Urinary Excretion of Albumin in Adolescents With Type 1 Diabetes

Persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control

REINHARD W. HOLL, MD
MATTHIAS GRABERT, PHD
ANGELIKA THON, MD
EBERHARD HEINZE, MD

OBJECTIVE — Urinary excretion of albumin is a marker for incipient diabetic nephropathy in adults. The intra-individual variability, as well as the relationship to duration of diabetes, onset of the disease, and long-term metabolic control, have not been evaluated in a large sample of pediatric patients.

RESEARCH DESIGN AND METHODS — A total of 5,722 nocturnal urinary albumin excretion rates were determined in 447 children, adolescents, and young adults with type 1 diabetes, comprising 1,821 years of observation. Excretion rates were related to duration of diabetes, age at onset of diabetes, sex, blood pressure, and metabolic control.

RESULTS — Based on repeated measurements in individual patients, the positive predictive value of one sample was 76%, the negative 99.5%. After a duration of diabetes of 11 years, 5% of patients displayed persistent microalbuminuria (10% after 13 years). The duration of diabetes until persistent microalbuminuria was identical for patients with prepubertal or pubertal onset of diabetes. In addition to duration, female sex ($P < 0.03$) and insufficient long-term metabolic control ($P < 0.03$) contributed significantly and independently to urinary albumin excretion.

CONCLUSIONS — Determination of urinary albumin excretion rate is useful in pediatric patients. Female subjects with a long duration of diabetes and insufficient metabolic control are especially at risk for microalbuminuria. Even if persistent microalbuminuria usually becomes evident in patients aged >11 years, the prepubertal duration of diabetes contributes equally to this risk. Good metabolic control therefore should be aspired to from the onset of diabetes.

Diabetes Care 22:1555–1560, 1999

The long-term prognosis of type 1 diabetes is clouded mainly by the development of organ complications. With respect to life expectancy, diabetic nephropathy plays a pivotal role. In the U.S. as well as in industrialized European countries, diabetes is the leading cause of renal failure: 36.3% of patients developing end-stage renal failure during 1992 were subjects with diabetes (1). In a 10-year follow-up study in 939 adults with type 1 diabetes, mortality was 15% for patients with normoalbuminuria, 25% for patients with microalbuminuria, and 44% for patients with macroalbuminuria at baseline (2).

Hypertension, poor metabolic control, smoking, and genetic factors are generally accepted risk factors for the development of diabetic nephropathy in adults (3–7). Several studies, including the Diabetes Control and Complications Trial (DCCT), have clearly established that better metabolic control, as reflected by lower HbA_{1c} values, reduces the incidence of diabetic microvascular complications (8–11). The question of a threshold of metabolic control, below which patients might be protected from microvascular complications, is controversial (12–17).

The excretion of albumin in the urine is an established marker for the future development of diabetic nephropathy, and screening is generally recommended with the exception of prepubertal patients with a very short duration of diabetes (18,19). In addition to diabetic nephropathy, elevated urinary albumin excretion independently predicts atherosclerotic vascular disease in patients with type 1 diabetes (20).

The aim of our study was to establish the relationship of nocturnal albumin excretion to duration of diabetes in relatively well-controlled pediatric patients. The effects of prepubertal or pubertal onset of diabetes and of long-term metabolic control were studied.

RESEARCH DESIGN AND METHODS

— A total of 447 patients with type 1 diabetes (215 males, 232 females) attending the pediatric diabetes center at Ulm participated in the study. Patient characteristics of this clinic-based population are summarized in Table 1. A total of 5,722 timed nocturnal urine samples for determination of the albumin excretion rate had been collected between January 1996 and December 1997 (2,685 samples from male and 3,037 from female patients). Informed consent for the scientific use of the urine samples was given by the patients and their parents. At the time of the most recent sample, the mean age of the patients was 15.5 ± 0.2 years (mean ± SEM) (range 3.5–30.5), the mean duration of diabetes was 7.6 ± 0.3 years (0–25.5).

Urinary albumin was quantitated by radioimmunoassay (Pharmacia, Freiburg, Germany). The detection limit is 0.4 mg/l; the interassay reproducibility is 7.1%. Urinary albumin values were only included in the evaluation when patients were not on antihypertensive drugs for at least 1 year before the date of urine sampling. The pres-

From the Department of Pediatrics, University of Ulm, Ulm, Germany.
Address correspondence and reprint requests to Priv-Doz. Reinhard W. Holl, MD, University Children's Hospital, Feulgenstr. 12, D35392 Giessen, Germany. E-mail: reinhard.w.holl@paediat.med.uni-giessen.de.
Received for publication 23 November 1998 and accepted in revised form 17 May 1999.
Abbreviations: DCCT, Diabetes Control and Complications Trial.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of patients included in the study*

	Subjects		
	All	Male	Female
n	447	215	232
Years of observation	1,791	871	920
Age (years)	15.5 ± 0.3	15.6 ± 0.4	15.3 ± 0.3
Duration of diabetes (years)	7.6 ± 0.3	7.9 ± 0.4	7.4 ± 0.3
Height (*z* score)	0.17 ± 0.05	0.07 ± 0.07	0.28 ± 0.07
Weight (*z* score)	1.06 ± 0.06	0.97 ± 0.08	1.13 ± 0.08
BMI (*z* score)	1.24 ± 0.06	1.25 ± 0.08	1.24 ± 0.08
Median HbA_{1c} (%)	7.05 ± 0.06	6.94 ± 0.08	7.16 ± 0.09
DCCT-corrected HbA_{1c} (%)	7.55 ± 0.06	7.44 ± 0.08	7.66 ± 0.09
Insulin dose (U/kg)	0.78 ± 0.01	0.77 ± 0.02	0.80 ± 0.02
Injections/day (*n*)	3.2 ± 0.04	3.1 ± 0.05	3.3 ± 0.09

Data are *n* or means ± SEM. The assay applied in the study for HbA_{1c} yields results ~0.5% lower than the reference DCCT assay; therefore, for better comparison with other studies, a mathematically corrected value is also given in the table.

ence of urinary tract infections or microhematuria was excluded by dipstick detection of urine leukocytes and erythrocytes (Combur dipstick) at each outpatient visit. Urine samples were not included in the study if either microhematuria or urinary tract infections were present; renal ultrasound was performed on diabetic subjects with persistent microalbuminuria. Nocturnal albumin excretion rates were expressed as $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$ of body surface area to correct for differences in body size (20). Height was measured by an electronic stadiometer (Busse Design, Ulm, Germany) and weight by a calibrated gauge. The formula by Dubois and Dubois (20a) was used to calculate body surface area. Persistent microalbuminuria was diagnosed if at least two of three urine samples were >15 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$. This cutoff level is based on numerous studies in the literature (21–23) and is consistent with a sample of 94 healthy children studied at our institution (range 0.2–12 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$).

To compare children and adolescents of different age and sex, *z* scores were calculated for height, weight, and BMI using the Zurich longitudinal growth study, which is suitable for children from our region (24,25). For systolic and diastolic blood pressure, the normative data provided by the Second Task Force on Hypertension in Childhood were used (26). The onset of puberty was defined by the chronological age at which the first signs of puberty are present (breast development stage 2 in girls at age 10.4 years, pubic hair stage 2 in boys at age 12.2 years) (27,28).

HbA_{1c} was measured by high-performance liquid chromatography (Microcolumn System; Pharmacia, Freiburg, Germany) every 3 months. The normal range for this method, based on 93 healthy control subjects, is 3.5–5.7%, which is 0.5% lower than the normal range obtained by the method applied by the DCCT reference lab (8). At our institution, we aim for an HbA_{1c} level of <7%, which is equivalent to ~5 SDs above the mean of healthy control subjects. Until 1991, ion exchange chromatography was applied for the measurement of HbA_{1c} at our clinic (normal range: 3.3–5.3%). These values were mathematically adjusted to the current normal range using the SD score method (29). Long-term metabolic control was reflected by the median of all HbA_{1c} measurements performed between the onset of diabetes and the date of the urine examination. On average, 28.5 HbA_{1c} values were available per patient.

All patients were treated with a free mixture of regular and NPH insulin; 17% of patients were on two injections per day, 36.6% on three, and 46.3% on four injections per day. Repeated daily blood glucose measurements and self-adjustment of insulin dose according to blood glucose was encouraged irrespective of age. All patients and their parents participated in a structured education program on diabetes-related topics at diagnosis as well as every 2–3 years thereafter. Patients were seen in our diabetes outpatient department on average 3.9 times per year (30). Every patient was assigned to one of two pediatric diabetes specialists (R.W.H., E.H.). While the intake of carbohydrates is calculated in all patients and adjusted to the insulin requirement, the consumption of protein and fat is not generally quantitated in our patients. However, dietary advice includes the recommendation to consume ~20% of total calories as protein and 30% as fat.

At our institution, all diabetes-related information is prospectively collected with a computer documentation system specifically designed for in- and outpatient care of diabetes patients (31). The Foxpro compiler is used for the current version of this program. The dBaseV software was used to extract relevant parameters. Data were then transferred to the SAS statistical software package (SAS Institute, Cary, NC) for further analysis. Data were expressed as percentiles or as means ± SEM. Nonparametric statistics (Wilcoxon's rank-sum test) were used for comparison between groups; a *P* value <0.05 was considered significant. To assess simultaneously the impact of duration of diabetes, prepubertal or pubertal onset, metabolic control, and blood pressure on urine albumin, a multiple regression analysis with backward selection of parameters was performed based on the most recent year of observation in each patient.

RESULTS — In 360 of a total of 5,722 timed nocturnal samples (6.3%), the urinary excretion of albumin exceeded the cutoff value of 15 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$. If 20 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$ was used as a cutoff, 236 samples (4.1%) exceeded this limit. Macroalbuminuria (>150 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$) was detected in 16 samples (0.3%).

In order to investigate the reproducibility of elevated urine albumin excretion rates, a subset of 4,447 urine samples from 398 patients was selected where at least two additional samples were available during the same yearly interval (on average 4.9 measurements per year for patients in this subgroup, range 3–15 measurements; mean interval 2.3 months, range 1–12 months). Persistent microalbuminuria was defined as an elevated albumin excretion rate in at least two of three samples. If >3 samples were measured during the respective year, persistent microalbuminuria was diagnosed when the median of all samples exceeded 15 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$. Of the individual samples, 305 (6.9%) exceeded this cutoff value and were therefore classified as pathologic. Among those, 124 samples (40.6%) represented persistent and 181 samples (59.3%) represented intermittent microalbuminuria. In contrast, among 4,142 samples in the normal range, 39 were false-negative, because the other two measurements performed during the

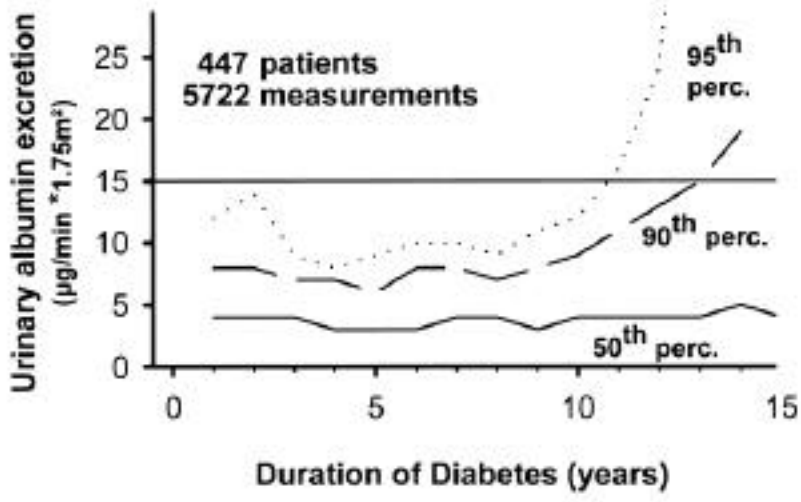

Figure 1—*Distribution of urinary albumin excretion rates related to the duration of diabetes. The 50th, 90th, and 95th percentiles are indicated. The horizontal line represents the cutoff between normo- and microalbuminuria of 15 µg · min^{-1} · 1.75 m^{-2}. For statistical background, see text.*

same year were elevated. The sensitivity of one elevated urinary albumin excretion rate to detect persistent microalbuminuria was therefore 76%, the specificity was 95.8%. In our patient population of adolescents and young adults, the positive predictive value of one urine albumin measurement was 40.6% and the negative predictive value was 99.5%. The high variability of repeated measurements in individual patients is also reflected by a coefficient of variation of 110%.

Persistent microalbuminuria was seen in three children <11 years of age (ages 8.5, 10.8, and 10.9; respective duration of diabetes 3.0, 2.7, and 2.9 years; two girls, one boy; median albumin excretion 15.1–22.7 µg · min^{-1} · 1.75 m^{-2}). When related to the duration of diabetes, 12 patients with persistent microalbuminuria had a duration of diabetes <5 years (range 0–3.1); their chronological ages ranged from 8.5–16.9 years; there were 6 boys and 6 girls; and the median albumin excretion rate ranged from 15.6–95.5 µg · min^{-1} · 1.75 m^{-2}. If only patients aged >11 years or with a duration of diabetes >5 years had been examined, three children with persistent microalbuminuria would have been missed.

We next related urinary albumin excretion to diabetes duration for the entire study population. In order to adjust for the different number of examinations per patient, the median urinary albumin excretion from all measurements performed within 1 year was calculated for each subject. The median value for a yearly interval in each patient was then weighted with the number of samples contributing to this value. The average number of urine samples per patient per year was 3.1 ± 0.05 (range 1–15). In Fig. 1, the relationship of albumin excretion to diabetes duration is depicted based on all 447 patients. The 50th percentile of albumin excretion during the first year of diabetes in 192 patients was 3.9 µg · min^{-1} · 1.75 m^{-2} (90th percentile: 8.43). The 50th percentile was stable for the first 15 years of diabetes (3.91 µg · min^{-1} · 1.75 m^{-2}). However, after 11 years of diabetes, 5% of the patients had microalbuminuria (>15 µg · min^{-1} · 1.75 m^{-2}). This proportion increased to 10% of the patients after 13 years of diabetes.

Elevated albumin excretion is seen after long duration of diabetes, but also at the onset, resulting in a biphasic curve for the 95th percentile of excretion rates. Repeated measurements during the 1st week of diabetes were available from 165 patients. Transient microalbuminuria (one sample >15 µg · min^{-1} · 1.75 m^{-2}) was present in 41 subjects (17 male, 24 female, average age 11.1 years), while persistent microalbuminuria was present in 2 subjects (both female, 13.9 and 14.3 years of age).

The prepubertal duration of diabetes has been hypothesized to be irrelevant for the development of complications (32,33). In order to objectively assess this question, 323 patients with a prepubertal onset of diabetes (average age 6.3 ± 0.17 years, 175 males, 148 females) were compared with 124 patients with a pubertal onset of diabetes (average age 13.2 ± 0.17 years, 40 males, 84 females). Using Wilcoxon's rank-sum test, no significant differences for urinary albumin excretion could be detected between children with a prepubertal onset of diabetes and children with a pubertal onset, but the same total duration of diabetes.

Multiple regression analysis was applied to detect factors related to albumin excretion. Analysis was based on the most recent year of observation in each patient. In addition to duration of diabetes, sex, long-term metabolic control, onset of diabetes (prepuberty or puberty), standardized blood pressure (systolic and diastolic), and standardized height, weight, and BMI were included as independent parameters into the model. Long-term metabolic control is represented by the median of all previous measurements of HbA_{1c} in the patient. Duration of diabetes, female sex, and high long-term HbA_{1c} were identified as significant contributors. Prepubertal or pubertal onset of diabetes again was not associated with high or low risk for incipient nephropathy. Table 2 gives the respective indices.

Table 2—*Multiple regression analysis of factors determining urinary albumin excretion rate per body surface area, based on the most recent year of observation in each patient*

Parameter	Estimate	*F* value	*P* value
Duration of diabetes	0.58	11.3	<0.001
Long-term metabolic control	1.68	5.1	<0.03
Female sex	4.2	5.2	<0.03
Prepubertal onset	—	—	NS
Systolic blood pressure	—	—	NS
Diastolic blood pressure	—	—	NS
Height	—	—	NS
Weight	—	—	NS
BMI	—	—	NS

CONCLUSIONS — While the predictive value of microalbuminuria in patients with diabetes is generally accepted, there is controversy about the optimal strategy for screening. Quantitative measurements in 24-h or in overnight timed urine specimens represent the "gold standard" for the detection of microalbuminuria, even if results obtained by the two collection methods are not equivalent (34). In outpatients, especially during adolescence, it is not possible to reliably collect 24-h urine specimens, while the quantitative collection of first morning urines is feasible. The rationale for nocturnal collection of urine is reduced intrasubject variability due to lack of orthostatic and exercise-induced albuminuria. Some centers use albumin concentration or albumin/creatinine ratio for screening; however, experiences reported with this approach are quite variable (21,35) and all patients with suspected microalbuminuria have to be reevaluated using a quantitative method and timed urine samples (36,37), which renders the logistics even more demanding. It has to be kept in mind that the predictive value of a positive screening result depends on the prevalence of the disease in the respective population. As persistent microalbuminuria is quite rare in pediatric subjects up to early adulthood, a specificity of ~70%, as reported for a dipstick method, means that the portion of false-positive results is considerably higher than the prevalence of microalbuminuria in adolescence (38). In addition, in order to achieve optimal sensitivity and specificity in pediatric patients, the cutoff level used for screening has to be chosen based on comparisons with a reference method in the respective age-group, rather than using values published for adults (39).

The high day-to-day variability of urinary albumin excretion has been pointed out as a caveat concerning urine albumin determination (39,40). In our study, a single value in the microalbuminuric range conveys only a 40% chance to indicate persistent microalbuminuria in pediatric patients, and the coefficient of variation within 1 year amounted to 110%. Medically, this demands that other potential causes of microalbuminuria have to be excluded (urinary tract infection and nondiabetic kidney diseases such as IgA nephritis, febrile proteinuria, etc.) and elevated albumin excretion has to be confirmed by at least one more measurement before a diagnosis of incipient diabetic nephropathy can be made and therapeutic consequences are justified. In addition, this high rate of false-positive results may lead to unnecessary psychological disturbance of patients and their families. However, the intra-individual variability of urinary albumin excretion should not be used to support a nihilistic approach to routine screening in pediatric patients. In view of the reversibility of microalbuminuria by improvement of metabolic control (41), reduced protein intake (42), or antihypertensive drugs (43), and the positive effect of intervention on long-term kidney function, early detection of persistent microalbuminuria is mandatory. In agreement with recommendations by the American Diabetes Association (18) and the International Society for Pediatric and Adolescent Diabetology (ISPAD) (19), the German Working Group on Pediatric Diabetology recommends screening for all patients with a duration of diabetes >5 years or with a chronological age >11 years (44). Following these guidelines, in our patient population only three patients with persistent proteinuria would have been missed. In the pediatric literature, the optimal cutoff for nocturnal albumin secretion rate has been a controversial subject. While several studies have determined the upper limit of normal in healthy control subjects to be ~7 $\mu g \cdot min^{-1} \cdot 1.75\ m^{-2}$, because of the large variability 15 or 20 μg/min has generally been recommended for clinical purposes (21–23).

After 11 years of diabetes 5%, and after 14 years of diabetes 10% of patients had persistent microalbuminuria, despite relatively tight metabolic control achieved at our institution (45). In our patient group, the prevalence of microalbuminuria after 10–15 years of diabetes is significantly lower compared with the Epidemiology of Diabetes Complications Study from the U.S. or the EURODIAB IDDM Complications Study from Europe (46). In agreement with the DCCT and other studies (8,9,13,41), the contribution of long-term metabolic control to the development of diabetic nephropathy is again supported by our data.

It has been suggested that the prepubertal duration of diabetes might not be relevant for the development of diabetic organ damage (32,33,47). This has led to the assumption that tight metabolic control is not a primary goal for prepubertal children with diabetes. However, such data are difficult to interpret, because metabolic control usually deteriorates during puberty and the time lag between the metabolic insult of hyperglycemia and the development of microalbuminuria is likely to be several years. In contrast to previous reports, several recent studies have demonstrated the importance of the prepubertal phase on the development of diabetic retinopathy (16,48). For diabetic nephropathy, impressive data from Sweden on 155 children followed for ~10 years demonstrate the importance of early metabolic control during the prepubertal period of diabetes (49). A prospective study from Switzerland described microalbuminuria during early—not late—puberty and recommends screening from the onset of puberty (22). Our study did not find any evidence for a "protective effect" of the prepubertal duration of diabetes, but the number of diabetic subjects with persistent microalbuminuria remains low. Our findings are in agreement with data from England comparing microalbuminuric and normoalbuminuric patients with similar duration of type 1 diabetes (50). The average age at onset was significantly younger in patients who developed microalbuminuria (10.0 years) compared with 15.6 years in patient who remained normoalbuminuric. This finding underlines the necessity to strive for good metabolic control from the onset of diabetes in order to prevent microvascular complications, even if retinopathy or nephropathy become manifest usually after the onset of puberty.

No relationship between microalbuminuria and height, weight, and BMI was found. In nondiabetic adult subjects, higher urine albumin excretion rates were seen in small men (51), but this relationship was not confirmed by others (52). Again in adult nondiabetic patients, higher albumin excretion was reported in massively obese compared with normal-weight subjects; however, this may well be explained by undetected type 2 diabetes in the overweight group, as both fasting and postprandial blood glucose were higher (53). In the multivariate analysis, in addition to long-term metabolic control, sex and duration of diabetes were independently related to urine albumin excretion. The higher albumin excretion rate in female subjects compared with male subjects may be explained by the higher HbA_{1c} values in female adolescents (45).

Our data confirm the usefulness of routine screening for microalbuminuria in pediatric subjects with diabetes. Long duration of diabetes, prolonged high HbA_{1c} levels, and female sex were significantly and

independently related to urinary albumin excretion rate, while age at disease onset was not. However, it has to be kept in mind that because of the large intra-individual variability, a study including an even larger number of subjects, more subjects with persistent microalbuminuria, and a longer observation period might uncover additional factors relevant for urinary albumin excretion. In addition, different results may be obtained using other methods to detect microalbuminuria (e.g., albumin/creatinin ratio and 24-h urine sampling). Early detection of incipient nephropathy together with appropriate treatment and intensive follow-up of patients identified by this approach are of pivotal importance to further reduce the incidence of nephropathy in diabetic subjects. Some encouraging reports on patients with type 1 or type 2 diabetes indicate that this aim may in fact be achievable (54,55).

Acknowledgments — Financial support to R.W.H. was available from the German Ministry of Health, the regional government of Baden-Württemberg, the German Diabetes Association, and the Dr. Bürger-Büsing-Fund from the Association of Diabetic Children and Adolescents, Kaiserslautern.

We thank U. Mann and H. Pinzer for excellent technical help with the measurement of urinary albumin, and Prof. Dr. E. Kohne and her staff for determination of HbA_{1c}. We are grateful to H. Nebenführ and U. Weinstein for excellent patient care and data entry into the computer system.

References

1. US Renal Data System: *USRDS 1995 Annual Data Report*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1995
2. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH: Predictors of mortality in insulin dependent diabetes: 10-year observational follow-up study. *BMJ* 313:779–784, 1996
3. Friedman EA: Renal syndromes in diabetes. *Endocrinol Metab Clin North Am* 25:293–324, 1996
4. Earle KA, Morocutti A, Viberti GC: Permissive role of hypertension in the development of proteinuria and progression of renal disease in insulin-dependent diabetic patients. *J Hypertens* 15:191–196, 1997
5. Quinn M, Angelico MC, Warram, JH, Krolewski AS: Familial factors determine the development of diabetic nephropathy in patients with IDDM. *Diabetologia* 39:940–945, 1996
6. Sawicki PT, Didjurgeit U, Mühlhauser I, Bender R, Heinemann L, Berger M: Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 17:126–131, 1994
7. Deckert T, Kofoed-Enevoldsen A, Norgaard K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen T: Microalbuminuria. *Diabetes Care* 15:1181–1191, 1992
8. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
9. Diabetes Control and Complications Trial Research Group: Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. *J Pediatr* 125:177–188, 1994
10. Klein R, Klein BEK, Moss SE, Davis MD, deMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Ophthalmol* 102:520–526, 1984
11. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications in diabetes. *N Engl J Med* 329:304–309, 1993
12. The Diabetes Control and Complications Trial Research Group: The absence of a glycemic threshold for the development of long-term complications. *Diabetes* 45:1289–1298, 1996
13. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
14. Danne TH, Weber B, Dinesen B, Mortensen HB: Threshold of HbA_{1c} for the effect of hyperglycemia on the risk of diabetic microangiopathy (Letter). *Diabetes Care* 19:183, 1996
15. Kovacs M, Mukerji P, Drash A, Iyengar S: Biomedical and psychiatric risk factors for retinopathy among children with IDDM. *Diabetes Care* 18:1592–1599, 1995
16. Donaghue KC, Fung ATW, Hing S, Fairchild J, King J, Chan A, Howard NJ, Silink M: The effect of prepubertal diabetes duration on diabetes. *Diabetes Care* 20:77–80, 1997
17. McNally PG, Raymond NT, Swift PGF, Hearnshaw JR, Burden AC: Does the prepubertal duration of diabetes influence the onset of microvascular complications? *Diabet Med* 10:906–908, 1993
18. American Diabetes Association: Diabetic nephropathy (Position Statement). *Diabetes Care* 21 (Suppl. 1):S50–S53, 1998
19. ISPAD-IDF/WHO Policy Group (Laron Z, Ed.): *Consensus Guidelines for the Management of Insulin-Dependent (Type 1) Diabetes Mellitus (IDDM) in Childhood and Adolescence*. London, Freund, 1995
20. Deckert T, Yokoyama H, Mathiesen E, Ronn B, Jensen T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen JS: Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *Br Med J* 312:871–873, 1996

20a. Dubois D, Dubois EF: A formula to estimate the approximate surface area if height and weight be known. *Arch Int Med* 17:863–871, 1996

21. Kouri TT, Viikari JSA, Mattila KS, Irjala KMA: Microalbuminuria: invalidity of simple concentration-based screening tests for early nephropathy due to urinary volumes of diabetic patients. *Diabetes Care* 14: 591–593, 1991
22. Janner M, Knill SE, Diem P, Zuppinger KA, Mullis PE: Persistent microalbuminuria in adolescents with type I (insulin-dependent) diabetes mellitus is associated to early rather than late puberty. *Eur J Pediatr* 153:403–408, 1994
23. Chase HP, Marshall G, Garg SK, Harris S, Osberg I: Borderline increases in albumin excretion rate and relation to glycemic control in subjects with diabetes. *Clin Chem* 37:2048–2052, 1991
24. Prader A, Largo RH, Molinari L, Issler C: Physical growth of Swiss children from birth to 20 years of age. *Helv Paediat Acta* 52:1–125, 1989
25. Holl RW, Seifert M, Grabert M, Heinze E: Longitudinal analysis of somatic development in paediatric patients with IDDM: genetic influences on height and weight. *Diabetologia* 37:925–929, 1994
26. Task Force on Blood Pressure Control in Children: Report of the Second Task Force. *Pediatrics* 79:1–25, 1987
27. Largo RH, Prader A: Pubertal development in Swiss boys. *Helv Paediat Acta* 38:211–228, 1983
28. Largo RH, Prader A: Pubertal development in Swiss girls. *Helv Paediat Acta* 38:229–243, 1983
29. Heinze E, Vetter U, Thon A, Kohne E: Is there a "risk-free" haemoglobin A1 concentration in type I diabetics. *Dtsch Med Wochenschr* 108:1632–1634, 1983
30. Holl RW, Grabert M, Hecker W, Klinghammer A, Renner C, Schweiggert F, Teller W, Heinze E: Quality control in the care of children and adolescents with diabetes. *Diab Stoffw* 6:83–90, 1997
31. Holl RW, Grabert M, Schweiggert F, Heinze E: A computer program for prospective documentation of pediatric patients with type I diabetes mellitus. *Diab Stoffw* 3:232–238, 1993
32. Kostraba JN, Dorman JS, Orchard TJ, Becker DJ, Ohki Y, Ellis D, Doft BH, Lobes LA, LaPorte RE, Drash AL: Contribution of

diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care* 12:686–693, 1989
33. Burger W, Hövener G, Düsterhus R, Hartmann R, Weber B: Prevalence and development of retinopathy in children and adolescents with type I diabetes mellitus. *Diabetologia* 29:17–22, 1986
34. Tomaselli L, Trischitta V, Vinci C, Frittitta L, Squatrito S, Vigneri R: Evaluation of albumin excretion rate in overnight versus 24-h urine. *Diabetes Care* 12:585–587, 1989
35. Shield JPH, Hunt LP, Baum JD, Pennock CA: Screening for diabetic microalbuminuria in routine clinical care: which method? *Arch Dis Child* 72:524–525, 1995
36. Schwab JS, Dunn FL, Feinglos MN: Screening for microalbuminuria: a comparison of single sample methods of collection and techniques of albumin analysis. *Diabetes Care* 15:1581–1584, 1992
37. Kouri T, Solakivi T, Harmoinen A: Performance of NycoCard-U-Albumin and MicralTest rapid methods for detecting microalbuminuria. *Eur J Clin Chem Clin Biochem* 32:419–423, 1994
38. Mogensen CE, Viberti GC, Peheim E, Kutter D, Hasslacher C, Hofmann W, Renner R, Bojestig M, Poulsen PL, Scott G, Thoma J, Kuefer J, Nilsson B, Gambke B, Mueller P, Steinbiss J, Willamowski KD: Multicenter evaluation of the Micral-Test II test strip, an immunologic rapid test for the detection of microalbuminuria. *Diabetes Care* 20:1642–1646, 1997
39. Phillipou G, Phillips PJ: Variability of urinary albumin excretion in patients with microalbuminuria. *Diabetes Care* 17:425–427, 1994
40. Shield JPH, Hunt LP, Karachaliou F, Karavanaki K, Baum JD: Is microalbuminuria progressive? *Arch Dis Childhood* 73:512–514, 1995
41. Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J: Glycemic control and prognosis in type I diabetic patients with microalbuminuria. *Diabetes Care* 19:313–317, 1996
42. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on progression of diabetic and nondiabetic renal diseases. *Ann Intern Med* 124:627–632, 1996
43. Laffel LMB, McGill JB, Gans DJ: The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. *Am J Med* 99:497–504, 1995
44. German Working Group for Pediatric Diabetology: Statement on quality control. *Monatsschr Kinderheilk* 143:1146–1149, 1995
45. Mortensen HB, Hougaard P: Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 nations. *Diabetes Care* 20:714–720, 1997
46. Lloyd CE, Stephenson J, Fuller JH, Orchard TJ: A comparison of renal disease across two continents. *Diabetes Care* 19: 219–225, 1996
47. Lawson ML, Sochett EB, Chait PG, Balfe JW, Daneman D: Effect of puberty on markers of glomerular hypertrophy and hypertension in IDDM. *Diabetes* 45:51–55, 1996
48. Holl RW, Lang GE, Grabert M, Heinze E, Lang GK, Debatin KM: Diabetic retinopathy in pediatric IDDM patients: effect of diabetes duration, prepubertal and pubertal onset of diabetes, and metabolic control. *J Pediatr* 132:790–794, 1998
49. Rudberg S, Dahlquist G: Determinants of progression of microalbuminuria in adolescents with IDDM. *Diabetes Care* 19:369–371, 1996
50. Powrie JK, Watts GF, Ingham JN, Taub NA, Talmud PJ, Shaw KM: Role of glycaemic control in the development of microalbuminuria in patients with insulin dependent diabetes. *BMJ* 309:1608–1610, 1994
51. Gould MM, Mohamed-Ali V, Goubet SA, Yudkin JS, Haines AP: Microalbuminuria: associations with height and sex in nondiabetic subjects. *BMJ* 306:240–242, 1993
52. McKeigue P, Leon D: Microalbuminuria, height, and sex. *BMJ* 306:653–654, 1993
53. Basdevant A, Cassuto D, Gibault T, Raison J, Guy-Grand B: Microalbuminuria and body fat distribution in obese subjects. *Int J Obes* 18:806–811, 1994
54. Bojestig M, Arnqvist HJ, Hermansson G, Karlberg GE, Ludvigsson J: Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 330: 15–18, 1994
55. Sievers ML, Nelson RG, Bennett PH: Sequential trends in overall and cause-specific mortality in diabetic and nondiabetic Pima Indians. *Diabetes Care* 19:107–111, 1996