Diabetes Complications: The Renal-Retinal Link

An epidemiological perspective

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The long-established close relationship between the renal and retinal complications of insulin-dependent diabetes mellitus (IDDM) (1) has been further described by Chavers et al. (2), who demonstrate considerable pathological concordance between these two often devastating complications. However, the concordance was not absolute, for while 57% of those with advanced retinopathy also had overt nephropathy (ON), 13% had normal measures of glomerular structure and only low-level microalbuminuria (MA) or normal urinary albumin excretion. This important study, investigating the association between pathological changes in the kidney and retinal tissues, was based on a relatively small sample of patients with IDDM (n = 86) who were being considered for pancreas transplantation. These subjects were, therefore, not likely to be fully representative of all IDDM patients. A further (understandable) limitation of the study was that the authors did not examine the relationship between risk factors other than hypertension and the above-mentioned complications.

To examine such issues in a broader epidemiological context, we review data on the concordance of renal and retinal disease from the Epidemiology of Diabetes Complications (EDC) Study, a large on-going prospective investigation of the development of IDDM complications in an incident-defined cohort of childhood-onset IDDM patients.

The EDC Study prevalence rates of the major complications based on information obtained at baseline (1986–1988) from this cohort (all diagnosed as children between 1950 and 1980) have been published (3). All subjects who agreed to take part (n = 658, mean age 28 years, mean duration 20 years) attended the Diabetes Research Center (Pittsburgh, PA) for a full clinical examination, including blood and urine analysis, the methods for which have been reported extensively elsewhere (3,4). At baseline, a prevalence of ON (defined as an albumin excretion rate >200 μg/min in multiple timed urine samples) of 29% for males and 23% for females was observed. For proliferative retinopathy (PR) (defined as grade 60 or higher in at least one eye, according to the modified Airlie House classification (5) of stereo fundus photographs), these figures were 33% for males and 30% for females. A strong association with duration of diabetes was observed for both complications, in common with other studies (6,7). For example, at 10 years' duration, prevalence rates for nephropathy were only 2% for males and 0% for females, while the rates for PR were 0% for males and 2% for females. By 30 years' duration, however, prevalence rates for nephropathy reached 50% for males and 40% for females. Rates for PR were even higher at 80% (males) and 70% (females) by this time. As the vast majority of patients will thus develop advanced retinopathy, considerable concordance of complications will occur simply because of the high prevalence rates and shared associations with duration.

In one approach, to account for duration effects, individuals who had had IDDM for 25 years or more were considered separately (4), based on the assumption that most subjects who have an accelerated course of complications will have developed such complications by this duration. In support of the report of Chavers et al. (2), considerable discordance between nephropathy and retinopathy was found. Of the subjects who had PR, 49% did not have ON. Indeed, 22% did not even have MA (defined as an albumin excretion rate 20–200 μg/min in multiple timed urine samples) (8). Thus, it seems unlikely that renal and retinal disease are linked genetically, unless two types of retinal disease exist—one linked to and the other independent of renal disease.

A further suggestion from EDC data, also consistent with the report by Chavers et al. (2), is that virtually all those with IDDM will develop some degree of most complications given sufficient duration and, at least for the microvascular complications of IDDM, hyperglycemic exposure. This is illustrated in Table 1, where EDC subjects are stratified (based on the median split of the distribution for the total EDC population) by both glycemic control (HbA_1) and duration of dia-

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AR, advanced background retinopathy; EDC, Epidemiology of Diabetes Complications; IDDM, insulin-dependent diabetes mellitus; LDL, low-density lipoprotein; MA, microalbuminuria; ON, overt neuropathy; OR, odds ratio; PR, proliferative retinopathy; RF, renal failure.

Table 1—*The EDC Study: prevalence of renal and retinal disease by duration of diabetes and glycemic control*

	Duration of diabetes	
	<18.5 years	≥18.5 years
Fair control (HbA_1 <10.2%)		
PR and ON	5(7)*	25(45)
AR/PR and MA/ON	17(26)*	42(75)
Poor control (HbA_1 ≥10.2%)		
PR and ON	6(11)*	34(51)
AR/PR and MA/ON	17(30)*	61(92)

Data are % (*n*). The ORs (95% confidence interval) for PR/ON and AR^+/MA^+ for control (poor vs. fair) are 1.3(0.8–1.9) and 1.4(1.0–1.9) and for duration (≥18.5 vs. <18.5 years) are 7.0(4.0–12.4) and 4.9(3.4–7.2), respectively. *$P < 0.001$, compared with duration ≥18.5 years.

betes. Saline incubated HbA_1 was measured initially by microcolumn cation-exchange chromatography (Isolab, Akron, OH). Approximately halfway through the baseline examination, a high-performance liquid chromatography method (Diamat, Bio-Rad, Hercules, CA) was introduced, which correlated strongly with the microcolumn method [$r = 0.96$; Diamat (HbA_1) = −0.18 + 1.00 Isolab (HbA_1)]. The proportion of those with both PR and ON or with at least both AR and MA at baseline is reported. Table 1 also illustrates the powerful effect of duration on the development of complications. Furthermore, while only 17% of subjects with <18.5 years' duration in fair control had both retinal and renal disease (i.e., at least AR and MA), these rates were over three times higher (61%) in those with poor control and a duration of 18.5 years or more. Interestingly, the level of glycemic control had a much smaller effect than the duration on the prevalence of these complications (odds ratio [OR] = 1.4 vs. 4.9, respectively). Adjusting the control ORs for duration and vice versa had minimal effect (i.e., 1.6 and 5.1, respectively). Because prospective data, including that from clinical trials (9,10), have confirmed a considerable role for glycemic control as a risk factor for the development of microvascular diabetes complications, these cross-sectional data may understate the role of glycemic control. However, they do help to put the dual roles of glycemia and duration into perspective. Thus, the key factor is likely to be the product of duration × hyperglycemia with glycemic control and duration being at least additive factors. Although poor control (hyperglycemia) will lead to earlier complications, eventually even those in good control will build up sufficient exposure (i.e., duration) to lower degrees of hyperglycemia to develop the complications.

Thus, much of the concordance of retinal and renal disease may relate to shared links with duration and hyperglycemia. However, other variables should also be considered as possible determinants of the concordance of these two complications. In particular, blood pressure may relate to the concordance between retinopathy and nephropathy, as it both has been implicated in the development of these complications (11–14) and, confusingly, is exacerbated by renal disease, potentially giving rise to a self-perpetuating cycle of complication production. Chavers et al. (2) and others (11–13) suggest that hypertension is a major mediator of the renal-retinal link. Chavers et al. (2) showed that 89% of the hypertensive subjects in their study had retinopathy and the vast majority (93%) of the 28 subjects with ON and hypertension also had advanced retinopathy (2). The association between hypertension and PR was also investigated in a recent EDC report on the 2-year incidence of PR. Interestingly, although hypertension was found to be significantly associated with subsequent PR, this was true only in subjects with ON (14). Blood pressure levels were not significantly higher in subjects who developed PR but who did not have ON at baseline. These data confirm the importance of hypertension in explaining the nephropathy-retinal link, data further confirmed by the 4-year incidence analyses from the EDC Study (15).

Other potential risk factor links include lipoproteins and fibrinogen (15,16). In a series of Cox Proportional Hazards models for the 4-year incidence of each complication in the EDC Study, namely PR, MA, ON, and renal failure (RF) (defined as on dialysis/post–kidney transplant or having a serum creatinine >5mg/dl), the best prediction models for all these endpoints included hypertension, with glycemic control also being important for both PR and the early stages of nephropathy (MA) (9). Other risk factors were lipoproteins (low-density lipoprotein [LDL] cholesterol in MA and ON, high-density lipoprotein cholesterol in PR, triglycerides in PR and RF, and fibrinogen in MA and ON, with total platelet count also contributing to PR). Interestingly, adding nephropathy did not improve the prediction of PR, suggesting that the link between nephropathy and PR is largely explained by common risk factors, in this case blood pressure and lipoproteins. This confirmed an earlier report using multiple logistic regression analyses rather than Cox modeling, which also showed that the association between nephropathy and the 4-year incidence of PR was predicted in multivariate models by the presence of hypertension, total platelet count, and fibrinogen just as well as it was predicted by the presence of nephropathy (15).

Further analyses from the EDC Study have shown strong lipid associations with renal disease, with LDL cholesterol being the major predictor of the incidence of MA (17) and the major

correlate of the regression of ON (18). These observations raise the possibility of another potential approach to preventing renal (and retinal) disease, i.e., lipid modulation.

In conclusion, the considerable concordance of nephropathy and retinopathy observed in various studies, including our own, is far from absolute. The association between these two serious complications may be largely mediated by shared associations with factors such as disease duration and the degree of hyperglycemia. In addition, hypertension and elevated lipoprotein concentrations, both of which may be further affected by the development of renal disease itself, appear to relate to the pathogenesis of both complications. While the importance of maintaining good glycemic control is now accepted and part of everyday clinical practice, it should also become a priority to reduce blood pressure levels (a recent angiotensin converting enzyme inhibitor trial should provide further impetus for this [19]) and to consider evaluation of aggressive treatment of lipid abnormalities to further attempt to delay the onset of both nephropathy and retinopathy.

References

1. Root HF, Pote WH, Frehner H: Triopathy of diabetes: a sequence of neuropathy, retinopathy and nephropathy. *Arch Intern Med* 94:931–941, 1954
2. Chavers BM, Mauer SM, Ramsay RC, Steffes MW: Relationship between retinal and glomerular lesions in IDDM patients. *Diabetes* 43:441–446, 1994
3. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH: Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 39:1116–1124, 1990
4. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Ellis D, LaPorte RE, Kuller LH, Wolfson SK, Drash AL: Factors associated with avoidance of severe complications after 25 yr of IDDM: Pittsburgh Epidemiology of Diabetes Complications Study I. *Diabetes Care* 13:741–747, 1990
5. Early Treatment of Diabetic Retinopathy Study Coordinating Center: *Manual of Operations*. Baltimore, MD, Diabetic Retinopathy Coordinating Center, Univ. of Maryland School of Medicine, 1980, Chapt. 5 and 18
6. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: Glycosylated hemoglobin predicts the incidence of and progression of diabetic retinopathy. *J Am Med Assoc* 260:2864–2871, 1988
7. Krolewski AS, Warram JH, Christlieb AR, Busick EJ, Kahn CR: The changing natural history of nephropathy in type 1 diabetes. *Am J Med* 78:785–794, 1985
8. Donahue RP, Orchard TJ: Diabetes mellitus and macrovascular complications. *Diabetes Care* 15:1141–1155, 1992
9. Orchard TJ, Drash A: Does glycosylated hemoglobin predict the incidence of late complications of IDDM? (Abstract). *Diabetes* 43 (Suppl. 1):25A, 1994
10. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
11. Chase HP, Garg SK, Jackson WE: Blood pressure and retinopathy in type 1 diabetes. *Ophthalmology* 97:155–159, 1990
12. Krolewski AS, Canessa M, Warram JH, Laffel MB, Christlieb AR, Knowler WC, Rand LI: Predisposition to hypertension and susceptibility to renal disease in insulin-dependent diabetes mellitus. *N Engl J Med* 318:140–145, 1988
13. Norgaard K, Feldt-Rasmussen, Deckert T: Is hypertension a major risk factor for retinopathy in Type 1 diabetes? *Diabetic Med* 8:334–337, 1991
14. Lloyd CE, Klein R, Maser RE, Kuller LH, Becker DJ, Orchard TJ: The progression of retinopathy over 2 years: the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. *J Diabetes and Its Complications*. In press
15. Orchard TJ: From diagnosis and classification to complications and therapy: DCCT Part II? The 1993 Kelly West Lecture. *Diabetes Care* 17:326–338, 1994
16. Kostraba JN, Klein R, Dorman JS, Becker DJ, Drash AL, Maser RE, Orchard TJ: The Epidemiology of Diabetes Complications Study: Correlates of diabetic background and proliferative retinopathy. *Am J Epidemiol* 133:381–391, 1991
17. Coonrod BA, Ellis D, Becker DJ, Bunker CH, Kelsey SF, Lloyd CE, Drash AL, Kuller LH, Orchard TJ: Predictors of microalbuminuria in individuals with insulin-dependent diabetes mellitus. *Diabetes Care* 16:1–8, 1993
18. Orchard T, Wilson R, Ellis D: Natural history of overt nephropathy in insulin dependent diabetes mellitus: correlates of regression (Abstract). *Diabetes* 42 (Suppl. 1):135A, 1993
19. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456–1462, 1993