From the Department of Child Health, University of the West Indies, Mount Hope Women's Hospital, and the Nutrition Laboratory, Ministry of Health, 15, Sackville Street, Port-of-Spain, Trinidad, West Indies.
Address correspondence and reprint requests to Dr. Zulaika Ali, 20, Schneider Gardens, Petit Valley, Port-of-Spain, Trinidad, West Indies.
Received for publication 5 September 1989 and accepted in revised form 15 November 1989.

ACKNOWLEDGMENTS

We thank Dr. D. Picou for advice.

REFERENCES

1. O'Sullivan JB: Long-term follow-up of gestational diabetes. In *Early Diabetes in Early Life*. Camerini-Davalos RA, Cole HS, Eds. New York, Academic, 1975, p. 503–10
2. Mestman JH, Anderson GV, Guadeloupe V: Follow-up study of 360 subjects with abnormal carbohydrate tolerance during pregnancy. *Obstet Gynecol* 39:421–25, 1972
3. Metzger BE, Bybee DE, Freinkel N, Phelps RL, Radvany RM, Vaisrub N: Gestational diabetes mellitus: correlations between the phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during the first year postpartum. *Diabetes* 34 (Suppl. 2):111–15, 1985
4. Hadden DR: Geographic, ethnic, and racial variations in the incidence of gestational diabetes mellitus. *Diabetes* 34 (Suppl. 2):8–12, 1985
5. Ali Z: The infant of the diabetic mother. *West Indian Med J* 36 (Suppl.):28–29, 1987
6. WHO Expert Committee on Diabetes Mellitus: *Second Report*. Geneva, World Health Org., 1980 (Tech. Rep. Ser., no. 646)
7. Freinkel N (Ed.): Summary and recommendations of the Second International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes* 34 (Suppl. 2):123–26, 1985

Low-Pigment Skin Type and Predisposition for Development of Type I Diabetes

Anette G. Ziegler, MD
Hans-J. Baumgartl, MD
Georgia Ede, BA
Martin Held, MD
Hermann-J. Vogt, MD
Helmut J. Kolb, MD
Eberhard Standl, MD

To ascertain whether skin pigmentation type and sensitivity to ultraviolet (UV) light are associated with susceptibility to type I (insulin-dependent) diabetes, 55 type I diabetic patients were examined, 38 new-onset and 17 long-term cases. They were compared to 72 control subjects of the same geographic region and nationality. To evaluate the individual skin pigmentation type, a standardized questionnaire was developed. Reactivity to UV light was determined by a stepwise-graded UV irradiation. Significantly more diabetic patients in southern Germany had blue eyes than nondiabetic control subjects (55 vs. 26%, $P < 0.01$), and significantly more diabetic patients had a low-pigment eye color (blue or green) than control subjects (66 vs. 38%, $P < 0.01$). In addition, more fair skin color was noted among diabetic versus control subjects (84 vs. 60%, $P < 0.01$). In response to UV irradiation, diabetic patients more often showed an increased UV-light sensitivity than control subjects (83 vs. 23%, $P < 0.001$). The relative risk for susceptibility to type I diabetes in subjects with low-pigment eye color was 3.1, in subjects with fair skin type 3.4, and in subjects with increased UV-light sensitivity 5.8. The highest risk for the development of diabetes was seen in subjects who had low-pigment eye color and/or increased UV-light sensitivity (95 vs. 51%, $P = 0.00002$, odds ratio 17.4). We conclude that a low-pigment skin type may predispose for the development of type I diabetes. *Diabetes Care* 13:529–31, 1990

Major geographic variations in the occurrence of type I (insulin-dependent) diabetes have been recognized with a north to south gradient in diabetic risk (1). However, what causes the extraordinary geographic differences in the distribution of type I diabetes—a host (genetic) factor, an environmental agent (virus, diet), or both—remains unknown. It has been reported that the risk for type I diabetes appears to correlate with average yearly temperature of environment, the distance from the equator, and the ethnicity of the population at risk (1). Therefore, an understanding of the geographic differences will be important to the identification of factors related to the etiology of type I diabetes. Because skin is an important immunological organ responsive to ultraviolet (UV) irradiation and environmental agents, we have begun to evaluate the dermis function of type I diabetes in southern Germany by studying skin pigmentation and reactivity to UV light in association with susceptibility to type I diabetes.

RESEARCH DESIGN AND METHODS

Fifty-five patients with type I diabetes were evaluated for skin pigmentation type, 38 newly diagnosed (group A) and 17 long-term (group B) diabetic patients. Group A was recruited from all new-onset patients hospitalized at the City Hospital Munich-Schwabing from September 1987 to May 1988 (18 females, 20 males; age range 6–28 yr, mean 20 ± 1 yr; diabetes duration 8 ± 5 days). Group B was recruited from diabetic patients who attended our outpatient department from January to February 1988 (9 females, 8 males; age range 17–35 yr, mean 25 ± 2 yr; diabetes duration 7 ± 4 yr). Inclusion criteria for patients and control subjects were German family origin, born in southern Germany, and living in southern Germany for 80% of their lives. Diabetic pa-

tients were compared to 72 healthy control subjects with no family history of diabetes (medical staff of our department: 33 nurses, 7 secretaries, 13 technicians, 19 physicians; 30 females, 42 males; age range 21–36 yr, mean 26 ± 2 yr). None of the subjects enrolled in the study had received any drugs during the preceding month or had a history of recent prolonged exposure to sunlight.

To evaluate individual skin pigmentation type, a standardized questionnaire was developed and administered by one researcher (blinded for the purpose of the study). Eye color (blue, green, gray, brown), hair color (blond, red, brown, black), skin color (fair, dark), hair form (straight, wavy, curly), hair thickness (thin, thick), and hair type/skin type (dry, oily) were examined by the interviewer. Based on tanning and burning histories, four tanning types were established (1: always burn, never tan; 2: always burn, then slight tan; 3: sometimes burn, always tan; 4: never burn, always tan [2]), and all subjects were classified according to their tanning type. In addition, all subjects were interviewed regarding history of white spots, allergies, and other skin diseases.

UV-light reactivity. Reaction to UV irradiation was tested in all 38 group A patients. Long-term diabetic patients were not tested because skin reactivity to UV light might change through diabetic side effects and complications. Diabetic subjects were compared to 61 control subjects. Reactivity to UV light was determined by a stepwise-graded UV irradiation (3). The UV light system used delivered UV-A and UV-B light with an intensity of 25.2 J/cm^2 and 8.4 mJ/cm^2, respectively. Eight fields on the skin of the back were irradiated for 2 min with decreasing intensity of UV light from 100 to 28% of the delivered dose. Readings were made at 22 h after irradiation; positivity was defined as a barely perceptible well-defined erythema. The number of positive fields represents the patient's threshold sensitivity to UV light. A reactivity of >3 fields (UV-light intensity <17.4 J/cm^2 for UV-A and <5.8 mJ/cm^2 for UV-B) is regarded as increased UV-light sensitivity (4,5).

Statistical analysis. Results were expressed as means ± SE. Comparisons were made on the basis of the χ^2-test and Fisher's exact test.

RESULTS

Table 1 summarizes results regarding eye color, skin color, and UV-light reactivity in type I diabetic versus control subjects. Significantly more diabetic subjects in southern Germany had blue eyes versus control subjects (55 vs. 26%, P = 0.001), and significantly more diabetic subjects had a low-pigment (light) eye color (blue or green) than control subjects (66 vs. 38%, P = 0.002). In addition, a higher frequency of fair skin color was noted among diabetic patients versus control subjects 84 vs. 60%, P = 0.003). In response to stepwise-graded UV irradiation, new-onset group A patients exhibited increased UV-light sensitivity more frequently than did control subjects (63 vs. 23%, P = 0.0001). The median UV-light threshold sensitivity in diabetic subjects was 14.6 J/cm^2 for UV-A and 4.9 mJ/cm^2 for UV-B (equivalent to 4 positive reacting fields) compared with 25.2 J/cm^2 for UV-A and 8.4 mJ/cm^2 for UV-B (equivalent to 1 field) in control subjects (Fig. 1). No difference was found in hair color (fair or red, 34 vs. 41%), hair form (straight, 61 vs. 46%), hair thickness (thin, 57 vs. 57%), hair type (dry, 38 vs. 42%), skin type (dry, 48 vs. 52%),

TABLE 1
Diabetic versus control subjects

	Diabetic (%)	Control (%)	P	Odds ratio
Blue eyes	55	26	=0.001	3.6
Light eyes	66	38	=0.002	3.1
Fair skin type	84	60	=0.003	3.7
Increased UV-light sensitivity	63	23	=0.0001	5.8
Subjects with light eye color				
Increased UV-light sensitivity	64	23	=0.01	6.0
Fair skin type	91	75	NS	
Subjects with fair skin color				
Increased UV-light sensitivity	51	27	NS	
Light eyes	69	47	=0.05	

UV, ultraviolet; NS, not significant.

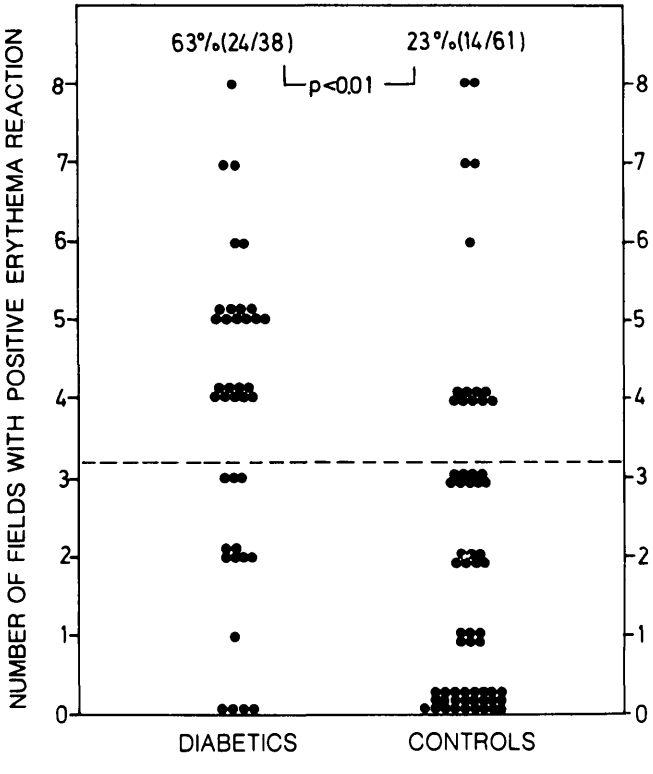

FIG. 1. Reaction to ultraviolet (UV) irradiation in recently diagnosed type I (insulin-dependent) diabetic and non-diabetic control subjects. The *y*-axis represents number of fields with positive erythema reaction. Reactivity of >3 fields (*dashed line*) is regarded as increased UV-light sensitivity (4).

histories of sunburn and ability to tan (tanning type 1 or 2, 19 vs. 27%), frequencies of white spots (10 vs. 8%), allergies (8 vs. 14%), or skin diseases (3 vs. 4%) between diabetic and control subjects.

Table 1 summarizes the relative risks using odds ratio for subjects with light eye color, fair skin type, or increased UV-light reactivity for susceptibility to type I diabetes. The risk for diabetes in subjects with blue eyes was 3.6, in subjects with light eyes 3.1, in subjects with fair skin type 3.4, and in subjects with increased UV-light sensitivity 5.8. By analyzing only subjects with light eye color, the risk for diabetes in subjects with increased UV-light sensitivity was 6.0 ($P = 0.01$). By analyzing only subjects with fair skin type, eye color and UV-light reactivity did not increase the risk for diabetes susceptibility. These data indicate that light eye color and increased UV sensitivity are independent variables associated with a higher risk for the development of type I diabetes. The relative risks for the combination of two or three of these variables are shown in Table 2. The highest risk for diabetes to develop was seen in subjects with light eyes and/or an increased UV-light sensitivity (95 vs. 51%, $P = 0.00002$, odds ratio 17.4). All diabetic subjects had either light eyes, fair skin, or increased UV-light sensitivity compared to 77% of control subjects ($P < 0.003$), thereby indicating that fair skin provides only a minimal increase in risk for diabetes to develop.

DISCUSSION

It has been shown that a significant proportion of the genetic susceptibility to type I diabetes is provided by class II genes near the HLA-DR subregion on chromosome 6. As reported, the relative risk for an HLA-DR4 or DR3 positive individual to develop type I diabetes is 5–7 times higher than for a DR3/DR4 negative subject (6). It is likely that a gene outside the major histocompatibility complex is also necessary for the development of type I diabetes in humans as it is in the animal models of type I diabetes, i.e., the nonobese diabetic mouse and the BB rat (7). In addition, the worldwide regional differences in the incidence of type I diabetes and the concordance for type I diabetes in only 50% of identical twins have been proposed as evidence for the presence of environmental factors initiating autoimmune β-cell destruction.

TABLE 2
Combination of variables (diabetic vs. control subjects)

	Diabetic (%)	Control (%)	P	Odds ratio
Light eyes or increased UV-light sensitivity	95	51	=0.00002	17.4
Light eyes or fair skin or increased UV-light sensitivity	100	77	=0.003	
Light eyes or fair skin	78	71	NS	

UV, ultraviolet; NS, not significant.

In this study, we demonstrated that significantly more type I diabetic subjects from southern Germany exhibit light eye color, fair skin type, and increased UV-light sensitivity compared with nondiabetic control subjects. The relative risk for subjects with either light eyes and/or increased UV-light sensitivity was 17.4. The association of diabetes with low-pigment skin type may be due to linkage of the genes determining eye color, skin color, sensitivity to radiation, and diabetes. It may also be possible that a low-pigment skin type favors the autoimmune process in type I diabetes in that subjects with low-pigment skin type have an immune system that is more susceptible to stimulation through diabetogenic agents or environmental factors. Differences in skin pigmentation, radiation sensitivity, and natural UV irradiation between races and countries could be one possible explanation for the major geographic variations in the occurrence of type I diabetes, with a north to south gradient in diabetes risk.

In conclusion, we believe that low-pigment skin type may be associated with type I diabetes in a way yet to be described. A combination of HLA typing and determination of skin pigmentation type should be studied in the future to ascertain whether both markers can assign greater risk for diabetes to develop.

From the Diabetes Research Institute and Schwabing City Hospital, the Technical University, and the Harlaching City Hospital, Munich, Federal Republic of Germany.

Address correspondence and reprint requests to A.G. Ziegler, MD, Schwabing City Hospital, Koelner Platz 1, D 8000 Munich 40, FRG.

Received for publication 31 July 1989 and accepted in revised form 14 November 1989.

ACKNOWLEDGMENTS

This work was supported by the Deutsche Diabetes-Stiftung, FRG.

We gratefully acknowledge the technical assistance of U. Helwig and Ø.C. Bruhn.

REFERENCES

1. Diabetes Epidemiology Research International Group: Geographic patterns of childhood insulin-dependent diabetes mellitus. *Diabetes* 37:1113–19, 1988
2. Wolff K, Gschnait F, Hönigsmann H, Konrad K, Parrish JA, Fitzpatrick TB: Phototesting and dosimetry for photochemotherapy. *Br J Dermatol* 96:1–10, 1977
3. Wucherpfennig V: Biologie und praktische Anwendung der Erythemschwelle des UV. *Strahlentherapie* 40:201–10, 1931
4. Fitzpatrick TB: Ultraviolet-induced pigmentary changes: benefits and hazards. In *Therapeutic Photomedicine Current Problems in Dermatology*. Vol. 15. Hönigsmann H, Stingl G, Eds. Basel, Karger, 1986, p. 25–38
5. Wucherpfennig V, Ehring FJ, Heite HJ: Die Beziehung des UV Erythems zu Konstitution und Umwelt. *Strahlentherapie* 92:212–19, 1935
6. Wolf E, Spencer KM, Cudworth AG: The genetic susceptibility to type I diabetes: analysis of the HLA-DR association. *Diabetologia* 24:224–30, 1983
7. Eisenbarth GS: Genes, generator of diversity, glycoconjugates, and autoimmune β-cell insufficiency in type I diabetes. *Diabetes* 36:355–64, 1987