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Original Article

Occurrence of Microalbuminuria among Children and Adolescents with Insulin-Dependent Diabetes Mellitus

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ABSTRACT. Microalbuminuria precedes the onset of diabetic nephropathy in insulin-dependent diabetes mellitus (IDDM) pediatric patients. Its prevention is among the most important challenges in managing IDDM. We attempted to determine the occurrence of microalbuminuria among IDDM Saudi children and adolescents and its associated risk factors. This is a retrospective cross-sectional study conducted on 409 IDDM children and adolescents attending the pediatric clinic at King Abdul-Aziz University Hospital from 2006 to 2010. Their ages ranged from 1 to 18 years and the mean ± standard deviation (mean ± SD) was 12.3 ± 4.1 years. Twenty-four-hour urinary albumin excretion (on two separate occasions or more, 3 - 6 months apart each), HbA1c, duration of IDDM, Tanner staging and body mass index (BMI) were reviewed. Prevalence of microalbuminuria in our cohort was 11.3%. IDDM duration was ≥2 years in 55.8% of our patients; of them, 15.6% had microalbuminuria while 45.2% had IDDM duration <2 years (6% had microalbuminuria) (P <0.01). The prevalence of microalbuminuria was higher among the post-pubertal subjects (50%) than that among the pre-pubertal (8.7%) and pubertal (41.5%) subjects. Furthermore, microalbuminuria was present in 16.7% of those with elevated blood pressure, but only in 8.5% among those with normal blood pressure (P <0.05). The enrolled overweight and obese subjects showed a higher prevalence of microalbuminuria (14%) when compared with that among those with a normal BMI (6.6%) (P <0.05). In our cohort, duration of IDDM, pubertal status, hypertension and BMI affected the prevalence of microalbuminuria. Annual screening for microalbuminuria in IDDM children and adolescents is imperative.

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Introduction

Diabetic nephropathy is a major cause of morbidity and mortality among children and adolescents with insulin-dependent diabetes mellitus (IDDM).[1-3] The prevalence of microalbuminuria in children and adolescents with IDDM varies from 10% to 40%. However, only 5-10% of these children and adolescents

demonstrate persistent elevations in urinary albumin excretion.[4-6] The high rate of regression and transient nature of microalbuminuria in young people with IDDM has been attributed to changing renal hemodynamics associated with pubertal growth and development.[5,7-9] Established risk factors for microalbuminuria in adolescents include diabetes duration,[5,10] poor metabolic control[11,12] and hypertension.[13] Intensified medical intervention represented in strict metabolic control of diabetes and aggressive management of hypertension, obesity and dyslipidemia have led to a decrease in the incidence of nephropathy over the past decades.[14,15]

Microalbuminuria has been established as an early marker of progressive kidney disease in diabetes,[16] starting at a pediatric age.[17,18] The presence of microalbuminuria predicts and precedes the onset of diabetic nephropathy, and it correlates with early diabetic glomerulopathy.[19] Indeed, among IDDM patients, microalbuminuria is often considered the first inexorable step toward progression to macroalbuminuria and, ultimately, end-stage renal failure.[1,2,20] Currently, the albumin excretion rate remains the best available non-invasive predictor for diabetic nephropathy and should be measured regularly according to the established guidelines.[21] Recent prospective studies, however, have shown that the elevated urinary albumin excretion in IDDM patients regresses to normoalbuminuria in a majority and advances toward proteinuria in only a minority of the patients.[7] Prevention of the renal complications of IDDM is one of the most important challenges in managing the disease. Indeed, improved long-term metabolic control has reduced the risk of developing the renal complications of IDDM among the affected children and adolescents.[22,23] We attempted to determine the occurrence of microalbuminuria among Saudi children and adolescents with IDDM and its relation to metabolic control, duration of IDDM, pubertal status, age and elevated blood pressure in these pediatric patients.

Methodology

Study design, patients and site

This is a retrospective cross-sectional study conducted on all children and adolescents with IDDM attending the pediatrics diabetes clinic at the King Abdul-Aziz University (KAAU) Hospital from 2006 to 2010. The study population comprised 409 children and adolescents with IDDM aged from 1 to 18 years. Inclusion criteria were: Patients who attended the pediatrics diabetes clinic for >3 months, patient ages between 1 and 18 years and HbA1c >6.5%. Patients with congenital renal anomalies seen by abdominal ultrasound and those with urinalysis positive for leukouria, hematuria, proteinuria or signs of urinary tract infection were excluded.

Number of insulin injections, insulin regimen, current age, Tanner staging, duration of IDDM, body mass index (BMI) and blood pressure readings of the enrolled children and adolescents were reviewed from their respective clinical records. Serum HbA1c, 24-h urinary albumin excretion (on two separate occasions or more, 3-6 months apart), urinalysis and abdominal ultrasound were reviewed from the KAAU Hospital laboratory and radiology phoenix database.

Metabolic control and microalbuminuria

All laboratory information was taken from the KAAU Hospital laboratory Phoenix system. Children and adolescents with a 24-h urinary albumin excretion rate of 30-300 mg/24 h (on two separate occasions or more, 3-6 months apart) were considered to have microalbuminuria. Patients were screened for microalbuminuria according to the established International Society for Pediatric and adolescent Diabetes (ISPAD) guidelines, which recommended annual screening from 11 years of age with 2 years' IDDM duration, from 9 years of age with 5 years' IDDM duration and after 2 years' IDDM duration in adolescents.[21] Metabolic control of the enrolled patients was assessed via the degree of HbA1c control. The ISPAD recommended that a target HbA1c level of <7.5% should be achieved without succumbing to episodes of severe hypoglycemia.[21] In this study, the ISPAD recommendations were used for assessing the degree of

HbA1c control in the enrolled subjects. Additionally, we defined the onset of normal puberty as the development of thelarche by the age of 8 years or older in girls and testicular enlargement of >4 mL in volume (measured by the Prader's orchidometer) by the age of 9 years or older in boys. All children on Tanner stage I were considered pre-pubertal. All children and adolescents on Tanner stages 2 to 4 were considered as pubertal. All adolescents on Tanner stage 5 were considered post-pubertal.

Hypertension

Hypertension in children and adolescents was defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) >95th percentile, plotted on the CDC age - gender-specific blood pressure charts and measured on three or more separate occasions.

Body mass index

Overweight and obesity for children and adolescents were defined respectively as a BMI the ≥85th and 95th percentiles plotted on Saudi population-specific BMI charts. Age- and gender-specific BMI z-scores were used as a continuous dependant variable for children and adolescents within our cohort. The BMI z-score was calculated using the World Health Organization age- and gender-specific BMI z-score charts. A BMI z-score between 1 and 2 was considered overweight and a BMI z-score >2 was considered obese. Weight and height measurements were taken according to the Saudi population-specific updated growth charts published by El-Mouzan et al.[24] Weight measurements were taken with clothes on.

Laboratory Method

Twenty-four-hour urinary albumin excretion was measured via the SEIMENS Dimension clinical chemistry system (Healthcare Diagnostics Inc. Newark, DE 19714. USA) MALB Flex reagent cartridges were used. This method is based on a particle-enhanced turbidimetric inhibition immunoassay (PETINIA), which allows direct quantitation of albumin in a urine sample. The MALB reagent cartridge contains particle reagents that aggregate to a monoclonal antibody. Both the particles and the albumin compete for the antibodies. The rate of aggregation is measured via a bichromatic turbidimetric reading (340 and 700 nm). Serum HbA1c was measured via the SEIMENS Dimension clinical chemistry system. GLU Flex reagent cartridges were used. The laboratory test used was the hexokinase method.

Statistical Analysis

This was primarily a descriptive study of the entire population of children and adolescents attending the pediatrics diabetes clinic at the KAAU Hospital with IDDM; therefore, for sample size calculations, *a priori* probabilities were not calculated. The distribution of all variables was examined graphically and, additionally, with the Shapiro–Wilk test to assess the normality of distribution for the gathered variables. Categorical variables are presented as percentages and continuous variables as means (SD) as appropriate. Student's t–test was used for comparisons of normal distributed continuous data and the Mann–Whitney *U* test and the Kruskal–Wallis test were used for comparisons of non–parametrically distributed data. The Chi-square test and cross-tabulation were used for the analysis of categorical data. In the univariate analysis, odds ratio was calculated for the risk factors. The level of significance was expressed as *P*-value; $P > 0.05$ = non-significant (NS), $P < 0.05$ = significant (S) and $P < 0.001$ = highly significant (HS). This study was approved by the biomedical ethics department at the KAAU, Faculty of Medicine.

Results

We conducted a chart review on a total of 484 children and adolescents with IDDM attending the pediatrics diabetes clinic at the KAAU Hospital from 2006 to 2010. Seventy-five patients were excluded from the study; 42 patients had leukouria, hematuria and signs urinary tract infection, 21 had <3 months follow-up at the KAAU pediatric endocrine clinic and 12 had congenital renal anomalies

confirmed by renal ultrasound.

A total of 46 of the 409 (11.3%) children and adolescents with IDDM had microalbuminuria in our cohort. In our cohort, the mean age was 12.3 ± 4.1 years, 178 were male (43.5%), 231 were female (56.5%), 128 were pre-pubertal (31.3%), 145 were pubertal (35.5%) and 136 were post-pubertal (33.3%). The mean levels of HbA1c in our cohort were 9.2 ± 2.4%; 315/409 (77%) had HbA1c ≥7.5%, of whom 34/315 (10.8%) had microalbuminuria while 94/409 (23%) had HbA1c <7.5%, of whom 12/94 (12.8%) had microalbuminuria (odds ratio = 0.8, *P* = 0.6). Furthermore, the SBP percentiles were 130.9 ± 15.6 and 119.7 ± 14.7 mmHg (*P* <0.05) and the IDDM duration was 3.6 ± 1.8 and 2.8 ± 1.2 years (*P* <0.05) among those with microalbuminuria and HbA1c ≥ 7.5% and HbA1c < 7.5%, respectively.

Duration of IDDM among the enrolled subjects was 2.8 ± 1.4 years; 224/409 (55.8%) had IDDM ≥2 years, of whom 35/224 (15.6%) had microalbuminuria while 185/409 had IDDM <2 years (45.2%), of whom 11/185 had microalbuminuria (6%) (odds ratio = 2.9, <0.01). The prevalence of microalbuminuria was higher among post-pubertal children and adolescents with IDDM (23/46 - 50%) than that among pre-pubertal (4/46 - 8.7%) and pubertal children (19/46 - 41.5%) (Table 1). All the IDDM pre-pubertal children who developed microalbuminuria had IDDM duration >4 years.

A total of 138/409 (33.7%) subjects had blood pressure >95 percentile, of whom 23/138 (16.7%) had microalbuminuria while 271/409 (66.3%) had normal blood pressure, of whom 23/271 (8.5%) had microalbuminuria (odds ratio = 2.2, *P* <0.05). Eleven IDDM patients with microabluminruia (47.8%) had elevated SBP, three (13%) had elevated DBP and nine (39.13%) had both elevated SBP and elevated DBP. In our cohort, 258/409 (63.1%) subjects had a BMI z-score >1, of whom 36/258 (14%) had microalbuminuria, while 151/409 (36.9%) were not overweight, of whom 10/151 (6.6%) had microalbuminuria (odds ratio = 2.2, <0.05). Twelve IDDM patients with microalbuminuria (26.1%) had a BMI z-score between 1 and 2 and 22 (47.8%) had a BMI z-score >2. More than half of our cohort were females [231/409 (56.5%)], of whom 30/231 (13%) developed microalbuminuria while 178/409 (43.5%) were male, of whom 16/178 (9%) developed microalbuminuria (odds ratio = 0.7, *P* = 0.3). Additionally, among those with microalbuminuria, females had mean SBP percentiles of 131.6 ±

Table 1. Comparison of the baseline patient characteristics between subjects with microalbuminuria and those without microalbuminuria.

	Subjects without microalbuminuria (n = 363)	**Subjects with microalbuminuria (n = 46)**	***P*-value**
Age (years)	13.9 ± 3	12 ± 2.8	0.06
Gender (female)	201 (55.4)	30 (65.2)	0.3
Pre-pubertal (total; 128)	124 (96.9)	4 (3.1)	<0.05*
Pubertal (total; 145)	126 (86.9)	19 (13.1)	
Post-pubertal (total; 136)	113 (83.1)	23 (16.9)	
IDDM duration (years)	2.7 ± 1.3	3.6 ± 1.6	<0.001
HbA1c (%)	8.8 ± 2.1	10.2 ± 2.9	<0.05
BMI z-score	1.1 ± 0.4	2.1 ± 1.4	<0.001
Number of insulin injections per day (for patients on injection therapy)	2.6 ± 0.6	2.8 ± 0.5	0.5
Insulin pump treatment (total; 20)	14 (3.9)	6 (13.1)	<0.05
Systolic BP percentile (mmHg)	121.6 ± 13.3	128.8 ± 14.8	<0.05
Diastolic BP percentile (mmHg)	73.8 ± 10.8	77.9 ± 11	<0.05

Values are n (%) or mean ± SD. *This *P*-value represents the comparison between post-pubertal and pre-pubertal - pubertal enrolled subjects combined.

IDDM: Insulin-dependent diabetes mellitus, HbA1c: Glycated hemoglobin, BMI z-score: Age- and Gender-adjusted body mass index, BP: Blood pressure

14.2 while males had mean SBP percentiles of 120.9 ± 13.6 mmHg, P <0.05.

Discussion

In our cohort of 409 pediatric patients, the prevalence of microalbuminuria was 11.3%. Several studies worldwide have attempted to establish the prevalence of microalbuminuria among children and adolescents with IDDM. In the Oxford Regional Prospective Study of young people with IDDM, the prevalence of microalbuminuria was 13–26%.[5] Several groups from Australia have reported prevalence rates of 6–18% for microalbuminuria among children and adolescents with IDDM.4,6 In a Swedish cohort of 426 pediatric patients with IDDM, the investigators found a prevalence of microalbuminuria of 5.6%.[25] In our study, microalbuminuria was associated with longer duration of IDDM, pubertal status, elevated blood pressure (mainly systolic) and above-normal BMI.

One-third of the patients with IDDM develop advanced nephropathy, and the renal status of probands of diabetic patients makes a difference of nearly 50% in risk.[26] Generalized glycocalyx damage occurs in diabetes and is associated with microalbuminuria.[27] Furthermore, IDDM patients have decreased systemic glycocalyx volume, and this correlates with the presence of microalbuminuria.[28] Progressive glomerular dysfunction was thought to be the primary mechanism causing increased urine protein excretion; however, tubulointerstitial disease may have an important role in the pathogenesis and progression of diabetic nephropathy.[29-32] Although it has been proposed that proximal renal tubule injury and dysfunction could be important in the early increases in urine albumin excretion, this issue has not been adequately investigated due to the lack of sensitive tests of proximal tubule injury in humans.[33,34] Although microalbuminuria has generally been attributed to glomerular injury, nephrotoxicity studies in animals reveal that microalbuminuria is a sensitive marker of early tubular toxicity.[35] Vaidya et al[36] suggested that early microalbuminuria observed in many IDDM patients may be partially due to tubular injury resulting from hyperglycemia and other metabolic factors, and that the degree of tubular injury may be associated with a more favorable microalbuminuria outcome. He also provided strong evidence that tubular injury is an important component of the natural history of microalbuminuria in IDDM.[36]

Metabolic control is imperative in the prevention of diabetic complications, particularly renal disease; several trials reported a 40% risk reduction for the development of microalbuminuria in intensively treated patients when compared with conventionally treated ones.[11,37] Elevated HbA1c, used as an indicator of hyperglycemia, is a reliable and well-established risk factor for diabetic kidney disease in pediatric-onset IDDM.[5,13,38,39] Both the Diabetes Control and Complications Trial Research Group and the follow-up Epidemiology of Diabetes Interventions and Complications study concluded that intensive management of IDDM rather than the conventional approach yielded fewer episodes of hyperglycemia and more of normal and near-normal glycemia, ultimately delaying the development and progression of diabetic nephropathy.[11,40] The majority of enrolled patients (77%) had poor metabolic control of their IDDM, of whom 10.8% developed microalbuminuria. Paradoxically, the incidence of microalbuminuria in the present study was higher (12.8% vs. 10.8%) among those with HbA1c <7.5%, which suggests that other factors might be associated with the prevalence of microalbuminuria in our cohort. Several studies have reported an increased risk of microalbuminuria in poorly controlled IDDM pediatric patients.[41-43]

The duration of IDDM affected, proportionately, the prevalence of microalbuminuria in our cohort; several studies reported similar findings.[42-44] Surprisingly, a higher percentage of young patients developed microalbuminuria in comparison with older patients (Table 1). Several studies reported that patients with microalbuminuria were generally older than those without microalbuminuria.[41,43] However, Alleyn et al reported no difference in the occurrence of microalbuminuria with respect

to patient age.[45] The prevalence of microalbuminuria increased in our cohort as children and adolescents advanced through the pubertal stages, with the highest prevalence of microalbuminuria noted in post-pubertal adolescents (Table 1). Several studies reported similar findings.[5,41] Interestingly, a number of studies have indicated that pre-pubertal duration of diabetes delays the onset of diabetic nephropathy.[5,10,25,42] Such reports must not be misinterpreted, however, as poor metabolic control in pre-pubertal children will ultimately increase the risk of microvascular complications among IDDM patients, but some evidence suggests that it will do so only at a lower rate.[46]

In the present study, a total of 33.7% subjects had elevated blood pressure, of whom 16.7% developed microalbuminuria compared with only 8.5% of those with normal blood pressure readings. Furthermore, SBP was found to be a contributing factor to the prevalence of microalbuminuria in our cohort (Table 1). Several studies concluded that arterial hypertension was a risk factor in the development of microalbuminuria among IDDM pediatric patients,[41,42] while Alleyn et al reported no difference in blood pressure percentiles with respect to the occurrence of microalbuminuria.[45] The prevalence of microalbuminuria among overweight and obese children was 14%; IDDM patients with normal BMI expressed a lower prevalence of microalbuminuria (6.6%). Additionally, those with microalbuminuria had a higher mean BMI when compared with children who did not develop microalbuminuria (Table 1). Stone et al[43] reported an increased risk of microalbuminuria among IDDM pediatric patients with above-normal BMI, while Alleyn et al[45] reported no difference in BMI with respect to the occurrence of microalbuminuria. The prevalence of microalbuminuria was higher among females. Several other studies also reported a female gender preponderance;[45,47] however, Raile et al. stated that male gender carried a higher risk of developing microalbuminuria.[42] In those who developed microalbuminuria, comparison of different genders showed that females had a higher SBP on average, which we believe to be the contributing factor to the female gender preponderance of microalbuminuria in our cohort.

Study Limitations

This is a retrospective study designed to describe the occurrence of microalbuminuria among Saudi children and adolescents with IDDM attending the KAAU pediatric endocrine clinic. Unfortunately, we were not able to assess the following: Intervals between onset of symptoms and start of treatment, compliance to therapy and family history of diabetes for enrolled subjects due to data collection obstacles. Furthermore, because of the limited access to a senior statistician, we were only able to perform univariate analysis in order to assess the relation between microalbuminuria and the collected variables. Multivariate analysis would provide a more accurate correlation. Future studies attempting to describe the prevalence of microalbuminuria and its associated risk factors among Saudi pediatric patients should pay attention to the above-mentioned variables and consider performing more advanced statistical techniques.

Conclusion

In our cohort of Saudi children and adolescents with IDDM, the prevalence of microalbuminuria was comparable with that from other international studies. Furthermore, duration of IDDM, pubertal status, hypertension and BMI affected the prevalence of microalbuminuria. This study has relevance for others attending to children and adolescents with IDDM, particularly in the Kingdom of Saudi Arabia. We emphasize the importance of annual screening for the detection of microalbuminuria among Saudi children and adolescents with IDDM.

References

1. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 1984;311:89-93.

2. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1: 1430-2.
3. Parving HH, Oxenboll B, Svendsen PA, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy: A longitudinal study of urinary albumin excretion. Acta Endocrinol 1982;100: 550-5.
4. Donaghue KC, Craig ME, Chan AK, et al. Prevalence of diabetes complications 6 years after diagnosis in an incident cohort of childhood diabetes. Diabet Med 2005;22:711-8.
5. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. Diabetes Care 1999;22:495-502.
6. Gallego PH, Bulsara MK, Frazer F, Lafferty AR, Davis EA, Jones TW. Prevalence and risk factors for microalbuminuria in a population-based sample of children and adolescents with T1DM in Western Australia. Pediatr Diabetes 2006;7:165-72.
7. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285-93.
8. Steinke JM, Sinaiko AR, Kramer MS, Suissa S, Chavers BM, Mauer M; International Diabetic Nephopathy Study Group. The early natural history of nephropathy in Type 1 Diabetes: III. Predictors of 5-year urinary albumin excretion rate patterns in initially normoalbuminuric patients. Diabetes 2005;54:2164-71.
9. Amin R, Williams RM, Frystyk J, et al. Increasing urine albumin excretion is associated with growth hormone hypersecretion and reduced clearance of insulin in adolescents and young adults with type 1 diabetes: The Oxford Regional Prospective Study. Clin Endocrinol (Oxf) 2005;62:137-44.
10. Donaghue KC, Fairchild JM, Craig ME, et al. Do all prepubertal years of diabetes duration contribute equally to diabetes complications? Diabetes Care 2003;26:1224-9.
11. 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: Diabetes Control and Complications Trial. J Pediatr 1994;125:177-88.
12. Couper JJ, Clarke CF, Byrne GC, et al. Progression of borderline increases in albuminuria in adolescents with insulin-dependent diabetes mellitus. Diabet Med 1997;14:766-71.
13. Rossing P, Hougaard P, Parving HH. Risk factors for development of incipient and overt nephropathy in type 1 diabetic patients. Diabetes Care 2002;25:859-64.
14. Nordwall M, Bojestig M, Arnqvist HJ, Ludvigsson J. Declining incidence of severe retinopathy and persisting decrease of nephropathy in an unselected population of type 1 diabetes: The Linkoping Diabetes Complications Study. Diabetologia 2004;47:1266-72.
15. Hovind P, Tarnow L, Rossing K, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care 2003;26:1258-64.
16. Perkins BA, Krolewski AS. Early nephropathy in type 1 diabetes: A new perspective on who will and who will not progress. Curr Diab Rep 2005;5:455-63.
17. Cowell CT, Rogers S, Silink M. First morning urinary albumin concentration is a good predictor of 24-hour urinary albumin excretion in children with type 1 (insulin-dependent) diabetes. Diabetologia 1986;29:97-9.
18. Gorman D, Sochett E, Daneman D. The natural history of microalbuminuria in adolescents with type 1 diabetes. J Pediatr 1999;134:333-7.
19. Walker JD, Close CF, Jones SL, et al. Glomerular structure in type 1 (insulin-dependent) diabetes patients with normo- and microabluminuria. Kidney Int 1994;41:741-8.
20. Mogensen CE. Microalbuminuria as a predictor of clinical diabetic nephropathy. Kidney Int 1987;31:673-89.
21. Rewers M, Pihoker C, Donaghue K, Hanas R, Swift P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes 2009;10:71-81.
22. Kofoed-Enevoldsen A, Borch-Johnsen K, Kreiner S, Nerup J, Deckert T. Declining incidence of persistent proteinuria in type 1 (insulin-dependent) diabetic patients in Denmark. Diabetes 1987;36:205-9.
23. Bojestig M, Arnqvist HJ, Hermansson G, Karlberg

BE, Ludvigsson J. Declining incidence of nephropathy in insulin-dependent diabetes mellitus (published erratum appears in N Engl J Med 1994;330:584). N Engl J Med 1994;330: 15-8.
24. El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Qurachi MM, Al-Omar AA. Growth charts for Saudi children and adolescents. Saudi Med J 2007;28:1555-68.
25. Svensson M, Nyström L, Schön S, Dahlquist G. Age at onset of childhood-onset type 1 diabetes and the development of end-stage renal disease: A nationwide population-based study. Diabetes Care 2006;29:538-42.
26. Quinn M, Angelico MC, Warram JH, Krolewski AS. Familial factors determine the development of diabetic nephropathy in patients with IDDM. Diabetologia 1996;39:940-5.
27. Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: A role for the glomerular endothelium? Diabetologia 2008; 51:714-25.
28. Nieuwdorp M, Mooij HL, Kroon J, et al. Endothelial glycocalyx damage coincides with microalbuminuria in type 1 diabetes. Diabetes 2006;55:1127-32.
29. Bangstad HJ, Seljeflot I, Berg TJ, Hanssen KF. Renal tubulointerstitial expansion is associated with endothelial dysfunction and inflammation in type 1 diabetes. Scand J Clin Lab Invest 2009;69:138-44.
30. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC. Structural–functional relationships in diabetic nephropathy. J Clin Invest 1984;74:1143-55.
31. Phillips AO, Steadman R. Diabetic nephropathy: The central role of renal proximal tubular cells in tubulointerstitial injury. Histol Histopathol 2002;17:247-52.
32. Wolkow PP, Niewczas MA, Perkins B, et al. Association of urinary inflammatory markers and renal decline in microalbuminuric type 1 diabetics. J Am Soc Nephrol 2008;19:789-97.
33. Abrass CK. Diabetic proteinuria. Glomerular or tubular in origin? Am J Nephrol 1984; 4:337-46.
34. Thomas MC, Burns WC, Cooper ME. Tubular changes in early diabetic nephropathy. Adv Chronic Kidney Dis 2005;12:177-86.
35. Yu Y, Jin H, Holder D, et al. Biomarkers of kidney tubule injury: Urinary trefoil factor 3 and albumin. Nat Biotechnol 2010;28:470-7.
36. Vaidya VS, Niewczas MA, Ficociello LH, et al. Regression of microalbuminuria in type 1 diabetes is associated with lower levels of urinary tubular injury biomarkers, kidney injury molecule-1, and N-acetyl-β-D-glucosaminidase. Kidney Int 2011;79:464-70.
37. The 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 1993;329:977-86.
38. Hovind P, Tarnow L, Rossing P, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: Inception cohort study. BMJ 2004;328:1105.
39. Holl RW, Grabert M, Thon A, Heinze E. Urinary excretion of albumin in adolescents with type 1 diabetes: Persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control. Diabetes Care 1999;22:1555-60.
40. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003; 290:2159-67.
41. Mathiesen ER, Saurbrey N, Hommel E, Parving HH. Prevalence of microalbuminuria in children with type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1986;29:640-3.
42. Raile K, Galler A, Hofer S, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: Effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Diabetes Care 2007;30:2523-8.
43. Stone ML, Craig ME, Chan AK, Lee JW, Verge CF, Donaghue KC. Natural history and risk factors for microalbuminuria in adolescents with type 1 diabetes: A longitudinal study. Diabetes Care 2006;29:2072-7.
44. Parving HH, Hommel E, Mathiesen E, et al. Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. Br Med J (Clin Res Ed) 1988;296:156-60.
45. Alleyn CR, Volkening LK, Wolfson J, Rodriguez-

Ventura A, Wood JR, Laffel LM. Occurrence of microalbuminuria in young people with Type 1 diabetes: Importance of age and diabetes duration. Diabet Med 2010; 27:532-7.
46. Chase HP. Glycemic control in prepubertal years. Diabetes Care 2003;26:1304-5.
47. Marcovecchio ML, Tossavainen PH, Dunger DB. Status and rationale of renoprotection studies in adolescents with type 1 diabetes. Pediatr Diabetes 2009;10:347-55.