

## Post Prandial Hyperglycemia: How Important Is Control of Post Prandial Hyperglycemia in Diabetes

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### Abstract

Post prandial hyperglycemia is the most neglected component of the glycemic parameters and seldom ordered to diagnose and treat patients with diabetes mellitus (DM). The reason is profound gaps of knowledge about the applicability of 1 hour or 2 hour post prandial glucose (1hPPG or 2hPPG) among the professionals. Four (4) hour glucose tolerance test is the ideal test to diagnose DM. However, it is a cumbersome test thus it is replaced by 2hPPG test. Fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) are the most publicized test and most commonly ordered to diagnosis and treat DM, but the sensitivity of these tests are low. Thus many people are labeled with type 2 DM using these test when they do not have DM. More important than the diagnosis is the relationship of 2hPPG to outcome measures. Most clinical trials used FBG and HbA1c for outcome measures. The preferred therapy is metformin which predictably lowers HbA1c. No clinical trials were ever done to determine if metformin lowers 2 HPPG. Author's studies which involve renal outcome have shown promising results with insulin therapy. Insulin predictably lowers 2hPPG. Thus it is important that we develop studies comparing insulin with oral antidiabetic agents in controlling post prandial hyperglycemia and determining its impact on outcome measures.

**Keywords:** Post prandial hyperglycemia; Diabetes; Retinopathy; postprandial glucose

### Introduction

Postprandial means after a meal; therefore, postprandial glucose (PPG) concentrations refer to plasma glucose concentration after a major meal. PPG is invalid after consuming tea and toast. In the western culture, breakfast is often a major meal whereas in eastern culture lunch is a major meal. The optimal time for measurement of PPG is 2 hours after a meal, generally approximating the peak value in patients with diabetes and providing a reasonable assessment of postprandial hyperglycemia. Specific conditions such as gestational diabetes may benefit by testing at 1 hour after the meal [1]. Author always orders fasting and 2 h postprandial basic metabolic panel (BMP) for every patient. BMP is a composite laboratory test that provides glucose levels, renal function tests with BUN, serum creatinine and the estimated glomerular filtration rate (eGFR), and electrolytes including sodium, potassium, chloride,  $\text{Co}_2$  and calcium.

It is not yet established the relationship of 2hPPG to diagnosis of DM. The criteria used to determine DM was recommended by National Diabetes Data Group [2] in 1979 and by the World Health Organizations (WHO) in 1980 [3]. They are based on the longitudinal studies conducted in the USA and UK on people with variable degrees of glucose intolerance. These people were followed prospectively for diabetic complications, primarily retinopathy as the end point. It was noted that whose 2hPPG was  $\geq 200$  mg/dl ( $\geq 11.1$  mmol/l), even when FBG was unequivocally normal were at the highest risk of developing diabetic complications. Thus the criteria of glucose levels are important. They are essential to determine the risk of developing complications specific to DM. In addition, virtually everyone with FBG of  $\geq 140$  mg/dL ( $\geq 7.8$  mmol/L) also has a 2 hPPG of  $\geq 200$  mg/dL. Thus the FBG is not needed to ascertain the diagnosis of DM. Finally 2 hPPG is the key for detecting DM [4]. This article is divided into several sections for complete understanding.

## Section A

### Importance of Post Prandial Hyperglycemia in Detection of undiagnosed Diabetes

The 2hPPG is the most satisfactory screening method. Using a value of  $\geq 200$ mg/dL sensitivity is 97%; only 3% of individuals have  $\leq 200$  mg/dL and considered to have DM, attributable to fasting values of  $\geq 140$  mg/dL only. Specificity is 100% because all non-diabetic individuals have 2 PPG  $< 200$ mg/dL. The positive predictive value is also 100 % because everyone with 2h PPG  $> 200$  mg/dL is considered to have diabetes. If a fasting glucose of  $\geq 100$  mg/dL (5.5 mmol/L) was used as a cut off value for screening, sensitivity would be 83% and specificity would be 76%, but positive predictive value would be 21% that is 4 of 5 individuals would not have diabetes.

Sensitivity is a measure of the false-negative rate (i.e., the number of negative results among people who have the disease), whereas specificity is a measure of false-positive rate (i.e. number of positive results among people who do not have the disease). The positive predictive value of a screening test depends primarily on the prevalence of disease in the population being screened higher the prevalence, the higher the positive predictive value [5].

## Section B

### Controversies in understanding post prandial hyperglycemia and relationship of post prandial hyperglycemia to complications

Profound gaps in knowledge exist among the professionals in understanding the validity of 2hPPG, in particular, defining the relationship of 2hPPG to development and progression of diabetic complications. The reason is simple, few or no professionals order 2hPPG or 2hBMP, thus no data has accumulated. A consistent body of data demonstrates a robust association between 2hPPG and cardiovascular risk. Large epidemiological studies have shown a continuous graded direct relation between the level of post challenge glycaemia and risk of events including coronary heart disease, stroke, sudden cardiac death and peripheral vascular disease [6]. The worst problem with the previous studies is that no information is available about how were these patients treated and whether did treatment help patients.

## Section C

### A Dilemma in the diagnosis of diabetes

The antihypertensive drugs including thiazide diuretics, beta blockers (BB), calcium channel blocker (CCB), renin- angiotensin inhibitors such as angiotensin converting enzyme inhibitors (ACE-I), or angiotensin receptor blocker (ARB) or vasodilator drugs all produce varying degrees of elevated glucose levels above the normal laboratory range (70 - 99 mg/dL). The elevation of blood glucose or hyperglycemia is much more common with thiazide diuretics such as hydrochlorothiazide (HCTZ) or chlorthalidone than with other antihypertensive drugs. Since hypertension is very prevalent, hyperglycemia associated with antihypertensive therapy is equally prevalent. Consequently, many hypertensive patients are labeled with Type 2 DM and treated with oral antidiabetic agents. Hypertensive patients treated with diuretic constitute a huge population with many of them showing hyperglycemia thus contributing to the assumption that diabetes is epidemic. Diabetes is not epidemic; it is a pretension. Therefore, the endpoints associated with hypertension are difficult to distinguish from those associated with diabetes. In this regard, it is important to know that many patients with diuretic induced hyperglycemia do not have overt diabetes. Here is an example of fortuitous epidemic of diabetes. 64y African American male was referred to the author for uncontrolled hypertension and hypokalemia. His home medication consisted of diltiazem 360 mg daily, amlodipine 10mg daily, triamterene/HCTZ 37.5/25 mg daily and potassium chloride 20 mEq TID. His serial laboratory studies are shown in table 1.

1. No evidence of diabetes mellitus
2. Hyperglycemia induced by HCTZ
- \*3. 2hPP lower than normal ( $\geq 140$ mg/dl) is due to high insulin response. Serum insulin (2hPP) 62.71u/L (n = 0 - 24.9)

Date	2009	2010	2011
Oct 26	Random 186 (10.3) Triam/HCTZ Discontinued		
Nov 17	Fasting 113 (6.2) 2hPP 153 (8.5) HbA1c 6.1%		
Dec 30	Random 147 (8.1) HbA1c 5.9%		
July 1		Fasting 104(5.7) 2hPP 09 (6) *	
Sept 15			2hPP 119 (6.6)*

**Table 1:** Glucose mg/d (mmol/L).

**Potential for overt diabetes**

Prevention: Low carbohydrate diet

Notably all antihypertensive drugs including thiazide diuretics, BB, CCB, ACE1 or ARB produce hyperglycemia. Among them thiazide diuretic is the worst, often mimicking overt DM [7].

The decode analysis of data from 25, 364 individuals reported that hazard ratios for death in individuals not previously known as diabetic, and with normal FBG, increased as 2hPPG increased. Over 7 years the presence of impaired glucose tolerance doubled the risk of CVD and death but fasting hyperglycemia had no effect on cardio vascular mortality [8].

**Section D**

**Pathophysiology of Postprandial Hyperglycemia**

Different mechanisms have been described at the molecular level which are interesting to read but are complex and multifactorial. Therefore, their applications in day to day diabetes care are far from practical. Thus from the standpoint of direct diabetes care, it is important to understand that chronic elevation of FBG or 2 h PPG can cause one or more of the following complications.

**These underlying complications are not in particular order**

1. Retinopathy leading to impaired vision
2. Nephropathy leading to progressive renal failure
3. Neuropathy leading to urinary retention, foot ulcer and sexual dysfunction
4. Vasculopathy leading to gangrene and amputation of digits or extremities, sexual dysfunction
5. Coronary heart disease leading to myocardial infarction
6. Neurogenic bladder leading to recurrent urinary tract infection
7. Gastroparesis and paralytic ileus leading to recurrent vomiting, loss of nutrition and cachexia.

When patients present to a doctor’s office with one complication, such as foot ulcers or gangrene, they usually have one or more additional complications.

These complications are due to microvascular and macrovascular lesion caused by undiagnosed or untreated persistent hyperglycemia. An important question is about glucose threshold above which complications are likely to develop. An even more important question is why glucose molecules in the normal range (70-99 mg/dL) do not produce any complications but do so when the glucose concentration

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increases to  $\geq 200$  mg/dL. Therefore, a big question is being glucose molecules the same or different in someone who is not diabetic versus who is diabetic?

Our laboratory research provides some insightful information about the mechanism of vascular injury caused by uncontrolled hyperglycemia. Research involving cell culture studies attest to the fact that elevated glucose levels in and of itself contribute to complications. In our laboratories vascular endothelial cells were cultured, then treated with normal concentration of glucose (90mg/dL or 5 mmol/L) or high concentration of glucose (540mg/dL or 30mmol/L) for a period of 2,6 or 10days. Additional cultured cells were treated with glucose of the same concentration as above plus insulin or insulin and heparin. In diabetes, endothelial cells and mesangial cells cannot reduce transport of glucose inside the cells when exposed to high glucose levels in the blood. In essence, a defect in membrane transport of endothelial cells permits excessive amount of glucose to enter inside the cells when glucose levels are high.

Therefore, complications that develops in diabetes likely concerns mechanisms involving excessive amount of glucose inside the endothelial cells rather than outside. We have demonstrated crystalline structures that are presumably glucose in severely damaged cells as published previously [9].

Many hypotheses have been proposed to explain high glucose- induced cellular damage that persists and perpetuates damage to various organs. However, there is no uniformity of the pathways. The author has proposed a unified theory, which is ischemia which may explain damage to all organs. Reduced blood flow in an indolent fashion causes atrophy. This is evident in heart as myocardial fibrosis and cardiomyopathy or atrophic tubules and interstitial fibrosis in the kidneys. Progressive Kidney failure in diabetes is more due to the loss of tubules and interstitial fibrosis rather than glomerular sclerosis. Inability to achieve penile erection is mainly due to lack of blood flow through penile microvasculature. Reduced blood flow can be associated with increased vascular permeability resulting in exudation of plasma proteins in the free surface outside of the vessels. This is best seen as hemorrhage and exudates in the retina and as proteinuria. Sustained reduction of hyperglycemia with insulin results in mitigation of endothelial damage and repair and consequently partial or complete recovery of organ function. Other authors have considered that diabetes-specific microvascular disease in the eyes, kidney glomeruli, and vasa nervorum (small vessel surrounding nerves in feet and penis) have similar pathophysiologic features [10]. Still other authors have determined that excessive filtration pressure caused by high glucose in the glomerular capillaries causes' glomerular sclerosis and kidney failure and by reducing glomerular filtration pressure by renin-angiotensin inhibitor drugs will reduce the risk of glomerular sclerosis and kidney failure [11]. The greatest pitfall of this theory is why will high glucose levels cause damage to the kidneys in a manner that is entirely different from its adverse effect to other organs such as heart, eyes or feet.

Thus our cell culture studies contend that unabated hyperglycemia with 2 h PPG  $\geq 200$  mg/dL ( $\geq 11.1$  mmol/L) causes necrosis of endothelial cells. These necrotic cells slough off into capillary lumen forming micro thrombi along with cholesterol and platelet deposits and resulting in occlusion of capillaries with slight or no blood flow to organs.

Author and colleagues have also considered that toxic oxygen radicals may be involved in ischemic injury to the organs. Glutathione is an important enzyme for oxidative stress. Therefore, by inhibiting glutathione oxidative injury may increase. We treated vascular endothelial cells with a potent glutathione inhibitor, buthionine sulfoximine for two and six days. After six days of treatment, endothelial cells had undergone severe necrosis. Thus this experiment suggests that deficiency of glutathione may be an important mechanism of microvascular complications [9]. Our cells culture studies have helped us to determine the mechanism of protection against high glucose- induced cellular damage. We treated cultured cells with insulin and heparin in the presence of high glucose and observed complete morphological protection. We have postulated that insulin reduces oxidative stress [12].

There is one mechanism by which heparin may synergize insulin. We have found that high glucose as well as insulin increase endothelin-1 production in cultures endothelial cells. Endothelin-1 is a potent vasoconstrictor and can aggravate ischemic injury to the endothelial cells. Heparin is an inhibitor of endothelin-1. Thus by inhibiting endothelin-production heparin may synergize insulin effect in protection against high glucose- induced cellular injury [13].

**Section E**

**Control of Hyperglycemia**

Since hyperglycemia is the culprit of diabetic complications, control of hyperglycemia is the logical answer for prevention of its complications. High glucose levels can be lowered by oral antidiabetic agents, insulin, a combination of both or dialysis against a glucose- free bath. The later was never put in practice.

No systemic studies were done to unequivocally show that lowering of blood glucose levels by oral antidiabetic agents, such as glyburide, metformin or sitagliptin will prevent diabetic complications. Occasional studies showed that use of metformin alone, or metformin in combination with insulin in Type 2 diabetes reduced the risk of myocardial infarction [14]. The most important caveat of the patients described to have Type 2 DM probably does not have diabetes but have drug- induced hyperglycemia [15]. In DM, where 2-hPPG is above 200 mg/dL (>11.1 mmol/L), oral antidiabetic agents can be used in addition to insulin to achieve better glucose control than either alone. However, the primary outcome such as microvascular complications, is not affected, despite better glucose control. For example, in 390 patients treated with insulin in the outpatient’s clinic of three hospitals for a period of 4.3 years received metformin (850mg) or placebo. The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality-, as separate aggregate scores. Metformin treatment prevented weight gain, improved glycemic control, and reduced insulin requirement but didn’t improve the primary end points [16]. In the authors cell culture studies where cells were treated with glucose and insulin, the glucose measurement in culture medium showed slight or no change in glucose concentration, although morphologically cultured cells appeared healthier than cultured cells treated with glucose alone. This finding suggests that insulin has a protective effect which may be independent of simply lowering of glucose. Thus combining clinical studies with the adjunct of cell culture studies, it is prudent to state that insulin is the cornerstone of therapy for endothelial cell integrity and hence mitigation of clinical complications.

**Section F**

**Renal Protection in Diabetes**

Our study has focused on renal protection in diabetes. Our hypothesis is that glycemic control with intensive insulin therapy is fundamental to renal protection in diabetes. Lowering of blood glucose levels to near normal levels in diabetes is a reality. However, trying to lower blood glucose levels with intensive insulin therapy is associated with a high risk of hypoglycemia. The goal of adequate glycemic control is to keep 2 h PPG at an optimal level which will not produce hypoglycemia. Hypoglycemia is a fearful experience which will distract patients to adhere to insulin injections. There is no yardstick available in the literature to determine optimal glycemic levels which will confer renal protection. However, it is evident that 2 h PPG > 200 mg/dL (>11.1mmol/L) is associated with discernible decrease in Kidney function. Here is an evidence to that effect. A 78-year Canadian male came to author’s office as a self- referral for diabetes control. He was initially treated with oral antidiabetic agents and Lisinopril which were gradually discontinued and started on insulin therapy. At the time of office visit he was receiving Glargine insulin (Lantus ®) 15 units subcutaneously after breakfast and 15 units after dinner. Here is a laboratory study on June 13, 2012.

Date	Glucose (mg/dL)		Scr (mg/dL)		eGFR (ml/min)	
	F	2hPP	F	2hPP	F	2hPP
June 13, 2012	114	235	1.18	1.28	>60	58

**Table 2:** Laboratory study on June 13, 2012.

Delta (d) glucose (2hPPG-FBG) was 121 mg/dL. His 24 h urine protein was < 111mg. Thus it is evident from a solitary example that 2h PPG above 200 mg/dL is associated with detectable increase of serum creatinine and corresponding decrease of eGFR. In order to validate this observation, data of FBG and 2hPPG and corresponding Scr and eGFR from 56 adults (29F, 27M) with diabetes were analyzed. Ages ranged from 19 to 91 years with a mean of age 68.7 ± 13.5 years. Diagnosis of diabetes was confirmed by 2h PPG ≥ 200 mg/dL. Before

diagnosis of diabetes was established, it was affirmed that no patients were taking thiazide diuretics, which causes or aggravates hyperglycemia mimicking diabetes. All patients were treated with a combination of long acting insulin Glargine insulin (Lantus®) after breakfast and dinner and short acting insulin on a sliding scale. Hypertension was treated with one or more of antihypertensive drug groups. These are beta blockers namely atenolol or metoprolol, second generation dihydropyridine calcium channel blockers, namely amlodipine or isradipine, sympathetic inhibitor, diuretic namely hydrochlorothiazide (HCTZ) or chlorthalidone in resistant cases. The most common combination used was atenolol and amlodipine. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers were excluded.  $\Delta$  levels (2hPP-F) for glucose, Scr and eGFR were calculated for each patient. Person correlation coefficients were calculated to determine if the changes in renal function ( $\Delta$  Scr and  $\Delta$  eGFR) were related to changes in glucose levels between F and 2hPP time points ( $\Delta$  glucose). For every 100mg/dl increase in  $\Delta$  glucose, the  $\Delta$  Scr increases by 0.08mg/dL and  $\Delta$  eGFR decreases by 2.73 ml/min. We have enhanced the predictive value of 2 hPPG by  $\Delta$  glucose (2hG-FBG). Our study further stresses that 2 hPPG  $\geq$  200mg/dL or  $\Delta$  glucose > 100 mg/dL is a determinant of renal function deterioration. In our initial observation, we have documented that in patients whose 2 h PPG is greater than 200 mg/dL, for every 100 mg/dL increase in  $\Delta$  glucose,  $\Delta$  Scr increases by 0.11 mg/dL and  $\Delta$  eGFR decreases by 3.73ml/min, while in patients whose 2h PPG < 200 mg/dL, for every 100 mg/dL increase in  $\Delta$  glucose little change is seen in  $\Delta$  Scr (+0.4mg/dL) or  $\Delta$  eGFR (-0.54ml/min) [17,18].

Since we have observed that renal function change is insignificant by keeping 2 PPG <200mg/dL with intensive insulin therapy, we have begun to study the long term effect of intensive glucose control on progression of renal function change. We have asked an important question: Can progression of chronic kidney disease be prevented by sustained glycemic control with intensive insulin treatment. Our recent study extending over 2 years showed that  $\Delta$  glucose (2h PPG-FBG)  $\geq$  50 mg/dL is associated with significant increase in serum creatinine. Therefore, the goal of renal protection will be to keep  $\Delta$  glucose under 50 mg/dL which can be accomplished by keeping 2hPPG <200mg/dL with intensive insulin therapy. Avoiding the use of ACE1/ARB drug is additive to renal protection (unpublished).

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