Role of Angiotensin-Converting Enzyme Inhibition in Glucose Metabolism and Renal Injury in Diabetes

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The role of angiotensin-converting enzyme (ACE) inhibition in glucose metabolism and renal injury in diabetes has been extensively investigated in diabetic humans, as well as in animal models of diabetes. Accumulated data indicate that ACE inhibitors have either no adverse effect on glucose control or insulin sensitivity or may even improve them. ACE inhibitors also appear to have neutral or positive effects on lipid metabolism. The variability of results between studies may relate to differences in experimental design, the degree of glycemia or insulin resistance, potassium balance, and dose or duration of ACE inhibitor treatment, among others. In contrast, ACE inhibitors have proved effective in limiting proteinuria and retarding renal function loss in insulin-dependent diabetes mellitus (IDDM) or non–insulin-dependent diabetes mellitus (NIDDM) patients. In rats with experimental or spontaneous diabetes, ACE inhibitors also reduce proteinuria and limit glomerular as well as tubulointerstitial damage, independent of their effects on systemic arterial pressure. How ACE inhibitors limit renal injury in diabetes is not entirely clear, but hemodynamic and nonhemodynamic mechanisms may be involved. Increasing evidence suggests that the intrarenal renin-angiotensin system (RAS) may be altered or activated in the diabetic kidney. Such activation may be specifically inhibited by ACE inhibitors and may explain the superiority of this class of agents over other antihypertensive agents in reducing proteinuria and slowing the progression of diabetic nephropathy.

DIABETES MELLITUS and hypertension often occur simultaneously and share metabolic features of impaired glucose tolerance and insulin resistance.[1,2] The common concurrence of these two conditions predisposes individuals to excess morbidity and mortality from cardiovascular disease and renal disease.[3-6] Furthermore, the risk of developing such complications is often related to the duration and/or severity of the two disorders. In fact, diabetes mellitus and hypertension currently rank as the two leading causes of end-stage renal disease in the United States.[7] Therefore, current strategies in the treatment of hypertension and diabetes have been directed not only to strict control of the blood pressure and blood glucose, but also to prevention or reduction of target organ damage associated with these conditions.

Angiotensin-converting enzyme (ACE) inhibitors are now widely used in the treatment of clinical hypertension. This class of agents is also increasingly used in hypertensive diabetic patients with diabetic nephropathy because of their proven ability to reduce proteinuria and slow renal disease progression. The mechanisms of this renal protective action of ACE inhibitors are still incompletely understood and remain the subject of intense investigation. ACE inhibitors have also been reported to have additional beneficial effects on glucose control and insulin sensitivity in hypertensive and diabetic patients, but such metabolic effects have not been consistently observed in other patients. Whether the influence of ACE inhibitors on glucose control and insulin resistance relates to their vasodilator effects or to their direct action on glucose metabolism is also uncertain and needs to be tested. This report briefly highlights the evidence for the role of ACE inhibition in glucose metabolism and renal injury in diabetic humans, as well as in animal models of diabetes.

ROLE OF ACE INHIBITION IN GLUCOSE METABOLISM IN DIABETES

The effects of various ACE inhibitors on carbohydrate metabolism in hypertensive and diabetic patients have been evaluated in many clinical trials. Some studies have shown that ACE inhibitors improve glucose control and/or insulin sensitivity in hypertensive and diabetic patients,[8-14] suggesting that ACE inhibitors have an additional effect on glucose metabolism. A number of possible mechanisms have been put forth to explain the improvement in insulin sensitivity by ACE inhibitors. These include reduction in circulating catecholamines, increased skeletal muscle blood flow due to ACE-induced vasodilatation, the potassium-sparing effect of ACE inhibition during insulin-induced hypokalemia, enhancement of bradykinin-mediated actions, and a direct action of ACE inhibitors on insulin receptors or postreceptor events. Whether each or all of these putative factors or mechanisms are operative during ACE inhibition in diabetic patients remains to be established. On the other hand, there are also studies that show no significant effects on glucose metabolism in patients treated with ACE inhibitors.[15-24] The reasons for these conflicting results are not clear, but they may relate to differences in subject selection, experimental design, the degree of glycemia or insulinemia among diabetic patients, concomitant use of agents that influence glucose metabolism, potassium balance, and dose or duration of ACE inhibitor treatment.

The effects of ACE inhibitors on glucose metabolism and insulin resistance have also been examined in some animal models of diabetes. Using the SHR/N-cp rat, a genetic model of non–insulin-dependent diabetes mellitus (NIDDM) and hypertension,[25,26] we have recently shown that chronic oral administration of perindopril in obese SHR/N-cp rats consistently lowered systemic arterial pressure to normal levels, but did not produce significant changes in either fasting or 1-hour re-

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sponses (after an oral glucose load) of serum glucose and insulin, suggesting that glucose metabolism and insulin responsiveness were not altered by the treatment.[27] Perindopril also had no appreciable effects on serum cholesterol and triglyceride levels, consistent with the lack of effect of the ACE inhibitor on hyperinsulinemia. These data support earlier observations in patients with hypertension and NIDDM showing that insulin sensitivity and secretion (as assessed by oral glucose tolerance and insulin tolerance tests) were unaffected by perindopril treatment[28] and complement other reports showing no effect of other ACE inhibitors on glucose control and serum lipid levels in hypertensive and diabetic patients.[16,19-21,29,30]

To obviate any possible influence of blood flow and circulating hormones on skeletal muscle glucose metabolism, we further performed in vitro experiments to examine the effects of perindopril on glucose metabolism in isolated soleus muscles of SHR/N-cp rats.[27] In these experiments, we measured basal and insulin-mediated glycogen synthesis into muscle, since a decrease in glycogenesis in skeletal muscle has been shown to be primarily responsible for the impaired glucose disposal in human NIDDM.[31,32] We found that the basal rate of muscle glycogen synthesis was significantly lower in obese compared with lean rats. The basal and maximal insulin-stimulated rates of muscle glycogen synthesis observed in these animals were approximately twofold to threefold lower than those reported by other groups using soleus muscles from nondiabetic male Wistar rats[33] and male Sprague-Dawley rats,[34] indicating the presence of severe insulin resistance. We further showed that perindopril had no significant effect on either basal or maximal insulin-mediated glucose conversion into glycogen in soleus muscle. Other groups using animal models have found different results with chronic ACE inhibition. Rosenthal et al showed that chronic treatment with enalapril lowered ambient blood glucose levels in the Cohen-Rosenthal diabetic hypertensive rat, an animal model with genetic hypertension and diabetes.[35] Henriksen and Jacob have shown that both short-term and long-term treatment with captopril improve insulin-stimulated glucose transport activity (as assessed by 2-deoxyglucose uptake) in the epitrochlearis muscle of obese Zucker rats and that pretreatment of the animals with a bradykinin antagonist abolished this effect.[36] However, the doses of ACE inhibitors used in these studies were very high (eg, 30 mg/kg/d for enalapril and 50 mg/kg/d for captopril) compared with the perindopril dose (0.5 to 0.1 mg/kg/d) used in our rats and the daily doses usually used for antihypertensive treatment in patients. The lack of an effect of perindopril on glucose control and muscle glycogen synthesis in obese SHR/N-cp rats may be related to their severe insulin-resistant state, which is not easily improved by ACE inhibitors, such as perindopril. It is possible that ACE inhibitors, if used in combination with antidiabetic agents that directly increase insulin sensitivity to treat NIDDM and hypertension, may produce additive or synergistic effects to enhance glucose disposal in insulin-resistant tissues. Further studies in animals and humans with both NIDDM and hypertension are needed to examine this point more fully.

On balance, it appears from these studies that the effect of ACE inhibition on glucose metabolism varies between patients. ACE inhibitors either have no adverse effect on glucose control or insulin sensitivity or may even improve them. These agents also appear to have neutral or positive effects on lipid metabolism.

RENAL STRUCTURAL-FUNCTIONAL RELATIONSHIPS IN DIABETIC NEPHROPATHY

Diabetic nephropathy is characterized structurally by early glomerular and tubular hypertrophy, followed by glomerular basement thickening and progressive expansion of the mesangial matrix, eventually leading to glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Mesangial expansion is generally considered the key lesion most closely related to the decline in renal function in patients with diabetic nephropathy.[37] However, morphometric studies indicate that tubulointerstitial pathology correlates just as well with reduced renal function as glomerulopathy. Bader et al evaluated kidney biopsy specimens from middle-aged diabetic patients and found that the degree of interstitial expansion correlated with the serum creatinine level and progression of glomerulosclerosis.[38] Similarly, Thomsen et al examined autopsy specimens from insulin-dependent diabetes mellitus (IDDM) patients and observed that both mesangial and interstitial lesions correlated with the serum creatinine level and the presence or absence of clinical nephropathy.[39] Moreover, Mauer et al observed a direct correlation between index of mesangial expansion and index of interstitial fibrosis in IDDM patients with varying degrees of nephropathy.[40] The same group of investigators found similar correlations between these two indices, both of which also correlated with urinary albumin excretion and glomerular filtration rate.[41] More recently, Ueno et al examined renal biopsy specimens from NIDDM patients and noted significant interstitial expansion that correlated with proteinuria, creatinine clearance, and blood pressure.[42] Taken together, these findings indicate that the pathologic lesions in the tubulointerstitium are as important as diabetic glomerulopathy in the development of clinical nephropathy and reduced renal function in both IDDM and NIDDM patients.

ROLE OF ACE INHIBITION IN RENAL INJURY IN DIABETES

The renin-angiotensin system (RAS) has been implicated in the pathogenesis of microvascular and renal lesions in diabetes. However, its precise role in renal injury in diabetes is not well understood. The RAS is generally thought to be suppressed in diabetes, since circulating levels of renin and aldosterone are usually low or normal in most diabetic patients. However, recent evidence suggests that a local or tissue RAS also exists in the kidney and other organs, which operates in an autocrine or paracrine manner, independent of the circulating RAS system.[43,44] All of the components of the RAS have been identified and localized in various structures of the kidney.[44] Molecular biological and immunohistochemical studies have shown that the levels of the different RAS components are increased in the diabetic kidney. For example, Anderson et al have found elevated levels of renal angiotensinogen mRNA and renin protein in kidneys of rats with experimental diabetes.[45] These investigators also noted increased immunostaining for ACE in glomeruli and renal vasculature in these animals. Other groups have also found increased renal renin content in glomeruli[46] or juxtaglomerular apparatus[47] of diabetic rats. These findings suggest that the renal RAS may be altered or activated in diabetes. Whether these changes in intrarenal RAS mediate

renal injury in diabetes is not clear and needs further intensive investigation.

Investigations on the effects of ACE inhibitors on diabetic renal disease in humans and animals have provided further evidence for the participation of the RAS in renal injury in diabetes. Many clinical studies have shown that treatment with ACE inhibitors reduces proteinuria in hypertensive diabetic patients[48,49] and slows the rate of renal functional deterioration in IDDM patients with diabetic nephropathy.[50-52] Similarly, other studies have also shown that ACE inhibitors limit the progression of renal disease in IDDM patients with microalbuminuria[53] and prevent the progression of albuminuria and loss of renal function in NIDDM patients with microalbuminuria and normal serum creatinine.[54] These beneficial renal effects of ACE inhibitors appear to be a class effect, since similar effects were observed using different ACE inhibitors. A recent meta-analysis indicated that the antiproteinuric effect of ACE inhibitors in diabetic patients exceeds that of most other antihypertensive agents.[55] More importantly, the Collaborative Study Group trial by Lewis et al has provided convincing evidence that ACE inhibition with captopril slows the progression of diabetic nephropathy, independent of its effect on blood pressure,[51] suggesting an additional specific effect on the kidney.

The effects of ACE inhibitors on diabetic renal lesions have been examined in several animal models of diabetes. In SHR rats made diabetic with streptozotocin (STZ), Cooper et al showed that ACE inhibition with enalapril limited albuminuria, mesangial expansion, and glomerular basement membrane thickening in the diabetic animals.[56] Similarly, Sassy-Prigent et al have shown that early treatment with trandolapril in STZ-induced diabetic rats completely abolished albuminuria and prevented the development of incipient glomerular lesions, namely, glomerular hypertrophy and mesangial expansion.[57] Anderson et al compared the effects of captopril and conventional triple therapy with hydrochlorothiazide, reserpine, and hydralazine in moderately hyperglycemic Munich-Wistar rats with STZ-induced diabetes and showed that both regimens equally reduced systemic arterial pressure, but captopril was more effective than triple therapy in preventing albuminuria and glomerulosclerosis in diabetic rats.[58] Similarly, our group has shown that treatment of obese SHR/N-cp rats with perindopril was more effective than triple-drug therapy in halting the progression of proteinuria.[59] Both regimens also significantly limited glomerular sclerosis and tubulointerstitial lesions but the magnitude of reduction was greater with perindopril compared with triple therapy. In addition, we found a significant positive correlation between the percentage of glomerular sclerosis and the index of severity of tubulointerstitial lesions, suggesting that the development of glomerulosclerosis and tubulointerstitial lesions in the diabetic kidney may have common pathophysiologic mechanism.

Several mechanisms have been suggested to contribute to the renal protective effect afforded by ACE inhibitors. Hemodynamic effects, such as reduction of intraglomerular pressure by ACE inhibitors, which has been amply demonstrated in diabetic rats,[58,60] may reduce pressure-related glomerular injury. ACE inhibitors may also reduce renal injury through inhibition of angiotensin II-mediated nonhemodynamic mechanisms.[61] Angiotensin II, in addition to its potent vasoconstrictor properties, is known to stimulate the proliferation and growth of mesangial cells[62] and to increase extracellular matrix protein synthesis.[63] Angiotensin II can also stimulate the production of various prosclerotic cytokines, such as transforming growth factor-beta, fibroblast growth factor, and platelet-derived growth factor.[64] ACE inhibitors may interfere with these trophic effects of angiotensin II by blocking its local production in the kidney.

CONCLUSION

In summary, accumulated evidence from clinical and experimental studies indicate that ACE inhibitors have either neutral or favorable effects on glucose control and insulin sensitivity. However, these agents have proven effective in reducing proteinuria and slowing the progression of diabetic nephropathy in both IDDM and NIDDM. Studies in animal models of diabetes have provided further evidence that the renoprotective effect of ACE inhibitors is associated with amelioration of glomerular and tubulointerstitial injury associated with diabetes and that these renal effects are independent of their effects on systemic arterial pressure. The mechanisms of how ACE inhibitors limit renal injury in diabetes are not entirely clear. Increasing evidence suggests that activation of the intrarenal RAS may play a role in renal injury in diabetes. Such activation may be specifically inhibited by ACE inhibitors and may explain the superiority of this class of agents over other antihypertensive agents in slowing the progression of diabetic nephropathy.

REFERENCES

1. Fuller JH: Epidemiology of hypertension with diabetes mellitus. Hypertension 7:II-113-II-117, 1985 (suppl 2)

2. Kannel WB, Wilson PWF, Zhang TJ: The epidemiology of impaired glucose tolerance and hypertension. Am Heart J 121:1268-1273, 1991

3. Eschwege P, Richard JL, Thibault N, et al: Coronary heart disease mortality in relation with diabetes, blood glucose, and plasma insulin levels. The Paris Prospective Study, ten years later. Horm Metab Res 15:41-46, 1985 (suppl)

4. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, et al: Coronary heart disease in young type I (insulin-dependent) diabetic patients with and without diabetic nephropathy: Incidence and risk factors. Diabetologia 30:144-148, 1987

5. Panzram G: Mortality and survival in type 2 (non–insulin-dependent) diabetes mellitus. Diabetologia 30:123-131, 1987

6. Mogensen CE: High blood pressure as a factor in the progression of diabetic nephropathy. Acta Med Scand Suppl 602:29-32, 1976

7. US Renal Data System: USRDS 1996 Annual Data Report. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, April 1996

8. Jauch KW, Hartl W, Guenther B, et al: Captopril enhances insulin responsiveness of forearm muscle tissue in non–insulin-dependent diabetes mellitus. Eur J Clin Invest 17:448-454, 1987

9. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med 321:868-873, 1989

10. Ferrier C, Ferrari P, Weidmann P, et al: Antihypertensive therapy with CA+2 antagonist verapamil and/or ACE inhibitor enalapril in NIDDM patients. Diabetes Care 14:911-914, 1991

11. Moore MP, Elliott TW, Nichols MG: Hormonal and metabolic

effects of enalapril treatment in hypertensive subjects with NIDDM. Diabetes Care 11:397-401, 1988

12. Paolliso G, Gambardella A, Verza M, et al: ACE inhibition improves insulin-sensitivity in aged insulin-resistant hypertensive patients. J Hum Hypertens 6:175-179, 1992

13. Santoro D, Natali A, Palombo C, et al: Effects of chronic angiotensin converting enzyme inhibition on glucose tolerance and insulin sensitivity in essential hypertension. Hypertension 20:181-191, 1992

14. Donnelly R: Angiotensin-converting enzyme inhibitors and insulin sensitivity: metabolic effects in hypertension, diabetes, and heart failure. J Cardiovasc Pharmacol 20:S38-S44, 1992 (suppl 11)

15. Corcoran JS, Perkins JE, Hoffbrand BI, et al: Treating hypertension in non–insulin-dependent diabetes: A comparison of atenolol, nifedipine, and captopril combined with bendrofluazide. Diabetic Med 4:164-168, 1987

16. Bilo HJG, Westerman RF, Nicolas-Mereus AM, et al: Effect of enalapril with and without hydrochlorothiazide in hypertensive patients with non–insulin-dependent diabetes mellitus. Diabetes Res 9:21-25, 1988

17. Prince MJ, Stuart CA, Padia M, et al: Metabolic effects of hydrochlorothiazide and enalapril during treatment of the hypertensive diabetic patient: Enalapril for hypertensive diabetics. Arch Intern Med 148:2363-2368, 1988

18. Seefeldt T, Orskov L, Mengel A, et al: Lack of effect of angiotensin-converting enzyme (ACE)-inhibitors on glucose metabolism in type 1 diabetes. Diabetic Med 7:700-704, 1990

19. Reneland R, Andersson PE, Haenni A, et al: Metabolic effects of long-term angiotensin converting enzyme inhibition with fosinopril in patients with essential hypertension: Relationship to angiotensin-converting enzyme inhibition. Eur J Clin Pharmacol 46:431-436, 1994

20. Haenni A, Andersson PE, Lind L, et al: Electrolyte changes and metabolic effects of lysinopril/bendrofluazide treatment. Am J Hypertens 7:615-622, 1994

21. Andersson PE, Lithell: Metabolic effects of doxazosin and enalapril in hypertriglyceridemic, hypertensive men: Relationship to changes in skeletal muscle blood flow. Am J Hypertens 9:323-333, 1996

22. Shionoiri H, Miyakawa T, Takasaki I, et al: Glucose tolerance during chronic captopril therapy in patients with essential hypertension. J Cardiovasc Pharmacol 9:160-164, 1987

23. Shionoiri H, Sugimoto K, Minamisawa K, et al: Glucose and lipid metabolism during long-term treatment with cilazapril in hypertensive patients with or without impaired glucose metabolism. J Cardiovasc Pharmacol 15:933-938, 1990

24. Ludvik B, Kueenburg E, Brunnbauer M, et al: The effects of ramipril on glucose tolerance, insulin secretion, and insulin sensitivity in patients with essential hypertension. J Cardiovasc Pharmacol 18:157-159, 1991

25. Michaelis OE IV, Ellwood KC, Judge JM, et al: Effect of dietary sucrose on the SHR/N-corpulent rat: A new model for insulin-independent diabetes. Am J Clin Nutr 39:612-18, 1984

26. Michaelis OE IV, Patrick DH, Hansen CT, et al: Spontaneous hypertensive/NIH-corpulent rat. Animal model for insulin-independent diabetes mellitus (type II). Am J Pathol 123:398-400, 1986

27. Striffler JS, Bhathena SJ, Michaelis OE IV, et al: Long-term effects of perindopril on metabolic parameters and the heart in the spontaneously hypertensive/NIH-corpulent rat with non–insulin-dependent diabetes mellitus and hypertension. Metabolism 47:1199-1204, 1998

28. Bak JF, Gerdes LU, Sorensen NS, et al: Effect of perindopril on insulin sensitivity and plasma lipid profile in hypertensive non-insulin-dependent diabetic patients. Am J Med 92:69S-72S, 1992

29. Baba T, Neugebauer S: The link between insulin resistance and hypertension: Effects of antihypertensive and antihyperlipidemic drugs on insulin sensitivity. Drugs 47:383-404, 1994

30. Gall M-A, Rossing P, Skott P, et al: Placebo-controlled comparison of captopril, metoprolol, and hydrochlorothiazide therapy in non–insulin-dependent diabetic patients with primary hypertension. Am J Hypertens 5:257-265, 1992

31. Meyer HU, Curchod B, Maeder E, et al: Modifications of glucose storage in nonobese diabetics, measured by continuous indirect calorimetry. Diabetes 29:752-756, 1980

32. Young AA, Bogardus C, Wolfe-Lopez D, et al: Muscle glycogen synthesis and disposition of infused glucose in humans with reduced rates of insulin-mediated carbohydrate storage. Diabetes 37:303-308, 1988

33. Leighton B, Cooper GJS: Pancreatic amylin and calcitonin gene-related peptide cause resistance to insulin in skeletal muscle in vitro. Nature 335:632-635, 1988

34. Kreutter DK, Orena SJ, Torchia AJ, et al: Amylin and CGRP induce insulin resistance via a receptor distinct from cAMP-coupled CGRP receptor. Am J Physiol 264:E606-E613, 1993

35. Rosenthal T, Erlich Y, Rosenmann E, et al: Effects of enalapril, losartan, and verapamil on blood pressure and glucose metabolism in the Cohen-Rosenthal diabetic hypertensive rat. Hypertension 29:1260-1264, 1997

36. Henriksen EJ, Jacob S: Effects of captopril on glucose transport activity in skeletal muscle of obese Zucker rats. Metabolism 44:267-272, 1995

37. Steffes ER, Osterby R, Chavers B, et al: Mesangial expansion as a central mechanism for loss of kidney function in diabetic patients. Diabetes 38:1077-1081, 1989

38. Bader R, Bader H, Grund KE, et al: Structure and function of the kidney in diabetic glomerulosclerosis: Correlations between morphological and functional parameters. Pathol Res Pract 167:204-216, 1980

39. Thomsen OF, Andersen AR, Christiansen JS, Deckert T: Renal changes in long-term type 1 (insulin-dependent) diabetic patients with and without clinical nephropathy. Diabetologia 26:361-365, 1984

40. Mauer SM, Steffes M, Ellis E, et al: Structural-functional relationships in diabetic nephropathy. J Clin Invest 74:1143-1155, 1984

41. Lane PH, Steffes MW, Fioretto P, et al: Renal interstitial expansion in insulin-dependent diabetes mellitus. Kidney Int 43:661-667, 1993

42. Ueno M, Kawashima S, Nishi S, et al: Tubulointerstitial lesions in noninsulin-dependent diabetes mellitus. Kidney Int 52:S-191-S-194, 1997 (suppl 63)

43. Dzau VJ: Circulating versus local renin-angiotensin system in cardiovascular homeostasis. Circulation I-4-I-13, 1988 (suppl 1)

44. Johnston CI, Fabris B, Jandeleit K: Intrarenal renin-angiotensin in renal physiology and pathophysiology. Kidney Int 44:S59-S63, 1993 (suppl 42)

45. Anderson S, Jung FF, Ingelfinger JR: Renin-angiotensin system in diabetic rats: Functional, immunohistochemical, and molecular biologic correlations. Am J Physiol 265:F477-F486, 1993

46. Jaffa AA, Chai KX, Chao J, et al: Effects of diabetes and insulin on kallikrein and renin genes in the kidney. Kidney Int 41:789-795, 1992

47. Everett AD, Scott J, Wilfomg N, et al: Renin and angiotensinogen expression during evolution of diabetes. Hypertension 19:70-78, 1992

48. Gambaro G, Morbiato F, Cicerello E, et al: Captopril in the treatment of hypertension in type I and type II diabetic patients. J Hypertens 3:153-154, 1985 (suppl 2)

49. Baba T, Murabayashi S, Takabe K: Comparison of the renal effects of angiotensin converting enzyme inhibitor and calcium antagonist in hypertensive type II (non–insulin-dependent) diabetic patients with microalbuminuria: A randomized controlled trial. Diabetologia 32:40-44, 1989

50. Bjork S, Nyberg G, Mulec H, et al: Benefical effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. Br Med J 293:471-474, 1986

51. Lewis EJ, Hunsicker LG, Bain RP, et al: The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. N Engl J Med 329:1456-1462, 1993

52. Mulec H, Johnsen SA, Bjork S: Long-term enalapril treatment in diabetic nephropathy. Kidney Int 45:S141-S144, 1994 (suppl 45)

53. Mathiesen ER, Hommel E, Giese J, et al: Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. Br Med J 303:81-87, 1991

54. Ravid M, Savin H, Jutrin I, et al: Long-term-stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 118:577-581, 1993

55. Kasiske BL, Kalil RSN, Ma JZ, et al: Effect of antihypertensive therapy on the kidney in patients with diabetes: A meta-regression analysis. Ann Intern Med 118:129-139, 1993

56. Cooper ME, Allen TJ, O'Brien RC, et al: Nephropathy in a model combining genetic hypertension with diabetes: Enalapril vs hydralzine and metoprolol therapy. Diabetes 39:1575-1579, 1990

57. Sassy-Prigent C, Heudes D, Jouquey S, et al: Morphometric detection of incipient glomerular lesions in diabetic nephropathy in rats. Lab Invest 73:64-71, 1995

58. Anderson S, Rennke HG, Garcia DL, et al: Short and long term effects of antihypertensive therapy in the diabetic rat. Kidney Int 365:26-536, 1989

59. Velasquez MT, Striffler JS, Abraham AA, et al: Perindopril ameliorates glomerular and renal tubulointerstitial injury in the SHR/N-corpulent rat. Hypertension 30:1232-1237, 1997

60. Zatz R, Dunn BR, Meyer TW, et al: Prevention of diabetic glomerulopathy by pharmacologic amelioration of glomerular capillary hypertension. J Clin Invest 77:1925-1930, 1986

61. Wolf G, Ziyadeh FN: The role of angiotensin II in diabetic nephropathy: Emphasis on nonhemodynamic mechanisms. Am J Kidney Dis 29:153-163, 1997

62. Wolf G, Haberstroh U, Neilson EG: Angiotensin II stimulates proliferation and collagen type I biosynthesis in cultured murine mesangial cells. Am J Pathol 140:95-107, 1992

63. Kagami S, Border WA, Miller DE, et al: Angiotensin II stimulates extracellular matrix protein synthesis through induction of transforming growth factor-beta expression in rat glomerular mesangial cells. J Clin Invest 93:232-237, 1996

64. Egido J: Vasoactive hormones and renal sclerosis. Kidney Int 49:578-597, 1997