmeal hyperglycaemia is common in diabetes

Postmeal hyperglycaemia occurs very frequently in people with type 1 and type 2 diabetes and occurs even when overall metabolic control appears to be adequate as assessed by HbA_{1c}. [43;44] For example a study which assessed daily plasma glucose profiles from 3,284 people with non-insulin-treated type 2 diabetes compiled over a one-week period, demonstrated that a postmeal plasma glucose value ›8.9 mmol/l (160 mg/dl) was recorded at least once in 84% of those studied. [44]

Question 1

Is postmeal hyperglycaemia harmful?

Epidemiological studies have shown a strong association between postmeal and postchallenge glycaemia and cardiovascular risk and outcomes.[45-48] Furthermore, a large and growing body of evidence shows a relationship between postmeal hyperglycaemia and oxidative stress,[49] carotid IMT[50] and endothelial dysfunction,[49;51] all of which are known markers of cardiovascular disease. Postmeal hyperglycaemia is also linked to retinopathy,[52;53] cognitive dysfunction in elderly people,[54] and certain cancers.[55-59]

Postmeal and postchallenge hyperglycaemia are independent risk factors for macrovascular disease [Level 1+]

The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) and the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) studies,[45;46] which analyzed baseline and two-hour postchallenge glucose data from prospective cohort studies including a large number of men and women of European and Asian origin, found two-hour plasma glucose to be a better predictor of cardiovascular disease and all-cause mortality than fasting plasma glucose.

Levitan and colleagues[47] performed a meta-analysis of 38 prospective studies and confirmed that hyperglycaemia in the non-diabetic range was associated with increased risk of fatal and non-fatal cardiovascular disease, with a similar relationship between events and fasting or two-hour plasma glucose. In the analysis, 12 studies reporting fasting plasma glucose levels and six studies reporting postchallenge glucose allowed for dose-response curve estimates. Cardiovascular events increased in a linear fashion without a threshold for two-hour postchallenge plasma glucose, whereas fasting plasma glucose showed a possible threshold effect at 5.5 mmol/l (99 mg/dl).

Similarly, in the Baltimore Longitudinal Study of Aging,[60] which followed 1,236 men for a mean of 13.4 years to determine the relationship between fasting plasma glucose and two-hour postmeal plasma glucose and all-cause mortality, all-cause mortality increased significantly above a fasting plasma glucose of 6.1 mmol/l (110 mg/dl) but not at lower fasting plasma glucose levels. However, risk increased significantly at two-hour postmeal plasma glucose levels above 7.8 mmol/l (140 mg/dl).

The observations also extend to people with diabetes with postmeal plasma glucose being a stronger predictor of cardiovascular events than fasting plasma glucose in type 2 diabetes, particularly in women[48], data which have been confirmed in a longer follow-up.[61]

However most of the epidemiological data supporting this concept are based on studies using the oral glucose tolerance test (OGTT). Since the OGTT cannot be considered a standard meal, questions have been raised about the relationship between the 2-h glucose values during an OGTT and postprandial hyperglycaemia after a meal. This concern is minimized by the demonstration of a strong relationship between the level of glycaemia during an OGTT and during a meal, particularly in terms of peak values.[62]

Postmeal hyperglycaemia is associated with increased risk of retinopathy [Level 2+]

While postchallenge and postmeal hyperglycaemia are associated with the development and progression of diabetic macrovascular disease, there are limited data on the relationship between postmeal hyperglycaemia and microvascular complications. Two observational prospective studies from Japan demonstrated that postmeal hyperglycaemia is a better predictor of diabetic retinopathy than HbA_{1c}. A multiple regression analysis revealed that not only postmeal hyperglycaemia independently correlated with the incidence of diabetic retinopathy [63;64], but also was a strong predictor of the progression of this complication. [64] This finding is consistent with the evidence that at 1- and 2-h after glucose ingestion, endothelial function decreases, while retinal vascular reactivity increases, compared with baseline values. [65] These data highlight that acute hyperglycaemia impacts on endothelial function simultaneously at both macrovascular and microvascular levels, inducing functional change which could contribute towards explaining the clinical evidence of an association between postprandial hyperglycaemia, cardiovascular disease and retinopathy.

Postmeal hyperglycaemia is associated with increased risk of cancer [Level 2+]

In addition to vascular disease, diabetes is associated with premature death from several cancers, infectious diseases, external causes, intentional self-harm, and degenerative disorders, independent of several major risk factors. [66]

Postmeal hyperglycaemia and factors known to promote postmeal hyperglycaemia are implicated in the development of pancreatic cancer. [55-57] A large, prospective cohort study of 35,658 adult men and women [55] found a strong correlation between pancreatic cancer mortality and postload plasma glucose levels. The relative risk for developing pancreatic cancer was 2.15 in people with postload plasma glucose levels of ›11.1 mmol/l (200 mg/dl) compared with people who maintained postload plasma glucose ‹6.7 mmol/l (121 mg/dl). This association was stronger for men than women.

In a study in northern Sweden which included 33,293 women and 31,304 men and 2,478 incident cases of cancer, relative risk of cancer over 10 years in women increased significantly by 1.26 in the highest quartile for fasting and 1.31 for postload glucose compared with the lowest quartile. No significant association was found in men. [67]

Postmeal hyperglycaemia is associated with impaired cognitive function in elderly people with type 2 diabetes [Level 2+]

Postmeal hyperglycaemia may also negatively affect cognitive function in older people with type 2 diabetes. One study [54] reported that significantly elevated postmeal plasma glucose excursions (11.1mmol; 200mg/dl) were associated with a disturbance of global, executive and attention functioning.

Postmeal hyperglycaemia is associated with increased carotid intima-media thickness (IMT) [Level 2+]

A clear correlation has been demonstrated between postmeal plasma glucose excursions and carotid IMT in 403 people without diabetes.[50] In multivariate analysis, age, male gender, postmeal plasma glucose, total cholesterol and HDL-cholesterol were found to be independent risk factors for increased carotid IMT.

Interestingly, it has been recently reported that incremental glucose peak (the maximal incremental increase in blood glucose obtained at any point after the meal), is associated with a significant increase of carotid IMT in type 2 diabetes[68] and that controlling postprandial hyperglycaemia significantly reduces IMT progression, independent of reduction in HbA_{1c}.[69] Another study has shown a slowing of progression of carotid IMT with treatment with acarbose, an agent known to reduce postprandial glucose excursions.[70]

Postmeal hyperglycaemia causes oxidative stress, inflammation and endothelial dysfunction [Level 2+]

Acute glucose fluctuations during postmeal periods have shown a more specific triggering effect on oxidative stress[71;72] and endothelial function[72] than chronic sustained hyperglycaemia in people with type 2 diabetes compared with people without diabetes. Another study demonstrated that people with type 2 diabetes and postmeal hyperglycaemia were exposed to meal-induced periods of oxidative stress during the day.[73]

Elevated levels of adhesion molecules, which play an important role in the initiation of atherosclerosis,[74] have been reported in people with diabetes.[75] Ceriello and colleagues[76] studied the effects of three different meals (high-fat meal, 75 g of glucose alone, high-fat meal plus 75 g of glucose) in 30 people with type 2 diabetes and 20 people without diabetes. The results demonstrated an independent and cumulative effect of postmeal hypertriglyceridaemia and hyperglycaemia on ICAM-1, VCAM-1 and E-selectin plasma levels.

Acute hyperglycaemia in response to oral glucose loading in people with normal glucose tolerance, IGT, or type 2 diabetes, rapidly suppressed endothelium dependent vasodilation and impaired endothelial nitric oxide release.[51] Other studies have shown that acute hyperglycaemia in normoglycaemic people impairs endothelium-dependent vasodilation,[77] may activate thrombosis[78] and increases circulating levels of soluble adhesion molecules.[79] Treating postprandial hyperglycaemia can improve oxidative stress[80], inflammation[81], endothelial dysfuncton[82] and thrombosis.[83]

Postmeal hyperglycaemia is associated with decreased myocardial blood volume and myocardial blood flow [Level 2+]

One study evaluated the effects of a standardized mixed meal on myocardial perfusion in 20 people without diabetes and 20 people with type 2 diabetes without macrovascular or microvascular complications.[84] No difference in fasting myocardial flow velocity (MFV), myocardial blood volume (MBV) and myocardial blood flow (MBF) between the control group and people with diabetes were observed. However, in the postmeal state, MBV and MBF decreased significantly in people with diabetes. Controlling postprandial hyperglycaemia has been demonstrated to improve myocardial blood flow and function.[85;86]

Question 2

Is the treatment of postmeal hyperglycaemia beneficial in improving clinical outcomes and glycaemic control (HbA_{1c})?

There is currently a lack of direct randomised clinical trial evidence that correcting postmeal hyperglycaemia improves clinical outcomes [Level 1-]

Two studies were specifically designed to asses the hypothesis that controlling postprandial hyperglycaemia can prevent cardiovascular complications.

The "Hyperglycaemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D)" study is a multinational, randomized, controlled trial designed to compare the effects of prandial versus fasting glycaemic control on risk for cardiovascular outcomes in people with type 2 diabetes after acute myocardial infarction (AMI).[87] People with type 2 diabetes aged 30-75 years were randomly assigned within 21 days after AMI to 1) prandial strategy (PRANDIAL) (three premeal doses of insulin lispro targeting 2-h postprandial blood glucose ‹7.5 mmol/l) or 2) basal strategy (BASAL) (NPH twice daily or insulin glargine once daily targeting fasting/premeal blood glucose ‹6.7 mmol/l). A total of 1,115 subjects were randomized (PRANDIAL n = 557; BASAL n = 558), and the mean patient participation time after randomization was 963 days (range 1-1,687 days). The trial was stopped for lack of efficacy. Risk of first combined adjudicated primary cardiovascular events in the PRANDIAL (n = 174, 31.2%) and BASAL (n = 181, 32.4%) groups was similar (hazard ratio 0.98 [95% CI 0.8-1.21]). Mean HbA_{1c} did not differ between the PRANDIAL and BASAL groups (7.7 ± 0.1 vs. 7.8 ± 0.1%; P = 0.4). The PRANDIAL group showed a lower daily mean postprandial blood glucose (7.8 vs. 8.6 mmol/l; P ‹0.01) and 2-h postprandial blood glucose excursion (0.1 vs. 1.3 mmol/l; P ‹0.001) compared with the BASAL group. The BASAL group showed lower mean fasting blood glucose (7.0 vs. 8.1 mmol/l; P ‹0.001) and similar daily fasting/premeal blood glucose (7.7 vs. 7.3 mmol/l; P = 0.233) compared with the PRANDIAL group.

Overall the HEART2D study did not show a beneficial effect of preferentially treating postprandial hyperglycaemia in reducing further cardiovascular events in people with diabetes who had had an acute myocardial infarction.

The ability of the short-acting insulin secretagogue, nateglinide, to reduce the risk of diabetes or cardiovascular events in people with impaired glucose tolerance has been evaluated in the NAVIGATOR Trial.[88] In a double-blind, randomized clinical trial, 9,306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors were assigned to receive nateglinide (up to 60 mg three times daily) or placebo, in a 2-by-2 factorial design with valsartan or placebo, in addition to participation in a lifestyle modification program. Participants were followed for a median of 5 years for incident diabetes. The effect of nateglinide on the occurrence of three co-primary outcomes was evaluated: the development of diabetes; a core cardiovascular outcome that was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; and

an extended cardiovascular outcome that was a composite of the individual components of the core composite cardiovascular outcome, hospitalization for unstable angina, or arterial revascularization. After adjustment for multiple testing, nateglinide, compared with placebo, did not significantly reduce the cumulative incidence of diabetes (36% and 34%, respectively; hazard ratio, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P=0.05), the core composite cardiovascular outcome (7.9% and 8.3%, respectively; hazard ratio, 0.94, 95% CI, 0.82 to 1.09; P=0.43), or the extended composite cardiovascular outcome (14.2% and 15.2%, respectively; hazard ratio, 0.93, 95% CI, 0.83 to 1.03; P=0.16). Nateglinide did, however, increase the risk of hypoglycaemia.

Unfortunately, neither the HEART2D Study [87] nor the NAVIGATOR Study [88] help in answering the question of whether lowering postprandial hyperglycaemia reduces cardiovascular disease. The HEART2D study failed to reach the study's prespecified difference in postprandial hyperglycaemia of 2.5 mmol/l (45mg/dl) with the mean difference at the end of the study being only 0.8 mmol/l (14mg/dl), less than 1/3 of the goal, even though there was a statistically significant different between the two groups. This small difference is unlikely to influence cardiovascular outcomes, particularly in such a short period. [89] Moreover, the study was under-powered as confirmed by the low rate of events. [89] Despite the overall negative result, a recent post hoc analysis suggested that older type 2 diabetes AMI survivors may have a lower risk for a subsequent cardiovascular event with insulin targeting postprandial versus fasting/premeal glycaemia. [90] The results of the NAVIGATOR study are difficult to reconcile. Nateglinide not only failed to improve glucose levels 2 hours after the glucose challenge in the annual OGTT, but glucose levels were actually higher in the nateglinide compared with the placebo group. [89] Furthermore the drop-out rate was very high. [89]

The Kumamoto study,[3] which used multiple daily insulin injections to control both fasting and postmeal glycaemia in people with type 2 diabetes, reported a curvilinear relationship between retinopathy and microalbuminuria with both fasting and two-hour postmeal plasma glucose levels. The study showed no development or progression of retinopathy or nephropathy with fasting blood plasma glucose ‹6.1 mmol/l (110 mg/dl) and two-hour postmeal blood plasma glucose ‹10 mmol/l (180 mg/dl). The Kumamoto study suggests that both reduced postmeal plasma glucose and reduced fasting plasma glucose are strongly associated with reductions in retinopathy and nephropathy.

Other considerations in interpreting these findings include the level of risk of study participants and their duration of diabetes [91]. As reviewed above, recent studies have suggested that control of hyperglycaemia may have a different impact in primary and secondary prevention of cardiovascular disease in type 2 diabetes and that the timing of initiation of more intensive glucose control may also be important. Starting too late may attenuate any possible beneficial effect of treating hyperglycaemia at an early stage of the disease.

At this time the impact of treating postprandial hyperglycaemia on cardiovascular disease is still a matter of debate.

Treatment with agents which target postmeal plasma glucose reduces vascular events in primary prevention [Level 1-].

A meta-analysis by Hanefeld and colleagues [92] showed significant positive trends in risk reduction for all selected cardiovascular event categories with

treatment with acarbose, an α-glucosidase inhibitor that specifically reduces postmeal plasma glucose excursions by delaying the breakdown of disaccharides and polysaccharides (starches) into glucose in the upper small intestine. In all of the seven studies of at least one year's duration, people treated with acarbose showed reduced two-hour postmeal levels compared with controls. Treatment with acarbose was significantly associated with a reduced risk for myocardial infarction and other cardiovascular events. These findings are consistent with findings from the STOP-NIDDM trial,[93] which showed that treating people with IGT with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension, although postmeal glucose was not routinely monitored. The ACE (Acarbose Cardiovascular Evaluation) study (www.clinicaltrials.gov NCT00829660) will provide further information on this question.

Targeting both postmeal plasma glucose and fasting plasma glucose is an important strategy for achieving optimal glycaemic control [Level 1+]

The relative contribution of postmeal plasma glucose to overall glycaemia increases as the HbA_{1c} level decreases. Monnier and colleagues[34] showed that in people with HbA_{1c} levels ‹7.3%, the contribution of postmeal plasma glucose to HbA_{1c} was ~70%, whereas the postmeal contribution was ~40% when HbA_{1c} levels were above 9.3%. Also nocturnal fasting plasma glucose levels remain at near-normal levels as long as the HbA_{1c} level remains ‹8%.[31] However, postmeal plasma glucose control deteriorates earlier, occurring when HbA_{1c} levels rise above 6.5%, indicating that people with relatively normal fasting plasma glucose values can exhibit abnormal elevations of glucose levels after meals. The same study also reported that the rate of deterioration of postmeal plasma glucose excursions after breakfast, lunch and dinner differs with postbreakfast plasma glucose being negatively affected first.

These findings are supported by interventions demonstrating that achieving target fasting plasma glucose alone is still associated with HbA_{1c} levels ›7%. Woerle and colleagues[94] assessed the relative contribution of controlling fasting and postmeal plasma glucose in people with type 2 diabetes and HbA_{1c} ≥7.5%. Only 64% of people achieving a fasting plasma glucose ‹5.6 mmol/l (100 mg/dl) achieved an HbA_{1c} ‹7% whereas 94% who achieved the postmeal target of ‹7.8 mmol/l (140 mg/dl) did. Decreases in postmeal plasma glucose accounted for nearly twice the decrease in HbA_{1c} compared with decreases in fasting plasma glucose. Postmeal plasma glucose accounted for 80% of HbA_{1c} when HbA_{1c} was ‹6.2% and about 40% when HbA_{1c} was above 9.0%.

These studies support the view that control of fasting hyperglycaemia is necessary but usually insufficient for achieving HbA_{1c} goals ‹7% and that control of postmeal hyperglycaemia is an important consideration for achieving recommended HbA_{1c} goals.

The efficacy of achieving HbA_{1c} target with different approaches to insulin therapy targeting or not targeting postprandial hyperglycaemia, has also recently been evaluated in two metaanalyses.[95;96] The overall conclusions were that a greater HbA_{1c} reduction may be obtained in type 2 diabetes using biphasic or prandial insulin rather than a basal regimen, but with increased risk of hypoglycaemia.

Rates of hypoglycaemia may different depending on whether treatment attempting to lower HbA_{1c} levels to ‹7% targets fasting or postprandial hyperglycaemia. In the "treat-to-target" study,[97] which used long-acting and intermediate-acting insulins to control fasting plasma glucose, only 25% of once-daily glargine-treated people achieved an HbA_{1c} of ‹7% without documented nocturnal hypoglycaemia. Conversely, Bastyr and colleagues,[98] demonstrated that targeting postmeal plasma glucose versus fasting plasma glucose was associated with lower levels of HbA_{1c}. Also no severe hypoglycaemia was observed in the study by Woerle and colleagues in which a reduction of mean HbA_{1c} from 8.7% to 6.5% was achieved, including targeting of postmeal plasma glucose.[94]

Question 3

Which therapies are effective in controlling postmeal plasma glucose?

Diets with a low glycaemic load are beneficial in improving glycaemic control [Level 1+]

Nutritional interventions, physical activity and weight control remain the cornerstones of effective diabetes management. Although few would dispute the importance and benefits of regular physical activity and maintenance of desirable body weight, there is considerable debate regarding optimum diet composition. Some forms of carbohydrate may exacerbate postmeal glycaemia. The glycaemic index (GI) is an approach to classifying carbohydrate foods by comparing the glycaemic effect (expressed as the postmeal incremental area under the curve) of equal amounts of carbohydrate of individual foods. Most modern starchy foods have a relatively high GI, including potatoes, white and brown bread, rice and breakfast cereals.[99] Foods with a lower GI (eg legumes, pasta and most fruits) contain starches and sugars that are more slowly digested and absorbed, or less glycaemic by nature (eg fructose, lactose). Dietary glycaemic load (GL), the product of the carbohydrate content of the diet and its average GI, has been applied as a "global" estimate of postmeal glycaemia and insulin demand. Despite early controversy, the GI and GL of single foods have been shown to reliably predict the relative ranking of postmeal glycaemic and insulinemic responses to mixed meals.[100;101] The use of GI can provide an additional benefit for diabetes control beyond that of carbohydrate counting.[102]

Meta-analyses of randomized controlled trials have shown that diets with a lower GI result in improvements in HbA_{1c} in the order of 0.5%.[103-105] A recent study compared a low GL with a low-fat diet in a randomized trial in 79 obese adults with type 2 diabetes over a 40-week period and found that HbA_{1c} reduction was 0.7% greater with the low GL diet.[106] Another 6 month study in people with type 2 diabetes compared a low GI diet with a high cereal fiber diet and showed an HbA_{1c} decrease of 0.5% with the low GI diet and a 0.18% decrease with the high cereal fiber diet ($P < 0.001$).[107]

Several classes of pharmacologic agents preferentially lower postmeal plasma glucose [Level 1+]

Although many agents improve overall glycaemic control, including postmeal plasma glucose levels, several pharmacologic therapies specifically target postmeal plasma glucose.

Therapies which have been available for some time include α-glucosidase inhibitors, glinides (rapid-acting insulin secretagogues), short-acting sulfonylureas, and insulins (rapid-acting human insulins/insulin analogues and biphasic [premixed] human insulins/ insulin analogues).

In addition, new classes of therapies for managing postmeal plasma glucose in people with diabetes (glucagon-like peptide-1 [GLP-1] derivatives, dipeptidyl peptidase-4 [DPP-4] inhibitors) have shown significant benefits in reducing postmeal plasma glucose excursions and lowering HbA_{1c}. These therapies address deficiencies in gut hormones that affect insulin and glucagon secretion, satiety and gastric emptying.

This section presents a description of the pharmacologic agents preferentially lowering postmeal plasma glucose, listed alphabetically. Specific combinations of therapies are not included in this summary.

α-glucosidase inhibitors

α-glucosidase inhibitors (AGIs) delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting postmeal plasma glucose excursions. Specifically, they inhibit α-glucosidases located in the brush border of the proximal small intestine that breaks down disaccharides and more complex carbohydrates. Through competitive inhibition of these enzymes, AGIs delay intestinal carbohydrate absorption and attenuate postmeal plasma glucose excursions.[108] Acarbose, miglitol and voglibose are commercially available AGIs.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors act by inhibiting the DPP-4 enzyme which degrades GLP-1, thereby increasing the active form of the hormone. This in turn stimulates glucose-dependent insulin secretion and suppresses glucagon release.[41] DPP-4 inhibitors decrease postmeal glucose and improve HbA_{1c} without causing hypoglycaemia.[109] Currently, aloglitin, linagliptin, saxagliptin, sitagliptin and vildagliptin are commercially available DPP-4 inhibitors.

Glinides

Glinides have a mechanism of action similar to sulfonylureas, but they act through a separate receptor and have a much shorter metabolic half-life. They stimulate a rapid but short-lived release of insulin from pancreatic *ß*-cells that lasts one to two hours.[110] When taken at mealtimes, these agents attenuate postmeal plasma glucose excursions and decrease the risk of hypoglycaemia during the late postmeal phase because less insulin is secreted several hours after the meal.[111] Two agents are commercially available: nateglinide and repaglinide.

Glucagon-like peptide-1 (GLP-1) derivatives

GLP-1 is an incretin hormone secreted from the gut that lowers glucose through its ability to stimulate insulin secretion, inhibit glucagon secretion, decelerate gastric emptying and induce satiety.[112] In people with type 2 diabetes, the incretin effect, i.e. the ability of an orally injested meal to stimulate insulin secretion, is diminished.[113] This defect can be attenuated by the administration of exogenous GLP-1 analogues or GLP-1 receptor agonists[41] GLP-1 derivatives diminish postmeal glucose excursions with a low risk of hypoglycaemic episodes , which is an advantage of the glucose dependent effect of GLP-1.[114] Exenatide and liraglutide are currently commercially available GLP-1 analogues.

Insulins

Rapid-acting human insulins / insulin analogues

Rapid-acting human insulins have been used for decades with the main goal of decreasing postmeal glucose excursions and thereby preventing postmeal hyperglycaemia. Rapid-acting insulin analogues were developed in order to better mimic the normal physiologic insulin response. The rapid-acting insulin analogues achieve a rapid onset, peak activity and a short duration of action [115]

Biphasic (premixed) human insulins / insulin analogues

Biphasic (premixed) insulins combine a rapid-acting with an intermediate acting insulin component, which is an alternative to addressing postmeal in addition to overall glucose control in people with type 2 diabetes.[116] Biphasic insulin analogues are associated with some advantages compared with biphasic human insulin preparations in controlling postmeal glucose.[117;118] Currently, there are several rapid-acting biphasic insulin formulations commercially available throughout the world, with different ratios of rapid and intermediate insulins, including 25/75, 30/70, 40/60 and 50/50 mixtures.

Short-acting sulfonylureas

Of the sulfonylureas, glipizide is short-acting and is occasionally used specifically for postmeal hyperglycaemia.[119]

Question 4

What are the targets for postmeal glycaemic control and how should they be assessed?

Postmeal plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) in people with normal glucose tolerance and typically return to basal levels two to three hours after food ingestion. [Level 1++]

Several studies using continuous glucose monitoring have shown that postmeal plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) in healthy people with normal glucose tolerance and typically return to basal levels two to three hours after food ingestion. [35-37]

Despite the postmeal plasma glucose levels being below 7.8 mmol/l (140 mg/dl) in people with normal glucose tolerance, glucose levels in healthy people are often difficult to achieve in people with diabetes without an undue risk of hypoglycaemia. Therefore, for reasons of safety, the IDF sets a glycaemic target slightly above the normal levels and for postmeal glucose this target is 9.0 mmol/l (160 mg/dl).

Self-monitoring of blood glucose (SMBG) is currently the optimal method for assessing plasma glucose levels [Level 1++]

SMBG allows people with diabetes to obtain and use information about "real-time" plasma glucose levels and facilitates timely intervention to achieve and maintain glycaemic control. SMBG in accepted as an integral part of diabetes management in people with diabetes requiring insulin therapy. Recently the IDF has published guidance on the use of SMBG in people with non-insulin treated diabetes and emphasized the need to ensure that there is an agreed purpose for using SMBG and that specific action should be linked to SMBG. [120] Recent studies have confirmed that structured SMBG followed by therapeutic interventions result in greater HbA_{1c} reduction in people with non-insulin-requiring type 2 diabetes compared with programmes without structured SMBG. [121-123]

SMBG is only one component of diabetes management. Its potential benefits require training of people to perform SMBG, interpret their test results and appropriately adjust their treatment regimens to achieve glycaemic control. Moreover, clinicians must be versed in interpreting SMBG data, prescribing appropriate medications and closely monitoring people in order to make timely adjustments to their regimens as needed.

The timing and frequency of SMBG must be individualized to each person's treatment regimen and level of glycaemic control. [120]

Emerging Technologies

Continuous glucose monitoring

The use of continuous glucose monitoring (CGM) for monitoring diabetes is increasing.[124] CGM employs a sensor, a data storage device and a monitor. The sensor measures glucose every 1 to 10 minutes and transmits this reading to a data storage device. Results can be either downloaded retrospectively by the physician, or displayed in "real time" in the monitor. CGM provides information on glucose levels, patterns and trends, thereby reflecting the effects of medication, meals, stress, exercise and other factors that affect glucose levels. Because CGM devices measure interstitial glucose, test values lag behind single "point in-time" measurements by several minutes.

1,5-Anhydroglucitol

Plasma 1,5-anhydroglucitol (1,5-AG), a naturally occurring dietary polyol, has been proposed as a marker for postmeal hyperglycaemia. Because 1,5-AG is sensitive and responds rapidly to changes in serum glucose, it accurately reflects transient elevations of glucose within a few days.[125] An automated assay for 1,5-AG has been used in Japan for over a decade.[126] A recent study suggests that 1,5-AG best reflects 2-h postprandial glucose values of the 2 previous weeks.[127] However there are no outcome studies using this measure of glycaemic control,

Clinical Implications

Most guidelines, including the updated IDF Global Guideline for Type 2 Diabetes, recommend a general HbA_{1c} target of < 7.0% while emphasising the need to take into account patient factors in determing the appropriate target for an individual.

The data reviewed in this guideline support the concept that postmeal glucose makes a significant contribution to overall glycaemia reflected in the HbA_{1c} level and that the relative contribution increases at lower levels of HbA_{1c}, especially below 8.0%. Therefore efforts to reach the HbA_{1c} target will often require specific attention to correcting postmeal glucose.

Consequently, particularly in people with HbA_{1c} levels between 7.0 and 8.0% in whom it is considered clinically appropriate to improve glycaemic control, assessing postmeal glucose is warranted and if found to be elevated, blood glucose lowering therapy should preferentially choose an agent which specifically lowers postmeal glucose. Similarly dietary interventions which lower postmeal glucose should be emphasized.

This approach complements the IDF Treatment Algorithm for people with type 2 diabetes.

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