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Cost-Effectiveness of Alternative Methods for Diabetic Retinopathy Screening

The paper by Lairson et al. (1) on the cost-effectiveness of alternative methods of screening for diabetic retinopathy rightly includes an analysis of the sensitivity of their conclusions to alterations in some of the program parameters. However they do not take into account the error in their estimation of the sensitivities of the four screening tests that they have compared. Because sensitivity and specificity are proportions, the 95% CIs can be calculated with the general formula for the SE of a proportion (2), yielding the results shown in Table 1.

The problem of accurately estimating the sensitivity of a test where the sensitivity is low is of particular relevance to screening for diabetic retinopathy because sensitivity is a major determinant of cost-effectiveness. Including CIs in the estimate of the cost per true-positive case detected is a critical step in the production of evidence with which to make important health-care policy decisions. As Table 2 demonstrates, recalculation of the results of the analysis in this paper make the conclusions less clear, because the CIs of the cost-effectiveness ratios overlap.

Table 1—*CIs for sensitivity and specificity*

	45° Photo without dilation	45° Photo with dilation	Ophthalmologist examination	Technician examination
Sensitivity	0.61	0.81	0.33	0.07
Upper 95% CI	0.72	0.90	0.44	0.14
Lower 95% CI	0.50	0.72	0.22	0
Specificity	0.85	0.96	1.00	0.99
Upper 95% CI	0.89	0.99	1.00	1.00
Lower 95% CI	0.81	0.94	0.99	0.97

Table 2—*System and patient cost per true-positive case detected*

	45° Photo without dilation	45° Photo with dilation	Ophthalmologist examination	Technician examination
System cost/true-positive ($)	378	295	390	794
Upper estimate	463	331	581	—
Lower estimate	320	265	294	379
Patient cost/true-positive ($)	171	139	306	1009
Upper estimate	209	156	454	—
Lower estimate	144	125	230	481

Nicholas J. Wareham, MRCP, MFPHM

From the Harvard School of Public Health, Boston, Massachusetts.

Address correspondence to Nicholas Wareham, MRCP, MFPHM, Harvard School of Public Health, 6778 Huntington Avenue, Boston, MA 02115.

CI, confidence interval.

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Prevalence of Diabetes in Asian Indians

Our observations (1–4) are similar to those of Ramachandran et al. (4a) and show that the prevalence of diabetes in Asian Indians is considerably higher in high risk (urban, upper socioeconomic groups) than in low risk (rural, low socioeconomic groups) populations. They attribute this disparity to altered life-style conditions prevailing in rural and urban areas. We have focused attention on dietary habits and fat intake and find that the prevalence of diabetes

in various subsets of Indian origin has a close linear relationship to the ratio of polyunsaturated n-6 fat to polyunsaturated n-3 fat (n-6/n-3 fat) in the diet. These data were presented recently (4) and are summarized below. The dietary habits of Indians offer a unique opportunity to assess the significance of n-6/n-3 fat ratio in the diet on insulin action and its relationship to the prevalence of diabetes and its complications.

Our studies (1–4) and those of the National Institute of Nutrition (5,6) show that in India, fish consumption is uncommon and that the "invisible" fat from cereals, pulses (beans), vegetables, and condiments is the main source of n-3 fat. Invisible fat from this source provides adequate n-6 fat but fails to provide the required quota of n-3 fat and has an undesirably high n-6/n-3 ratio. Consequently, the Indian diet has a partial deficiency of the precursor n-3 fat; namely, α-linolenic acid-C18:3 n-3 and an absolute deficiency of longer-chain n-3 derivatives. At the same time, "visible" fat in the diet rises sharply with rise in socioeconomic status and urbanization. Visible fat intake in rural areas is 10–15 g/day but this rises to 40–90 g/day in the diet of urban upper-socioeconomic groups. For generations, Indians have consumed traditional low n-6 fats without ill effects, but recently vegetable oils with high n-6 fat content have replaced them. This change has resulted in a wide disparity in n-6/n-3 ratio in dietary fats and a sharp rise in prevalence of diabetes in some subsets of the population. The prevalence of diabetes and its complications in various subsets at present is broadly parallel to this ratio. Before the change in cooking fat, the prevalence of diabetes in the subcontinent, as shown by West and Klebfleisch (7) or the multicenter Indian Council of Medical Research study (8) was low even in a high-risk urban population.

The following observations give further support to the above postulation: *1*) animal studies (9); 2) epidemiological observations in India and other countries (4,10); and 3) our ongoing study, which shows that >30% of unselected high-risk adults (n = 340), both diabetic and nondiabetic, had elevated plasma concentrations of triglycerides (>200 mg/dl) and depressed HDL cholesterol (<35.0 mg/dl). These lipid abnormalities, like upper body adiposity, indicate insulin resistance (11) and had close correlation to the n-6/n-3 ratio in dietary lipids (4). Mean values of HDL cholesterol in this study are much lower than those we obtained in 1984 (12), both in diabetic patients (41.1 vs. 45.1 mg/dl) and nondiabetic subjects (40.6 vs. 54.5 mg/dl). This possibly reflects the ill effect of increased and widespread use of fats with high n-6 content with a consequential rise in the n-6/n-3 ratio. In addition, intervention studies done on free-living high-risk adults with NIDDM or dyslipidemia indicate that supplementation with fish oil alone is not enough to achieve the desired results. Also required is a lowering of the elevated n-6/n-3 ratio in dietary fats either by drastic reduction in visible n-6 fat intake or, preferably, its substitution with traditional low n-6 fats (4). When substituting traditional low n-6 fats for visible n-6 fat, insulin action was improved (euglycemic clamp study), lipid abnormalities were corrected without lipid-lowering agents, and remission was induced in recent-onset NIDDM subjects without changes in body weight.

These observations suggest that the high prevalence of diabetes seen in some subsets of Asian-Indians cannot be attributed to ethnic or genetic predisposition (as commonly stated) but is possibly the result of faulty fat intake, which elevates the n-6/n-3 ratio in dietary fats and impairs insulin action to induce insulin resistance and its cluster of metabolic disorders (2–4).

BIHARI S. RAHEJA, MD
SHAUKAT M. SADIKOT, MD
RAGHUNATH B. PHATAK, MD
M.B. RAO, MSC, PHD

FROM THE ALL INDIA INSTITUTE OF DIABETES, S.L. RAHEJA HOSPITAL, AND THE JASLOK HOSPITAL AND RESEARCH CENTRE, BOMBAY, INDIA.

ADDRESS CORRESPONDENCE TO B.S. RAHEJA, MD, ALL INDIA INSTITUTE OF DIABETES, S.L. RAHEJA HOSPITAL, BOMBAY 400 016, INDIA.

HDL, HIGH-DENSITY LIPOPROTEIN; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS.

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Lipoprotein(a) Levels in Japanese Children With IDDM

High levels of Lp(a) have been proposed as one of the risk factors for CHD. It has been shown by some that diabetic subjects have higher levels of Lp(a) and that there might be a genetic difference in mean levels and response of Lp(a) to hyperglycemia (1,2). We evaluated blood concentrations of Lp(a) and correlations with glycemic control in Japanese children with IDDM.

The study included 31 patients (17 boys and 14 girls) with IDDM and 19 normal control subjects (12 boys and 7 girls). Mean ± SE ages were 14.1 ± 1.1 and 15.9 ± 1.1 yr, respectively. Four girls in each group had begun menstruation. Patients with obesity (obesity index >20%), short stature (SD score < −2 SD), familial history of hyperlipidemia, or hypothyroidism (free T_4 <0.8 ng/dl) were omitted from this study. The patients were divided into well-controlled (HbA_{1c} < 8%, n = 15) and poorly controlled groups (HbA_{1c} ≥8%, n = 16). The duration of diabetes, insulin dose, and age were not different between the two groups of IDDM patients. No patient had continuous microalbuminuria. Blood samples were obtained before the morning insulin injection. The concentrations of serum Lp(a), serum fructosamine, and HbA_{1c} were measured by a highly specific enzyme-linked sandwich immunoassay (3), high-performance liquid chromatography, and enzymatic assay, respectively. Statistical analyses were performed by regression analysis and Mann-Whitney U test. Data are means ± SE.

HbA_{1c} and fructosamine levels in the poorly controlled group, well-controlled group, and control subjects were 9.1 ± 0.3% and 497.6 ± 16.9 μM, 7.1 ± 0.1% and 414.9 ± 9.6 μM and, 4.6 ± 0.1% and 259.5 ± 3.8 μM, respectively. Both levels were significantly higher in the poorly controlled group than in other groups ($P < 0.01$). The levels of Lp(a) in the poorly controlled group (24.6 ± 1.6 mg/dl) were significantly higher than those in the well-controlled group and control subjects (15.5 ± 1.2 and 13.2 ± 0.6 mg/dl, respectively, $P < 0.01$). In diabetic patients, Lp(a) levels showed a positive correlation with the levels of HbA_{1c} ($r = 0.69$, $P < 0.01$) and fructosamine ($r = 0.46$, $P < 0.01$). No correlation could be found between the levels of Lp(a) and blood glucose.

The mean levels of LP(a) in the control subjects were higher than reported values in black or white populations (1,2). The levels of Lp(a) were higher in the poorly controlled diabetic patients. Although an explanation for high levels of Lp(a) in poorly controlled diabetic children has yet to be fully established, some have reported that the high levels of Lp(a) in diabetic subjects decline with improved glycemic control (4,5). In this study, a significant correlation was noted between the levels of Lp(a) and HbA_{1c} or fructosamine. These data indicate that glycemic control may have an effect on the levels of Lp(a) in Japanese children with IDDM. If elevated Lp(a), attributable to hyperglycemia, is a risk factor for early CHD in diabetic subjects, strict glycemic control may be essential. From previous reports and our data, we propose that blood levels of Lp(a) should be evaluated in the management of diabetic patients.

KANJI NAGASHIMA, MD, PHD
SHIGENORI YUTANI, MD
HIROSHI MIYAKE, MD
KAZUMICHI ONIGATA, MD
HIDEKI YAGI, MD, PHD
TAKAYOSHI KUROUME, MD, PHD

FROM THE DEPARTMENT OF PEDIATRICS, GUNMA UNIVERSITY SCHOOL OF MEDICINE, MAEBASHI, GUNMA, JAPAN.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO KANJI NAGASHIMA, MD, DEPARTMENT OF PEDIATRICS, GUNMA UNIVERSITY SCHOOL OF MEDICINE, 3-39-22 SHOWA-MACHI, MAEBASHI, GUNMA, 371, JAPAN.

Lp(a), LIPOPROTEIN(a); IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; CHD, CORONARY HEART DISEASE.

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