Mini Review

Post-prandial hyperglycemia

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ABSTRACT

Isolated post prandial hyperglycaemia (PPHG) has been shown to double the risk for cardiovascular mortality. It also makes a significant contribution to overall glycaemia reflected in the HbA1c level. The harmful effects of PPHG are increased cardiovascular mortality, association with mic rovascular complications, cognitive decline and cancers. A variety of both pharmacologic and non-pharmacologic trherapies are available to target PPHG.

Key words: Post-prandial hyperglycemia, cardiovascular mortality, HbA1c

Introduction

Isolated post-prandial hyperglycemia (PPHG), as occurs in impaired glucose tolerance (IGT), has been shown to double the risk for cardiovascular (CV) mortality. PPHG also appears to be the rate limiting factor for achieving optimal glycemic control in T2DM.

Prandial regulation of glucose is a complex process. The magnitude and time of the peak plasma glucose (PG) depends on a variety of factors, including the timing, quantity and composition of the meal. In non-diabetic individuals , PG peaks about 60 minutes after the start of a meal, rarely exceeds 140 mg/dl, and returns to pre-prandial levels within 2 – 3 hours.[1,2] Grilinger *et al.* observed that in diabetics with HbA1c<7% , 80% had PPPG>200 mg/dl and 17% had FPG>126 mg/dl, whereas in individuals with HbA1c>8%, the corresponding figures were 100% (PP) and 99% (Fasting).[3] Monnier *et al.* found that the relative contribution of PPPG was higher (70%) in patients with fairly good control of diabetes (HbA1c <7.3%) and decreased progressively (30%) with worsening diabetes (HbA1c>10.2%).[4]

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Decreases in PPG accounted for nearly twice the decrease in HbA1c compared with decreases in FPG.[1]

There are different targets for PPPG control: <180 mg/dl (ADA); <140 mg/dl (AACE); IDF target is 145 mg/dl (plasma) and 160 mg/dl (capillary). SMBG is currently the optimal method for assessing PG levels. Plasma 1,5 – anhydro – glucitol (1,5 – AG) best reflects 2 h PPG of the previous 2 weeks.[1]

The harmful effects of PPPG are related to ROS and mediated by PKC, AGE, Polyol and Hexoseamine pathway.[1]

Harmful effects of PPHG:

a. **PPHG and CV Mortality:** Studies by Levitan *et al.* have shown that PPPG appears to have a linear relation with CVD, even across the non - diabetic range.[1,5] In DECODA, 2 h PPG was superior to FPG in predicting premature CVD mortality. In a recently published meta-analysis, the pooled relative risk for CVD was 1.18, representing a 1% increase in HbA1c in persons with T2DM [Figure 1 and 2]. Controlling PPHG has been demonstrated to improve myocardial flow and function.[1]
b. **PPHG and oxidative stress, inflammation, and endothelial dysfunction:** Treating post-prandial hyperglycemia can improve oxidative

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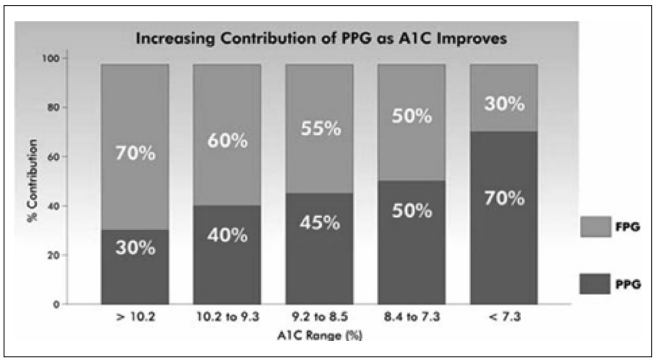

Figure 1: Contribution of PPHG to HbA1c

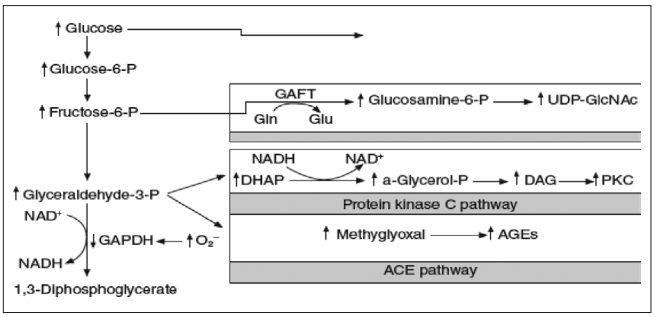

Figure 2: Mechanisms of PPHG-induced harmful effects

stress, inflammation, endothelial dysfunction, and thrombosis.[1,6]

c. **PPHG and CIMT**: Carotid intima – media thickness (CIMT) was significantly increased in the top quintile of 2 h PPPG (148 – 200 mg/dl).[1,7]
d. **PPHG and micro-vascular complications:** PPHG had a stronger correlation with the incidence of diabetic microangiopathy compared with HbA1c levels.[1,8]
e. **PPHG and cognitive function:** Exaggerated PPG excursions are associated with a derangement of both global, executive and attention functioning.[1,9]
f. **PPHG and cancer:** PPHG and factors known to promote post-meal hyperglycemia are implicated in the development of cancer.[1,10]

PPHG – Management Strategies

A variety of both non – pharmacologic and pharmacologic therapies should be considered to target PPG. Diets with a low glycemic load are beneficial in improving post-meal glycemia. Therapies which are available for PPHG include AGI, Glinides, short-acting SU (Glipizide), and rapidly acting human insulins/ insulin analogues and biphasic (pre-mixed) insulins/insulin analogues, DPP4 Inhibitors, and GLP -1 derivatives.[1]

One of the earlier studies to show that targeting PPHG has the potential to improve clinical outcome was done by de Veciana *et al.* who found that pregnant women with GDM requiring insulin therapy did better when PPPG rather than FPG was used to guide management. Ceriello *et al.* reported that insulin aspart reduced PP oxidative stress more effectively than regular insulin in patients with T2DM.

Beisswenger *et al.* found a highly significant correlation between PPPG, excursions and AGE in T1DM subjects.[2]

In a small study, once – daily glipizide GITS, twice-daily immediate-release glipizide, or thrice-daily nateglinide resulted in equivalent control of PPPG in type 2 DM.[2]

In a seminal study organized by the Campanian Post-prandial Hyperglycemia Study Group, the reduction in CIMT was associated with changes in PPHG but not fasting hyperglycemia, and those who had the greatest reduction in PPHG had the greatest CIMT regression. In this study, repaglinide was more effective in blunting the PPG peak and showed greater CIMT regression and greater reduction in IL – 6 and CRP compared with glyburide.[2]

The STOP – NIDDM trial, in patients with IGT, found a 49% RR reduction for any CV event in patients treated with acarbose over a mean follow – up of 3.3 years. There was significant reduction in progression of CIMT. In a meta-analysis, there was a significant 35% RR reduction for any CV event and 64% RR reduction for myocardial infarction with acarbose.[2]

There may be enhancement of post-prandial glucose control and some diminution of fasting glucose control with shorter – acting GLP – 1 receptor agonist (exenatide BID) compared to longer-acting agonist (exenatide once – weekly, Liraglutide).[11] 2 h PPPG decreased by a mean 76 mg/dl when patients switched from Sitagliptin to Exenatide (and increased by 73 mg/dl when the reverse switch was made).[12] Post-prandial glucose after supper and breakfast were significantly lower in T2DM taking Vildagliptin (100 mg/day) than those taking Sitagliptin (100 mg/day) who had lower glucose level after dinner. Sitagliptin has been reported to effectively reduce PPG fluctuations and block the AGE – RAGE axis. Rizzo *et al.* reported that reductions in oxidative stress and markers of inflammation were greater in T2DM patients taking Vildagliptin than those taking Sitagliptin.[13]

There is currently a lack of direct randomized clinical trial evidence that correcting post-meal hyperglycemia improves clinical outcomes. The HEART 2D study, assigned T2DM patients to prandial (lispro) and basal (NPH or glargine) strategy, did not show a beneficial effect of preferentially

treating PPHG in reducing further CV events in people with diabetes who had an acute MI. A recent post-hoc analysis, however, suggested that older patients may have a lower risk for a subsequent CV event.[1]

PPHG makes a significant contribution to overall glycemia reflected in the HbA1c level, and blood glucose lowering therapy should preferentially choose an agent, which specifically lowers PPG. Similarly, dietary interventions which lower PPHG should be emphasized.

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