

Tracking ancient pathways to a modern epidemic: Diabetic end-stage renal disease in Saskatchewan aboriginal people

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Tracking ancient pathways to a modern epidemic: Diabetic end-stage renal disease in Saskatchewan aboriginal people.

Background. Saskatchewan aboriginal people are experiencing an epidemic of type 2 diabetes (T2DM) and diabetic end-stage renal disease (ESRD). The purpose of these investigations was to study the role of the intrauterine environment in the emergence of these diseases.

Methods. Epidemiologic studies were carried out using data from the Provincial Department of Health databases, the Saskatoon Health Region obstetrical unit, the Saskatchewan Renal Transplant Program, surveys of Saskatchewan aboriginal communities, and the Canadian Organ Replacement Registry. Parameters analyzed included rates, risk factors, and outcomes of T2DM, gestational diabetes (GDM), and ESRD; birth registration information; anthropometric measurements; and human leukocyte antigen profiles.

Results. Aboriginal ethnicity is an independent predictor of GDM. High rates of GDM appear in remote aboriginal communities before the significant appearance of T2DM and are associated with increasing rates of high birth weight. A significant relationship between high-birth-weight rates and T2DM was strengthened over several decades. Finally, higher birth weights and older mother's age (both associated with GDM), and increased frequencies of the human leukocyte antigen-A2/DR4 and A2/DR8 haplotypes are associated with ESRD among aboriginal people.

Conclusion. It is likely that diabetic pregnancies play a key role in the initiation, progression, and perpetuation of the T2DM epidemic among Canadian aboriginal peoples, and may additionally increase the risk for ESRD. We speculate that an ancient survival advantage that promoted caloric conservation in young women and their unborn children is now a risk factor for prepregnancy obesity, GDM, and excess fetal nutrition. Infants are often large and have an increased risk for T2DM and its complications (hefty fetal-type hypothesis).

Resumen

Antecedentes. El grupo étnico Saskatchewan está viviendo en la actualidad una epidemia de diabetes tipo 2 (DMT2) y de enfermedad renal crónica terminal secundaria a nefropatía diabética (ERCTD). El objetivo de este estudio es el determinar el papel que juega el ambiente intrauterino en la aparición de estas enfermedades.

Key words: type 2 diabetes mellitus, diabetic ESRD, aboriginal, gestational diabetes, birth weight, maternal age, HLA, hefty fetal type hypothesis, thrifty genotype hypothesis.

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Método. Se realizaron estudios epidemiológicos utilizando la información contenida en las bases de datos del Departamento de Salud Provincial, de la unidad de obstetricia de la Región Sanitaria Saskatoon, del Programa de Trasplante Renal de Saskatchewan, así como de encuestas de las comunidades Saskatchewan y del Registro Canadiense de Reemplazo de Órganos. Los parámetros analizados incluyeron índices, factores de riesgo y consecuencias de la DMT2, diabetes gestacional (DMG) y ERCTD; información al nacer, medidas antropométricas y perfiles de HLA.

Resultados. El factor étnico predice independientemente la DMG. Los elevados índices de DMG se presentan en comunidades aborígenes remotas antes de la aparición de DMT2 y se asocian a índices elevados de alto peso al nacer (APN). Una relación significativa entre los índices de APN y DMT2 se ha acentuado en las últimas décadas. Finalmente, el alto peso al nacer, la mayor edad materna (ambos asociados con DMG), así como la presencia de los haplotipos HLA-A2/DR4 y A2/DR8, se asocian con ERCTD en esta población aborigen.

Conclusion. La diabetes gestacional probablemente juega un papel importante en el inicio, progresión y perpetuación de la epidemia de DMT2 entre los aborígenes canadienses; adicionalmente, pudiera incrementar el riesgo de ERCTD. Sospechamos que la ventaja ancestral que promovía la conservación de calorías en las mujeres jóvenes y en el feto, es actualmente un factor de riesgo de obesidad pregestacional, DMG, y de excesiva nutrición fetal. Sus hijos son robustos y con un riesgo elevado de desarrollar DMT2 (hipótesis del feto robusto).

Saskatchewan aboriginal people are experiencing an epidemic of type 2 diabetes (T2DM) and diabetic end-stage renal disease (ESRD). Although a tuberculosis survey in 1937 disclosed no cases of diabetes among 1500 registered Indians [1], point prevalence studies carried out in Saskatchewan aboriginal communities showed almost a tripling of diabetes prevalence rates from 1980 to 1990 [2]. By 1996, almost 16% of aboriginal adults in Saskatchewan had diabetes, with rates exceeding 30% in older age groups. Overall rates in nonaboriginal adults were under 5% [3].

Rates of ESRD have also increased dramatically [4]. During the period of 1982 to 1985, the incidence of ESRD among Saskatchewan aboriginal people was 3.8 cases/10,000 adults. This increased to 15.1 cases/10,000 adults by 1994 to 1997. Among nonaboriginal people, rates increased from 0.6 cases to 1.6 cases/10,000

adults during the same time. Furthermore, this dramatic increase in DESRD rates is not wholly explained by increasing rates of T2DM. After adjusting for differences in the prevalence of T2DM between aboriginal and non-aboriginal people, aboriginal people with diabetes were 7 times more likely to develop DESRD than nonaboriginal people with diabetes [5]. Thus, DESRD in this population represents an epidemic within an epidemic, and accounts for 60% of all new cases of ESRD among Saskatchewan aboriginal people.

These alarming statistics translate into a devastating toll on patients and their families, as well as an alarming demand on health care resources. Accordingly, it is imperative that effective strategies for the prevention, identification, and treatment of T2DM and its complications be developed for a burgeoning aboriginal population. Increasingly, we have focused our investigations on the diabetogenic potential of the intrauterine milieu. This article will summarize our research to date and review a working hypothesis that provides a possible evolutionary explanation for this modern epidemic [6].

THE ROLE OF THE INTRAUTERINE ENVIRONMENT IN THE EPIDEMIC OF T2DM AMONG SASKATCHEWAN ABORIGINAL PEOPLE

Although there is ample evidence that Saskatchewan aboriginal people are experiencing an epidemic of T2DM and diabetic complications, the relative importance of genetic and various environmental factors in the emergence of T2DM has not been clearly established. We believe that a key factor in this epidemic is the diabetogenic potential of the intrauterine milieu. Pregnant aboriginal women with gestational diabetes (GDM) or preexisting T2DM experience have elevated blood glucose levels that can lead to fetal hyperinsulinemia, increased fuel utilization, and high birth weight (HBW [7]). Freinkel suggested that fetal anthropometric and metabolic changes might continue and contribute to insulin resistance later in life [8]. What is the epidemiologic evidence that diabetic pregnancies are important in the epidemic of T2DM among indigenous peoples? In Saskatchewan, we observed very high rates of GDM in remote, northern aboriginal communities before the significant appearance of T2DM [9]. In an isolated Dene community, 13.9% of women reported a pregnancy complicated by GDM (In contrast, GDM rates in the nonaboriginal Saskatchewan population are currently only 3.5% [10]), while only 4.9% of women (and 2.5% of men) in the same community had T2DM. We subsequently demonstrated that aboriginal ethnicity is an independent risk factor for GDM when combined with prepregnancy obesity [10]. Aboriginal women whose prepregnancy body mass index was <27 had GDM rates only slightly higher than comparable nonaboriginal women; however, abo-

original women whose prepregnancy body mass index was ≥ 27 had GDM rates 5 times higher than rates in obese nonaboriginal women.

We reasoned that high rates of GDM in aboriginal communities would lead to increasing rates of HBW (≥ 4000 g) among aboriginal infants. We subsequently demonstrated an increase in HBW rates in northern Saskatchewan (predominantly aboriginal people) from 14% to 18.3% between 1975 and 1986, whereas HBW rates rose from only 11% to 13% in southern Saskatchewan (predominantly nonaboriginal people) during the same time period [11]. Interestingly, low-birth-weight (LBW <2500 g) rates in both northern and southern Saskatchewan steadily fell during this time to approximately 5% by 1986 [12].

We were aware of the seminal work done among the Pima showing that offspring of women with T2DM and GDM had a propensity to develop early-age onset T2DM [13]. Because we were unable to retrospectively identify women who had experienced diabetic pregnancies, we used HBW as a proxy for this condition. Our next step, therefore, was to examine the relationship between HBW and the future development of T2DM among registered adult Indians in Saskatchewan. We subsequently made the unique Canadian observation that aboriginal people with diabetes are significantly more likely than control populations to have been born with HBW [6]. Moreover, this association between HBW and T2DM strengthened progressively from the middle to the late twentieth century, suggesting that HBW and its causes may be assuming an ever more important role in the T2DM epidemic. It also suggested that the younger the age of T2DM diagnosis in this population, the stronger its relationship with HBW. Young and his colleagues have now shown a direct relationship between diabetic pregnancies and the development of childhood T2DM among native Canadians [14], a finding consistent with earlier reports from the Pima. Importantly, we did not find a relationship between LBW and T2DM as reported elsewhere ("thrifty phenotype" hypothesis [15]). Furthermore, fetal deprivation would be unlikely to contribute to the T2DM epidemic in populations whose LBW rates are decreasing (see above).

In summary, epidemiologic evidence suggests that GDM may represent the earliest manifestation of carbohydrate intolerance among indigenous peoples experiencing acculturation, and play a key role in the initiation, progression, and perpetuation of the T2DM epidemic in such populations.

FETAL DETERMINANTS OF DESRD IN SASKATCHEWAN'S ABORIGINAL POPULATION

If the diabetic intrauterine environment is important in the epidemic of T2DM among aboriginal people, do

diabetic pregnancies play an additional role in the epidemic of DESRD? That question has not been completely answered; however, there is emerging evidence that diabetic pregnancies may have some impact on the development of diabetic nephropathy in offspring.

We have recently carried out a study in Saskatchewan that was designed to identify possible links between birth-related factors and ESRD [16]. A secondary objective was to determine if any observed relationships differed on the basis of ethnicity or diabetic status. This was a 1:3 age-, sex-, and ethnicity-matched case-control study in which patients were Saskatchewan residents born after 1949 with ESRD diagnosed between January 1, 1981 and December 31, 1998. Control subjects were randomly selected from the provincial health registry. Birth registration data analyzed included birth weight, gestational age, and maternal age and parity. For the final analysis, birth registration data existed for 334 cases and 828 controls. Matched birth weight data were obtained for 277 cases (48 aboriginal and 229 nonaboriginal) and 601 controls (112 aboriginal and 489 controls).

Overall, there was a trend for increased rates of LBW in patients with ESRD compared with controls; however, none of the differences was statistically significant. An increased HBW rate among aboriginal patients with ESRD was also not statistically significant. When patients with ESRD were subdivided by diabetic status and ethnicity, however, the most striking finding was that 40% of aboriginal patients with DESRD were born with HBW compared with 15% of controls. Again, this difference was not statistically significant, possibly because of small numbers. Overall, only female patients with ESRD were found to have a significantly higher proportion of LBW compared with controls (odds ratio [OR] = 2.7; confidence intervals [CI] = 1.05, 6.95). This finding was stronger for nonaboriginal women (OR = 3.7; CI = 1.05, 12.73) and for those with non-DESRD. In contrast, aboriginal women with DESRD were more likely to be born with HBW (OR = 6; CI = 0.54, 66.2); however, this latter finding was not statistically significant, again possibly because of small numbers.

Multivariate analysis using conditional logistic regression led to the most unique finding of this study. After adjusting for all other variables, increasing maternal age was the sole birth-related independent predictor for ESRD in Saskatchewan. Patients with ESRD were more than twice as likely to have mothers 30 years of age or older than controls (OR = 2.14; CI = 1.21, 3.78). For cases with non-DESRD (particularly nonaboriginal), those with older mothers had lower mean birth weights (3245 g vs. 3418 g; $P = 0.02$). For female aboriginal cases with DESRD, those with older mothers had higher mean birth weights (3776 g vs. 3247 g; $P = 0.099$).

These findings suggest that different prenatal factors may be operational in the pathogenesis of DESRD versus non-DESRD, possibly modulated by differences in

sex and ethnicity. The finding of lower mean birth weights in patients with non-DESRD whose mothers are older is consistent with the Brenner hypothesis that fetal deprivation may lead to a decrease in nephron numbers and an increased risk for glomerulosclerosis and progressive renal damage [17]. In contrast, the finding of higher mean birth weights in aboriginal patients with DESRD whose mothers are older is consistent with an exposure to a diabetic intrauterine environment. We have previously shown that Saskatchewan aboriginal women aged 30 years or older are approximately 6 times more likely to develop GDM than their nonaboriginal counterparts [10].

Studies from other populations provide additional support for the role of diabetic pregnancies in the development of diabetic nephropathy. Among both Pima Indians [18] and a predominantly black population from South Carolina [19], diabetic nephropathy was more significantly associated with HBW than LBW. In fact, diabetic pregnancies may have a direct effect on fetal kidneys. Nelson has found that Pima diabetic subjects whose mothers had diabetic pregnancies were more likely to have microalbuminuria than diabetic offspring of mothers who did not experience a diabetic pregnancy [20]. This suggests that a diabetic intrauterine environment may have an adverse impact on developing kidneys that compounds the risk for diabetic nephropathy.

THE HEFTY FETAL-TYPE HYPOTHESIS

We have presented evidence that excess fetal nutrition related to diabetic pregnancies can predispose susceptible populations to the later development of T2DM and can possibly increase the risk for diabetic nephropathy. Is there a teleologic rationale that might explain why the intrauterine environment is potentially diabetogenic? Neel speculated that a thrifty genotype enabled people to conserve calories when food supplies were uncertain, but suggested that this had become a risk factor for obesity and T2DM when food supplies were unlimited [21]. In this way, an ancient asset has become a contemporary liability. Would Neel's hypothesis retain its underlying reasoning if taken a step further? By specifically favoring caloric conservation in young women and their unborn children, we have suggested that the thrifty genotype would facilitate optimal fetal nutrition and a "healthy" birth weight [6], thus increasing the chances for survival of both mother and infant. However, modern changes in lifestyle would predispose young women with this genotype to obesity before and during pregnancy, high rates of GDM, and a tendency to have large infants. Our hefty fetal-type hypothesis proposes that an ancient mechanism that evolved as a survival advantage now contributes to a diabetogenic intrauterine environment, which leads to an exponential transfer of risk for T2DM in successive

generations of affected populations as proposed by Petit et al [13, 22].

An evolutionary survival advantage implies a genetic basis that, despite the longevity of Neel's hypothesis, has remained elusive. It also implies that a large proportion of the affected population would have the protective genotype. Although we have not had an opportunity to conduct more sophisticated genetic studies in our center, we have recently reported intriguing findings based on almost 20 years of (human leukocyte antigen) HLA data from our Renal Transplant Program [23]. We reasoned that the younger the age of DESRD diagnosis, the more likely there would be a genetic basis. We found that aboriginal people with DESRD diagnosed in individuals aged <50 years had higher frequencies of the HLA-A2, HLA-DR4, and DR8 antigens than older aboriginal people with DESRD and aboriginal patients with non-DESRD. More significantly, younger aboriginal patients with DESRD were much more likely to have an HLA-A2/DR4 or HLA-A2/DR8 haplotype than the other 2 groups (OR = 5.09; CI = 1.35, 20.15) when compared with older aboriginal patients with DESRD (OR = 3.32; CI = 1.2, 9.3) and when compared with aboriginal patients with non-DESRD. Moreover, 40% of the younger patients with DESRD were homozygous for at least one of A2, DR4, or DR8. An interesting facet to these findings is that HLA-A2, DR4, and DR8 have previously been associated with type 1 diabetes (T1DM) in different populations [24–26]. We also observed high frequencies of other diabetes-associated HLA antigens (A24, B62, DQ3, and DQ4 [27–30]) in all aboriginal ESRD groups in our study, but differences between subgroups were not statistically significant.

It is not clear from this study whether the associations that we have identified are between specific HLA antigens and DESRD, or between HLA antigens and T2DM. In any case, the fact that other North American Indian populations are also known to have high frequencies of A2, A24, DR4, and DR8 [31, 32] lends support to our findings. It also raises the intriguing possibility that these diabetes-associated HLA antigens may reflect a role for the major histocompatibility complex in conferring an evolutionary survival advantage on affected populations.

CONCLUSIONS

The epidemic of T2DM and DESRD among Saskatchewan aboriginal people appears to be due to a complex interaction of genetic and environmental factors. We have provided evidence to support a key role of the diabetic intrauterine milieu in the initiation, progression, and perpetuation of this epidemic. We speculate that an ancient survival advantage that promoted caloric conservation in young women and their unborn children

is now a risk factor for prepregnancy obesity, GDM, and excess fetal nutrition. Infants are often large and have an increased risk for T2DM (hefty fetal-type hypothesis [6]). Emerging evidence suggests that the diabetic intrauterine environment may additionally increase the risk for diabetic nephropathy.

These findings have important implications with respect to the primary prevention of T2DM and diabetic nephropathy. Prevention and/or optimal management of GDM (and T2DM during pregnancy) through promotion of healthy lifestyles could play a major role in this effort. Aboriginal ethnicity is an independent predictor of GDM, particularly when combined with prepregnancy obesity [10]. Accordingly, targeting obesity in pregravid women may be especially beneficial in the prevention of GDM. Because exercise can prevent T2DM in susceptible individuals [33–35], we have also been interested in the use of physical activity in the prevention and management of GDM [36, 37]. We have subsequently found an inverse relationship between frequency of exercise during pregnancy and rates of GDM in aboriginal women [10]. We believe that young aboriginal women are an ideal group for GDM/T2DM prevention programs [38], because they are motivated to engage in healthy lifestyles for the benefit of their unborn children, and the time required for beneficial intervention may be relatively brief. Second, they can be encouraged to breast-feed their infants, a practice that may reduce rates of juvenile T2DM [14]. Finally, healthy lifestyles adopted before and during pregnancy may persist indefinitely; these women can serve as role models for families and communities.

Further studies such as longitudinal analyses are necessary to substantiate these findings and to validate our hypothesis. If confirmed, prevention strategies as we have described could play a pivotal role in breaking an exponential transfer of risk for T2DM and its complications in successive generations of aboriginal people. Although a genetic susceptibility to T2DM and diabetic nephropathy in North American aboriginal peoples may be instrumental in their emergence, it is important to put this in perspective. T2DM was distinctly uncommon, if not absent, in these populations before the middle of the last century. Therefore, it is clear that environmental factors including the intrauterine environment are responsible for the appearance of T2DM and T2DM complications that are ravaging indigenous peoples worldwide.

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REFERENCES

1. CHASE LA: The trend of diabetes in Saskatchewan, 1905 to 1934. *Can Med Assoc J* 36:366–369, 1937

2. PIORO MP, DYCK RF, GILLIS DC: Diabetes prevalence rates among First Nations adults on Saskatchewan reserves in 1990: Comparison by tribal grouping, geography and with non-First Nations people. *Can J Public Health* 87:325–328, 1996
3. REPORT OF THE SASKATCHEWAN ADVISORY COMMITTEE ON DIABETES: Diabetes 2000. Recommendations for a strategy on diabetes prevention and control in Saskatchewan. Saskatchewan Health; March 2000
4. DYCK RF: Mechanisms of renal disease in indigenous populations: Influences at work in Canadian indigenous peoples. *Nephrology* 6:3–7, 2001
5. DYCK RF, TAN L: Rates and outcomes of diabetic end-stage renal disease among registered native people in Saskatchewan. *Can Med Assoc J* 150:203–208, 1994
6. DYCK RF, KLOMP H, TAN L: From “thrifty genotype” to “hefty fetal phenotype”: The relationship between high birthweight and diabetes in Saskatchewan registered Indians. *Can J Public Health* 92:340–344, 2001
7. PEDERSON J: Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol* 16:330–342, 1954
8. FREINKEL N: Of pregnancy and progeny. *Diabetes* 29:1023–1035, 1980
9. DYCK RF, TAN L, HOEPPNER VL: Relationship of body mass index and self-reported rates of gestational diabetes and diabetes mellitus with geographic accessibility: A comparison of three northern Saskatchewan aboriginal communities. *Chronic Dis Can* 16:24–26, 1995
10. DYCK R, KLOMP H, TAN LK, *et al*: A comparison of rates, risk factors, and outcomes of gestational diabetes between aboriginal and non-aboriginal women in the Saskatoon Health District. *Diabetes Care* 25:487–493, 2002
11. DYCK RF, TAN LK: Differences in high birth weight rates between northern and southern Saskatchewan: Implications for aboriginal peoples. *Chronic Dis Can* 16:107–110, 1995
12. TAN LK, IRVINE J, HABBICK B, WONG A: *Vital Statistics in Northern Saskatchewan, 1974–1988*. Saskatoon, Canada, Northern Medical Services, Department of Family Medicine, University of Saskatchewan, 1992
13. PETTITT DJ, KIRK A, ALECK KA, *et al*: Congenital susceptibility to NIDDM: Role of the intrauterine environment. *Diabetes* 37:622–628, 1988
14. YOUNG TK, MARTENS PJ, TABACK SP, *et al*: Type 2 diabetes mellitus in children: Prenatal and early infancy risk factors among native Canadians. *Arch Pediatr Adolesc Med* 156:651–655, 2002
15. HALES CN, BARKER DJ: Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. *Diabetologia* 35:595–601, 1992
16. DYCK R, KLOMP H, TAN L, STANG MR: An association of maternal age and birth weight with end-stage renal disease in Saskatchewan. *Am J Nephrol* 23:380–389, 2003
17. BRENNER BM, CHERTOW GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171–175, 1994
18. 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
19. 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
20. NELSON RG: Intrauterine determinants of diabetic kidney disease in disadvantaged populations. *Kidney Int* 63:S13–S16, 2003
21. NEEL JV: Diabetes mellitus: A “thrifty genotype” rendered detrimental by “progress”? *Am J Hum Genet* 14:353–362, 1962
22. PETTITT DJ, SAAD MF, BENNETT PH, *et al*: Familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 33:438–443, 1990
23. DYCK RF, BOHM C, KLOMP H: Increased frequency of HLA A2/DR4 and A2/DR8 haplotypes in young Saskatchewan aboriginal people with diabetic end-stage renal disease. *Am J Nephrol* 23:178–175, 2003
24. FENNESSY M, METCALFE K, HITMAN GA, *et al*: A gene in the HLA class I region contributes to susceptibility to IDDM in the Finnish population. Childhood diabetes in Finland (DiMe) study group. *Diabetologia* 37:937–944, 1994
25. FIELD LL, TOBIAS R: Unravelling a complex trait: The genetics of insulin-dependent diabetes mellitus. *Clin Invest Med* 20:41–49, 1997
26. NOBLE JA, VALDES AM, COOK M, *et al*: The role of HLA class II genes in insulin-dependent diabetes mellitus: Molecular analysis of 180 Caucasian, multiplex families. *Am J Hum Genet* 59: 1134–1148, 1996
27. HONEYMAN MC, HARRISON LC, DRUMMOND B, *et al*: Analysis of families at risk for insulin-dependent diabetes mellitus reveals that HLA antigens influence progression to clinical disease. *Mol Med* 1:576–582, 1995
28. FREEDMAN BI, ESPELAND MA, HEISE ER, *et al*: Racial variation in human leukocyte antigen frequency in insulin-dependent diabetic nephropathy. *J Am Soc Nephrol* 3:1467–1473, 1993
29. BAISCH JM, WEEKS T, GILES R, *et al*: Analysis of HLA-DQ genotypes and susceptibility in insulin-dependent diabetes mellitus. *N Engl J Med* 322:1836–1841, 1990
30. RONNINGEN KS, KEIDING N, GREEN A: Correlations between the incidence of childhood-onset type I diabetes in Europe and HLA genotypes. *Diabetologia* 44:B51–B59, 2001
31. LEE TD, ZHAO TM, CHOW MP, LEE G: HLA, GM, KM, and Diego blood group typing of Chippewa Indians. *Transfusion* 30:728–732, 1990
32. STRONCEK DF, STRAND RD, NOREEN HJ, *et al*: HLA class I and II antigen phenotypes of North American Indians from Minnesota: Implications for marrow transplants using unrelated donors. *Transfusion* 30:521–527, 1990
33. HELMRICH SP, RAGLAND DR, LEUNG RW, *et al*: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1995
34. MANSON JE, NATHAN DM, KROLEWSKI AS, *et al*: A prospective study of exercise and the incidence of diabetes among US male physicians. *JAMA* 268:63–67, 1992
35. TUOMILEHTO J, LINDSTROM J, ERIKSSON JG, *et al*: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
36. DYCK RF, SHEPPARD MS, KLOMP H, *et al*: Using exercise to prevent gestational diabetes among Aboriginal women: Hypothesis and results of a pilot/feasibility project in Saskatchewan. *Can J Diabetes Care* 23:32–38, 1999
37. KLOMP H, DYCK RF, SHEPPARD S: Description and evaluation of a prenatal exercise program for urban aboriginal women: Trials and tribulations. *Can J Diabetes* 27:231–238, 2003
38. DYCK RF, KLOMP H: Preventing non-insulin dependent diabetes among aboriginal peoples: Is exercise the answer? *Chronic Dis Can* 16:175–177, 1995