Senile Cataract and Glucose Intolerance: The Israel Study of Glucose Intolerance Obesity and Hypertension (The Israel GOH Study)

AVRAHAM KARASIK, M.D., MICHAELA MODAN, M.Sc., HILLEL HALKIN, M.D., GIORA TREISTER, M.D., ZAHAVA FUCHS, M.Sc., AND AYALA LUSKY, M.Sc.

Association of "senile" cataract (SC) with glucose intolerance (impaired tolerance and diabetes) was assessed by sex and age in a random population sample comprising 930 individuals aged 40–70 yr, who underwent concurrent oral glucose tolerance test and ophthalmoscopy. The eye examination was performed without knowledge of the glucose tolerance status. SC was defined as lens opacification preventing visualization of the eyeground or as surgical aphakia due to SC. To assess the independent effect of hyperglycemia, glycosylated hemoglobin (HbA_1) was determined in 769 participants. In men, no association was found between SC, glucose intolerance, and HbA_1. In women of all ages, glucose intolerance was associated with an SC risk ratio of 6.1 (95% confidence limits 3.3–11.1; $P < 0.001$). Furthermore, SC was associated in women with increased HbA_1 independently of the effect of glucose intolerance ($P < 0.01$). These findings confirm the reported association of SC with diabetes (although unlike the Framingham and HANES population studies, the association was confined to women), indicate its presence at all degrees of glucose intolerance, and suggest a possible independent role of nonenzymatic glycosylation in its pathogenesis. DIABETES CARE 7: 52–56, JANUARY–FEBRUARY 1984.

Increased risk of "senile" cataract (SC) in diabetes has been demonstrated in a number of studies comparing diabetic patients with control subjects.[1-5] Two main points of view prevail regarding this association. One, based on reanalysis of two large population studies, reaffirms the increased prevalence of SC in diabetic patients under age 65 yr.[1] The other questions the validity of this association on the grounds that they may merely reflect a greater likelihood of cataract diagnosis in diabetes due to frequent eye examinations or biased interpretation of ophthalmologic findings in diabetic patients.[2-5] With regard to the entire range of glucose intolerance and SC, only indirect evidence from one study indicates a positive association.[6] These disparate opinions, the lack of data regarding the effect of the whole range of glucose intolerance on the risk of SC, as well as the experimental demonstration of cataract formation due to lens protein glycosylation in a variety of animal species[7-9] led us to the present study. Our objective was to evaluate the association of cataract with age, sex, glucose tolerance level, and ambient plasma glucose as reflected by glycosylated hemoglobin (HbA_1), in a representative population sample.

MATERIAL AND METHODS

The subjects were participants of the Israel Study of Glucose Intolerance Obesity and Hypertension (The Israel GOH Study). This is a 10-yr longitudinal study of a nationwide sample of the total Jewish population in Israel born between 1912 and 1941, equally representing the various sex, ethnic origin, and length of residence groups in the country, which was obtained from the Central Population Registry. The study was aimed at comparing associations, risk factors, and complication of glucose intolerance obesity and hypertension in the four main ethnic groups of Israeli Jews. The detailed study design is given elsewhere;[10] methodologic aspects relevant to this report are presented below. A total of 5711 participants was first seen in 1968–71. At that time, 10 blood pressure readings, body weight, and height were measured, and regular use of medications as well as smoking habits were recorded. Since 1977, participants have been reexamined at home for the same variables and invited to their regional medical center. At the center, an overnight fasting blood sample was obtained and, unless known to have diabetes,

participants were requested to undergo an oral glucose tolerance test (OGTT). Of those examined at home, 67.2% agreed to undergo this test. Case accrual was scheduled by area of residence. During May 1979 to May 1981, HbA_1 determinations and ophthalmoscopic examinations were also performed at the study center on OGTT examinees as well as on individuals known to have diabetes. The data reported herein pertain to 930 consecutive participants who underwent ophthalmoscopy and whose glucose tolerance category was known (i.e., either by OGTT or by virtue of being known to have diabetes); of these, HbA_1 was available in 769. The total group and the subgroup with HbA_1 determinations did not differ significantly from the original sample in the distribution of age, sex, ethnic group, length of residence, body mass index [(weight in kilograms/height in meters)^2], systolic and diastolic blood pressure levels, and smoking history, and can be considered to be representative of the total sample.[10]

HbA_1 (in percentage of total hemoglobin) was determined in the fasting state by a commercial minicolumn method [Helena Laboratory minicolumn kits (Helena Laboratories, Beaumont, Texas) and instructions with temperature control] chosen for the sake of feasibility in population screening. The OGTT was based on plasma glucose levels in the fasting state and 1 and 2 h after a 100-g oral glucose load. No specific dietary instructions were given for the period preceding the OGTT since assurance of compliance was not feasible; however, dietary interviews indicated a daily intake of at least 250 g carbohydrates in practically all participants, while only a daily intake under 150 g affects the test results appreciably.[11] While the recommended load for diagnosis is 75 g, a 100-g load was chosen for other purposes;[10] however, the difference between loads is known to have little influence on blood glucose levels.[11] Plasma glucose (PG) level (in mg/dl) was measured by an automated Technicon Autoanalyzer II method (Technicon Corp., Tarrytown, New York) based on potassium ferricyanide reduction. Glucose tolerance was classified according to the National Diabetes Data Group (NDDG) criteria[11] as follows: normal tolerance = fasting PG (FPG) < 115, 1-h PG < 200, 2-h PG < 140; impaired tolerance = FPG < 140, 1-h PG ≥ 200, 2-h PG 140–199; and diabetes mellitus = FPG ≥ 140 or both 1- and 2-h PG ≥ 200. Intermediate combinations between normal and impaired tolerance were defined as borderline (the nondiagnostic group by NDDG criteria). For statistical analysis, normal and borderline tolerance were grouped together and termed "satisfactory tolerance." The impaired tolerance and diabetes categories were grouped under the term "glucose intolerance."

Ophthalmoscopic examinations were carried out concurrently with the glucose tolerance test by eight third-year residents, four each from the departments of internal medicine and ophthalmology. Participants were scheduled for examination at their convenience with no reference to their medical condition. Physicians were assigned examination days by administrative considerations, independently of the participants' schedules. The examinations were performed by direct ophthalmoscopy with fully dilated pupils. Ophthalmoscopy was the method of choice since the prime purpose of the eye examination was detection of eyeground changes, while slit lamp examination and visual acuity tests could not be employed, due to technical limitations. Criteria for SC were (1) intraocular lens opacification interfering with visualization of the eyeground; or (2) surgical aphakia due to SC. Cataracts of metabolic congenital or traumatic etiology were not found by case history. Uveitis and vitreal hemorrhage were not observed in our series. Use of medications that might lead to cataract formation was excluded by drug history during the home interview and verified by inspection of drug receptacles. Although the definition of SC based on lens opacification is subjective to some extent, diagnostic bias on the part of the examining physician was precluded since the persons with impaired glucose tolerance and diabetes discovered by the OGTT were asymptomatic, and the physicians were unaware of the glucose tolerance status of the participants (with the exception of known diabetes) at the time of the ophthalmoscopy. Obviously only the more progressive and denser cataracts would be revealed by this method.

STATISTICAL ANALYSIS

Excess prevalence of SC due to glucose intolerance was estimated by comparing the relative risk of SC in the combined group of impaired tolerance and diabetes (glucose intolerance) to that of the combined groups of normal and borderline tolerance (satisfactory tolerance).

Confidence intervals for relative risks were computed by the test-based method.[12] Tests for sex–glucose-tolerance interaction were performed by the method of Breslow and Day.[13]

Association of HbA_1 level with SC was examined by the χ^2 test comparing the observed number of SC cases presenting HbA_1 levels greater than the median HbA_1 for cases without cataract at similar levels of glucose tolerance with the expected number, i.e., one-half of the cases.

RESULTS

Fifty-seven SC cases were observed in the study group: 26 (5.3%) in men (including two surgical aphakias) and 31 (7.1%) in women (including four surgical aphakias). The rate of SC did not differ significantly ($P > 0.25$) in cases examined by the ophthalmologists (25/550) from those examined by internists (26/430) nor between individual physicians, and this was true for both sexes and for all levels of glucose intolerance.

Rates of SC by sex and glucose tolerance category are given in Table 1. The overall higher SC prevalence in women was not significant. However, when comparison was stratified by glucose tolerance, a significantly different trend emerged between the sexes. In men, the rates in the various tolerance groups did not differ signficantly, while in women, glucose intolerance was associated with a significantly increased SC rate ($P < 0.001$). In the subgroup with normal tolerance,

TABLE 1
Rate of senile cataract (SC) by sex and glucose tolerance*

Glucose tolerance	Men			Women		
		SC			SC	
	No. exam.	No.	Percent	No. exam.	No.	Percent
Total group	495	26	5.3	435	31	7.1
Total satisfactory tolerance	353	19	5.4	354	13	3.7
Normal	265	15	5.7	285	8	2.8
Borderline	88	4	4.6	69	5	7.2
Total glucose intolerance	142	7	4.9	81	18	22.2
Impaired	39	—	0.0	20	5	25.0
Diabetes:						
Newly found	44	2	4.5	16	3	18.8
Previously known	59	5	8.4	45	10	22.6

*Including six cases with aphakia: two with normal tolerance (one male and one female) and four with previously known diabetes (one of them a male).

the rate in women was lower than in men (2.8% versus 5.7%); in the borderline subgroup, the trend was reversed (7.2% versus 4.6%); and in the total group with glucose intolerance, the rate was considerably higher in women (22.2% versus 4.9%). It is of interest to note that the rate of SC in women with diabetes newly found by the glucose tolerance test was similar to the rate in individuals previously known to have diabetes (95% of the known cases of diabetes in both sexes were non-insulin-dependent). The difference between the sexes was highly significant as reflected by the significant sex–glucose-tolerance interaction ($P < 0.01$). Of the six cases with surgical aphakia, two had normal tolerance (one male, one female), while four were previously known to have diabetes (three female). This excess of aphakias in diabetes was highly significant ($P < 0.001$).

The rate of SC in persons with satisfactory tolerance as compared with those with glucose intolerance in each age and sex stratum is presented in Figure 1. There was a significant increase of the total rate of SC with age in both sexes ($P < 0.01$). The association of glucose intolerance with increased SC prevalence in women was apparent in all ages as evidenced by the significant sex–glucose-tolerance interaction in the three age groups (Table 2). This effect was greater in the younger age group, although the confidence limits overlapped those of the other two age groups.

In women with satisfactory tolerance, the rate of SC was 3.7%. As the rate in the total female group was 7.1%, it follows that this excess rate of 3.4%, or 47.9% of all SC in women, was associated with glucose intolerance.

In addition, an association was found in women between SC and hyperglycemia, which was independent of the association with glucose intolerance (Table 3). Thus, HbA_1 values among the male SC cases were equally distributed below and above the median HbA_1 value of cases without SC in the respective glucose tolerance category, in complete accordance with the expected frequency of 50%. In contrast, among the 25 female SC cases, 19 had HbA_1 levels above the median value in the respective glucose tolerance category, a significantly higher proportion than expected ($P < 0.01$). It should be noted that the median HbA_1 values in cases without SC were practically identical in men and women at all levels of glucose intolerance.

DISCUSSION

Our study indicates a significant role of the entire range of glucose intolerance in the prevalence of SC in women but not in men. In the large HANES and Framingham popu-

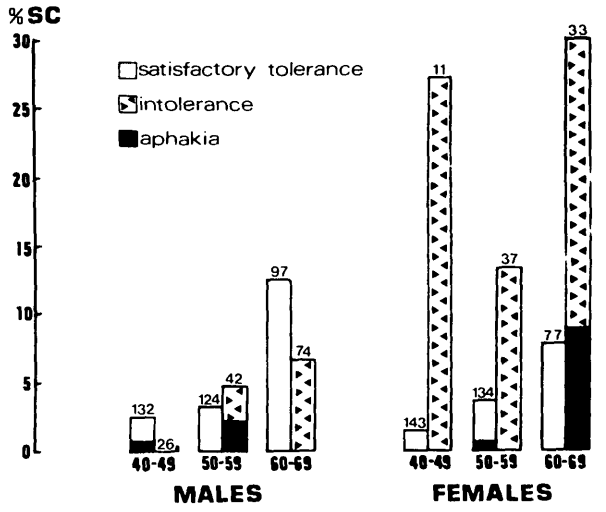

FIG. 1. Rate of senile cataract (SC) and aphakia by glucose tolerance, age, and sex. Each column represents the percentage of SC (including aphakia) cases in a specific subgroup by sex, age, and glucose tolerance. The numbers on the top of the column represent the total number of cases in that subgroup, i.e., the denominator for the percentage SC.

TABLE 2
Risk ratio of senile cataract in glucose intolerance by sex and age*

Age (yr)	Men	Women	Test for sex interaction
40–49	<0.7 (0.1–4.2)†	19.5 (5.6–110.0)	P < 0.001
50–59	1.5 (0.2–8.8)	3.6 (1.6–9.3)	P < 0.01
60–69	0.5 (0.16–1.1)	3.9 (1.6–9.3)	P < 0.01
Total	0.9 (0.32–2.5)	6.1 (3.3–11.1)	P < 0.001

*95% confidence limits are given in brackets. The large upper limit in women age 40–49 is due to the small number of glucose-intolerant cases.
†As the number of cases in the cell representing senile cataract with glucose intolerance was zero, risk ratio and confidence limits were calculated by adding one-half a case to each of the four cells in this age and sex category.

lation studies,[1] the risk of SC was increased to the same extent in diabetic patients of both sexes. On the other hand, a British study demonstrated, in line with our findings, a higher rate of diabetes and greater response to glucose challenge among female patients with cataracts than among controls, while in male patients no such differences were found.[6] In the HANES study, diabetic patients of all ages had a higher SC prevalence, while in the Framingham study this was true only in regard to the younger age group. In our study, which comprises ages 40–70, the effect in women, while present in all age groups, seemed considerably larger in those under 50. It should be noted, however, that in these younger women the high risk observed in the group with glucose intolerance was based on 11 cases only.

The possibility has been raised that the increased prevalence of SC and aphakia among diabetic patients found in other studies as well as our own is due to more meticulous eye examinations in this condition.[2,3] Our study, which is the only reported population-based study of this association in which glucose tolerance was tested in the entire population, provides an opportunity to examine this suggestion, since, unlike all other studies, the physicians performing the ophthalmoscopic examination were unaware of patients' glucose tolerance status. The results in the women indicate a gradual increase of lens opacifications with increasing glucose intolerance, with a similar rate in those with previously unknown and known diabetes. Thus, excess risk of SC in our study group cannot be attributed to examiner bias.

The fact that our patients were examined by ophthalmoscopy rather than by slit lamp, and the criteria employed for definition of SC, would suggest lesser sensitivity. As noted above, only the more progressive denser lens opacifications would be revealed by our method. Notwithstanding, the rates of SC were similar to the respective age-specific rates of cases defined as SC (not including precataract) in the HANES and Framingham population studies, where persons were examined by slit lamp.[1]

Our data indicate independent and additive effects of the HbA_1 level and of the glucose intolerance on the rate of SC formation in women, while in the men no association with HbA_1 level was found. The potential ability of the individual to handle glucose loads is measured by OGTT; HbA_1 reflects the actual integrated levels of ambient blood glucose over the preceding period of 2 mo.[14] Our data thus seem to emphasize the role of actual blood glucose level in the formation of cataract. Animal studies showed that experimental diabetes leads to cataract. Moreover, the rate of cataract formation was correlated with the severity of the diabetes.[7,15] The lens is freely permeable to glucose and does not require insulin for glucose penetration and hence is directly affected by the ambient blood glucose level through the aqueous humor and vitreous body.[16] Two mechanisms have been suggested to explain the way in which high glucose levels contribute to lens opacification. The first is the sorbitol pathway in which high blood sugar levels activate aldose reductase that converts the sugar to polyol, the accumulation of which results in osmotic swelling and changes in membrane permeability. Consequent chronic changes in water and ion content of the lens lead to opacification.[17]

The second mechanism, suggested only recently, is nonenzymatic glycosylation of ε-amino groups of lysine in the lens crystallin proteins. In vitro glycosylation of crystallin proteins of the bovine and rat lens lead to their precipitation and aggregation and thus to opacification of the lens material. Animal and human studies of lens composition show that

TABLE 3
Rate of cases with senile cataract cases presenting HbA_1 level above the median HbA_1 for cases without cataract, by sex

Glucose tolerance	Men				Women			
	No. without cataract	Median HbA_1	No. with cataract	No. above median	No. without cataract	Median HbA_1	No. with cataract	No. above median
Normal	206	6.7	13	7	225	6.7	8	4
Borderline	75	7.1	3	2	59	7.0	4	3
Impaired	30	7.1	—	—	9	7.1	3	2
Newly found diabetes	37	7.6	2	1	11	7.3	3	3
Previously known diabetes	40	7.7	2	—	32	7.7	7	7
			20	10			25	19
			P = 1.00				P < 0.01	

the same product of glycosylation is produced in vivo.[8,9] The reaction in the erythrocyte yielding glycosylated hemoglobin is practically identical to the glycosylation in the lens.[9]

In our study both indicators of the blood glucose level to which the lens is exposed, namely, postload glucose and HbA_1 levels, showed an independent positive association with the prevalence of SC in females. The increased HbA_1 level found in the female SC cases might reflect an increased rate of glycosylation of lens proteins, as a possible etiologic factor. The difference between the sexes does not seem to be due to higher ambient blood glucose levels in the women in general since HbA_1 level in persons without SC was similar in both sexes. The reason for the apparent resistance of the male lens to this effect is unclear, but it is known that factors other than ambient glucose level affect the glycosylation rate.[18]

By the same token, nonenzymatic glycosylation of collagen has been implicated as a possible etiologic factor in micro- and macrovascular complications of diabetes, such as occlusive disease of the lower-limb arteries and atherosclerotic heart disease.[19] A stronger deleterious effect of glucose intolerance among women as compared with men has been found in these morbid manifestations of diabetes as well.[20]

Finally, it should be noted that in our female population about one-half of the SC cases could be attributed to glucose intolerance and that lens opacification in persons with normal tolerance of both sexes occurred even in the youngest age group in our study, namely, the 40–49-yr-old. Also, external factors such as solar irradiation and others have been implicated in cataract formation.[21] It thus seems that the term "senile" cataract implying a nonspecific etiologic role of aging in lens opacification should be reconsidered.

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From the Departments of Clinical Epidemiology, Internal Medicine, and Ophthalmology, the Chaim Sheba Medical Center, Tel Hashomer, affiliated with the Tel-Aviv University Sackler School of Medicine, Israel.

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