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Intrauterine determinants of diabetic kidney disease in disadvantaged populations

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Intrauterine determinants of diabetic kidney disease in disadvantaged populations. Disadvantaged populations worldwide are experiencing an increasing incidence of kidney disease, much of which is attributable to diabetes. This report reviews the evidence that intrauterine exposure to growth retardation, diabetes, and vitamin A deficiency contribute disproportionately to the rising incidence of kidney disease in disadvantaged people, because they encounter these exposures more frequently than people from developed countries. These abnormal intrauterine exposures reduce nephron mass by impairing nephrogenesis, thereby increasing the susceptibility to kidney damage from diseases such as hypertension and diabetes that commonly affect disadvantaged people.

A growing body of evidence suggests that fetal exposure to an abnormal intrauterine environment has lasting effects on anthropomorphic and metabolic development that lead to increased risk of disease later in life. Offspring exposed to diabetes in utero, for example, are prone to obesity and diabetes at a young age, and offspring with intrauterine growth retardation, reflected by a low birth weight, are prone to ischemic heart disease, chronic obstructive pulmonary disease, diabetes, and hypertension.

This report reviews the evidence that intrauterine exposure to growth retardation, diabetes, and vitamin A deficiency predispose the offspring to kidney disease. These exposures were selected because of their disproportionately elevated frequency in many disadvantaged populations. Since much of the increase in the incidence of kidney disease in these populations is attributable to diabetes, this report focuses primarily on the effects of exposure to an abnormal intrauterine environment in people with diabetes. Nevertheless, these exposures also appear to enhance the risk of non-diabetic kidney disease. Portions of this report were published recently in a review of the genetic and environmental determinants of kidney disease in disadvantaged populations [1].

Key words: birth weight, diabetic nephropathy, type 2 diabetes mellitus, vitamin A deficiency, intrauterine environment, neonate, nephron mass.

SCOPE OF THE PROBLEM

Diabetes

About 135 million adults worldwide had diabetes in 1995 and the vast majority of them had type 2 diabetes. The highest prevalence was found in the developed countries, but the global distribution of diabetes is changing [2]. Over the next 30 years, the number of people with diabetes is expected to increase by 170% in developing countries and by 42% in developed countries [2]. Unlike the developed countries, where most cases of diabetes are found in people ≥65 years of age, most cases in developing countries occur in those between 45 and 64 years of age, and a substantial number are found in those between 20 and 44 years of age, the childbearing years [2]. The earlier onset of diabetes in developing countries also is found in some disadvantaged groups in developed countries. Examples include American Indians, Black Americans, Mexican Americans, Australian Aborigines, and migrant Chinese and Asian Indians. The greater frequency of diabetes during the childbearing years in these populations means that the offspring are more likely to be exposed to a diabetic intrauterine environment and suffer the consequences of that exposure.

Diabetic kidney disease

Substantial ethnic differences in the incidence of end-stage renal disease (ESRD) attributable to type 2 diabetes are found in several large population-based studies [3, 4]. Pugh and coworkers reported that even after adjusting for differences in the prevalence of diabetes, the incidence of ESRD in black Americans was nearly four times as high as in non-Hispanic whites, and the rate in Mexican Americans was 2.5 times as high [4]. Burden and coworkers noted that Asians in the United Kingdom had 14 times the incidence of diabetic end-stage renal disease as the Caucasians in the same region [5], and we found that the rate in diabetic Pima Indians was 14 times as high as the estimated rate in the U.S. diabetic population aged 45 to 64 years [6]. Numerous factors account for these differences, but exposure to an abnormal intra-

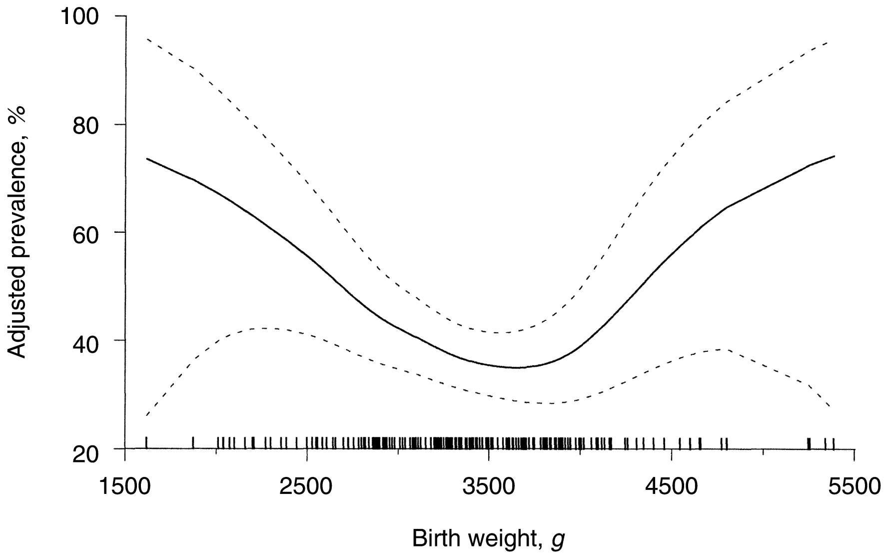

Fig. 1. Prevalence of elevated urinary albumin excretion (albumin-to-creatinine ratio ≥30 mg/g) in diabetic Pima Indians, by birth weight, adjusted for age, sex, duration of diabetes, HbA_{1c}, and mean arterial pressure. Dashed lines represent twice the point-wise asymptotic standard errors of the estimated curve, and the vertical tics on the x-axis are a frequency plot of birth weights. Values of the covariates were set to their sample means (Reprinted with permission from Nelson et al [15]).

uterine environment may contribute to a greater acceleration in the rate of kidney disease in disadvantaged populations than in the rest of the developed world, because of the higher frequency of such exposure in disadvantaged people.

Abnormal intrauterine exposures are important in the pathogenesis of kidney disease because they occur during nephrogenesis. Nephron development begins during the fifth week of gestation and continues into the third trimester. Induction of about 60% of the normal complement occurs during the third trimester. Under normal circumstances, new nephron formation ceases between 28 and 36 weeks of gestation. Since additional nephrons do not form after birth, damage that occurs as a result of exposure to an abnormal intrauterine environment may have long-lasting effects that are more likely to become clinically apparent when the individual is exposed to diseases, such as hypertension and diabetes, that further damage the kidney. Several such exposures are considered in the next section.

ABNORMAL INTRAUTERINE EXPOSURES

Intrauterine growth retardation

Brenner and Chertow proposed that nephron development is impaired in people of low birth weight because of a critical shortage of the fuels necessary for fetal development [7]. The low nephron mass, in turn, heightens the risk of kidney disease later in life. Consistent with this hypothesis are two autopsy studies, which found that infants of low birth weight had fewer glomeruli than those of normal birth weight [8, 9]. Furthermore, low birth weight was associated with reduced kidney volume by ultrasound in Australian Aboriginal children examined at ages 5 to 18 years [10], and the prevalence of elevated urinary albumin excretion (urinary albumin-to-creatinine ratio ≥300 mg/g) was twice as high in Aboriginal adults of low birth weight than in those with normal birth weight, regardless of whether or not they had diabetes [11]. Low birth weight is common in Aborigines, since over one fourth of them weigh less than 2500 g at birth, presumably as a consequence of poverty and malnutrition [12]. Lackland and coworkers extended these observations by reporting that low birth weight contributes to the early onset of kidney failure from multiple causes in blacks and whites of both sexes in South Carolina [13].

Birth weight may affect the development of kidney disease in both major types of diabetes. In type 1 diabetes, Rossing and coworkers reported that 75% of women below the 10^{th} percentile of birth weight (≤2700 g) had persistent albuminuria (≥300 mg/24 h) compared with 35% of those above the 90^{th} percentile [14]. No relationship was found, however, between urinary albumin excretion and birth weight in the diabetic men. In Pima Indians with type 2 diabetes, the prevalence of elevated urinary albumin excretion (urinary albumin-to-creatinine ratio ≥30 mg/g) was twice as high in men and women of low birth weight than in those of normal birth weight (Fig. 1) [15].

Whereas these studies suggest that low birth weight increases the frequency of kidney disease, Zidar and coworkers suggested that impaired nephron development also might increase the severity of kidney disease [16, 17]. They reported more relapses and a higher incidence of steroid dependency among low birth weight children with minimal change nephrotic syndrome than among children of normal birth weight [16], and an increased risk of hypertension and glomerulosclerosis among low birth weight children with IgA glomerulonephritis than among those of normal birth weight [17]. The higher risk of low birth weight in many disadvantaged populations, in comparison with the populations of developed coun-

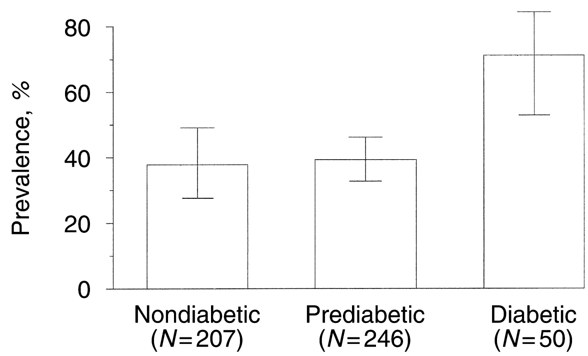

Fig. 2. Predicted prevalence (95% CI) of elevated urinary albumin excretion (albumin-to-creatinine ratio ≥30 mg/g) in diabetic Pima Indians, by maternal diabetes status, adjusted for age, sex, duration of diabetes, HbA_{1c}, and mean arterial pressure. Values of the covariates were set to their sample means (Reprinted with permission from Nelson et al [20]).

tries, may be responsible, in part, for the higher rates and more rapid progression of diabetic and non-diabetic kidney disease reported in many parts of the world.

Intrauterine diabetes exposure

A shortage of maternal fuels is not the only mechanism of injury to developing nephrons. Freinkel proposed that fetal exposure to fuel-mediated alterations in maternal metabolism in pregnancies complicated by diabetes may preferentially harm poorly replicating, terminally differentiated cells—such as those found in the nephron—perhaps by reducing the number of such cells or by altering their functional capacity [18]. The adverse effect of hyperglycemia on nephrogenesis was demonstrated experimentally by exposing pregnant rats to hyperglycemia, either by inducing diabetes on day zero of gestation with a single injection of streptozotocin or by infusing glucose from gestational days 12 to 16, and counting the nephrons in the offspring [19]. The number of nephrons was reduced by up to 35% in the offspring of the streptozotocin treated rats. In vitro experiments from the same study, which examined metanephroi from 14-day-old fetuses exposed to various glucose concentrations, indicated that even minor elevations of glucose concentration were associated with impaired metanephros development [19].

In Pima Indians, the odds of having elevated urinary albumin excretion was nearly four times as high in subjects exposed to diabetes in utero than in those exposed to a normal intrauterine environment [20]. Figure 2 shows the predicted prevalence of elevated urinary albumin excretion (urinary albumin-to-creatinine ratio ≥30 mg/g) by maternal diabetes status, after adjusting for age, sex, duration of diabetes, HbA_{1c}, and mean arterial pressure.

Maternal diabetes during pregnancy is believed to lead to a vicious cycle in which each successive generation has a higher risk of having diabetes by the time it reaches the childbearing years than the preceding generation. Given the heightened risk of elevated urinary albumin excretion associated with exposure to maternal diabetes during pregnancy, this vicious cycle could lead also to a corresponding increase in the incidence of diabetic kidney disease in subsequent generations [20]. Evidence for a vicious cycle is provided by Dabelea and coworkers, who reported that the proportion of Pima children exposed to diabetes in utero increased nearly fourfold over the past 30 years, rising from 2% of births in 1967 to 1976 to nearly 8% of births in 1987 to 1996 (Table 1) [21]. The increased frequency of exposure to maternal diabetes was associated with a doubling of the cases of diabetes attributable to that exposure [21]. Coincident with the rise in diabetes prevalence was a doubling of the incidence of proteinuria that occurred despite improvements in plasma glucose and blood pressure control (Fig. 3) [22]. This finding is in sharp contrast with a 30 to 50% decline in the risk of proteinuria among patients diagnosed with type 1 diabetes since the 1930s. Although the increasing incidence of proteinuria cannot be attributed with certainty to the increasing frequency of intrauterine exposure to diabetes, the temporal relationship between these two phenomena is compelling.

Table 1. Frequency of exposure to diabetes in utero and attributable risk of diabetes, in three time periods

Years of examination	1967–76	1977–86	1987–96
Exposure to diabetes in utero %	2.1	4.0	7.5
Odds ratio for diabetes	13.5	10.3	10.4
Attributable risk[a] %	18.1	23.7	35.4

Adapted with permission from Dabelea et al [21].
[a] Attributable risk = (OR-1)P/OR, where OR is the odds ratio and P is the proportion of cases exposed

Vitamin A deficiency

Vitamin A (retinol) and its main derivative, retinoic acid, are involved in nephrogenesis, and rats exhibit a dose-dependent effect of vitamin A on nephron number [23]. Both retinol and retinoic acid are potent stimulators of nephrogenesis, with a single injection of retinoic acid given to a pregnant rat at mid-gestation inducing supernumerary nephrons. Although human data on the relationship between vitamin A and nephron mass are not available, the existing animal data suggest that a mild vitamin A deficiency during pregnancy could lead to a nephron deficit in the offspring that enhances the risk of kidney disease. Although vitamin A deficiency is not a major health problem in developed countries, it is frequently encountered in developing countries, particularly in pregnant women, in whom intake of vitamin A may be inadequate to meet the increased demands encountered during pregnancy. Accordingly, fetal vitamin A deficiency may disproportionately affect minority and disadvantaged populations and contribute to their increasing incidence of kidney disease.

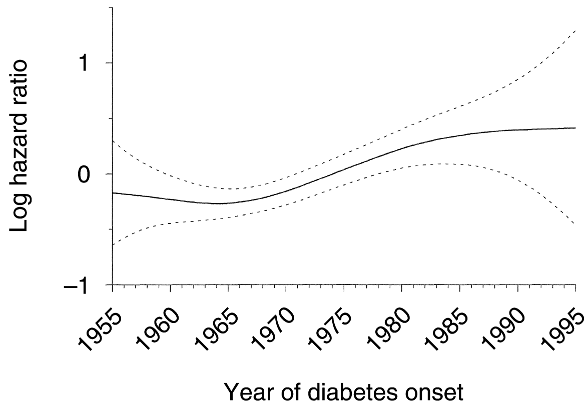

Fig. 3. Function plot for the effect of year of onset of diabetes on the incidence rate of proteinuria in the additive proportional hazards model. The curve is centered to have an average of zero over the range of the data. The dashed lines represent the approximate point-wise 95% confidence intervals (Reprinted with permission from Nelson et al [22]).

CONCLUSIONS

The incidence of kidney disease, particularly diabetic kidney disease, is increasing rapidly in many disadvantaged populations throughout the world. Exposure to an abnormal intrauterine environment may be a contributing factor to this rise, since each of the exposures reviewed in this report occur more frequently in the developing world and in the disadvantaged populations of the developed world. The reduction in nephron mass that follows each of these exposures reduces the reserve capacity of the kidneys, thereby increasing the susceptibility to kidney damage from diseases such as hypertension and diabetes that commonly affect disadvantaged people. The rapidly increasing frequency of intrauterine diabetes exposure in successive generations of Pima Indians suggests that the worldwide epidemic of kidney disease, particularly diabetic kidney disease, may actually accelerate in the future as diabetes becomes more prevalent during the childbearing years. To counter this epidemic of kidney disease will require inexpensive and effective ways to address the numerous public health needs of disadvantaged people.

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REFERENCES

1. Nelson RG: Diabetic renal disease in transitional and disadvantaged populations. *Nephrol* 6:9–17, 2001
2. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025. Prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
3. Cowie CC, Port FK, Wolfe RA, *et al*: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989
4. Pugh JA, Medina RA, Cornell JC, Basu S: NIDDM is the major cause of diabetic end-stage renal disease. More evidence from a tri-ethnic community. *Diabetes* 44:1375–1380, 1995
5. Burden AC, McNally PG, Feehally J, Walls J: Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. *Diabetic Med* 9:641–645, 1992
6. Nelson RG, Newman JM, Knowler WC, *et al*: Incidence of end-stage renal disease in type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians. *Diabetologia* 31:730–736, 1988
7. Brenner BM, Chertow GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171–175, 1994
8. Hinchliffe SA, Lynch MR, Sargent PH, *et al*: The effect of intrauterine growth retardation on the development of renal nephrons. *Br J Obstet Gynaecol* 99:296–301, 1992
9. Mañalich R, Reyes L, Herrera M, *et al*: Relationship between weight at birth and number and size of renal glomeruli in humans: A histomorphometric study. *Kidney Int* 58:770–773, 2000
10. Spencer J, Wang Z, Hoy W: Low birth weight and reduced renal volume in Aboriginal children. *Am J Kidney Dis* 37:915–920, 2001
11. Hoy WE, Rees M, Kile E, *et al*: Low birthweight and renal disease in Australian aborigines. *Lancet* 352:1826–1827, 1998
12. Hoy WE, Mathews JD, McCredie DA, *et al*: The multidimensional nature of renal disease: Rates and associations of albuminuria in an Australian Aboriginal community. *Kidney Int* 54:1296–1304, 1998
13. Lackland DT, Bendall HE, Osmond C, *et al*: Low birth weights contribute to the high rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med* 160:1472–1476, 2000
14. Rossing P, Tarnow L, Nielsen FS, *et al*: Low birth weight. A risk factor for development of diabetic nephropathy? *Diabetes* 44:1405–1407, 1995
15. Nelson RG, Morgenstern H, Bennett PH: Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol* 148:650–656, 1998
16. Zidar N, Cavic MA, Kenda RB, Ferluga D: Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation. *Kidney Int* 54:1320–1323, 1998
17. Zidar N, Čavic MA, Kenda RB, *et al*: Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. *Nephron* 79:28–32, 1998
18. Freinkel N: Banting Lecture 1980: Of pregnancy and progeny. *Diabetes* 29:1023–1035, 1980
19. Kaouthar A, Freund N, Vilar J, *et al*: Adverse effects of hyperglycemia on kidney development in rats. In vivo and in vitro studies. *Diabetes* 48:2240–2245, 1999
20. Nelson RG, Morgenstern H, Bennett PH: Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. *Diabetes* 47:1489–1493, 1998
21. Dabelea D, Hanson RL, Bennett PH, *et al*: Increasing prevalence of Type II diabetes in American Indian children. *Diabetologia* 41:904–910, 1998
22. Nelson RG, Morgenstern H, Bennett PH: An epidemic of proteinuria in Pima Indians with type 2 diabetes mellitus. *Kidney Int* 54:2081–2088, 1998
23. Merlet-Bénichou C: Influence of fetal environment on kidney development. *Int J Dev Biol* 43:453–456, 1999