

# GUIDELINE FOR MANAGEMENT OF POSTMEAL GLUCOSE



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## Correspondence and related literature from IDF

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These companies did not take part in the development of the guideline. However, these and other commercial organizations on IDF's communications list were invited to provide comments on draft versions of the guideline (see *Methodology*).

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## METHODOLOGY

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](http://www.idf.org)). In summary:

- The process involved a broadly based group of people, including people with diabetes, healthcare professionals from diverse disciplines and people from non-governmental organizations. The project was overseen by a Steering Committee (see *Steering Committee*) and input was provided by the entire Guideline Development Group (see *Members of the Guideline Development Group*).
- The Guideline Development Group included people with considerable experience in guideline development and healthcare development and delivery and living with diabetes.
- Geographical representation included all IDF regions and countries in different states of economic development (see *Members of the Guideline Development Group*).
- 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). A scientific writer with knowledge of diabetes obtained relevant reports through a computerized search of the literature using PubMed and other search engines; scanning of incoming journals in the medical library and review of references in pertinent review articles, major textbooks and syllabi from national and international meetings, on the subjects of diabetes, using relevant title and text words (eg postprandial, postmeal, hyperglycaemia, mealtime, self-monitoring, oxidative stress, inflammation) as search criteria. Evidence relating to both postmeal and postchallenge plasma glucose was reviewed and cited as appropriate. A review of recent guidelines, position statements and recent articles not identified in the universal search was also conducted to obtain additional information that was potentially applicable to the questions. An electronic database was created to include full reference information for each report; abstracts for most of the reports were included in the database. Members of the Steering Committee were asked to identify any additional

reports or publications relevant to the questions. In total, 1,659 reports were identified.

- Key reports, whether supportive or not, were included and summarized based on their relevance to the questions to be addressed by this document. The evidence was graded according to criteria presented in Table 1. The evidence cited to support the recommendations was reviewed by two independent external reviewers who were not part of the Guideline Development Committee. Comments from the external reviewers were then reviewed by the Steering Committee.
- Evidence statements were compiled based upon review of the selected reports. These statements and supporting evidence were sent to Steering Committee members for their review and comment.
- The Guideline Development Committee met to discuss the evidence statements and supporting data and to develop the 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 Steering Committee formulated a consensus recommendation.
- The draft guideline was sent out for wider external review to IDF member associations, global and regional IDF elected representatives, interested professionals, industry and others on IDF contact lists, for a total of 322 invitations. Thirty-eight comments from 20 external reviewers from five of the seven IDF regions (Africa, South East Asia, Western Pacific, North America, Europe) were received. These comments were reviewed by the Steering Committee and considered in developing the final document.
- The final guideline is being made available in paper form and on the IDF website. The evidence resources used (or links to them) will also be made available.
- IDF will consider the need to review and update this guideline within three years.

## Members of the Guideline Development Committee

### Steering Committee

- Antonio Ceriello, Chair, Coventry, UK
- Stephen Colagiuri, Sydney, Australia
- John Gerich, Rochester, United States
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### Duality of interest

Members of the Guideline Development Committee 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 Committee members in connection with the current activity.

### IDF Executive Office

Anne Pierson

**TABLE 1****Evidence-Grading Criteria\***

LEVEL	TYPE OF EVIDENCE
1++	<ul style="list-style-type: none"> <li>• High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias</li> </ul>
1+	<ul style="list-style-type: none"> <li>• Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</li> </ul>
1-	<ul style="list-style-type: none"> <li>• Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</li> </ul>
2++	<ul style="list-style-type: none"> <li>• High-quality systematic reviews of case-control or cohort studies</li> <li>• High-quality case control or cohort studies with a very low risk of confounding bias and a high probability that the relationship is causal</li> </ul>
2+	<ul style="list-style-type: none"> <li>• 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</li> <li>• Well-conducted basic science with low risk of bias</li> </ul>
2-	<ul style="list-style-type: none"> <li>• Case-control or cohort studies with a high risk of confounding bias or chance and a significant risk that the relationship is not causal</li> </ul>
3	<ul style="list-style-type: none"> <li>• Non-analytic studies (for example case reports, case series)</li> </ul>
4	<ul style="list-style-type: none"> <li>• Expert opinion</li> </ul>

\* From the Scottish Intercollegiate Guidelines Network.  
*Management of Diabetes: A national clinical guideline.* November, 2001.

The image features a dark red background with several overlapping circles in lighter shades of red and pink. The circles are arranged in a way that they appear to be part of a larger, abstract composition. The number ".01" is prominently displayed in the center of one of the circles.

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# INTRODUCTION

An estimated 246 million people worldwide have diabetes.<sup>(1)</sup> 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.<sup>(1)</sup>

Poorly controlled diabetes is associated with the development of such complications as neuropathy, renal failure, vision loss, macrovascular diseases and amputations.<sup>(2-6)</sup> Macrovascular complications are the major cause of death in people with diabetes.<sup>(7)</sup> Furthermore, a strong association between poorly controlled diabetes and depression has been reported,<sup>(8;9)</sup> which in turn can create significant obstacles to effective diabetes management.

Large controlled clinical trials have demonstrated that intensive treatment of diabetes can significantly decrease the development and/or progression of microvascular complications of diabetes.<sup>(2-4;10)</sup> Furthermore, intensive glycaemic control in people with type 1 diabetes or impaired glucose tolerance (IGT) lowers the risk for cardiovascular disease.<sup>(11;12)</sup> There appears to be no glycaemic threshold for reduction of either microvascular or macrovascular complications; the lower the glycated haemoglobin (HbA<sub>1c</sub>), the lower the risk.<sup>(13)</sup>

The progressive relationship between plasma glucose levels and cardiovascular risk extends well below the diabetic threshold.<sup>(14-18)</sup> Furthermore, a recent meta-analysis by Stettler and colleagues<sup>(13)</sup> demonstrated that improvement in glycaemic control significantly reduced the incidence of macrovascular events in people with type 1 or type 2 diabetes.

Until recently, the predominant focus of therapy has been on lowering HbA<sub>1c</sub> levels, with a strong emphasis on fasting plasma glucose.<sup>(19)</sup> 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,<sup>(20)</sup> or perhaps more important for achieving HbA<sub>1c</sub> goals.<sup>(3;21-25)</sup>

## OBJECTIVE

The purpose of this guideline is to present data from reports that describe the relationship between postmeal glucose and the development of diabetic complications. Based on these data, recommendations for the appropriate management 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 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, given the uncertainties regarding a causal association between postmeal plasma glucose and macrovascular complications, as well as the utility of self-monitoring of blood glucose (SMBG) in non-insulin-treated people with type 2 diabetes, additional research is needed to clarify our understanding in these areas. Logic and clinical judgment remain critical components of diabetes care and implementation of the guideline recommendations.

## 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?

### MAJOR EVIDENCE STATEMENT

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

### OTHER EVIDENCE STATEMENTS

- Postmeal hyperglycaemia is associated with increased risk of retinopathy. [Level 2+]
- Postmeal hyperglycaemia is associated with increased carotid intima-media thickness (IMT). [Level 2+]
- Postmeal hyperglycaemia causes oxidative stress, inflammation and endothelial dysfunction. [Level 2+]
- Postmeal hyperglycaemia is associated with decreased myocardial blood volume and myocardial blood flow. [Level 2+]
- Postmeal hyperglycaemia is associated with increased risk of cancer. [Level 2+]
- Postmeal hyperglycaemia is associated with impaired cognitive function in elderly people with type 2 diabetes. [Level 2+]

### RECOMMENDATION

**Postmeal hyperglycaemia is harmful and should be addressed.**

## QUESTION 2

Is treatment of postmeal hyperglycaemia beneficial?

### EVIDENCE STATEMENTS

- Treatment with agents that target postmeal plasma glucose reduces vascular events. [Level 1-]
- Targeting both postmeal and fasting plasma glucose is an important strategy for achieving optimal glycaemic control. [Level 2+]

### 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 controlling postmeal plasma glucose. [Level 1+]
- Several 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) in people with normal glucose tolerance and typically return to basal levels two to three hours after food ingestion. [Level 2++]
- IDF and other organizations define normal glucose tolerance as <7.8 mmol/l (140 mg/dl) two hours following ingestion of a 75-g glucose load. [Level 4]
- The two-hour timeframe for measurement of plasma glucose concentrations is recommended because it conforms to guidelines published by most of the leading diabetes organizations and medical associations. [Level 4]
- Self-monitoring of blood glucose (SMBG) is currently the optimal method for assessing plasma glucose levels. [Level 1++]
- It is generally recommended that people treated with insulin perform SMBG at least three times per day; SMBG frequency for people who are not treated with insulin should be individualized to each person's treatment regimen and level of control. [Level 4]

### RECOMMENDATIONS

- **Two-hour postmeal plasma glucose should not exceed 7.8 mmol/l (140 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.**
- **Efficacy of treatment regimens should be monitored as frequently as needed to guide therapy towards achieving postmeal plasma glucose target.**



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**BACKGROUND**

### 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.<sup>(26;27)</sup> The World Health Organization defines normal glucose tolerance as <7.8 mmol/l (140 mg/dl) two hours following ingestion of a 75-g glucose load in the context of an oral glucose tolerance test.<sup>(28)</sup> In this guideline, *postmeal hyperglycaemia* is defined as a plasma glucose level >7.8 mmol/l (140 mg/dl) two hours after ingestion of food.

### 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  $\beta$ -cell function and hence insulin secretion.<sup>(29;30)</sup> 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.<sup>(29-31)</sup> Emerging evidence shows that postmeal plasma glucose levels are elevated by deficiencies in the following substances: amylin, a glucoregulatory peptide that is normally cosecreted by the  $\beta$ -cells with insulin;<sup>(32;33)</sup> and glucagon-like peptide-1 (GLP-1) and glucose-dependent gastric inhibitory peptide (GIP), incretin hormones secreted by the gut.<sup>(34;35)</sup> There is evidence that the gradual loss in daytime postmeal glycaemic control precedes a stepwise deterioration in nocturnal fasting periods with worsening diabetes.<sup>(36)</sup>

### Postmeal hyperglycaemia is common in diabetes

Postmeal hyperglycaemia is a very frequent phenomenon in people with type 1 and type 2 diabetes<sup>(37-40)</sup> and can occur even when overall metabolic control appears to be adequate as assessed by HbA<sub>1c</sub>.<sup>(38;40)</sup> In a cross-sectional study of 443 individuals with type 2 diabetes, 71% of those studied had a mean two-hour postmeal plasma glucose of >14 mmol/l (252 mg/dl).<sup>(37)</sup> A study<sup>(40)</sup> looking at 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 (160 mg/dl) was recorded at least once in 84% of those studied.

### People with diabetes are at increased risk for macrovascular disease

Macrovascular disease is a common diabetic complication<sup>(41)</sup> and the leading cause of death among people with type 2 diabetes.<sup>(7)</sup> A recent meta-analysis<sup>(42)</sup> reported that the relative risk for myocardial infarction (MI) and stroke increased by almost 40% in people with type 2 diabetes compared with people without diabetes. A meta-regression analysis by Coutinho and colleagues<sup>(43)</sup> showed that the progressive relationship between glucose levels and cardiovascular risk extends below the diabetic threshold. The increased risk in people with IGT is approximately one-third of that observed in people with type 2 diabetes.<sup>(17;18;42;44;45)</sup> Earlier studies demonstrated that both carotid and popliteal IMT were directly related to clinically manifest cardiovascular disease affecting cerebral, peripheral and coronary artery vascular systems, and were associated with an increased risk of MI and stroke.<sup>(46;47)</sup>

### Several mechanisms are related to vascular damage

Numerous studies support the hypothesis of a causal relationship between hyperglycaemia and oxidative stress.<sup>(48-53)</sup> Oxidative stress has been implicated as the underlying cause of both the macrovascular and microvascular complications associated with type 2 diabetes.<sup>(54-56)</sup> Current thinking proposes that hyperglycaemia, free fatty acids and insulin resistance feed into oxidative stress, protein kinase-C (PKC) activation and advanced glycated endproduct receptor (RAGE) activation, leading to vasoconstriction, inflammation and thrombosis.<sup>(57)</sup>

Acute hyperglycaemia and glycaemic variability appear to play important roles in this mechanism. One study<sup>(58)</sup> examined apoptosis in human umbilical vein endothelial cells in cell culture that were subjected to steady state and alternating glucose concentrations. The study demonstrated that variability in glucose levels may be more damaging than a constant high concentration of glucose.

The same relationship between steady-state glucose and alternating glucose has been observed with PKC-

$\beta$  activity in human umbilical vein endothelial cells in cell culture. PKC- $\beta$  activity was significantly greater in cells exposed to alternating glucose concentrations compared with steady-state glucose concentrations (low or high).<sup>(59)</sup> This effect also applies to nitrotyrosine formation (a marker of nitrosative stress) and the generation of various adhesion molecules, including E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and interleukin-6 (IL-6).<sup>(60)</sup>

## QUESTION 1: IS POSTMEAL HYPERGLYCAEMIA HARMFUL?

Epidemiological studies have shown a strong association between postmeal and postchallenge glycaemia and cardiovascular risk and outcomes.<sup>(17;20;22;61)</sup> Furthermore, a large and growing body of evidence clearly shows a causal relationship between postmeal hyperglycaemia and oxidative stress,<sup>(62)</sup> carotid IMT<sup>(25)</sup> and endothelial dysfunction,<sup>(53;63)</sup> all of which are known markers of cardiovascular disease. Postmeal hyperglycaemia is also linked to retinopathy,<sup>(21)</sup> cognitive dysfunction in elderly people,<sup>(64)</sup> and certain cancers.<sup>(65-69)</sup>

### **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,<sup>(17;18)</sup> 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<sup>(22)</sup> 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 postmeal 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,<sup>(20)</sup> 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.

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

While it is well known that postchallenge and postmeal hyperglycaemia are related to the development and progression of diabetic macrovascular disease,<sup>(17;22)</sup> there are limited data on the relationship between postmeal hyperglycaemia and microvascular complications. A recent observational prospective study from Japan<sup>(21)</sup> demonstrated that postmeal hyperglycaemia is a better predictor of diabetic retinopathy than HbA<sub>1c</sub>. Investigators performed a cross-sectional study of 232 people with type 2 diabetes mellitus who were not being treated with insulin injections. A multiple regression analysis revealed that postmeal hyperglycaemia independently correlated with the incidence of diabetic retinopathy and neuropathy. Additionally, post-prandial hyperglycaemia was also associated, although not independently, with the incidence of diabetic nephropathy.

### **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.<sup>(25)</sup> 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.

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

A study<sup>(70)</sup> of acute glucose fluctuations showed that glucose fluctuations during postmeal periods exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycaemia in people with type 2 diabetes compared with people without diabetes. Another study<sup>(71)</sup> demonstrated that people with type 2 diabetes and postmeal hyperglycaemia were exposed to meal-induced periods of oxidative stress during the day.

Elevated levels of adhesion molecules, which play an important role in the initiation of atherosclerosis,<sup>(72)</sup> have been reported in people with diabetes.<sup>(48)</sup> Ceriello and colleagues<sup>(48;62)</sup> 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; 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.<sup>(63)</sup> Other studies have shown that acute hyperglycaemia in normal people impairs endothelium-dependent vasodilation,<sup>(53)</sup> and may activate thrombosis, increase the circulating levels of soluble adhesion molecules and prolong the QT interval.<sup>(52)</sup>

### **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.<sup>(73)</sup> No difference in fasting myocardial flow velocity (MFV), myocardial blood volume (MBV) and myo-

cardial 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.

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

Postmeal hyperglycaemia may be implicated in the development of pancreatic cancer.<sup>(65-67)</sup> A large, prospective cohort study of 35,658 adult men and women<sup>(65)</sup> 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. Increased risk for pancreatic cancer associated with elevated postmeal plasma glucose has also been shown in other studies.<sup>(66;67)</sup>

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.<sup>(74)</sup> No significant association was found in men.

### **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<sup>(64)</sup> has reported that significantly elevated postmeal plasma glucose excursions (>200 mg/dl [11.1 mmol]) were associated with a disturbance of global, executive and attention functioning.

## QUESTION 2: IS TREATMENT OF POSTMEAL HYPERGLYCAEMIA BENEFICIAL?

Findings from large, randomized, clinical trials demonstrate that intensive management of glycaemia, as assessed by HbA<sub>1c</sub>, can significantly decrease the development and/or progression of chronic complications of diabetes.<sup>(2-4;15)</sup> Moreover, there appears to be no glycaemic threshold for reduction of complications.<sup>(15)</sup> Because HbA<sub>1c</sub> is a measure of average fasting plasma glucose and postprandial plasma glucose levels over the preceding 120 days, treatment regimens that target both fasting and postmeal plasma glucose are needed to achieve optimal glycaemic control.

### Treatment with agents that target postmeal plasma glucose reduces vascular events [Level 1-]

As yet, no completed studies have specifically examined the effect of controlling postmeal glycaemia on macrovascular disease. However, there is some evidence which supports using therapies that target postmeal plasma glucose.

A meta-analysis by Hanefeld and colleagues<sup>(23)</sup> revealed significant positive trends in risk reduction for all selected cardiovascular event categories with treatment with acarbose, an  $\alpha$ -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 MI and other cardiovascular events. These findings are consistent with findings from the STOP-NIDDM trial,<sup>(75)</sup> which showed that treating people with IGT with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension.

A significant positive effect of postmeal plasma glu-

cose control on carotid IMT has also been reported in drug-naïve people with type 2 diabetes.<sup>(76)</sup> Treatment with repaglinide, a rapid-acting insulin secretagogue that targets postmeal plasma glucose and treatment with glyburide achieved similar HbA<sub>1c</sub> levels; after 12 months, carotid IMT regression, defined as a decrease of >0.02 mm, was observed in 52% of people taking repaglinide and in 18% of those receiving glyburide. Significantly greater decreases in interleukin-6 and C-reactive protein were also seen in the repaglinide group compared with the glyburide group.

An interventional study in people with IGT also showed a significant reduction in the progression of carotid IMT in people treated with acarbose versus placebo.<sup>(11)</sup>

There is also indirect evidence of benefit in reducing surrogate markers of cardiovascular risk. Treatment with rapid-acting insulin analogues to control postmeal plasma glucose has shown a positive effect on cardiovascular risk markers such as nitrotyrosine,<sup>(77)</sup> endothelial function,<sup>(78)</sup> and methylglyoxal (MG) and 3-deoxyglucosone (3-DG).<sup>(79)</sup> Similar improvement has been reported with acarbose therapy.<sup>(80)</sup> Furthermore, controlling only postmeal hyperglycaemia using the rapid-acting insulin aspart may increase myocardial blood flow, which is reduced in type 2 diabetes following a meal.<sup>(81)</sup> A similar relationship between postmeal hyperglycaemia and MG and 3-DG in people with type 1 diabetes has also been shown.<sup>(79)</sup> In people with type 1 diabetes, treatment with insulin lispro significantly reduced excursions of MG and 3-DG, and these reductions were highly correlated with lower postmeal plasma glucose excursions compared with regular insulin treatment.

The Kumamoto study,<sup>(3)</sup> 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 control. 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.

### Targeting both postmeal plasma glucose and fasting plasma glucose is an important strategy for achieving optimal glycaemic control [Level 2+]

Recent studies have reported that the relative contribution of postmeal plasma glucose to overall glycaemia increases as the HbA<sub>1c</sub> level decreases. Monnier and colleagues<sup>(82)</sup> showed that in people with HbA<sub>1c</sub> levels <7.3%, the contribution of postmeal plasma glucose to HbA<sub>1c</sub> was ≈70%, whereas the postmeal contribution was ≈40% when HbA<sub>1c</sub> levels were above 9.3%. Also nocturnal fasting plasma glucose levels remain at near-normal levels as long as the HbA<sub>1c</sub> level remains <8%.<sup>(86)</sup> However, postmeal plasma glucose control deteriorates earlier, occurring when HbA<sub>1c</sub> 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 intervention trials demonstrating that achieving target fasting plasma glucose alone is still associated with HbA<sub>1c</sub> levels >7%.<sup>(24;83)</sup> Woerle and colleagues<sup>(24)</sup> assessed the relative contribution of controlling fasting and postmeal plasma glucose in people with type 2 diabetes and HbA<sub>1c</sub> ≥7.5%. Only 64% of people achieving a fasting plasma glucose <5.6 mmol/l (100 mg/dl) achieved an HbA<sub>1c</sub> <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<sub>1c</sub> compared with decreases in fasting plasma glucose. Postmeal plasma glucose accounted for 80% of HbA<sub>1c</sub> when HbA<sub>1c</sub> was <6.2% and about 40% when HbA<sub>1c</sub> was above 9.0%.

These studies support the view that control of fasting hyperglycaemia is necessary but usually insufficient for achieving HbA<sub>1c</sub> goals <7% and that control of postmeal hyperglycaemia is essential for achieving recommended HbA<sub>1c</sub> goals.

Targeting postmeal plasma glucose is not associated with an increased risk of hypoglycaemia. However the risk of hypoglycaemia may be increased by attempting to lower HbA<sub>1c</sub> levels to <7% by targeting only fasting plasma glucose. In the “treat-to-target” study,<sup>(84)</sup> which used long-acting and intermediate-

acting insulins to control fasting plasma glucose, only 25% of once-daily glargine-treated people achieved an HbA<sub>1c</sub> of <7% without documented nocturnal hypoglycaemia. Conversely, Bastyr and colleagues,<sup>(85)</sup> demonstrated that targeting postmeal plasma glucose versus fasting plasma glucose was associated with similar and lower rates of hypoglycaemia. Also no severe hypoglycaemia was observed in the study by Woerle and colleagues in which a reduction of mean HbA<sub>1c</sub> from 8.7% to 6.5% was achieved, including targeting of postmeal plasma glucose.<sup>(24)</sup>

### QUESTION 3: WHICH THERAPIES ARE EFFECTIVE IN CONTROLLING POSTMEAL PLASMA GLUCOSE?

#### Diets with a low glycaemic load are beneficial in controlling postmeal plasma glucose [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 carbohydrate weight in individual foods. Most modern starchy foods have a relatively high GI, including potatoes, white and brown bread, rice and breakfast cereals.<sup>(86)</sup> 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.<sup>(87;88)</sup> The use of GI can

provide an additional benefit for diabetes control beyond that of carbohydrate counting.<sup>(89)</sup>

In a meta-analysis of randomized controlled trials, diets with a lower GI are associated with modest improvements in HbA<sub>1c</sub>.<sup>(90)</sup> Observational studies in populations without diabetes suggest that diets with a high GI are independently associated with increased risk of type 2 diabetes,<sup>(91;92)</sup> gestational diabetes<sup>(93)</sup> and cardiovascular disease.<sup>(94)</sup> Glycaemic load has been shown to be an independent risk factor for MI.<sup>(94)</sup>

Despite inconsistencies in the data, sufficient positive findings suggest that nutritional plans based on the judicious use of the GI positively affect postmeal plasma glucose excursions and reduce cardiovascular risk factors.<sup>(95)</sup>

### Several 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. This section presents a description of the mechanism(s) of action of the commercially available therapies, listed alphabetically. Specific combinations of therapies are not included in this summary.

Traditional therapies include the  $\alpha$ -glucosidase inhibitors, glinides (rapid-acting insulin secretagogues) and insulin (rapid-acting insulin analogues, biphasic [premixed] insulins, inhaled insulin, human regular insulin).

In addition, new classes of therapies for managing postmeal plasma glucose in people with diabetes (amylin analogs, 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<sub>1c</sub>.<sup>(96-99)</sup> These therapies address deficiencies in pancreatic and gut hormones that affect insulin and glucagon secretion, satiety and gastric emptying.

#### $\alpha$ -glucosidase inhibitors

$\alpha$ -glucosidase inhibitors (AGIs) delay the absorption of carbohydrates from the gastrointestinal tract, thereby limiting postmeal plasma glucose excursions. Specifically, they inhibit  $\alpha$ -glucosidase, an enzyme

located in the proximal small intestinal epithelium that breaks down disaccharides and more complex carbohydrates. Through competitive inhibition of this enzyme, AGIs delay intestinal carbohydrate absorption and attenuate postmeal plasma glucose excursions.<sup>(100;101)</sup> Acarbose and miglitol are commercially available AGIs.

#### Amylin analogues

Human amylin is a 37-amino acid glucoregulatory peptide that is normally cosecreted by the  $\beta$ -cells with insulin.<sup>(99;102)</sup> Pramlintide, which is commercially available, is a synthetic analogue of human amylin that restores the natural effects of amylin on glucose metabolism by decelerating gastric emptying, lowering plasma glucagon and increasing satiety, thereby blunting postmeal glycaemic excursions.<sup>(103-108)</sup>

#### Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors work by inhibiting the DPP-4 enzyme that degrades GLP-1, thereby extending the active form of the hormone.<sup>(96)</sup> This in turn stimulates glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying and increases satiety.<sup>(34)</sup> Currently, sitagliptin phosphate is the only commercially available DPP-4 inhibitor.

#### Glinides

Glinides have a mechanism of action similar to sulfonylureas, but have a much shorter metabolic half-life. They stimulate a rapid but short-lived release of insulin from pancreatic  $\beta$ -cells that lasts one to two hours.<sup>(109)</sup> 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.<sup>(110;111)</sup> 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, increase  $\beta$ -cell neogenesis, inhibit  $\beta$ -cell apoptosis, inhibit glucagon secretion, decelerate gastric emptying and induce satiety.<sup>(112-115)</sup> In people with type 2 diabetes, secretion of GLP-1 is diminished.<sup>(34)</sup> Exenatide, the only currently commercially



available GLP-1 receptor agonist, shares a 53% sequence homology with GLP-1 and has been shown to exhibit many of the same effects.<sup>(116)</sup>

## Insulins

### • Rapid-acting insulin analogues

Rapid-acting insulin analogues were developed to mimic the normal physiologic insulin response.<sup>(117)</sup> Rapid-acting insulins have a rapid onset and peak activity and a short duration of action.<sup>(117)</sup>

### • Biphasic insulins

Biphasic (premixed) insulins combine a rapid-acting insulin analogue with an intermediate-acting insulin to mimic the normal physiological insulin response and reduce postmeal plasma glucose levels.<sup>(118-121)</sup> Currently, there are several rapid-acting biphasic insulin formulations commercially available throughout the world.

### • Inhaled insulin

Inhaled insulin consists of human insulin inhalation powder, which is administered using an inhaler. The inhaled insulin preparation has an onset of action similar to rapid-acting insulin analogues and a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin.<sup>(122)</sup> Currently, exubera is the only commercially available inhaled insulin preparation.

## 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 2++]**

As previously discussed, 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.<sup>(26;27)</sup>

**IDF and other organizations define normal glucose tolerance as <7.8 mmol/l (140 mg/dl) two hours following ingestion of a 75-g glucose load [Level 4]**

IDF and other organizations define normal glucose tolerance as <7.8 mmol/l (140 mg/dl) two hours following ingestion of a 75-g glucose load,<sup>(1;123;124)</sup> thus a two-hour postmeal plasma glucose goal of <7.8 mmol/l (140 mg/dl) is consistent with this definition. Furthermore, because postmeal plasma glucose usually returns to basal level two to three hours following food ingestion, a plasma glucose goal of <7.8 mmol/l (140 mg/dl) would seem to be a reasonable and conservative target. Table 2 presents recommended goals for glycaemic control.

**The two-hour timeframe for measurement of plasma glucose concentrations is recommended because it conforms to guidelines published by most of the leading diabetes organizations and medical associations [Level 4]**

Although testing timeframes from one to four hours postmeal correlate with HbA<sub>1c</sub>,<sup>(125)</sup> the two-hour timeframe for measurement is recommended because it conforms to glucose guidelines published by most of the leading diabetes organizations and medical associations.<sup>(124;126;127)</sup> Furthermore, two-hour measurement may be a safer timeframe for people treated with insulin, particularly those who are inexperienced with insulin therapy or have received inadequate education. These people may tend to respond inappropriately to elevated one-hour plasma glucose levels with additional insulin boluses without waiting for their initial bolus insulin to take full effect. This behaviour is often referred to as “insulin stacking,” and can lead to severe hypoglycaemia.

**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. This facilitates timely intervention to achieve and maintain near-normal glycaemia and provides feedback to people with diabetes. Thus, most diabetes organizations and other medical associations advocate use of SMBG in people with diabetes.<sup>(126-128)</sup>

While much of the literature has focused primarily on the utility of SMBG in people treated with insulin,<sup>(2;129)</sup> a number of studies have demonstrated that therapeutic management programmes that include structured SMBG result in greater HbA<sub>1c</sub> reduction in people with non-insulin-requiring type 2 diabetes compared with programmes without SMBG.<sup>(130-134)</sup>

Nonetheless, debate continues on the clinical benefits of SMBG, particularly in non-insulin-treated type 2 diabetes. Some studies have shown little or no difference in glycaemic control (HbA<sub>1c</sub>) when comparing use of SMBG and urine glucose testing,<sup>(135;136)</sup> whereas other reports have demonstrated that SMBG has distinct advantages in terms of improved glycaemic control.<sup>(133)</sup>

A recent meta-analysis by Jansen and colleagues,<sup>(133)</sup> which looked at 13 randomized controlled trials investigating the effects of SMBG, found that interventions with SMBG showed a reduction in HbA<sub>1c</sub> of 0.40% compared with interventions without SMBG. Moreover, when regular medical feedback was provided to people, the HbA<sub>1c</sub> reduction more than doubled, whereas self-monitoring of urine glucose showed comparable results to interventions without self-monitoring of blood glucose or urine glucose. However the recently published DiGEM study failed to show that SMBG significantly reduced on HbA<sub>1c</sub> which was only 0.17% lower in the group using intensive SMBG compared with usual care without SMBG.<sup>(137)</sup>

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.

**It is generally recommended that people treated with insulin perform SMBG at least three times per day; SMBG frequency for people who are not treated with insulin should be individualized to each person's treatment regimen and level of control [Level 4]**

Because of their absolute insulin deficiency, most

people with type 1 diabetes require multiple daily insulin injections to manage glycaemia. In addition, many people with type 2 diabetes use insulin therapy to manage their disease. Given the potential for insulin-induced hypoglycaemia, most medical organizations recommend that people treated with insulin perform SMBG at least three times per day.<sup>(128;138)</sup>

As discussed previously, there is ongoing debate regarding the clinical utility of SMBG in non-insulin treated diabetes. However, despite a lack of evidence regarding timing and frequency of SMBG, most medical organizations recommend that the frequency of SMBG in non-insulin-treated diabetes be individualized to each person's treatment regimen and level of glycaemic control.<sup>(128;138)</sup>

## EMERGING TECHNOLOGIES

### Continuous glucose monitoring

Continuous glucose monitoring (CGM) is an emerging technology for monitoring diabetes.<sup>(139-142)</sup> 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.<sup>(143;144)</sup> An automated assay for 1,5-AG has been used in Japan for over a decade;<sup>(145)</sup> a similar assay has recently been approved in the United States.<sup>(146)</sup> There are no outcome studies using this measure of glycaemic control.

The image features a dark red background with a series of overlapping, semi-transparent circles in various shades of red and pink. The circles are arranged in a way that creates a sense of depth and movement, with some circles appearing to be in front of others. The overall composition is abstract and modern.

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**CONCLUSIONS**

With an estimated 246 million people worldwide with diabetes,<sup>(1)</sup> this epidemic is a significant and growing global concern. Poorly controlled diabetes is a leading cause of death in most developed countries and is associated with the development of such complications as diabetic neuropathy, renal failure, blindness and macrovascular disease.<sup>(5;6)</sup> Macrovascular complications are the major cause of death in people with diabetes.<sup>(7)</sup>

There is a strong association between postmeal and postchallenge glycaemia and cardiovascular risk and outcomes in people with normal glucose tolerance, IGT and diabetes,<sup>(17;18;20;22;61)</sup> as well as an association between postmeal hyperglycaemia and oxidative stress, inflammation, carotid IMT and endothelial dysfunction, all of which are known markers of cardiovascular disease.<sup>(25;52;53;63;71;73)</sup> Furthermore, a growing body of evidence shows that postmeal hyperglycaemia may also be linked to retinopathy,<sup>(21)</sup> cognitive dysfunction in elderly people with type 2 diabetes,<sup>(64)</sup> and certain cancers.<sup>(65-69)</sup>

Because there appears to be no glycaemic threshold for reduction of complications,<sup>(14;15)</sup> the goal of diabetes therapy should be to achieve glycaemic status as near to normal as safely possible in all three measures of glycaemic control, namely HbA<sub>1c</sub>, fasting premeal and postmeal plasma glucose. Within these parameters, and subject to the availability of therapies and technologies for treating and monitoring postmeal plasma glucose, a two-hour postmeal plasma glucose goal of <7.8 mmol/l (140 mg/dl) is both reasonable and achievable.

Regimens that target both fasting and postmeal glycaemia are needed to achieve optimal glucose control. However, optimal glycaemic control cannot be achieved without adequate management of postmeal plasma glucose.<sup>(36;82;83)</sup> Therefore, treatment of fasting and postmeal hyperglycaemia should be initiated simultaneously at any HbA<sub>1c</sub> level. Although cost will remain an important factor in determining appropriate treatments, controlling glycaemia is ultimately much less expensive than treating the complications of diabetes.

## TABLE 2

### Glycaemic goals for clinical management of diabetes\*

HbA <sub>1c</sub>	<6.5%
Premeal (fasting)	5.5 mmol/l (<100 mg/dl)
2-hour postmeal	7.8 mmol/l (<140 mg/dl)

\* The overriding goal for diabetes management is to lower all glucose parameters to as near to normal as safely possible. The above goals provide a framework for initiating and monitoring clinical management of glycaemia, but glycaemic targets should be individualized. These goals are not appropriate for children and pregnant women.



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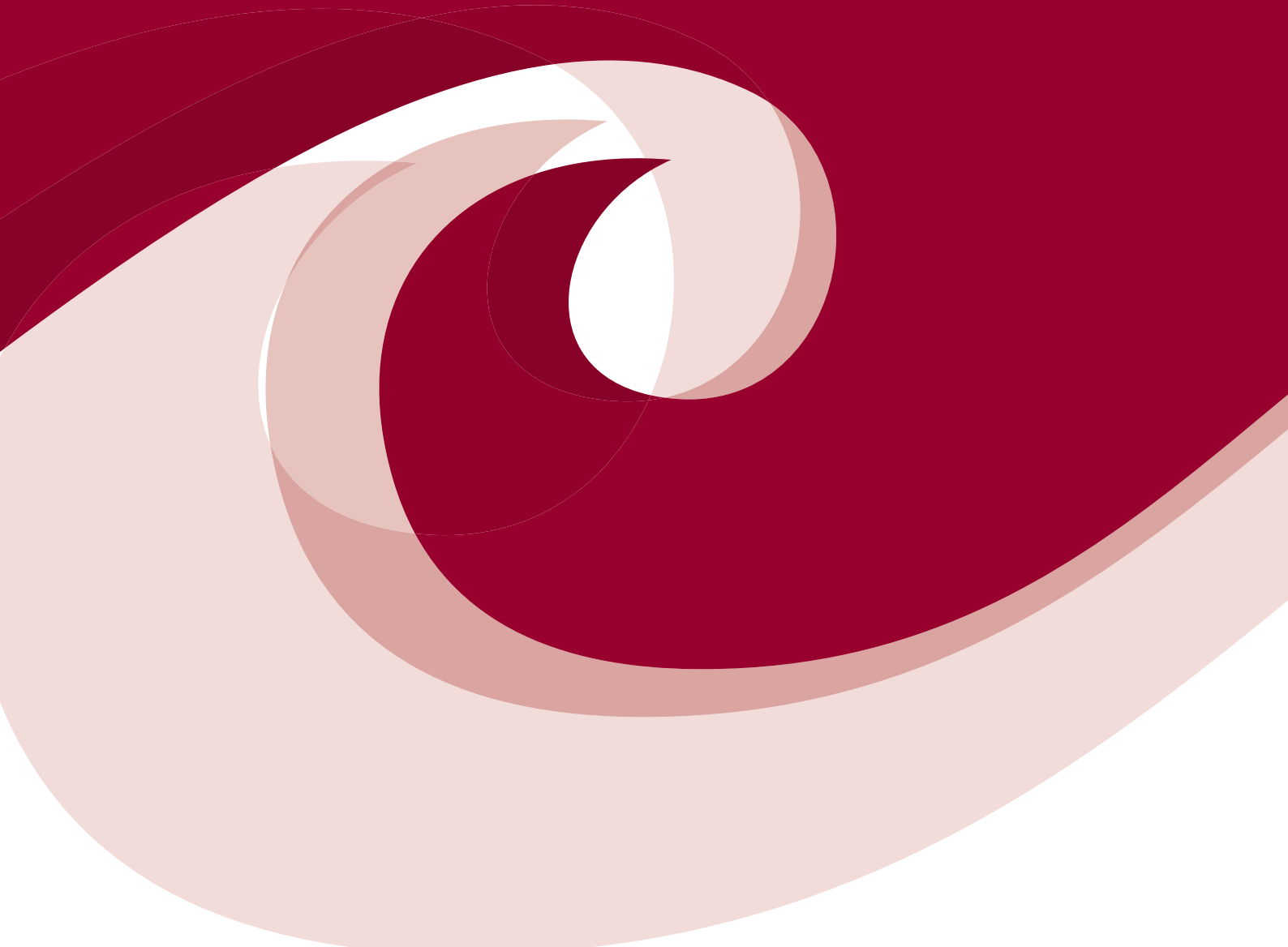
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