In treating diabetes, what is important? Glucose levels or outcome measures?

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Abstract

Gaps in knowledge prevail in recognizing which glycemic parameters to order and in determining glycemic control. However glycosylated hemoglobin (HbA1c) is most commonly ordered to determine glycemic control. HbA1c provides information of overtime glycemic control but does not inform post meal glycemic excusions. The latter may be significant in outcome measure such as cardiovascular disorder (CVD), renal failure or amputation in diabetes. In order to obviate the dilemma in the importance between fasting blood glucose (FBG) and 2-h post prandial glucose (2hPPG), we innovated delta (d) which is the difference between 2hPPG minus FBG. There is much information available relating 2hPPG or postprandial hyperglycemia to CVD and some information relating 2hPPG to renal failure or amputation. Thus much emphasis is laid upon glycemic control with little or no emphasis on the complications of diabetes or the outcome measures. The focus of this editorial is to draw attention to outcome measures by ordering fasting and 2-h postprandial (2hPP) basic metabolic panel (BMP) which provides glucose levels, renal function test and electrolytes. HbA1c significantly relates to 2hPPG, thus by ordering F and 2hPP BMP instead of HbA1c alone will serve both purposes: Glycemic control and outcome measure. Delta (d) glucose (dhPPG-FBG) is a stronger predictor than 2hPPG of renal function deterioration.

Key words: Diabetes; Outcome measures; Amputation; Renal failure; Glycosylated hemoglobin; Postprandial hyperglycemia; 2-h postprandial glucose

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Core tip: Postprandial glucose level (2-h after major meal: Breakfast or lunch) is the cornerstone of laboratory test for diabetes to monitor glycemic control and prognosticate development or progression of diabetic
Mandal AK. In treating diabetes, what is important? Glucose levels or outcome measures? World J Diabetes 2015; 6(13): 1243-1245 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i13/1243.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i13.1243

INTRODUCTION

Lowering of blood glucose levels to normal or near normal levels in diabetes mellitus is a legitimate consideration. But why and which glycemic parameters are to follow in therapeutic strategy. There are three glycemic parameters to consider: Glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG) and 2-h postprandial blood glucose (2hPPG). The latter is obtained after a major meal or by oral glucose tolerance test. There are valid reports in the literature to suggest that lowering of blood glucose to normal levels with intensive insulin therapy will prevent microvascular complications[1,2]. The pitfalls of previously published reports are that no information is provided which glycemic parameters were used to determine outcome. However FBG and HbA1c were most commonly used in outcome studies. There is no indication that 2hPPG was used to monitor prevention or progression of microvascular complications. Author orders FBG and 2hPPG in all patients with diabetes prior to their office visits. HbA1c is ordered quarterly which is permitted by health insurance. 2hPPG is the pivotal glycemic marker for author’s studies. We initially observed that elevation of blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) or even ≥ 50 mg/dL above FBG at 2-h postprandial (2hPP) period is associated with a discerning increase of serum creatinine (Scr) and a proportionate decrease of estimated glomerular filtration rate (eGFR) when sampled on the same day. The above renal function changes are less noticeable when 2hPPG is less than glucose is a stronger predictor of renal function changes.

Thus with delta (d) glucose of 121 mg/dL, increase of Scr and decrease of eGFR are very noticeable. He was being treated with metformin and Lisinopril. These medication were discontinued and he was placed on Glargine insulin (Lantus®), subcutaneously 15 units after breakfast and 15 units after dinner. He is also hypertensive; hypertension is kept under control with spironolactone and chlorthalidone. His 24 h Urine total protein was less than 111 mg. Close to two years later his blood pressure is 120/60 mmHg and his 2hPPG is decreased to 191 mg/dL (10.8 mmol/L) and renal function improved with decrease of Scr from 1.28 mg/dL to 1.17 mg/dL and increase of eGFR from 58 to 59 mL/ min. In his subsequent office visit, renal function is stable or better.

The greatest pitfall in Advance Trial and many similar trials using oral anti diabetic agents is the renal outcome defined by diabetic nephropathy. This is an unmeaningful way to determine the renal outcome. Nephropathy defined clinically as the presence of microalbuminuria is a common complication of type 2 diabetes. There was no mention whether any renal function tests were done in the assessment of nephropathy in Advance trial or other clinical trials. Thus the serious deficiency in the assessment of significant risk reduction of nephropathy in Advance Trial is the lack of use of renal function test such as Scr or GFR in defining nephropathy[3]. It should also be noted that many subjects with diabetes are also hypertensive; hence proteinuria can result from diabetic or hypertensive nephropathy. Thus, without kidney biopsy, it would be most difficult to determine cause of proteinuria whether due to diabetes or hypertension.

Renal biopsy was seldom done in outcome studies. In our studies, renal function test as already defined is the mirror of glycemic control. Our goal is to determine the staging of diabetes-related chronic kidney disease (CKD) by the available eGFR and treat them with a combination of insulin therapy to determine if progression of CKD into end stage renal disease can be halted.

In Advance trial, intensive glucose control had considerable renoprotective effects compared with standard control, with 21% risk reduction ratio for new or worsening nephropathy. The component of nephropathy that was clearly reduced was macroalbuminuria (risk reduction ratio of 30%); 0 < 0:001).

The purpose of this editorial is to reveal which glycemic parameters are most predictive of renal function changes.

We already reported that delta (d) glucose (2hPPG-FBG) relates significantly to renal function changes. For every 100 mg/dL increase in dglucose, dScr increases by 0.11 mg/dL and d eGFR decreases by 3.73 mL/min. Thus dglucose is a stronger predictor of renal function than 2hPPG[4].

Our current study is an expanded study and for a longer duration. All patients are treated with a combination of Glargine (Lantus®) or detemir insulin twice daily after breakfast and dinner and one of the regular or fast acting insulin before each meal and at bedtime. This is similar to what Frederick G. Banting used for his patients at University of Toronto[5]. We have noted essentially no change in renal function in a period of 26 mo. Although FBG or 2hPPG did not decrease between the two periods, dglucose was significantly reduced from baseline 63.5 ± 68.1 to 36.6 ± 65.6 mg/dL. We have noted that as dglucose increases above 50 mg/dL (2.7 mmol/L), serum creatinine increases in step wise fashion[6].

We have found in our previous study (unpublished) that although glucose levels did not decrease despite insulin therapy, renal function remained unchanged during the two periods of 14.2 mo. This indicates that insulin therapy is important for renal protection which

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may not be entirely dependent on tight glycemic control.

Hypertension control is achieved as always in author's patients by beta blockers, calcium channel blocker either alone or in combination, sympathetic inhibitor and in resistant cases, chlorthalidone. Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is excluded to reduce the risk of acute or chronic renal failure in diabetes[6,7].

We have previously reported that use of ACEI/ARB drug is associated with high risk of recurrent attack of acute renal failure or development of CKD in diabetes[7]. Other authors characterized acute kidney injury as a significant risk factor for CKD independent of other risk factors of progression in diabetes[8].

The pearl of wisdom of this editorial is the first step to establish the diagnosis of diabetes. The most sensitive test to establish the diagnosis is to order a post challenge glucose 2-h after a major meal. Blood glucose greater than 200 mg/dL, establishes the diagnosis of diabetes[9]. In order to monitor outcome measures in particular renal failure, it is important to order fasting and 2hPP basic metabolic panel which will provide glucose and renal function tests. The cornerstone of therapy of established diabetes is insulin therapy. Although evidence is tenuous for prevention of many of the complications of diabetes, author’s studies confirm that insulin therapy is conducive to protection against renal failure and dialysis. Equally important in author’s studies is to exclude use of renin-angiotensin inhibitors drugs to treat diabetes as a complimentary measure of protection for renal failure.

Table 1  A 78-year white male with established diabetes showed the following results in his first office visit

| Glucose (mg/dL) | Scr (mg/dL) | eGFR (mL/min) |
|-----------------|------------|---------------|
| F 2hPP          | F 2hPP     | F 2hPP        |
| 114 (6.3 mmol/L)| 235 (13 mmol/L) | 1.18 | 1.28 | > 60 | 58 |

2hPP: 2-h postprandial; 2hPPG-FBG: 2-h postprandial blood glucose - fasting blood glucose; eGFR: Estimated glomerular filtration rate; Scr: Serum creatinine; F: Fasting.

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P- Reviewer: Beltowski J, Garcia Mayor R, Gomez-Saez J, Hoskote SS
S- Editor: Ji FF L- Editor: A E- Editor: Liu SQ

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