Association of HELLP Syndrome With Autoimmune Antibodies and Glucose Intolerance

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OBJECTIVE — HELLP syndrome is a severe form of preeclampsia, characterized by hemolysis (H), elevated liver enzymes (EL), and low platelets (LP), whose pathogenesis is unclear. Autoimmunity is thought to play an important role. After the observation of development of type 1 diabetes in a patient with HELLP syndrome, we assumed a possible disease association based on autoimmune reactions.

RESEARCH DESIGN AND METHODS — We examined 70 women with HELLP syndrome for the presence of autoimmune markers and glucose intolerance. Free thyroxine, triiodothyronine, thyroid-stimulating hormone, anti-thyroglobulin antibodies, thyroperoxidase antibodies, thyrotropin receptor antibodies, antinuclear antibodies (ANAs) and anti-DNA, islet cell antibodies, GADA, an oral glucose tolerance test, and HbA_{1c} were determined postpartum. Patients with positive autoimmune markers or glucose intolerance were prospectively followed and repeated testing was performed. There were 60 women with a normal course of pregnancy matched for age, BMI, and number of pregnancies, which served as a control group.

RESULTS — From the HELLP patients, 22 (31%) compared with only 6 (10%) control subjects had autoimmune antibodies ($P < 0.01$). There were 16 HELLP patients (23%) who exhibited only 1 kind of autoantibody (5 ANA, 9 thyroid antibodies, and 2 GADA), whereas in 6 HELLP patients (8.5%) 2 different antibodies were found. In all but 4 patients of the study group, these antibodies disappeared during 3 ± 1.5 years of follow-up. Glucose intolerance was detected in 22 (31%) of the HELLP patients, 17 of them had impaired glucose tolerance (IGT), and 5 had diabetes, whereas only 4 subjects (6.5%) with IGT at postpartum were found in the control group ($P < 0.01$). During the follow-up, 2 HELLP patients were still diabetic and another 2 HELLP patients (1 GADA positive) had IGT versus 1 control subject.

CONCLUSIONS — Our data give evidence that HELLP syndrome is associated with various autoimmune antibodies and glucose intolerance. Because glucose intolerance and/or autoimmune markers persisted during long-term follow-up in 6 patients with HELLP syndrome versus 1 in the control group, it may become advisable to reexamine patients with HELLP syndrome for detection of diabetes and autoimmune disorders.

Diabetes Care 23:786–790, 2000

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Received for publication 20 December 1999 and accepted in revised form 7 March 2000.

Abbreviations: ANA, antinuclear antibody; APCA, anti-parietal cell antibodies; GADA, GAD antibodies; ICA, islet cell antibody; IGT, impaired glucose tolerance; OGTT, oral tolerance glucose test; TGAB, thyroglobulin antibodies; TPAB, thyroperoxidase antibodies; TRAB, thyrotropin receptor antibodies; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

HELLP syndrome is a rare but severe form of preeclampsia with an incidence of 1:250 pregnancies in our hospital, characterized by hemolysis (H), elevated liver enzymes (EL), and low platelets (LP) (1–5). Obstetricians advocate early detection of the disease to induce labor or perform a cesarean section for prompt recovery of the patient and normalization of symptoms and pathological findings (2–5). In patients with HELLP syndrome, autoimmune platelet antibodies and cytotoxic antibodies have been detected, thus making the presence of an autoimmune disorder most likely (6,7). In pregnancy, autoimmunity has been found to be related to reproductive failure and recurrent miscarriage (8–11). Highly abnormal levels of anti-phospholipid antibodies have been detected in pregnancies associated with maternal hypertension and fetal growth retardation (7,12). Antinuclear antibodies (ANAs) were found to occur more often in patients with preeclampsia, intrauterine growth retardation, fetal death, or abruptio placentae (12,13). However, for patients with HELLP syndrome, data on autoimmunity are not conclusive so far. Because of the observation of development of type 1 diabetes in 1 of our patients with HELLP syndrome (14), we investigated a possible association of HELLP syndrome with autoimmune-related disorders. In our study, we report the findings of various autoimmune antibodies and glucose intolerance at postpartum in patients with HELLP syndrome. All patients positive for autoimmune antibodies or glucose intolerance at postpartum were followed prospectively for a mean of 3 years.

RESEARCH DESIGN AND METHODS

Patients

From all 74 patients who were admitted to our hospital with HELLP syndrome during the last 7 years, 4 women were excluded from further evaluation because of incomplete data in 3 cases and prednisone treatment before examination in 1 case. In the 70 patients who were eligible for the study,

Table 1—*Clinical data of patients with HELLP syndrome and control subjects*

	HELLP patients				
	All	With autoimmune antibodies	With glucose intolerance	Control subjects	*P*
n	70	22	22	60	—
Age (years)	28 ± 5	29 ± 5	29 ± 6	27 ± 5	NS
Pregnancies (*n*)	1.7 ± 1	1.2 ± 0.5	1.6 ± 1	1.6 ± 0.8	NS
Age of gestation (weeks)	33 ± 4.5	34 ± 4	33 ± 4.9	37.5 ± 3.5	<0.001
BMI (kg/m^2)	26.5 ± 3.3	25 ± 3.5	25 ± 2.6	26.7 ± 3.2	NS
AST (U/l)	226 ± 212	235 ± 148	234 ± 188	13 ± 6.9	<0.001
ALT (U/l)	206 ± 194	255 ± 165	198 ± 150	8 ± 4.1	<0.001
LDH (U/l)	889 ± 507	811 ± 396	927 ± 582	254 ± 77	<0.001
Platelets (×10^9/l)	60 ± 31	62 ± 35	62 ± 38	226 ± 54	<0.001

Data are *n* or means ± SD; *P* values given for control subjects against all HELLP patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

HELLP syndrome was diagnosed at our Department of Gynecology and Obstetrics according to the definition by Sibai et al. (2). Besides a physical examination directed toward signs of autoimmune disease, the history of collagen disease, thyroid disorder, or diabetes in the patient and her first-grade relatives was stated at postpartum.

Laboratory measurements

Routine laboratory parameters, especially blood cell count (Max M; Instrumentation Laboratories, Vienna), coagulation, and liver and renal function parameters, performed on a Hitachi automated analyzer (Roche Diagnostics, Mannheim, Germany), were determined daily (until values normalized) during each patient's stay in the obstetrics unit. The highest values for aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase, and the lowest values for platelets measured were used to determine the patient's characteristics (Table 1). Seven to 14 days after initiation of labor or a cesarean section, the following laboratory measurements were performed: an oral glucose tolerance test (OGTT) with 75-g glucose load evaluated according to World Health Organization (WHO) criteria (14); plasma glucose by glucose oxidase method using a Beckman Analyzer 2 (Beckman, Palo Alto, CA); HbA_{1c} by high-performance liquid chromatography (HPLC Diamat; Bio-Rad, Hercules, CA) with a normal range in our laboratory of 4.2–6.0% (range 2 SD); islet cell antibodies (ICAs) by immuno-fluorescence method (16); for GAD antibodies (GADA), a radio immunoassay (GAD-RIA; Brahms Diagnostica, Berlin), normal range <7 mU/ml was used; free thyroxine (T4), normal range 0.8–1.8 ng/dl, and thyroid stimulating hormone, normal range 0.5–3.5 mU/l, were measured by chemoluminescence method (Bayer Diagnostics, Leverkusen, Germany); and triiodothyronine (T3), normal range 3–7.5 pmol/l, was measured by electro-chemo-luminescence (Roche Diagnostics, Mannheim, Germany); for measurement of thyroglobulin antibodies (TGAB), normal range <100 U/ml, and thyroperoxidase antibodies (TPAB), normal range <100 U/ml, an immunoenzyme-assay (Pharmacia & Upjohn, Freiburg, Germany) was used; for thyrotropin receptor antibodies (TRAB), normal range <7 U/ml, a radioimmunoassay (Iason Labormedizin, Graz, Austria) was used; ANAs, IgG, and anti-parietal cell antibodies (APCA), positive with titers >1:40, were determined by indirect immunofluorescence method (Sanofi/Pasteur, Vienna, and Bios, Munich); and anti-DNA antibodies, normal range <25 U/ml, were measured by enzyme-linked immunosorbent assay (Elias Medizintechnik, Freiburg, Germany).

Control subjects

Sixty women with a normal course of pregnancy, matched for age, BMI (kg/m^2), and number of pregnancies, served as a control group. Recruitment encompassed all women within a defined period of 3 months who were admitted to our Department of Gynecology and Obstetrics for delivery and who had given written consent for performance of the above-mentioned laboratory examinations. Patients with gestational diabetes, for whom there is a higher probability to develop diabetes during follow-up compared with normal pregnant women, were excluded from the control group. A selection bias between our study group and the control subjects due to the difference in gestational age could be excluded as OGTTs were performed 1–2 weeks postpartum.

Follow-up

Patients with positive autoantibodies or diabetes at postpartum were prospectively followed and repeated testing was performed. Also, patients who were antibody negative but had IGT or diabetes were followed and tested again for the underlying disorder. Mean follow-up for all of these patients was 3 ± 1.5 years (range 0.8–6.8).

Statistical analysis

Comparison of data is given for patients with HELLP syndrome versus control subjects. Subgroup analysis was performed for patients with HELLP syndrome either with or without autoimmune markers. Patients with glucose intolerance were also evaluated separately. Data are given as means ± SD. Significance of differences between study groups has been determined by the use of the Mann-Whitney *U* test; $P < 0.05$ was considered significant.

RESULTS

Seventy patients with HELLP syndrome were included in our analysis. HELLP syndrome was diagnosed according to the criteria of Sibai et al. (2). All patients showed hemolysis, elevated liver enzymes, and low platelet counts (clinical data are presented in Table 1).

Postpartum findings

From the HELLP patients, 22 (31%) exhibited autoimmune antibodies: 16 (23%) had only 1 kind of antibody, 5 of them had elevated ANA titers, 2 had TGAB, 7 had TRAB, and 2 had GADA. In 6 patients (8.5%), 2 different autoimmune antibodies could be detected (Table 2). One patient (age 30 years), who had already developed a HELLP syndrome in 2 previous pregnancies, showed elevated ANA IgG of 1:160, APCA IgG 1:1280, TRAB 9 U/ml, and impaired glucose tolerance (IGT). From the 60 control subjects, autoimmune antibodies were found in only 6 women (10%): 3 had elevated ANA, 1 had elevated TGAB, and 2 had GADA. The difference in the frequency of antibodies between HELLP patients and control subjects was highly significant ($P < 0.01$). Three patients in the HELLP group had a history of Hashimoto thyroiditis, but had no thyroid antibodies at postpartum examination.

Glucose intolerance was diagnosed in 22 (31%) of the 70 patients with HELLP syndrome: 17 (24%) had IGT

Table 2—*HELLP patients with autoimmune antibodies at postpartum*

Patient, age (years)	Glucose intolerance	ANA titer	Thyroid antibodies (U/ml)			GADA (mU/ml)
			TGAB	TPAB	TRAB	
V.R., 25		1:160	101			
G.G., 27		1:640			8	
M.G., 18		1:80				
M.R., 24		1:80				
S.M., 25		1:80				
E.F., 29		1:160				
G.S., 29	IGT	1:160				
E.G., 30	IGT	1:160			9	
U.R., 26					7	
S.K., 29					7	
R.M., 31	IGT				8	17
C.L., 37	D			232		10
E.W., 31	D		138			
E.E., 38	D		137			
T.B., 21	IGT				13	
H.R., 23	IGT				8	
T.M., 38					11	
A.S., 27			115	317		
M.W., 35					8	
I.L., 29					7	
R.P., 24						8
M.B., 29						550

D, diabetes.

and 5 (7%) had diabetes according to WHO criteria. Glucose values during the OGTT in these patients were as follows: fasting, 4.8 ± 1.1; at 1 h, 9.3 ± 1.4; and at 2 h, 8.8 ± 1.0 mmol/l. Of these HELLP patients with glucose intolerance, 8 were positive for autoimmune antibodies (ANA, TGAB, TPAB, TRAB, and GADA) (Table 2). In the control group, only 4 (6.5%) women had IGT and none had diabetes. OGTT glucose values in the 4 control patients with IGT are as follows: fasting, 3.5 ± 1.1; at 1 h, 9 ± 0.8; and at 2 h, 8.9 ± 0.5 mmol/l. The difference in the frequency of glucose intolerance between HELLP patients and control subjects was significant ($P < 0.01$). Two HELLP patients with IGT and 2 patients without glucose intolerance had elevated GADA and all were ICA negative. One of the GADA-positive patients had developed a HELLP syndrome during her first and fourth pregnancies. HbA_{1c} was normal in all patients (4.8 ± 0.6 vs. 4.6 ± 0.7% in the control subjects, P = NS). The clinical data of HELLP patients with autoimmune antibodies or glucose intolerance taken separately were not different compared with data for all HELLP patients (P = NS) (Table 1).

For all other subjects (48 HELLP patients and 56 control subjects), values of the OGTTs were normal according to the WHO criteria. However, blood glucose values were significantly higher for HELLP patients compared with those for the control subjects (fasting glucose 4.6 ± 0.5 vs. 3.5 ± 0.7 mmol/l, $P < 0.001$; 1-h glucose 7.8 ± 1.6 vs. 6.6 ± 1.5 mmol/l, $P = 0.003$; 2-h glucose 6.3 ± 1.1 vs. 5.4 ± 1.0 mmol/l, $P < 0.001$).

Findings during the follow-up period

All patients with autoantibodies and/or glucose intolerance at postpartum were reexamined 6 months later. From the 22 patients with autoantibodies at postpartum, only 4 had autoantibodies 6 months later: 2 had GADA (18 and 500 mU/ml), 1 had TGAB (193 U/ml), and 1 had TPAB (991 U/ml). From the 22 patients with glucose intolerance at postpartum, only 2 had diabetes and 2 had IGT 6 months later. One of the 2 patients with diabetes was classified as type 1 diabetic with negative C-peptide; the other patient had type 2 diabetes, which was well controlled by diet (Table 3). BMI in these patients with glucose intolerance was normal (between 20–25 kg/m^2); only 1 patient was overweight (C.L., age 37 years, BMI 30 kg/m^2). All patients with autoantibodies or glucose intolerance 6 months postpartum remained positive in repeated follow-up examinations after another 6 months, and once a year thereafter.

In the control group, all 6 subjects with autoimmune antibodies at postpartum were negative 6 months later, and of the 4 subjects with IGT at postpartum, only 1 patient, with a BMI of 28 kg/m^2, had IGT 6 months later.

CONCLUSIONS — To date, the etiology and pathogenesis of the HELLP syndrome are not well understood. Gleicher

Table 3—*Characteristics of all patients with persisting autoimmune antibodies or glucose intolerance during follow-up*

Patients (n = 7)	Autoimmune antibodies, glucose intolerance	Patient's age (years)	Age of gestation (weeks)	Pregnancies (n)	BMI (kg/m^2)	Platelets ($\times 10^9$/l)	AST (U/l)	Follow-up (years)
E.W.	Type 2 diabetes	31	38	1	25	9	152	5.0
G.L.	Type 1 diabetes	30	35	1	20	25	150	4.1
C.L.	IGT, TPAB	37	37	4	31	99	62	0.8
R.M.	IGT, GADA	31	35	1	22	46	420	1.0
M.B.	GADA	29	26	2	24	83	91	1.5
V.R.	TGAB	25	36	1	25	15	618	3.0
S.V.	IGT	24	41	1	28	177	7	2.6

S.V., control subject; all others, HELLP patients. AST, aspartate aminotransferase.

(6,7) described the occurrence of antiplatelet and cytotoxic antibodies in patients with HELLP syndrome. To our knowledge, no other data with respect to antibodies have been reported for the HELLP syndrome. In our study, autoantibodies were found in 31% of the HELLP patients, whereas in the control group, only 10% had autoantibodies. The frequency of autoantibodies in our control subjects is higher compared with data from Rosenberg et al. (17) and Kiuttu et al. (18), who found ANA in 4 and 5%, respectively, of normal pregnancies and no difference compared with nonpregnant female control subjects. This finding is confirmed in a larger survey by Piura et al. (19). For higher-risk pregnancies, Matthiesen at al. (13) reported a significantly higher percentage of positive ANA. Our study shows that autoimmune phenomena, in particular of transient predominance, are a frequent finding in HELLP syndrome. Although in our HELLP patients only 6% had kept their autoantibodies 6 months postpartum, all of them stayed positive during further follow-up. It is presumed that autoimmune mechanisms play a role in the pathogenesis of the HELLP syndrome because the fetus acts as an antigen source for the mother and that transfer of fetal proteins to the mother may mediate autoimmunity, representing a subclinical rejection mechanism of the fetal allograft (6,20). Strong evidence for an autoimmune etiology of the HELLP syndrome is, on the other hand, derived from the observation of IgG antibody–mediated passive disease transfer to the fetus. It has been reported that up to 83% of infants born of mothers with HELLP syndrome show signs of hemolysis (bilirubinemia and abnormal peripheral blood smears with burr cells and/or schistocytes) and that 26% were thrombocytopenic at birth (6). In HELLP patients, comparable with predictive markers for type 1 diabetes such as ICA and GADA (21–24), the persistence of ANA and thyroid antibodies could lead to the development of collagen vascular or thyroid disorders later on. Data for some of our patients in the study group support this hypothesis: Patients who were positive for >1 autoantibody at postpartum had a higher probability to keep their autoimmune antibodies when reexamined. Persistent (resting) autoimmunity could lead to the later onset of autoimmune disease, as known for diabetes. However, the 2 subjects who remained positive for TGAB and TPAB during follow-up did not show any symptom of thyroid disorder or any other disease.

Glucose intolerance was only partly associated with signs of autoimmunity in our study. Only 8 (Table 2) of 22 patients with glucose intolerance at postpartum also had autoimmune antibodies. Thyroid antibodies as an additional sign for autoimmunity were associated with glucose intolerance in 28% of patients in the study group. Of the 2 patients who continued to exhibit GADA during the follow-up, 1 had IGT. It is possible that, in this case, HELLP syndrome caused persistent glucose intolerance, leading to type 1 diabetes or latent autoimmune diabetes in adults (25) later on. This hypothesis is supported by the previous description of the development of type 1 diabetes in a patient with HELLP syndrome (14). Only 1 of the 2 patients with diabetes diagnosed postpartum had type 1 diabetes but was possibly already antibody negative. In our study, 31% of the HELLP patients had glucose intolerance at postpartum, whereas in the control group only 6.6% had glucose intolerance. According to data published by the American Diabetes Association (26), glucose intolerance is found in ~4% of normal pregnancies. No data about the frequency of glucose intolerance in gestosis or HELLP syndrome patients have been reported so far. Of our HELLP patients, 5.7% had persisting glucose intolerance during follow-up. This finding is consistent with the assumption that HELLP syndrome is a risk factor for the development of glucose intolerance. Furthermore, our HELLP patients, with normal OGTTs at postpartum, had significantly higher glucose values at fasting, 1 h, and 2 h compared with control subjects. Besides immunological causes, we may speculate that insulin resistance could play an additional role in augmenting the development of IGT and diabetes in these patients. This association is already known for patients with gestational diabetes who are at increased risk for the development of type 2 diabetes when obesity and other factors that promote insulin resistance are present.

In conclusion, our study, for the first time, describes a high frequency of autoimmune phenomena and glucose intolerance in patients with HELLP syndrome. Although part of these alterations are only transient, we believe that this observation is of clinical relevance. If our results are confirmed by long-term follow-up and additional studies, it may become advisable to repeatedly test patients with a history of HELLP syndrome for the presence of glucose intolerance. If the development of autoimmune disease will also be shown, it may become recommendable to test such patients for autoimmune antibodies, too.

Acknowledgments — We thank Dr. Gabriele Pohla-Gubo, Immunological Laboratory, Department of Dermatology, for measurements of ICA, ANA, and anti-DNA; and Dr. Guenther Galvan and Ingrid Gruber, Institute for Nuclear Medicine and Endocrinology, for technical support with measurements of GADA and thyroid parameters. We also thank Brigitta Gappmayer, Ana Kobas, and Dr. Claus Baumann from our laboratory for their assistance.

References

1. Weinstein L: Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol* 142:159–167, 1982
2. Sibai BM, Taslimi MM, El-Nazer A, Amon E, Mabie BC, Ryan GM: Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia/eclampsia. *Am J Obstet Gynecol* 155:501–509, 1986
3. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA: Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 169:1000–1006, 1993
4. Stone JH: HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets. *JAMA* 280:559–562, 1998
5. Egerman RS, Sibai BM: HELLP syndrome. *Clin Obstet Gynecol* 42:381–389, 1999
6. Gleicher N: Pregnancy and autoimmunity. *Acta Haemat* 76:68–77, 1986
7. Gleicher N: Autoantibodies in normal and abnormal pregnancy. *Am J Reprod Immunol* 28:269–273, 1992
8. Geva E, Amit A, Lerner-Geva L, Lessing JB: Autoimmunity and reproduction. *Fertil Steril* 67:599–611, 1997
9. Kovacs L, Szabo J, Molnar K, Kovacs A, Pokorny G: Antineutrophil cytoplasmic antibodies and other immunologic abnormalities in patients with habitual abortion. *Am J Reprod Immunol* 41:264–270, 1999
10. Bussen S, Steck T: Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. *Hum Reprod* 10:2938–2940, 1995
11. Wilson R, Ling H, MacLean MA, Mooney J, Kinnane D, McKillop JH, Walker JJ: Thyroid antibody titer and avidity in patients with recurrent miscarriage. *Fertil Steril* 71: 558–561, 1999
12. El-Roeiy A, Myers SA, Gleicher N: The relationship between autoantibodies and intrauterine growth retardation in hyper-

tensive disorders of pregnancy. *Am J Obstet Gynecol* 164:1253–1261, 1991
13. Matthiesen LS, Berg G, Ernerudh J, Skogh T: A prospective study on the occurrence of autoantibodies in low-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 83:21–26, 1999
14. Weitgasser R, Schnoell F, Haidbauer R: Type-1 diabetes mellitus developing during HELLP syndrome (Case Report). *Acta Diabetol* 30:173–174, 1993
15. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
16. Marner B, Lernmark A, Nerup J, Molenaar JL, Tuk CW, Bruining GJ: Analysis of islet cell antibodies on frozen sections of human pancreas. *Diabetologia* 25:93–96, 1983
17. Rosenberg AM, Bingham MC, Fong KC: Antinuclear antibodies during pregnancy. *Obstet Gynecol* 68:560–562, 1986
18. Kiuttu J, Hartikainen-Sorri AL, Makitalo R: Occurrence of antinuclear antibodies in an unselected pregnancy population. *Gynecol Obstet Invest* 33:21–25, 1992
19. Piura B, Tauber E, Dror Y, Sarov B, Buskila D, Slor H, Shoenfeld Y: Antinuclear antibodies in healthy non-pregnant and pregnant women and their offspring. *Am J Reprod Immunol* 26:28–31, 1991
20. Knobloch V, Miler I: The development of immunological relationship between mother and fetus under physiological and pathological conditions. *Allerg Immunol* 34: 219–231, 1988
21. Betterle C, Presotto F, Magrin L, Pedini B, Moro L, Caretto A, Zanchetta R: The natural history of pre-type 1 (insulin-dependent) diabetes mellitus in patients with autoimmune endocrine diseases. *Diabetologia* 37:95–103, 1994
22. Bach J-F: Insulin-dependent diabetes mellitus as an autoimmune disease. *Endocr Rev* 15:516–542, 1994
23. Lernmark A, Kolb H, Mire-Sluis T: Towards a World Health Organization (WHO) approved standard sample for islet cell antibodies, GAD65 and IA-2 autoantibodies. *Diabetologia* 42:381–382, 1999
24. Leslie RD, Atkinson MA, Notkins AL: Autoantigens IA-2 and GAD in type 1 (insulin-dependent) diabetes. *Diabetologia* 42:3–14, 1999
25. Zimmet P, Turner R, McCarthy D, Rowley M, Mackay I: Type 2 diabetes or slow type 1 diabetes. *Diabetes Care* 22 (Suppl. 2): B59–B64, 1999
26. American Diabetes Association: Clinical practice recommendations 1999. *Diabetes Care* (Suppl. 1):S74–S76, 1999