Point: Postrandial Glucose Levels ARE a Clinically Important Treatment Target

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Introduction

- NAVIGATOR Trial (NEJM 2010; 362: 1477-90)
  - Looked at Nateglinide and Valsartan in patients with impaired glucose tolerance.
  - Nateglinide lowers postprandial hyperglycemia by increasing the first phase of insulin secretion.
  - Conclusions of study:
    - There was not a significant decrease in new cases of diabetes nor new cardiovascular events with use of nateglinide.
    - Valsartan reduced onset of DM (but no change in CV events).
Introduction

- Postprandial hyperglycemia has been linked to increased risk of CVD, so its treatment (in this case with nateglinide) was expected to decrease CV events.
- The negative result of the NAVIGATOR trial suggested that postprandial hyperglycemia treatment may not improve CV risk in diabetes.
**Background**

- Evidence suggests that type 2 DM occurs from both:
  - 1.) impaired pancreatic beta-cell glucose sensitivity and whole body insulin sensitivity
  - 2.) defects in acute insulin secretion

**First phase insulin secretion (FPIS)**
- FPIS is impaired early on in the progression from normal glucose tolerance to diabetes.
- It first becomes impaired or sluggish until eventually it is lost in diabetes.
- The end result is *postprandial hyperglycemia.*
Background

- Importance of postprandial hyperglycemia:
  - Hemoglobin A1C
    - Postprandial glucose affects overall glycemic control.
    - HgA1C is affected by postprandial glucose especially in tight glycemic control (HgA1C <7.5%).
    - To achieve tight control, postprandial glucose ultimately needs to be under control.
Background

- Cardiovascular Disease
  - Many studies have supported a linear relationship between postprandial hyperglycemia and risk of CVD death.
  - However, these studies mainly looked at postprandial glucose following oral glucose tolerance test.
    - This finding was questioned because the OGTT is not an a meal and it was felt that actual food would not show the same relationship.
  - Another study did show correlation between 2 hour postprandial levels after OGTT as well as after a meal².
Postprandial hyperglycemia and CVD

- Is there evidence that treating postprandial hyperglycemia reduces risk of CVD?
  - The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) showed that new CV events (secondary endpoint) may be reduced by treating postprandial hyperglycemia in impaired glucose tolerance patients.\(^3\)
  - This was confirmed in diabetic patients in a meta-analysis with acarbose.\(^4\)
  - The HEART2D\(^5\) trial and NAVIGATOR study failed to confirm this.
Postprandial hyperglycemia and CVD

- Limitations of the NAVIGATOR Trial:
  - It only showed that nateglinide does not reduce cardiovascular events.
  - The nateglinide group did not have improved postprandial hyperglycemia.
  - The nateglinide group had higher postprandial glucose levels 2 hours after OGTT compared to placebo.
  - The incidence of new DM was higher in nateglinide group than placebo.
Limitations of Navigator Trial:

- Multiple studies (ACCORD, ADVANCE, VADT, UKPDS) have shown that control of overall hyperglycemia if started too late in CVD loses its beneficial effect.
- The NAVIGATOR subjects in the primary prevention who had hx of CV event were pooled together which could have affected the end results.
- Also, there was a very high drop out rate.
The effect of postprandial hyperglycemia on CVD is still unclear.

- The Acarbose Cardiovascular Evaluation (ACE) is a large trial that may give more information.

Postprandial hyperglycemia is becoming part of the treatment targets and is the most important contributor to A1C, especially if lower than 7.5%.

- One study showed that further reducing strict glycemic control (HgA1C 6.5 to 6.1%) in diabetes reduced carotid intima-media thickness in diabetes.7
Conclusions

- Oxidative stress has been thought to be the cause of diabetic complications with hyperglycemia\(^6\).
  - Postprandial hyperglycemia likely produces oxidative stress resulting in endothelial damage.
  - Irbesartan reduces oxidative stress and valsartan may have worked in the NAVIGATOR study for this reason.
  - There is significant evidence that widely fluctuating glucose is associated with worsening prognosis and diabetic complications.
Conclusions

- In nondiabetics, glucose is very closely maintained within a small range suggesting also that postprandial hyperglycemia needs to be controlled.
- Therefore, the NAVIGATOR study did not help clarify the issue and only suggests that nateglinide did not reduce risk of cardiovascular disease in this study.
References