Postprandial glycemia (PPG): Should we keep it low? If yes, how?

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Impaired beta-cell function in normal glucose tolerance

From Insulin Resistance to Diabetes

- Reduced Insulin Secretion
- Fasting Glucose
- Post-Meal Glucose
- Impaired 1st phase insulin secretion
- Reduced Insulin Secretion

Cardiovascular Disease

Microvascular Disease

Years: -10, -5, 0, 5, 10, 15, 20, 25, 30


Ins Res – insulin resistance
IGT – impaired glucose tolerance
Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes?
Blood Glucose Levels Over 24 Hours

Meal-related Plasma Glucose Excursions

Over 3 months
\( \text{HbA}_1^C \)
Hamburgerology
Where the sacred ground is. BY JANE AND MICHAEL STERN

BEST BURGERS
Clockwise from above: eyeing a fully dressed SoCal patty from The Cottage, stopping for a Bobcat Bite in New Mexico, going for a triple at South Dakota's Hamburger Inn and dropping by for one with fried onions at the White Hut in Massachusetts.
Glucose $\rightarrow$ Glycolysis $\rightarrow$ Acetyl-CoA

Fats $\rightarrow$ Beta-oxidation $\rightarrow$ Acetyl-CoA
I

II

Q+

III

Cyt C

IV

ATP syntase

Δµ H⁺

H⁺

NADH

NAD+

FADH₂

FAD

O₂⁻ → O₂

H₂O ← O₂

ATP ← ADP+Pi

Acetyl-CoA
Acetyl-CoA Overload
Oxidative Stress

Overnutrition
Decreased Physical Activity

Glucose
FFA
Cellular Overload

Oxidative Stress

Endothelial cells
Endothelial Dysfunction

Muscle Adipocyte
Insulin Resistance

β cells
Altered Insulin Secretion

IGT (Post Prandial Hyperglycemia)

CVD

Metabolic Syndrome

Diabetes (Chronic Hyperglycemia)

The Common Soil Hypothesis Revisited
A. Ceriello ATVB, 2004
Hyperglycemia

Mitochondria

O$_2^-$

PKC

NF-kB

NAD(P)H oxidase

O$_2^-$

iNOS

eNOS

NO

Peroxynitrite

DNA damage

PARP

NAD$^+$

GAPDH

Endothelial dysfunction

Polyol Pathway

AGE Formation

Hexosamine Flux

Adhesion molecules

Proinflammatory Cytokines

Nitrotyrosine

Diabetic Complications

Ceriello A, Diabetes Care 2010
Glutathione reverses systemic haemodynamic changes induced by acute hyperglycaemia in healthy subjects

Acute hyperglycemia and endothelial dysfunction: the role of oxidative stress

Endothelial dysfunction induced by hyperglycaemia

NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = diabetes mellitus

*Kawano H et al. J Am Coll Cardiol 1999;34:146–54*
Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation in vivo.


Diabetes 2006;55:1127-32
glucose (●), mannitol (■), or glucose-NAC (▲) infusion

*Nieuwdorp M et al. Diabetes 2006;55:1127-32*
Glycemia, NT, triglycerides and FMD variations:

Acarbose therapy reduces coagulation marker levels in diabetic patients

Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia

Diene peak (min)

Ceriello A et al. Metabolism, 1999;48:1503-8
Effects of different insulin regimes on postprandial myocardial perfusion defects in type 2 diabetic patients

Scognamiglio R, Negut C, de Kreutzenberg SV, Tiengo A, Avogaro A.

Diabetes Care 2006;29:95-100
### Insulin and postprandial myocardial perfusion defects

<table>
<thead>
<tr>
<th></th>
<th>MBF&lt;sub&gt;f&lt;/sub&gt;</th>
<th>MBF&lt;sub&gt;pp&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subject</td>
<td>5,6 ± 2,0</td>
<td>9,9 ± 2,8</td>
</tr>
<tr>
<td>Type 2 placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>5,4 ± 1,5</td>
<td>3,4 ± 0,9</td>
</tr>
<tr>
<td>Regular insulin</td>
<td>5,4 ± 1,9</td>
<td>4,2 ± 0,9</td>
</tr>
<tr>
<td>Insulin analog</td>
<td>5,4 ± 2,0</td>
<td>7,2 ± 1,9</td>
</tr>
</tbody>
</table>

Scognamiglio R et al. Diabetes Care 2006;29:95-100
Regression of carotid atherosclerosis by control of postprandial hyperglycaemia in type 2 diabetes mellitus

- Number of patients: 175
- Follow-up: 12 months

Improved CIMT and other CVD markers with PGR


CIMT = carotid intima-media thickness
CVD = cardiovascular disease
FPG = fasting plasma glucose
IL-6 = interleukin-6
CRP = C-reactive protein
FFA-induced endothelial dysfunction can be corrected by vitamin C.
The Role of Hyperglycemia and Hypertriglyceridemia in Postprandial Oxidative Stress Generation In Diabetic Patients (Ceriello A et al. Circulation 2002 106:1211-8)
Epidemiological Evidences
Relation between postprandial blood glucose levels and cardiovascular mortality

1. DECODE Study Group. Lancet 1999;354:617
San Luigi Gonzaga Diabetes Study

- 529 (284 men and 245 women) consecutive type 2 diabetic patients\(^1\)
- 77 events over 5 years\(^1\)
- Multivariate analysis including HbA1c, pre- and postprandial glucose showed only post-lunch glucose to be predictive\(^1\)
- Long-term follow-up (10 years) confirms this evidence\(^2\)

\(^1\) JCEM 2005;91,813-819
\(^2\) Diabetes Care 2011; 34:2237-2243
Excess glycaemic excursions after an oral glucose tolerance test compared with a mixed meal challenge and self-measured home glucose profiles: is the OGTT a valid predictor of postprandial hyperglycaemia and vice versa?

J. J. Meier, B. Baller, B. A. Menge, B. Gallwitz, W. E. Schmidt and M. A. Nauck

Diabetes, Obesity and Metabolism 2009; 11: 213–222
Glucose concentrations measured during an oral glucose tolerance test [75 g oral glucose; (a)], after a standardized test meal (b) and during self-measured home glucose profiles in subjects with normal (NGT), impaired (IGT) and diabetic (DM) glucose tolerance. Data are presented as means ± s.e.m., and p values were calculated by repeated-measures ANOVA and denote (A) differences between groups, (B) differences over time and (AB) differences because of the interaction of group and time. Asterisks denote significant (p < 0.05) differences vs. NGT subjects.
(A and B) Linear regression analysis between the 2-h glucose concentrations after oral glucose ingestion (75 g) and the respective glucose levels 2 h after a standardized test meal (A) as well as the self-measured glucose levels 2 h after breakfast under everyday conditions (B) in subjects with a normal (NGT), impaired (IGT) and diabetic (DM) glucose tolerance.

*Meier JJ et al. Diabetes, Obesity and Metabolism 2009; 11: 213–222*
Studies have investigated postprandial glycaemic excursions and CV risk

- Intervention trials:
  - Positive in primary prevention (STOP-NIDDM)\(^1\)
  - Negative in secondary prevention (HEART2D-NAVIGATOR)\(^2,3\)
    (In both HEART2D\(^2\) and NAVIGATOR\(^3\) the goal of reducing PPG was not achieved)
  - Positive, in a post-hoc analysis of the HEART2D Study, in the older patients and in patients with longer duration of the disease\(^4\)

Pre- and postprandial glycemic levels in 3,284 non-insulin treated type 2 diabetic patients

Bonora E et al. Diabetologia 2006;49:846-54
Principle of MAGE assessment
(from Molnar and Service)
Objective:

- This study examined the relation of dietary intake to glycemic response when foods are consumed under free-living conditions.

Design:

- Participants were 26 overweight or obese adults with T2DM who participated in a RCT of lifestyle modification. Participants wore a CGM and simultaneously kept a food diary for 3 d. The dietary variables included Glycemic Index (GI), Glycemic Load (GL), and intakes of energy, fat, protein, carbohydrate, sugars, and fiber. The glycemic response variables included Area Under the Curve (AUC), mean and SD of continuous glucose monitoring (CGM) values, percentage of CGM values in euglycemic and hyperglycemic ranges, and mean amplitude of glycemic excursions. Relations between daily dietary intake and glycemic outcomes were examined.
Main results

Dietary Glycemic Index and Glycemic response:
Bivariate correlation analyses showed that dietary GI was positively related to AUC, mean glucose and the percentage of values in the hyperglycemic range. GI was also negatively related to the percentage of values in the euglycemic range.

Dietary Glycemic Load and Glycemic response:
No significant relations between GL and glycemic outcomes were found in the uncontrolled bivariate correlations.
Conclusion

- The data support the ecologic validity of the GI and GL constructs in free-living obese adults with type 2 diabetes. GI was the strongest and the most consistent independent predictor of glycemic stability and variability.
This study aims to determine the peak timing of postprandial blood glucose level (PBGL) of two breakfasts with different glycemic index (GI) in gestational diabetes mellitus (GDM).

Ten women with diet-controlled GDM who were between 30 and 32 weeks of gestation were enrolled in the study. They consumed two carbohydrate controlled, macronutrient matched bread-based breakfasts with different GI (low vs. high) on two separate occasions in a random order after an overnight fast. PBGLs were assessed using a portable blood analyser.
Timing of Peak Blood Glucose after Breakfast Meals of Different Glycemic Index in Women with Gestational Diabetes

Jimmy Chun Yu Louie ¹,², Tania P. Markovic ²,³, Glynis P. Ross ³, Deborah Foote ⁴ and Jennie C. Brand-Miller ²,*

Figure 1. Mean ± SEM postprandial blood glucose level of the 10 subjects. NS: non-significant.

Nutrients 2013, 5, 1-9; doi:10.3390/nu5010001
Conclusion:

• the low GI breakfast produced lower postprandial glycemia, and the peak PBGL occurred closer to the time recommended for PBGL monitoring (i.e., 1 h postprandial) in GDM than a macronutrient matched high GI breakfast.
Randomized Control Trials

Effects of hypocaloric diets with different glycemic indexes on endothelial function and glycemic variability in overweight and in obese adult patients at increased cardiovascular risk

Silvio Buscemi*, Loretta Cosentino, Giuseppe Rosafio, Manuela Morgana, Alessandro Mattina, Delia Sprini, Salvatore Verga, Giovam Battista Rini


SUMMARY

Background & aims: The role of glycemic index of the diet in glucose control and cardiovascular prevention is still not clear. The aim of this study was to determine the effects of hypocaloric diets with different glycemic indexes and glycemic loads on endothelial function and glycemic variability in nondiabetic participants at increased cardiovascular risk.

Methods: Forty nondiabetic obese participants were randomly assigned to a three-month treatment with either a low glycemic index (LGI; n = 19) or high glycemic index (HGI; n = 21) hypocaloric diet with similar macronutrient and fiber content. Endothelial function was measured as flow-mediated dilatation
Randomized Control Trials

Effects of hypocaloric diets with different glycemic indexes on endothelial function and glycemic variability in overweight and in obese adult patients at increased cardiovascular risk

Silvio Buscemi*, Loretta Cosentino, Giuseppe Rosafio, Manuela Morgana, Alessandro Mattina, Delia Sprini, Salvatore Verga, Giovam Battista Rini

Table 4
Glycemic variables at continuous subcutaneous glucose monitoring in the study participants before and 3 months after randomization to hypocaloric diets with different glycemic indexes.

<table>
<thead>
<tr>
<th>Glycemic index diet</th>
<th>Low (n = 11)</th>
<th>3 Months</th>
<th>High (n = 13)</th>
<th>3 Months</th>
<th>ph</th>
<th>p&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td>Baseline</td>
<td></td>
<td>Time</td>
<td>Time × treatment</td>
</tr>
<tr>
<td>48 h-CSGM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>95 ± 12 (74–113)</td>
<td>90 ± 13 (64–102)</td>
<td>106 ± 16 (76–125)</td>
<td>97 ± 14 (74–119)</td>
<td></td>
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<tr>
<td>SD</td>
<td>22.3 ± 6.8 (15.2–35.2)</td>
<td>18.1 ± 5.0 (12.1–28.4)</td>
<td>24.1 ± 8.2 (13.5–41.1)</td>
<td>26.2 ± 8.6 (16.8–46.8)</td>
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<tr>
<td>95% CI</td>
<td>17.7–26.9</td>
<td>14.8–21.5</td>
<td>19.2–29.0</td>
<td>18.6–33.9</td>
<td></td>
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<tr>
<td>CV %</td>
<td>23.5 ± 5.5 (17.0–34.5)</td>
<td>20.0 ± 4.2 (13.3–36.4)</td>
<td>23.6 ± 6.2 (12.4–38.8)</td>
<td>26.6 ± 6.2 (16.8–41.8)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>19.9–27.2</td>
<td>17.2–22.8</td>
<td>19.8–27.4</td>
<td>22.9–30.4</td>
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</table>

CSGM: continuous subcutaneous glucose monitoring; and CV: coefficient of variability.

- Values are presented as means ± SD (range in parenthesis) or as confidence intervals.
- Student’s unpaired t-test.
- 2 × 2 repeated-measures ANOVA with diet × time interaction for the change.
Conclusions: Endothelial function and glycemic variability ameliorate in association with the adherence to an LGI hypocaloric diet in nondiabetic obese persons.
Characterizing Glucose Exposure for Individuals with Normal Glucose Tolerance Using Continuous Glucose Monitoring and Ambulatory Glucose Profile Analysis

R.S. Mazze, E. Strock, D. Wesley, S. Borgman, B. Morgan, R. Bergenstal and R. Cuddihy

Diabetes Technology & Therapeutics 2008 ;10:149-598
The modal day and the AGP depict 3,628 continuous glucose readings measured for 30 days. The modal day shows each data point graphed without regard to date. The AGP replaces the individual data points with five smoothed frequency curves, which represent the underlying glycemic pattern (accounting for outlier values). The statistical summary (shown separately, but contained in the AGP report) is customizable.

Center solid line is the median, next two outer solid lines (25th and 75th percentiles) represent the IQR, the dotted lines depict the 10th and 90th percentiles.

Mazze RS et al. Diab Technol Therap 2008;10:149-159
Hyperglycaemia

LDL oxidation

Antioxidant consumption

F VIIa

Oxidative stress

Endothelium

Endothelial dysfunction

Atherosclerosis

Ceriello A: Annual Meeting Italian Society of Diabetology, 1998

Ceriello A: Diabetologia 2003; 46 Suppl 1:M9-16
Guideline for PPG management was published by the IDF in 2008.

Updated in 2011.
Is postprandial hyperglycaemia harmful?

Postprandial and postchallenge hyperglycaemia are independent risk factors for macrovascular disease

Postprandial hyperglycaemia is associated with:

- Increased risk of retinopathy, increased CIMT, decreased myocardial blood volume/blood flow, increased risk of cancer, impaired cognitive function in the elderly
- Postprandial hyperglycaemia causes oxidative stress, inflammation and endothelial dysfunction

CIMT = carotid-intima-media thickness
Is postprandial hyperglycaemia harmful?

IDF Recommendation:

Postprandial hyperglycaemia is harmful and should be addressed
Is treatment of postprandial hyperglycaemia beneficial?

Conclusion

There is currently a lack of randomised clinical trial evidence that correcting postprandial hyperglycaemia improves clinical outcomes

[Level 1]

Treatment with agents which target postprandial plasma glucose reduces vascular events in primary prevention

[Level 1-]

Targeting both postprandial plasma glucose and fasting plasma glucose is an important strategy for achieving optimal glycaemic control

[Level 1+]
Is treatment of postprandial hyperglycaemia beneficial?

IDF Recommendation:

Implement treatment strategies to lower postprandial plasma glucose in people with postprandial hyperglycaemia.
Which therapies are effective in controlling postprandial plasma glucose?

**Conclusion**

<table>
<thead>
<tr>
<th>Evidence grade</th>
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<tbody>
<tr>
<td>[Level 1+]</td>
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</table>

<table>
<thead>
<tr>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Diets with a low glycaemic load are beneficial in improving glycaemic control</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Evidence grade</th>
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<tr>
<td>[Level 1++]</td>
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<table>
<thead>
<tr>
<th>Conclusion</th>
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<tr>
<td>Several pharmacological agents preferentially lower postprandial plasma glucose</td>
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</table>
Which therapies are effective in controlling postprandial plasma glucose?

IDF Recommendation:

A variety of both non-pharmacologic and pharmacologic therapies should be considered to target postprandial plasma glucose.
What are the targets for postprandial glycaemic control and how should they be assessed?

**Conclusion**

**Evidence grade**

| Postprandial plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) after food ingestion in healthy non-pregnant people | [Level 1++] |
| Self-monitoring of blood glucose (SMBG) is currently the optimal method for assessing plasma glucose levels | [Level 1++] |
What are the targets for postprandial glycaemic control and how should they be assessed?

IDF Recommendation:

Postprandial plasma glucose should be measured 1-2 hours after a meal. The target for postprandial plasma glucose is 9.0 mmol/L (162 mg/dl). Self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring postprandial glucose.