

vitamin D during the first year of life, thus the comparative population was rather small. The increased prevalence of this disease (3x) among children in this Finnish study, who were suspected of having rickets, is impressive. However the data are not very compelling since there was no radiologic or biochemical evidence of rickets presented.

The infants who took 2000 IU of vitamin D as a daily supplement had a 78% lower risk of developing diabetes. This dose of vitamin D, however, is high and not recommended by most authorities. (The Committee of Nutrition of the American Academy of Pediatrics, among others, state that an adequate intake of this vitamin is 200 IU per day.) Others have recommended dosages ranging from 400 to 1000u per day,³ where there may be lack of sunlight exposure, particularly during the long winter months in the northern hemisphere. Although there is no single recommendation for the amount of vitamin D supplemented, exposure to the sun usually will satisfy the requirements to prevent rickets and vitamin D deficiency. As little as 1 minimal erythemal dose (MED) of sunlight is equivalent to ingesting about 10,000 IU of vitamin D. Simple exposure of hands and face two or three times per week provides a third to a half of the MED (about 5 minutes for fair-skinned people) is more than adequate. Moreover, sunlight is without risk of hypervitaminosis D which may occur when large amounts of vitamin D supplements are ingested. Thus, caution should be exercised to the possible temptation of increasing vitamin D supplementation in an attempt to prevent type I diabetes. Further studies are needed

to assess if there are other factors to ascertain why there is a high prevalence of type I diabetes among populations who also are exposed to insufficient sunlight such as found in Finland.

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References

1. Stene L, et al. *Diabetologia* 2000;43:1093-1098.
2. The EURODIAB Substudy 2 Study Group *Diabetologia* 1999;42:51-54.
3. Canadian Pediatric Society *CMAJ* 1988;138:229-230.

Second Editor's Comment: In the early 19th Century, cod liver oil was given to prevent rickets. The classical role of vitamin D in the prevention of rickets is to assist absorption of calcium and phosphate. Vitamin D also appears to play a role in preventing some cancers and autoimmune diseases. Ideally, in a study such as the one reported here, evaluation would include plasma 25(OH) D or 1,25(OH) 2D₃ concentrations. When sun exposure is limited, as in northern Finland, supplementation or dietary intake is an important source of vitamin D. Breast milk does not contain enough vitamin D to cover an infant's needs. The role of vitamin D in the pathogenesis of type 1 diabetes certainly deserves follow-up. If vitamin D does impair the immune system functioning in infancy, there may be other long-term effects. Interesting as well, Finland has the highest incidence of type 1 diabetes in the world.

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Beneficial Effects of Intensive Therapy of Diabetes during Adolescence: Outcomes after the Conclusion of the Diabetes Control and Complications Trial (DCCT)

The DCCT, in 1994, reported the results of intensive diabetes therapy of adolescents (age 13-17 years at the time of enrollment into the study). Those results demonstrated a significant reduction in the risk for the development, and progression of retinopathy and microalbuminuria. Since that time, subjects from both the intensive and conventional therapy groups have been offered the opportunity to participate in the epidemiologic study of diabetes interventions and complications (EDIC). EDIC is a long-term observational study of the DCCT cohort. In this manuscript the DCCT/EDIC research group presents their latest findings. Of the original 195 adolescents, 175 agreed to participate in the EDIC study. At the end of the DCCT all subjects returned to their health care providers in the community for continuing diabetes care, and all conventionally treated subjects were offered instruction in the use of

intensive therapy. Approximately 50% of the subjects continued to receive their care at a DCCT/EDIC site. Subjects were seen on a yearly basis for determination of HbA1c and the recording of severe hypoglycemic episodes. Retinopathy was assessed by stereoscopic fundus photography at year 4, and classified according to the criteria described in the DCCT trial. A 3-step or more progression was classified as significant. Renal function was determined every other year by measurement of albumin excretion.

At year 4, 1/3 of the subjects who were originally randomized to conventional therapy continued to use 1 or 2 injections a day. The rest switched to multiple daily injections or insulin pump therapy. Ninety percent of former intensive therapy subjects continued to use multiple daily insulin injections or pump therapy. Total insulin doses and frequency of blood glucose monitoring

were similar between the 2 treatment groups. The difference in HbA1c between treatment groups was highly significant at the closeout of the DCCT, but by the end of the first year of the EDIC study there were no significant differences in HbA1c levels between the two groups. This was the result of both an increase in HbA1c by the intensive therapy group, and a decrease by the conventionally controlled group. These HbA1c values remained stable over the next 3 years (8.38% vs. 8.45%, intensive vs. conventional). In addition, the relative risk of severe hypoglycemia for patients in the former intensive treatment group was < 1 , which was a decrease from the rates during the DCCT, and an increase in hypoglycemic occurrence for the conventionally controlled group. There was no difference in body weight, BMI, or percentage of subjects overweight at year 4 of the EDIC study.

After 4 years of follow-up in the EDIC study, 65% of the original conventionally treated patients showed a 3-step or more progression in retinopathy as compared with 32% of the former intensive group patients. This represents an odds ratio reduction of 74% for those having been in the intensive control group. Thus, the benefits of intensive therapy persisted for an additional 4 years in a significant number despite increased levels of glucose control. Similar findings were observed for the progression of nephrological disease. There was an 85% reduction in the adjusted odds ratio for developing albuminuria in the former intensive treated patients vs. the former conventionally controlled group. Thus, the benefits of previous intensive therapy continued for another 4 years with regard to renal function.

The authors state that these results demonstrate conclusively that the benefits of intensive therapy outweigh any associated risks of hypoglycemia and weight gain, and persist for at least four years. In addition, the data suggest that less than optimal glycemic control during the early years of diabetes (in adolescence) has a long lasting, detrimental effect on

the development of complications even after better glycemic control is established. Thus the recommendation is that intensive therapy be the standard of care for adolescents with type I diabetes mellitus. The DCCT/EDIC study is planned to continue for at least 10 years.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes of Interventions and Complications research group: *J Pediatr* 2001;139:804-812.

Editor's Comment: *The results of the DCCT/EDIC at year 4 in adolescents are not different from those presented for the entire group (New Engl J Med 2000;342:381-389). The findings are important and have significant implications for the treatment of adolescents starting at diagnosis, and perhaps pre-adolescent children with type I diabetes mellitus. Some have assumed that the intensive therapy achieved by the DCCT research group, while important in reducing complications, might not be a reasonable and cost-effective treatment regimen for all adolescents with diabetes. These data prove otherwise. Intensive therapy initiated early in the course of diabetes has prolonged and long-lasting effects of reducing the risks of microvascular complications. Alternatively, diabetes management resulting in poor glucose control during the early adolescent years may be associated with an increased risk of microvascular complications, even after intensive therapy and a reduction in HbA1c has been achieved. Thus, these data support the initiation of intensive diabetes therapy designed to achieve near normal glucose control as early as possible in newly diagnosed adolescents. This must be the standard of care. Patients, their parents, and third-party payers must be educated to understand, demand, and compensate for such treatment.*

William L. Clarke, MD

Growth in Human Immunodeficiency Virus Type 1-Infected Children Treated with Protease Inhibitors

About 33% of children infected with HIV have impaired growth. The extent of such impairment may be regarded as a clinical criterion predicting progression to AIDS. The addition of protease inhibitors (PIs) has been demonstrated to frequently reduce plasma HIV RNA levels, to increase CD4 lymphocyte numbers, and to improve the general condition of children and adults with HIV retrovirus type I infections.

Steiner et al present data on the long-term (72 week) impact of PI treatment on growth of infected children.

Data are reported on 44 children between the ages of 0-17 years with confirmed infection. They were observed for 72 weeks prior to starting PI treatment. Nintavanir or nelfinavir were added to the previous treatment of two nucleoside analogue reverse transcriptase inhibitors. Growth, HIV-1 RNA plasma levels, and CD4 lymphocyte counts were determined at 0, 24, 48, and 72 weeks of treatment. Heights were reported in SD scores as determined from normal aged and gender individuals. Data from 44 children were analyzed in 3 age groups [6