DO POSTPRANDIAL GLYCEMIC EXCURSIONS IMPACT CARDIOVASCULAR RISK?

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Declaration of potential conflict of interest

I have no conflict of interest to declare
DYSGLYCAEMIA

FPG

PPG

Acute glucose fluctuations from peaks to nadir

CHRONIC HYPERGLYCEMIA

EXCESS OF GLYCATION (HbA1c)

GLYCEMIC VARIABILITY

Activation of oxidative stress

DIABETIC COMPLICATIONS
PPG

Magnitude of PPG

Contribution to acute glucose fluctuations (Glycemic Variability [MAGE])

Duration of PPG increment contributes to chronic sustained hyperglycaemia (HbA1c)
Daily glycemic variation with worsening type 2 diabetes

Monnier, C Colette, G Dunseath and D Owens, Diabetes Care. 2007;30:263-269
Exaggerated postmeal glucose excursions are common in patients with diabetes.

PPHG precedes elevation of fasting glucose by 4-7 yrs.

Diabetic complications develop during this period of PPHG even though FPG remains in the normal range.

We spend the majority of the day in a postprandial state.

Yet the vast majority of metabolic studies are done in the fasting state.
POSTPRANDIAL GLUCOSE SPIKES – THE POTENTIAL IMPACT

- **Short term**
  - Increased atheromatous factors (Ceriello 1998)
  - Oxidative Stress (Ceriello 1998)
  - Hypertriglyceridemia (Ceriello 2000)
  - Endothelial dysfunction (Ceriello 2000)

- **Medium term**
  - Glucose is toxic to the β-cell, therefore hyperglycemia impairs β-cell responsiveness, which may accelerate the deterioration of the β-cells (Yki-Jarvinen 1992)

- **Long term**
  - PPG spikes are an independent risk factor for cardiovascular disease

Reduces glomerular filtration rate and renal plasma flow

Reduces retinal blood flow

Reduces motor and sensory nerve conduction velocity
POSTPRANDIAL HYPERGLYCEMIA AND MACROVASCULAR DAMAGE
PROPOSED PATHOPHYSIOLOGIC MECHANISMS

- Increased intracellular formation of advanced glycation end products (AGE)
- Impairs endothelial NO-mediated function
- Induces pro-coagulative state
- Increases adhesion proteins
- Induces oxidative stress

Oxidative Stress: Why is it Important?

Free radicals (reactive oxygen species) are known to fuel diabetic vascular complications.
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Free radicals (reactive oxygen species) are known to fuel diabetic vascular complications.

How Does One Measure oxidative stress?

- Urinary isoprostanes: best marker of oxidative stress in total body
- “HbA1c of oxidative stress”
Correlation between 24 hour urinary excretion rates of 8-iso Prostaglandin F2α (isoprostanes) and Mean Amplitude of Glycemic Excursions (MAGE)

Monnier L et al, JAMA, 2006, 295, 1681 - 1687

R=0.86, p<0.001
## STRONG LINK BETWEEN PPBG AND CV EVENTS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Key Findings</th>
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<tbody>
<tr>
<td><strong>Macrovascular Complications</strong></td>
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<td><strong>DECODE study</strong></td>
<td>15,388 men; 7126 women from 10 prospective studies; not previously diagnosed with diabetes</td>
<td>2-h blood glucose levels following 75-g OGTT better predictor of all cause and cardiovascular deaths than FBG</td>
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<td><strong>Chicago Heart Association</strong></td>
<td>12,220 men with diabetes or asymptomatic hyperglycemia</td>
<td>Increased risk of CVD mortality with higher post load (50-g OGTT)</td>
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<td><strong>Temelkova-Kurktschiev et al.</strong></td>
<td>582 men and women at risk for type 2 diabetes</td>
<td>2-h blood glucose levels and spikes more strongly associated with carotid IMT than FPG or HbA1c</td>
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<td><strong>Diabetes Intervention Study</strong></td>
<td>1139 men and women with newly diagnosed type 2 diabetes</td>
<td>PPHG, but not FPG, significant risk factor for MI and mortality</td>
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<td><strong>Campanian Postprandial Hyperglycemia Study</strong></td>
<td>93 men and 82 women with type 2 diabetes; not previously drug-treated</td>
<td>Reduction of PPHG, but not FPG, associated with reductions in carotid IMT</td>
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</tbody>
</table>

*Hurel SJ and Mohan V, J. Assoc. Physicians India, 2006,54,871 - 876*
DECODE Study: Relative Risk of Mortality Increased with Increasing 2-Hr Glucose Level

DIABETES INTERVENTION STUDY: POSTPRANDIAL, NOT FASTING GLUCOSE, ASSOCIATED WITH INCREASED ALL-CAUSE MORTALITY

Mortality rate per 1,000

Fasting Glucose

- <140 mg/dl: P=NS
- >140 mg/dl

Postprandial Glucose

- <180 mg/dl
- >180 mg/dl: P<0.05

RISK FOR CAD IN INDIANS

Chennai Urban Population Study (CUPS)

Mohan V et al, J Am Coll Cardiol. 2001; 38; 682-687
Relative odds ratio for CAD by quartiles of 2 hour post plasma glucose

2 hr Post prandial blood sugar (mg/dl)

Reference

<=74

75 - 94

95 - 121

>=123

p < 0.001

p < 0.0001

Pharmacotherapeutic strategies to lower PPG

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Class</th>
<th>Examples</th>
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<tr>
<td>Augment insulin concentration</td>
<td>Benzoic acid derivatives</td>
<td>Repaglinide</td>
</tr>
<tr>
<td></td>
<td>Amino acid derivatives</td>
<td>Nateglinide</td>
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<td>Reduce intestinal breakdown of complex carbohydrates</td>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose</td>
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<td></td>
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<td>Miglitol</td>
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<td></td>
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<td>Voglibose</td>
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<tr>
<td>Decrease gastric emptying rates; reduce postprandial glucagon secretion; promote glycogen storage</td>
<td>Amylin analogs</td>
<td>Pramlintide</td>
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<tr>
<td>Enhance glucose-dependent insulin secretion; increase glucose disposal, lipogenesis, and glycogen synthesis; decrease gastric motility and delay gastric emptying</td>
<td>GLP-1 analogs</td>
<td>Exenatide</td>
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<tr>
<td>Insulin-like actions</td>
<td>Rapid-acting insulin analogs</td>
<td>Insulin lispro</td>
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In DM, PP state is characterized by rapid & large increase in blood sugar levels.

Post prandial hyperglycemic peaks are linked to cardiovascular complications.

Correcting PP hyperglycemia may form part of the strategy for the prevention & management of cardiovascular disease in DM.

New and emerging medications specifically target PPHG in patients experiencing postprandial glycemic excursions.

The combination of improved detection and monitoring of PPHG and effective medications to address it may help establish optimal glycemic control and reduce the risk of microvascular and macrovascular complications of diabetes.