Original Articles

Reduction of Glomerular Hyperfiltration in Normoalbuminuric IDDM Patients by 6 mo of Aldose Reductase Inhibition

MARGRETHE MAU PEDERSEN, JENS S. CHRISTIANSEN, AND CARL ERIK MOGENSEN

Hyperglycemia causes enhanced glucose metabolism by the polyol pathway in tissues not requiring insulin for glucose uptake. It has been suggested that the high level of aldose reductase activity may cause functional and structural abnormalities in diabetes and may be involved in the development of late complications. To elucidate the effect of an aldose reductase inhibitor (ponalrestat) on kidney function in uncomplicated insulin-dependent diabetes mellitus (IDDM), 20 normoalbuminuric IDDM patients were randomized to follow either 6 mo of treatment with ponalrestat (n = 11, mean ± SD age 30 ± 8 yr, diabetes duration 10 ± 6 yr) or 6 mo of placebo (age 33 ± 7 yr, diabetes duration 12 ± 6 yr). The glomerular filtration rate (clearance of [^{125}I]iothalamate) was significantly reduced from 140 ± 18 to 129 ± 10 ml · min^{-1} · 1.73 m^{-2}, $2P$ = 0.02) in the ponalrestat-treated patients, whereas no change was seen after placebo (142 ± 12 vs. 141 ± 12 ml · min^{-1} · 1.73 m^{-2}). The renal plasma flow (clearance of ^{131}I-labeled hippuran), urinary albumin excretion rate (radioimmunoassay), fractional albumin clearance, and renal vascular resistance were unchanged in both groups. HbA_{1c} showed a modest increase during ponalrestat (7.9 ± 1.8 vs. 8.7 ± 1.5%, $2P$ = 0.01) but was unchanged during placebo. No side effects of ponalrestat were observed. Thus, inhibition of aldose reductase may reduce the characteristic hyperfiltration in uncomplicated IDDM. *Diabetes* 40:527–31, 1991

In tissues with insulin-independent glucose uptake, hyperglycemia gives rise to enhanced glucose metabolism by the polyol pathway. Thus, the primary pathways for glucose are saturated, and the high intracellular glucose concentration leads to flux through the polyol pathway despite the low affinity of aldose reductase for glucose. The possibility that increased polyol-pathway activity could be a link between hyperglycemia and diabetic complications has attracted much interest and has been widely studied in experimental models of diabetes. Studies in rats with chemically induced diabetes have indicated that the biochemical and metabolic alterations that accompany a high level of polyol-pathway activity may be involved both in functional and structural renal abnormalities (1,2).

In human insulin-dependent diabetes mellitus (IDDM), the characteristic functional abnormality during the early stage is glomerular hyperfunction with hyperfiltration and some degree of hyperperfusion (3–5). The aim of this study was to elucidate the possible influence of long-term inhibition of aldose reductase on glomerular filtration rate (GFR) and renal plasma flow (RPF) in normoalbuminuric IDDM patients.

RESEARCH DESIGN AND METHODS

Twenty male IDDM patients were studied. The patients were characterized as normoalbuminuric with a urinary albumin excretion rate (UAER) ≤20 μg/min. Clinical data are given in Table 1 for the patients being randomized to active treatment (ponalrestat) and placebo, respectively (see below). The patients were normotensive, and none had proliferative retinopathy. They were taking no medication other than insulin and did not have a history of chronic disease of any kind other than diabetes. Informed consent was given by the patients. The study protocol was approved by the Regional Ethical Committee and the Danish National Board of Health.

The study followed a double-blind parallel design. The patients were randomized to receive 6 mo of either ponalrestat (Statil, ICI-128436, Prodiax, and MK-538 brands were used, ICI, Macclesfield, UK) 600 mg daily (n = 11) or placebo (n = 9). The treatment period was preceded by a 4-wk placebo run-in in both groups to assess treatment compliance. Kidney function was measured at the beginning of the run-in period and before and at the end of the treatment

From the Second University Clinic of Internal Medicine, Aarhus Kommunehospital, Aarhus, Denmark.

Address correspondence to M. Mau Pedersen, MD, Second University Clinic of Internal Medicine, Medical Department M (Endocrinology and Diabetes), Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.

Received for publication 4 January 1990 and accepted in revised form 19 December 1990.

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/40/5/527/336711/40-5-527.pdf by guest on 26 March 2023

TABLE 1
Baseline clinical data and renal hemodynamics of 20 patients with insulin-dependent diabetes randomized to ponalrestat or placebo

	Ponalrestat (n = 11)	Placebo (n = 9)
Age (yr)	30 (19–44)	33 (24–44)
Diabetes duration (yr)	10 (2–18)	12 (3–23)
Blood pressure (mmHg)	116/78 (101–128/62–87)	119/77 (106–131/70–87)
HbA_{1c} (%)	7.9 (5.9–10.3)	8.7 (7.1–10.1)
GFR (ml · min^{-1} · 1.73 m^{-2})	140 ± 18	142 ± 12
RPF (ml · min^{-1} · 1.73 m^{-2})	554 ± 93	568 ± 78
UAER (μg/min)	5.4 ×/÷ 1.9	6.1 ×/÷ 1.3

Data are means with ranges in parentheses. Values are means ± SD where appropriate. Blood pressure was measured as systolic/diastolic. GFR, glomerular filtration rate. RPF, renal plasma flow. Urinary albumin excretion rate (UAER) is measured as geometric mean ×/÷ tolerance factor instead of mean ± SD due to log transformation. All comparisons were NS.

period. The patients were instructed to follow their usual diet throughout the study period.

GFR and RPF were measured by constant infusion technique with [^{125}I]iothalamate and ^{131}I-labeled hippuran as markers (6). Five 20-min clearance periods were conducted. The patients fasted overnight before measurement of kidney function, and no insulin was given the morning of the investigation. UAER was measured by radioimmunoassay (7) on urine samples from the clearance studies.

Blood glucose (standard enzymatic technique) and plasma concentration of human growth hormone (radioimmunoassay [8]) were measured during all clearance periods. Blood pressure (standard sphygmomanometer, Korotkoff phase V for diastolic pressure) and heart rate were determined in each clearance period. At each kidney function study and in addition after 3 mo of ponalrestat or placebo, a hematological and biochemical blood screen was performed with conventional laboratory techniques. HbA_{1c} was measured by cation-exchange chromatography (9) (mean ± SD normal level 5.5 ± 0.5%).

GFR and RPF were adjusted to 1.73 m^2 body surface. The mean of results from clearance periods 1–5 was calculated. Filtration fraction (FF) was calculated as GFR/RPF, renal vascular resistance as mean arterial pressure (MAP) (1 − hematocrit)/RPF, and fractional albumin clearance (ΘAlb) as UAER/(plasma albumin × GFR). Results are given as means ± SD. UAER and ΘAlb were log transformed before statistical analysis to achieve normal distribution and are therefore given as geometric mean ×/÷ tolerance factor instead of mean ± SD.

Clinical data and baseline parameters of the ponalrestat-treated patients and the placebo patients were compared by an unpaired Student's t test. The t test for paired comparison was used for analysis of possible changes during the treatment period in the ponalrestat group and placebo group, respectively. In case of any statistically significant changes, an additional comparison was performed between the values before treatment in each of the groups and likewise between the values after treatment (unpaired t test). Comparisons were considered statistically significant at $2P < 0.05$. Correlations were calculated as Pearson's product moment correlation coefficient r.

RESULTS

The ponalrestat-treated group of patients and the group of patients receiving placebo were comparable with respect to clinical data and baseline renal hemodynamics (Table 1). Coefficient of variance for the five baseline GFR measurements during each kidney function test was 5.5 ± 2.6.

Renal effects are shown in Fig. 1. The 6-mo administration of ponalrestat was accompanied by an 8% reduction in GFR from 140 ± 18 to 129 ± 10 ml · min^{-1} · 1.73 m^{-2}, $2P = 0.02$. During placebo, no change in mean GFR (142 ± 12 vs. 141 ± 12 ml · min^{-1} · 1.73 m^{-2}, NS) was seen. Comparison of GFR values after ponalrestat and after placebo showed a statistically significant difference ($2P = 0.03$).

The decreases in GFR during ponalrestat were significantly correlated to the baseline GFR values ($r = 0.82$, $2P = 0.004$). In the placebo group, no significant correlation was found between these parameters ($r = 0.47$). One month before the beginning of the treatment period, GFR showed mean values and SDs not different from those at the start of treatment (ponalrestat group 139 ± 15 ml/min, placebo group 136 ± 15 ml/min). No significant correlations were found between ΔGFR in the ponalrestat patients and baseline or mean HbA_{1c} during the 6-mo treatment period.

RPF was not significantly changed during either ponalrestat (554 ± 93 vs. 539 ± 87 ml · min^{-1} · 1.73 m^{-2}) or placebo (568 ± 78 vs. 602 ± 70 ml · min^{-1} · 1.73 m^{-2}). The mean value of FF decreased slightly in both groups, although it was only statistically significant in the placebo group (0.25 ± 0.03 vs. 0.24 ± 0.02, $2P = 0.03$). When

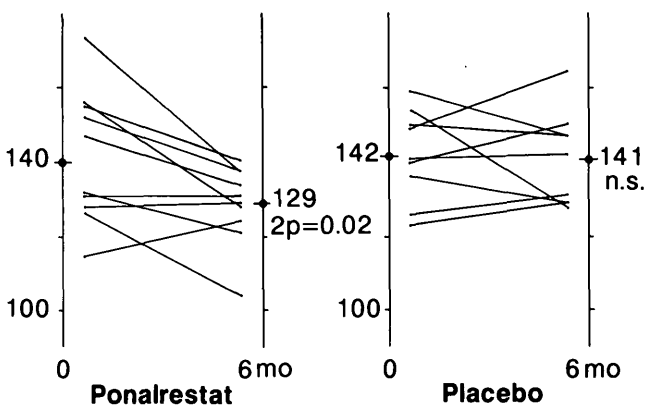

FIG. 1. Glomerular filtration rate (ml · min^{-1} · 1.73 m^{-2}) before and at end of 6-mo administration of ponalrestat (n = 11) and placebo (n = 9) in insulin-dependent diabetic patients. ●, Mean values. Statistical significance was determined by comparison of values before with values after ponalrestat or placebo.

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/40/5/527/336711/40-5-527.pdf by guest on 26 March 2023

comparing FF between the two groups, no differences were found in the values before and after the treatment period. UAER and ΘAlb did not show significant changes in any of the groups, and renal vascular resistance was also unchanged after 6 mo of both ponalrestat and placebo.

During ponalrestat, a slight decrease in diastolic blood pressure was seen (78 ± 7 vs. 74 ± 5 mmHg, $2P = 0.05$). No changes in systolic blood pressure or MAP were observed. In the placebo group, the blood pressures were similar before and after the 6-mo period. No significant difference between diastolic blood pressure before or after ponalrestat versus placebo was found. The decrease in diastolic blood pressure during ponalrestat did not correlate with the fall in GFR ($r = 0.04$, NS). Heart rate was unchanged in both groups.

Regarding metabolic effects, mean blood glucose (and fasting blood glucose) on the day of the kidney function measurement was unchanged before and after ponalrestat and placebo. HbA_{1c} showed a modest increase during ponalrestat (7.9 ± 1.8 vs. 8.7 ± 1.5%, $2P = 0.01$), whereas it was unchanged during placebo (8.7 ± 1.0 vs. 8.7 ± 0.8%). No statistically significant differences were found between HbA_{1c} before ponalrestat and before placebo. Likewise, the values after the two treatment periods were not different. Insulin dose and body weight were constant in both groups. Growth hormone was unchanged during the 6 mo of ponalrestat and placebo.

The hematological and biochemical blood screen showed no significant changes during ponalrestat or placebo with respect to cellular blood elements, parameters of liver function, serum protein and albumin, urea, and electrolytes. Serum concentration of uric acid decreased from 0.21 ± 0.04 to 0.16 ± 0.03 μmol^{-1} during ponalrestat ($2P = 0.02$, $n = 8$), whereas no change was seen during placebo.

No adverse events that could be ascribed to the ponalrestat treatment were reported or observed.

DISCUSSION

Our study suggests that the abnormal activity of the polyol pathway caused by the diabetic state may be involved in the hyperfiltration phenomenon in IDDM. In the normoalbuminuric patients, 6-mo administration of a highly selective reductase inhibitor (10) was accompanied by a reduction of the elevated GFR level. GFR was found unchanged during a parallel placebo period, and although the baseline GFR levels in the two groups were comparable, there was a significant difference between the results after 6 mo. Before the ponalrestat and placebo periods, GFR values were stable judged by measurements obtained with 1-mo intervals. The strong correlation between the size of the GFR reductions during ponalrestat and the baseline GFR values suggests that individual differences in the influence of the polyol pathway may exist. Because baseline and mean HbA_{1c} during the study period did not correlate to the GFR changes, it is indicated that such differences between diabetic subjects are not closely related to the glycemic control. Correspondingly, Berger et al. (11) demonstrated that in vitro sorbitol accumulation in glucose-incubated erythrocytes is heterogenous in diabetic patients and highest in those patients suffering from severe diabetic neuropathy. The ΔGFR/GFR correlation could have been influenced by regression toward mean. However, as mentioned above, the reproducibility of GFR measurements during the run-in period appeared to be high, and no correlation was observed during placebo administration.

Discussion on the possible role of polyol-pathway activity in diabetic hyperfiltration has so far been based on experimental studies in diabetic animals. The results obtained have not been uniform. Because various models of diabetes and different treatment periods have been used, the findings are difficult to compare. Tilton et al. (1) and McCormack et al. (12,13) reported that increased GFR and RPF levels in diabetic animals were reduced after aldose reductase inhibition. Also, Wilkes and Silverman (14) and Goldfarb et al. (15) demonstrated a GFR decrease, whereas Daniels and Hostetter (16), who investigated insulin-treated rats, found no influence of aldose reductase inhibition of GFR. In the study by Mauer et al. (2) dealing with both structural and functional diabetic abnormalities in long-term diabetic rats, GFR was unchanged but, as noted by the researchers, the diabetic model used did not give rise to hyperfiltration. Apparently, the application of different aldose reductase inhibitors does not explain the varying results. Studies with the same inhibitor have given opposite results (1,2,12,15), and Tilton et al. (1) reported normalization of GFR with three structurally different inhibitors. Thus, no overall conclusion can be made on GFR and polyol-pathway activity in experimental diabetes. However, in certain models of diabetes, aldose reductase inhibition reduces hyperfiltration. Regarding the mechanisms involved in this GFR reduction, Tilton et al. suggest that the effect is partly mediated by a lowering of RPF and partly by an altered balance between afferent and efferent arteriolar resistance, which decreases the glomerular transcapillary hydraulic pressure difference (ΔP).

In human diabetes, this study could not clearly identify which GFR determinants were responsible for the decrease in GFR. We did not find any change in RPF during ponalrestat. However, reservations must be made that ponalrestat might influence the tubular secretion of hippuran. In addition, hippuran extraction could be influenced by the diabetic state (17). Because plasma albumin was unchanged during ponalrestat, it is probable that the oncotic pressure difference was unchanged. Accordingly, ΔP and/or the ultrafiltration coefficient may have been reduced. The observed decrease in diastolic blood pressure was minor and thus unlikely to account for a decrease in GFR through a lowering of ΔP. In former experimental and clinical studies, no reports on changes in blood pressure during aldose reductase inhibition have appeared (1,2,16,18,19). However, a recent multicenter trial concerning diabetic neuropathy showed a small but significant blood pressure reduction during tolrestat treatment (20).

UAER and ΘAlb was not influenced by the 6-mo ponalrestat treatment. In a preliminary report concerning patients with incipient diabetic nephropathy, a reduction in UAER was seen (21). In the experimental models of diabetes, the results on UAER, like those on GFR and RPF, are not uniform, although most evidence favors a lowering effect on albumin excretion with inhibition of the polyol pathway (1,2,16,22–25).

Animal studies on aldose reductase inhibition have indicated a close relationship between normalization of bio-

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/40/5/527/336711/40-5-527.pdf by guest on 26 March 2023

chemical and functional parameters (1,22,23). Correspondingly, aldose reductase inhibitors have induced no changes in GFR in healthy control animals (2,15). In contrast to animal studies, it was not possible in this study to monitor renal sorbitol accumulation. It has been shown that ponalrestat reduces aldose reductase activity in human erythrocytes, the IC_{50} being achieved by oral doses of 600–1000 mg (26). The application of these results to kidney sorbitol is complicated, e.g., by tissue-specific characteristics of aldose reductase (27,28). However, in animal studies, both erythrocyte and kidney sorbitol has been lowered by ponalrestat administration (16,24,29). Concerning the suggested causality between the GFR reduction and aldose reductase inhibition, changes in protein intake and glycemic control might act as confounding factors. In this study, it is unlikely that a systematic decrease in protein intake took place in the patients given ponalrestat (and not in those receiving placebo). Likewise, systematic confounding changes in other well-known GFR modulators, e.g., growth hormone and glucagon (30), are improbable. Concordantly, growth hormone levels, based on repetitive clearance measurements but not 24-h profile, were unchanged during ponalrestat. Because HbA_{1c} apparently rose during ponalrestat, changes in glycemic control could not account for the decrease in GFR. The explanation for the increase in HbA_{1c} is not obvious. Neither human (18) nor experimental studies (1,2,15,16,31) have indicated that aldose reductase influences total glucose disposal.

Many hypotheses have been put forward on the possible pathogenetic factors associated with high polyol-pathway activity. It has been suggested that a decrease in intracellular *myo*-inositol (32,33), an increase in lactate formation (29,34,35), and changes in redox state (36,37,38) may be involved. Some suggest an increased production of vasodilatory prostaglandins (25,39,40) and abnormalities in ascorbic acid metabolism (41). In our study, the fact that renal vascular resistance was unchanged during aldose reductase inhibition does not confirm the importance of vasoactive prostaglandins. Apart from ponalrestat, no medicine was taken that might have influenced the prostaglandin system. The 6-mo administration of ponalrestat to the normoalbuminuric IDDM patients appeared to be safe. No clinical, biochemical, or hematological side effects were seen. In conclusion, 6 mo of aldose reductase inhibition reduced the characteristic hyperfiltration in uncomplicated IDDM, thereby suggesting a possible pathophysiological role of increased polyol-pathway activity in early hemodynamic changes in diabetic kidney function.

ACKNOWLEDGMENTS

The technical assistance of laboratory technicians M. Møller and E. Bang and the secretarial assistance of A. Andersen are gratefully acknowledged.

Ponalrestat and placebo were kindly supplied by ICI-Pharma.

This study was presented at the meeting of the European Association for the Study of Diabetes 20–23 September 1989 in Lisbon, Portugal.

REFERENCES

1. Tilton RG, Chang K, Pugliese G, Eades DM, Province MA, Sherman WR, Kilo C, Williamson JR: Prevention of hemodynamic and vascular albumin filtration changes in diabetic rats by aldose reductase inhibitors. *Diabetes* 38:1258–70, 1989
2. Mauer SM, Steffes MW, Azar S, Brown DM: Effects of sorbinil on glomerular structure and function in long-term–diabetic rats. *Diabetes* 38:839–46, 1989
3. Mogensen CE: Kidney function and glomerular permeability to macro-molecules in juvenile diabetes. *Dan Med Bull* 19 (Suppl. 3):1–36, 1972
4. Christiansen JS, Gammelgaard J, Tronier B, Svendsen PA, Parving H-H: Kidney function and size in diabetics before and during initial insulin treatment. *Kidney Int* 21:683–88, 1982
5. Christiansen JS, Gammelgaard J, Frandsen M, Parving H-H: Increased kidney size, glomerular filtration rate and renal plasma flow in short-term insulin-dependent diabetics. *Diabetologia* 20:451–56, 1981
6. Mogensen CE: Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. *Scand J Clin Lab Invest* 28:91–100, 1971
7. Miles DW, Mogensen CE, Gundersen HJG: Radioimmunoassay for urinary albumin using a single antibody. *Scand J Clin Lab Invest* 26:5–11, 1970
8. Ørskov H, Thomsen AG, Yde H: Wick-chromatography for rapid and reliable immunoassay of insulin, glucagon and growth hormone. *Nature* (Lond) 219:193–95, 1968
9. Poulsen JH, Jespersen J: A comparison of the determination of glucosylated haemoglobin by isoelectric focusing and cation-exchange chromatography on minicolumns. *Scand J Clin Lab Invest* 46:259–63, 1986
10. Poulsom R: Inhibition of hexonate dehydrogenase and aldose reductase from bovine retina by sorbinil, statil, M79175 and valproate. *Biochem Pharmacol* 35:2955–59, 1986
11. Berger W, Lehner D, Flückiger R: Heterogeneity of sorbitol accumulation in glucose incubated erythrocytes: a possible explanation for the inherent susceptibility to neural complications in diabetic patients (Abstract). *Diabetologia* 29:517A, 1987
12. McCormack AJ, Hak LJ, Finn WF: Effects of aldose reductase inhibition on renal function in long-term experimental diabetes mellitus. In *Proc Satellite Symp Uremic Diabetic, Int Congr Nephrology, 10th, Jerusalem, Israel, 1987*, p. 24
13. McCormack AJ, Finn WF: The effects of aldose reductase inhibitors in diabetic nephropathy. *J Diabetic Complications* 3:18–26, 1989
14. Wilkes B, Silverman S: Metabolic factors in the development and reversal of hyperfiltration in diabetic (DM) rats (Abstract). *Kidney Int* 33:387, 1988
15. Goldfarb S, Simmons DA, Kern EFO: Amelioration of glomerular hyperfiltration in acute experimental diabetes mellitus by dietary *myo*-inositol supplementation and aldose reductase inhibition. *Trans Assoc Am Physicians* 49:67–72, 1986
16. Daniels BS, Hostetter TH: Aldose reductase inhibition and glomerular abnormalities in diabetic rats. *Diabetes* 38:981–86, 1989
17. Nyberg G, Granerus G, Aurell M: Renal extraction ratios for ^{51}Cr-EDTA, PAH, and glucose in early insulin-dependent diabetic patients. *Kidney Int* 21:706–708, 1982
18. Cohen DL, Allawi J, Brophy K, Keen H, Viberti GC: Tolerance, safety and effects of Statil, an aldose reductase inhibitor in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria (Abstract). *Diabetologia* 31:477A, 1989
19. Jennings PE, Nightingale S, Le Guen C, Lawson N, Williamson JR, Hoffman P, Barnett AH: Prolonged aldose reductase inhibition in chronic peripheral diabetic neuropathy: effects on microangiopathy. *Diabetic Med* 7:63–68, 1990
20. Boulton AJM, Levin S, Comstock J: A multicentre trial of the aldose-reductase inhibitor, tolrestat, in patients with symptomatic diabetic neuropathy. *Diabetologia* 33:431–37, 1990
21. Blohmé G, Smith U: Aldose reductase inhibition reduces urinary albumin excretion rate in incipient diabetic nephropathy (Abstract). *Diabetologia* 31:467A, 1989
22. Beyer-Mears A: The polyol pathway, sorbinil, and renal dysfunction. *Metabolism* 35 (Suppl. 1):46–54, 1986
23. Williamson JR, Chang K, Rowold E, Marvel J, Tomlinson M, Sherman WR, Ackermann KE, Kilo C: Sorbinil prevents diabetes-induced increases in vascular permeability but does not alter collagen cross-linking. *Diabetes* 34:703–705, 1985
24. McCaleb ML, Sredy J, Millen J, Ackerman DM, Kvornik D: Prevention of urinary albumin excretion in 6 month streptozotocin-diabetic rats with the aldose reductase inhibitor tolrestat. *J Diabetic Complications* 2:16–18, 1988
25. Larkins RG, Chang WP, Dimitriadis E, Brown S, Dunlop ME: Aldose reductase inhibitors reduce glomerular prostaglandin production and urinary albumin excretion in experimental diabetes (Abstract). *Diabetologia* 31:508A, 1989
26. Norris SC, Perkins CM, Bastain W, Mirrlees D, Yates RA: Studies on the pharmacokinetics and pharmacodynamics of 'Statil' (ICI 128,436), an aldose reductase inhibitor (Abstract). *Clin Sci* 69 (Suppl. 12):22p, 1985
27. Flynn TG: Aldose and aldehyde reductase in animal tissues. *Metabolism* 35 (Suppl. 1):105–108, 1986

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/40/5/527/336711/40-5-527.pdf by guest on 26 March 2023

28. Kador PF, Kinoshita JH, Sharpless NE: The aldose reductase inhibitor site. *Metabolism* 35 (Suppl. 1):109–13, 1986
29. Sochor M, Kunjara S, McLean P: The effect of aldose reductase inhibitor statil (ICI 128436) on the glucose over-utilization in kidney of diabetic rats. *Biochem Pharmacol* 37:3349–56, 1988
30. Christiansen JS: On pathogenesis of the increased glomerular filtration rate in short-term insulin-dependent diabetes. *Dan Med Bull* 31:349–61, 1984
31. Stribling D, Mirrlees DJ, Harrison HE, Earl DCN: Properties of ICI 128,436, a novel aldose reductase inhibitor, and its effects on diabetic complications in the rat. *Metabolism* 34:336–44, 1985
32. Greene DA, Lattimer SA, Sima AAF: Sorbitol, phosphoinositides, and sodium-potassium-ATPase in the pathogenesis of diabetic complications. *N Engl J Med* 316:599–606, 1987
33. Kinoshita JH, Nishimura C: The involvement of aldose reductase in diabetic complications. *Diabetes Metab Rev* 4:323–37, 1988
34. Harrison HE, Stribling D, Armstrong FM, Perkins CM: Aldose reductase in the etiology of diabetic complications. I. Introduction. *J Diabetic Complications* 3:6–11, 1989
35. Poulsom R, Mirrlees DJ, Earl DCN, Heath H: The effects of an aldose reductase inhibitor upon the sorbitol pathway, fructose-1-phosphate and lactate in the retina and nerve of streptozotocin-diabetic rats. *Exp Eye Res* 36:751–60, 1983
36. Barnett PA, Gonzalez RG, Chylack LT Jr, Cheng H-M: The effect of oxidation on sorbitol pathways kinetics. *Diabetes* 35:426–32, 1986
37. Gonzalez A-M, Sochor M, Hothersall JS, McLean P: Effect of aldose reductase inhibitor (Sorbinil) on integration of polyol pathway, pentose phosphate pathway, and glycolytic route in diabetic rat lens. *Diabetes* 35:1200–205, 1986
38. Carroll PB, Thornton BM, Greene DA: Glutathione redox state is not the link between polyol pathway activity and *myo*-inositol–related Na^+-K^+-ATPase defect in experimental diabetic neuropathy. *Diabetes* 35:1282–85, 1986
39. Craven PA, DeRubertis FR: Sorbinil suppresses glomerular prostaglandin production in the streptozotocin diabetic rat. *Metabolism* 38:649–54, 1989
40. Frey J, Zager P, Jackson J, Eaton P, Scavini M: Aldose-reductase activity mediates renal prostaglandin production in streptozotocin diabetic rats (Abstract). *Kidney Int* 35:292, 1989
41. Yue DK, McLennan S, Fisher E, Heffernan S, Capogreco C, Ross GR, Turtle JR: Ascorbic acid metabolism and polyol pathway in diabetes. *Diabetes* 38:257–61, 1989

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/40/5/527/336711/40-5-527.pdf by guest on 26 March 2023