Relationship between Blood Glucose Control, Pathogenesis and Progression of Diabetic Nephropathy

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Abstract. The present review briefly discusses evidence that the risk of a rapid decline of glomerular function abruptly increases when glycated hemoglobin is steadily higher than 7.5% and postprandial blood glucose is >200 mg/dl. The capacity to accomplish and to maintain steadily tightly controlled blood glucose levels is scanty using the currently implemented hypoglycemic drugs. Moreover, it must be highlighted that most patients with type 2 diabetes, particularly when renal damage does occur, have arterial hypertension. Several studies suggested that the development of ESRD is prevented significantly better by drugs that modulate the renin angiotensin system than by other compounds in patients with type 1 and 2 diabetes with overt diabetic nephropathy. However, a recent trial, the study Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which compared lisinopril, chlorthalidone, and amlodipine in a large population of patients with arterial hypertension, either associated or not with diabetes, demonstrated that the development of both coronary heart diseases and renal complications was equally prevented by the three drugs. One word of caveat, however, needs to be raised concerning one of the results of the ALLHAT study: the higher risk of developing new-onset diabetes among hypertensive patients who are not treated with lisinopril. Even if it is true that this latter side effect was not accompanied by a worse outcome of macrovascular and renal complications during the 5-yr follow-up period, one cannot rule out the possibility that this might be the case during more prolonged periods of follow-up in the future. Thus, the advantage of a lower cost in the treatment of hypertension with diuretics as compared with other drugs, with similar degree of success in the prevention of vascular complications, should be weighed also taking into consideration the burden of a higher rate of occurrence of new-onset diabetes.

The relationship between hyperglycemia and cardiac complications and that between hyperglycemia and renal complications are different. In fact, the occurrence rate of coronary artery disease doubles in patients with blood glucose levels >95% mg/dl after an oral glucose tolerance test (1), thus in patients with only impaired glucose tolerance or even with circulating glucose patterns in the upper normal range. Conversely, convincing evidence has been reported that renal damage rarely occurs both in patients with type 1 and 2 diabetes when postprandial blood glucose levels are <200 mg/dl and glycated hemoglobin A1c is <7.5 to 8.0% (2,3). Hyperglycemia is the “conditio sine qua non” antecedent to the occurrence of renal complications in diabetes. Two different points of view have been suggested to describe the relationship between the abnormalities of blood glucose level and the development of renal complications. Data from the Diabetes Control and Complications Trial Research Group (4) trial in type 1 diabetes and the UK Prospective Diabetes Study Group (5) in type 2 diabetes showed a linear inverse relationship between hyperglycemia and renal-retinal complications. More particular, a 37% decrease in the incidence rate of micro-macroalbuminuria and retinal complications was observed in the UK Prospective Diabetes Study Group study for any decrease of HbA1c by 1% (5). This was also the case for decreases of HbA1c <7.0 to 6.5%. On the contrary, data from the Joslin Clinic in the United States suggested that the incidence rate of diabetic nephropathy in type 1 diabetes is very low when HbA1c levels are <8.0% (2). This is not a trivial issue as a 7.5% level of HbA1c might be accomplished in large cohorts of patients with type 2 diabetes, whereas a level of HbA1c <6.5% is rarely achieved in the overall population of patients with type 2 diabetes despite intensive therapeutic efforts.

To understand better the nature of the mechanisms underlying differences in the time courses of GFR among an apparently uniform diabetic population, we studied the individual relationship between HbA1c concentrations and postprandial plasma glucose and fasting plasma glucose levels during a 4-yr follow-up period in 74 patients with type 2 diabetes and abnormalities of albumin excretion rate in the range of 20 to 3000 μg/min and arterial hypertension (3). Tight BP control was accomplished in all of the patients who were using angiotensin-converting enzyme inhibitors (ACE) along with calcium channel blockers and diuretics aiming for BP values <140/90 mmHg. This target was successfully accomplished and maintained in 94% of the patients (3). The target of the metabolic therapy was to reduce HbA1c levels to <7.5% using sulfonylureas, metformin, and metformin with insulin. The patients were seen every 6 mo for 1 wk during which GFR and HbA1c were measured once a week along with daily blood glucose levels.
evaluations after overnight fast and during postprandial periods. Our aim was to investigate the contributions of high postprandial plasma glucose and fasting plasma glucose levels in addition to HbA1c patterns to determine the progression of renal damage in white patients with type 2 diabetes and altered albumin excretion rate. More particular, we tried to assess whether the measurement of postprandial plasma glucose and fasting plasma glucose substantially improves the prediction of a worse course of GFR. Approximately 75% of the patients had a decrease of GFR. These patients had HbA1c values >7.5 to 8.0%. No change of GFR was found in 25% of the patients who conversely had HbA1c values <7.5 to 8.0%. These findings suggest that HbA1c levels >7.5 to 8.0% are closely associated with a rapid decay of renal function in type 2 diabetes. Also, postprandial plasma glucose values were closely linked to a rapid decay of GFR. More particular, all but two of the patients with postprandial plasma glucose >200 mg/dl had a decay of GFR, whereas no or trivial change was observed when postprandial plasma glucose was <200 mg/dl (Figure 1). Also, fasting plasma glucose values were significantly related to the changes of GFR, although less closely than with the other two parameters. This finding of a closer relationship of postprandial than fasting plasma glucose with the changes of GFR may be explained by the fact that most of the day during the morning, in the afternoon, and during the first hours of the night, the patients are in postprandial phase (3).

Whatever the relationship between blood glucose and renal complications in diabetes, most authors agree that coronary heart disease (CHD) does occur usually at levels of blood glucose significantly lower than those observed in patients with diabetic nephropathy. This is not merely an academic issue, as it is evident that the available therapeutic approaches might, relatively frequently, accomplish HbA1c <7.5%, whereas a reduction of HbA1c <6.5 to 7.0% is rarely feasible in an overall population of patients with diabetes. This can explain why the coronary artery disease (CHD) is the main cause of mortality in diabetes and can account for the observation that tight glycemic control significantly prevents microangiopathic but not macroangiopathic complications.

The reasons explaining the different relationship between hyperglycemia and renal and cardiac complications in diabetes might be due also to different meanings of the pathogenesis if micro-macroalbuminuria in patients with diabetes and such abnormality. In other words, one can suggest that the pathogenetic mechanisms that lead to albuminuria in hypertensive patients with diabetes and cardiac ischemic complications are different from those that cause albuminuria in renal complications. In fact, the epidemiology of renal complications in patients with diabetes is completely different from that of cardiac complications. Renal complications tend to occur after 5 yr of duration of the disease, to reach a peak after 5 to 10 yr and thereafter rarely to occur in the same patients (2). On the

Figure 1. Relationship between percentage change of GFR from baseline values and average postprandial plasma glucose values measured 12 times after lunch and supper during admission into the ward every 6 mo in 74 patients with type 2 diabetes and abnormalities of albumin excretion rate in the range of 20 to 3000 µg/min during a follow-up period of 4 yr with tight antihypertensive control, aiming for BP values <140/90 mmHg by using ACE inhibitors along with other drugs. This target was accomplished and maintained in 94% of the patients. The target of the metabolic therapy was to reduce HbA1c levels to <7.5% using sulfonylureas, metformin, and metformin with insulin. A line was drawn through the null value to visually distinguish the patients with a decay of GFR from those who showed no change or even a slight increase of GFR.
contrary, the cumulative incidence of cardiac complications tends to increase continuously during the duration of the disease until values of 80 to 90% after 20 to 30 yr of duration (1.5).

**Role of BP Control and Its Implications with That of Glycemic Control in the Prevention of New-Onset Diabetes in Nondiabetic Hypertensive Patients**

If it is true that the accomplishment of tight glycemic control in diabetes is not an easy task, then one is prompted to adopt subsidiary therapeutic approaches in the attempt to curb the burden of diabetic complications. One of the most satisfying among these approaches has been antihypertensive therapy. Numerous trials have shown convincingly that lowering BP levels using diuretics, β blockers, calcium channel antagonists, ACE inhibitors (6), and, more recently, the blockers of AT1 receptor (7,8) markedly delay the progression of renal damage and decrease overall mortality.

Use of drugs that impair glucose tolerance constitutes another set of modifiable risk factors for type 2 diabetes. Anti-hypertensive medications arouse greater concern because they are used by millions of adults. Initially, short-term metabolic studies of thiazide diuretics aroused concern about the diabetogenic potential of these drugs (9). Subsequently, the results of some epidemiologic studies and clinical trials suggested a causal link between the use of β blockers or thiazide diuretics and the subsequent development of type 2 diabetes (10). Given such evidence, investigators in the Diabetes Prevention Program, sponsored by the National Institutes of Health, excluded individuals who used thiazide diuretics or β blockers for the treatment of hypertension, despite their proven benefit in reducing the risk of death from cardiovascular causes (11) and despite their status as first-line agents in the Sixth Report of the Joint national Committee on Prevention, Detection, Evaluation, and Treatment of High BP (6). Previous trials of antihypertensive therapy have consistently documented that diuretic-based drug regimens substantially reduce the risk of stroke (6).

However, the benefits of diuretic therapy on CHD, although evident in quantitative overview, were less than expected (9).

It has been postulated that diuretic-induced metabolic effects (i.e., hypokalemia, dyslipidemia, and insulin resistance) might have reduced the effects of BP decrease. Such patterns of reasoning led in part to a progressive shift from thiazide diuretic therapy to nondiuretic, particularly ACE inhibitors and calcium channel blockers. Furthermore, a study provided evidence that dihydropyridinic calcium channel blockers (CCB) were associated with an increased risk of myocardial infarction in both nondiabetic (12) and diabetic (13) patients.

Five recent large trials reported important findings that clarify, maybe definitively, several of the above-mentioned open questions. First, four of five studies so far have shown unequivocally that drugs that inhibit the renin angiotensin system prevent the onset of newly developed diabetes in patients with hypertension (Table 1) (14–18). The Captopril Prevention Project randomized trial followed for 5 yr 10,985 hypertensive patients who were randomly assigned to captopril or conventional antihypertensive treatment (diuretics, β blockers) (14). This study clearly showed a lower rate of occurrence of new-onset diabetes in hypertensive patients treated with ACE inhibitors (Table 1). Also, the Heart Outcomes Prevention Evaluation Study Investigators (15) confirmed that patients with hypertension associated with at least one additional risk factor for cardiovascular diseases developed significantly less new-onset diabetes when treated with CCB, β blockers, and diuretics in association with ramipril rather than placebo (Table 1).

A similar lower occurrence rate of new diabetes was demonstrated using inhibition of the renin angiotensin system with losartan (an AT1 receptor of angiotensin II blocker) in comparison with the β blocker atenolol (Table 1) (17).

More recently, the ALLHAT study randomly compared three distinct medications—amlodipine, lisinopril, and chlorthalidone—in 33,357 participants aged 55 yr or older with hypertension and at least one other CHD risk factor during a follow-up period of 5 yr (16). This study showed similar effects of diuretics and ACE inhibitors as far as myocardial infarction, whereas diuretics better prevented stroke (16). Also, heart failure occurrence was lower with diuretics than with lisinopril and amlodipine (16). Similar beneficial effects among the three drugs used during the trial were observed with

**Table 1. Risk of diabetes according to antihypertensive medications using ACE inhibitors, AT1 blockers, CCB diuretics, and β blockers among nondiabetic patients with arterial hypertension**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPPP ((14)) (captopril versus diuretics versus β-blockers)</td>
<td>0.86 (0.7–0.9)</td>
<td>0.03 (C versus others)</td>
</tr>
<tr>
<td>HOPE ((15)) (ramipril versus placebo)</td>
<td>0.66 (0.5–0.8)</td>
<td>0.001 (R versus P1)</td>
</tr>
<tr>
<td>LIFE ((17)) (losartan versus atenolol)</td>
<td>0.75 (0.63–0.88)</td>
<td>0.001 (L versus A)</td>
</tr>
<tr>
<td>ALLHAT ((16)) (Lisinopril versus amlodipine versus chlorthalidone)</td>
<td>0.68 (0.5–0.8)</td>
<td>0.01 (L versus C)</td>
</tr>
<tr>
<td>ARIC ((18)) (β blocker versus none) (ACE, β blocker CCB diuretics versus none)</td>
<td>0.79 (0.66–0.91)</td>
<td>0.04 (A versus C)</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; CAPPP, Captopril Prevention Project; HOPE, Heart Outcomes Prevention Evaluation; LIFE, Losartan Intervention for End point Reduction in Hypertension Study; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
regard to renal function (16), even if a slightly better performance seemed to be associated with CCB treatment (16). A particularly important clinical feature of the ALLHAT trial, irrespective of the conclusions that one can draw on the comparison between the individual drugs adopted by the protocol, is the success that the authors accomplished in lowering BP levels. In fact, >60% of the patients had systolic BP levels <140 mmHg in all three branches of treatment (Table 1). This last point particularly deserves to be emphasized as the majority of the previous trials conducted in hypertensive patients with similar clinical characteristics were able to accomplish systolic BP levels <140 mmHg in only 40% of the patients.

In summary, the two major findings of four of five of the large studies mentioned before were 1) that the occurrence of CHD was virtually identical in the CCB, ACE, and diuretic groups and 2) that ACE inhibitors better prevented the onset of diabetes in nondiabetic hypertensive patients.

The editorial comment concerning the ALLHAT study report (17) concluded that there is compelling evidence that thiazide diuretics should be the initial drug of choice for patients with hypertension because diuretics are as effective and even more as compared with other agents, despite adverse metabolic effects of diuretics as compared with ACE inhibitors, such as hypokalemia, hypercholesterolemia, and evidence of insulin resistance and greater risk of developing new-onset diabetes.

Three important issues need to be raised and discussed with regard to the results of the ALLHAT study and particularly to the final comments concerning this study as reported by the editorial that accompanies the original report of the study (19). In fact, despite the adverse metabolic effect of chlorthalidone, Appel et al. (19) emphasized that there was no excess of cardiovascular events or mortality from chlorthalidone in the entire population or among patients with diabetes. Such findings reaffirm the importance of relying on hard clinical outcome rather than on surrogate markers for clinical decision making. However, it must be pointed out that the group of patients who were treated with chlorthalidone had always on average 1 to 1.5 mmHg of systolic BP lower than those on lisinopril and amlodipine. This result could help to explain the better outcome of the patients during chlorthalidone therapy with regard to heart failure and stroke. However, this difference between chlorthalidone and the other treatments was not observed with regard to diastolic BP levels, which were even better during amlodipine therapy than with the two other drugs. Thus, this argument may be used for systolic but not for diastolic BP levels. We believe that a second word of caution should be spent to analyze better all of the consequences of such a statement. Although it is true that no excess of cardiovascular events was observed in patients who were taking chlorthalidone, despite the negative side effects of the antihypertensive therapy, it must be pointed out that the period of follow-up was too short to draw strong conclusions concerning this issue. In fact, it is well known that diabetic complications occur at least after 3 to 5 yr of duration of the disease; thus, no one can rule out the hypothesis that such complications might more frequently develop in patients after diuretic therapy, after a more prolonged period of follow-up. Indeed, the duration of diabetes in the ALLHAT study was only 2 to 3 yr. Thus, this clinical feature of antihypertensive therapy needs to be clarified further before drawing definitive conclusions on the adoption of diuretics as first-choice drugs in the treatment of large populations of hypertensive patients. A second word of caution before drawing definitive conclusions on the strategy of adopting diuretics as the first drug of choice in the treatment of hypertension, at least among patients with diabetic and abnormalities of albumin excretion rate, is raised by the findings of Lewis et al. (20) in type 1 diabetes using ACE inhibitors and of the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin Antagonist Losartan (RENAAL) (7) and the Irbesartan Diabetes Nephropathy Trial (IDNT) studies in type 2 diabetes (8), which used AT1 blockers losartan and irbesartan. Lewis et al. (20) demonstrated that ACE significantly delayed the onset of clinically sound renal outcomes, such as dialysis, renal transplantation, death, and doubling of baseline serum creatinine in approximately 200 patients with type 1 diabetes and overt proteinuria as compared with a matched group on conventional antihypertensive therapy as compared with diuretics and β blockers (20). The IDNT (8) and the RENAAAL (7) studies compared the angiotensin II type 1 receptor antagonists, either with amlodipine alone or with a combined therapy encompassing CCB, β blockers, and diuretics. Both of these studies suggested that the development of ESRD is better prevented by AT1 blockers than by the other compounds in the patients with type 2 diabetes and overt diabetic nephropathy, confirming a previous report, almost 25 yr ago, in Japanese patients with type 2 diabetes using captopril in proteinuric patients (21).

References


