Effect of Exercise on Urinary N-Acetyl-Beta-D-Glucosaminidase Activity and Albumin Excretion in Children with Type I Diabetes Mellitus

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Urinary N-acetyl-beta-D-glucosaminidase (NAG), a proximal tubule lysosomal enzyme, has been used as an indicator of subtle renal injury. Since it has been positively and significantly correlated with hemoglobin A_{1c} and microalbuminuria, it has been suggested that this enzyme may also reflect metabolic control. Albumin excretion is exacerbated in adult diabetic individuals during exercise; such exercise-induced albuminuria may be a forerunner of diabetic nephropathy. Metabolic control, degree of exertion, and duration of diabetes have been suggested to influence this increase in albuminuria during exercise. Studies of children are few and have produced inconsistent results. Thus we studied 28 insulin-dependent diabetic children ranging in age from 5 yr to 16 yr and 27 age-matched controls using treadmill exercise; two exercise periods consisting of (1) graded increases in speed and grade at 3-min intervals until exhaustion and (2) a constant speed and grade necessary to produce $\frac{2}{3}$–$\frac{3}{4}$ maximal heart rate for 30 min were performed. Capillary blood glucose, urinary NAG/creatinine (cr) ratios (U_{NAG}/U_{cr}) and urinary albumin/creatinine ratio (U_{alb}/U_{cr}) were measured before and after each exercise period; hemoglobin A_{1c} was also measured. The latter averaged 11.8 ± 0.6% (x ± SEM); contrary to previous studies, this was not correlated with pre- or postexercise U_{NAG}/U_{cr}. During both exercise periods, blood glucose dropped 271 ± 19 mg/dl to 213 ± 21 mg/dl (period 1) and 230 ± 22 mg/dl to 157 ± 21 mg/dl (period 2). U_{alb}/U_{cr} was slightly but not significantly elevated at rest in the diabetic subjects (0.020 ± 0.005 versus 0.016 ± 0.003 mg/mg) (P = NS); however, U_{NAG}/U_{cr} was significantly higher (7.3 ± 0.7 versus 2.9 ± 0.3) ($P < 0.05$). Regardless of age, duration of disease, or metabolic control as measured by hemoglobin A_{1c}, no significant differences in albumin excretion were noted between diabetic subjects and controls after exercise; nor did U_{alb} excretion increase significantly in either group during either exercise period. However, U_{NAG}/U_{cr} was elevated in all groups in the diabetic subjects compared with the controls ($P < 0.05$). Furthermore, during both exercise periods U_{NAG}/U_{cr} consistently decreased in the controls (−6% and −8% for periods 1 and 2, respectively), whereas U_{NAG} activity consistently rose in the diabetic subjects (27% and 36%); the differences were significant ($P < 0.05$ and $P < 0.01$). Thus, U_{alb} excretion is not significantly different in children with insulin-dependent diabetes compared with controls before or after either maximal or submaximal exercise. However, U_{NAG} activity showed significant differences before exercise and a significantly different response to exercise in the diabetic subjects and controls. Such enzymuria appears to be a more sensitive indicator of exercise-induced renal abnormalities than does albuminuria in children. Whether such changes will be useful in predicting early nephropathy or selecting those patients at risk for nephropathy requires further study. DIABETES CARE 1985; 8:466–72.

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Urinary N-acetyl-beta-D-glucosaminidase (NAG), a lysosomal hydrolase located in the proximal tubule of the kidney,[1] has been shown to be a marker for subtle renal injury.[2] Not only is this urinary enzyme a marker for glomerular and interstitial renal disease,[3] but it is also increased in the urine of patients with diabetes mellitus without overt nephropathy.[4-6] Patients with microvascular complications have higher levels of U_{NAG} activity than do those without such complications;[5] furthermore, the urinary activity is higher in newly diagnosed patients compared with treated diabetic individuals.[7] Thus, it has been suggested that U_{NAG} activity may not only detect renal disease but may also reflect metabolic control in the diabetic subject. This enzymuria has been positively and significantly correlated with hemoglobin A_{1c} levels and microalbuminuria.[6,8] The latter has been shown to be responsive to blood glucose control and has been shown to be a predictor of nephropathy.[9-12]

Exercise testing has been shown to increase urinary albumin (U_{alb}) excretion in adults with diabetes.[13-15] However, such testing in children has produced less consistent results. In three studies evaluating bicycle exercise in children and adolescents with insulin-dependent diabetes, two found no change in albumin excretion with the duration of exercise varying from 16 min to 30 min,[16,17] while the third found significant increases with such exercise.[18] Factors that have been suggested to influence increased albuminuria with exercise include degree of exertion,[15] metabolic control,[10] age,[16] and albustix-positive proteinuria.[18] Since U_{NAG}/U_{cr} (urinary creatinine) ratios have also been correlated with microalbuminuria,[6] we investigated the response of U_{NAG} activity and microalbuminuria in children with insulin-dependent diabetes and nondiabetic controls during two exercise periods with varying time intervals using the treadmill as the method of exercise.

METHODS

Twenty-eight insulin-dependent diabetic children and 27 age-matched controls exercised between 10:00 a.m. and noon on two consecutive days. The diabetic children were referred to our center for education usually after initial diagnosis or for evaluation of metabolic control and thus were hospitalized at the time of the studies. This may explain the relatively poor control of the group as reflected by an average hemoglobin A_{1c} of 11.8%. None were acutely ill at the time of the studies. Before the exercise period began, an appropriately sized blood pressure cuff was applied to the left upper arm for automatic blood pressure measurement every 3 min; 12 electrodes were attached for continuous EKG monitoring. Also at this time, blood sugar was determined using Dextrostix and Glucometer (Ames, Evansville, Indiana). The Glucometer was calibrated before each exercise period by one of the investigators (B.H.B. or K.A.). This method has been shown to be positively and significantly correlated with the laboratory determination of blood glucose and thus serves as a reliable indicator of blood glucose.[19] A random urine specimen was collected for creatinine, albumin, and U_{NAG} activity immediately before both exercise periods. After a 3-min warm-up period, the exercise session was begun using the Bruce protocol[20] modified by Cumming et al.[21] with the Quinton Status 1000 Treadmill (Seattle, Washington). This protocol allows testing of smaller children without using a bicycle ergometer. The speed and grade increased every 3 min. For the first exercise period, the children were encouraged to continue until exhaustion. A 3-min cool-down period followed the exercise; then another blood glucose and urine sample were obtained. The next day the same procedure was followed except that the children, after attaining a heart rate of $\frac{2}{3}$–$\frac{3}{4}$ of the maximum attained the previous day, exercised at that speed and grade for 30 min.

TABLE 1
Comparison of hemodynamic data for the first exercise period

	Controls (N = 27)	Diabetic subjects (N = 28)
Age (yr)	10.6 (5–17)	12.8 (5–17)
Heart rate (bpm)		
Rest	97 ± 3 (x ± SEM)	101 ± 3
Maximum	180 ± 4	193 ± 4
Systolic blood pressure (torr)		
Rest	108 ± 3	105 ± 3
Maximum	155 ± 7	148 ± 6
Diastolic blood pressure (torr)		
Rest	65 ± 2	61 ± 2
Maximum	82 ± 4	81 ± 4
Time exercised (min)		
in period 1	14 ± 0.5	12 ± 0.6*

*$P < 0.05$.

Hemoglobin A_{1c} (BioRad Laboratories, Richmond, California) was drawn within 2–3 days of the exercise testing. Before assay, the red cells were washed with normal saline to remove the labile fraction; each sample was run in duplicate. Normal values for our laboratory are 3–6%. U_{NAG} activity was measured using the spectrophotometric method of Lockwood and Bosmann[22] with p-nitrophenyl-2-acetamido-2-deoxy-beta-D-glycopyranoside as the substrate, liberating p-nitrophenyl as the product. U_{alb} was measured by a nephelometric technique using antisera to human albumin and the Beckman Immunochemistry Analyzer (Beckman Instruments, Inc., Fullerton, California). This method has a lower detection limit of 5 μg/ml. U_{cr} was measured using the Beckman Creatinine Analyzer II (Beckman Instruments). Ratios of U_{NAG}/U_{cr} and U_{alb}/U_{cr} were then calculated. For U_{NAG}/U_{cr}, 1 U was defined as 1 μg substrate liberated/h/1 mg/dl creatinine. For U_{alb}/U_{cr}, U_{alb} (in mg/dl) was divided by U_{cr} (in mg/dl) to give mg albumin/mg creatinine. Expressing U_{NAG} and U_{alb} as ratios of creatinine have been previously found to compare favorably with timed urine samples (0.08 and 0.85, respectively) as determined in our laboratory.[6]

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TABLE 2
U_{NAG} and albumin excretion data for both exercise periods

	Control	Diabetic	Control vs. diabetic
Period 1			
U_{NAG}/U_{cr} (U)			
Pre	2.9 ± 0.3*	7.3 ± 0.7	$P < 0.05$
Post	2.6 ± 0.3	9.3 ± 1.4	$P < 0.05$
U_{alb}/U_{cr} (mg/mg)			
Pre	0.016 ± 0.003	0.020 ± 0.005	
Post	0.041 ± 0.011	0.036 ± 0.007	
Period 2			
U_{NAG}/U_{cr}			
Pre	3.3 ± 0.4	7.2 ± 1.1	$P < 0.05$
Post	2.6 ± 0.3	9.8 ± 1.8	$P < 0.05$
U_{alb}/U_{cr}			
Pre	0.022 ± 0.011	0.042 ± 0.009	
Post	0.026 ± 0.009	0.041 ± 0.017	

*x ± SEM.

The protocol was approved by the Institutional Review Board, University of Texas Medical Branch, Galveston.

Data were analyzed using Student's *t*-test for paired and unpaired data as appropriate, the F-test, the Wilcoxon two-sample test, and Pearson's coefficient; $P < 0.05$ was considered significant.

RESULTS

The age of the children ranged from 5 yr to 17 yr. Duration of disease ranged from 0.3 yr to 8 yr. The hemoglobin A_{1c} averaged 11.8 ± 0.6%, with a range from 5.5% to 17.3% (N = 18).

Table 1 gives the ages and hemodynamic data of the diabetic children and controls for the first exercise period. Initial blood glucose of the diabetic subjects for the first exercise period dropped from 271 ± 19 to 213 ± 21 (x ± SEM) mg/dl and from 230 ± 22 to 157 ± 21 mg/dl for the longer exercise period. Table 2 shows that U_{alb}/U_{cr} for the diabetic subjects was slightly but not significantly elevated above the control values before both exercise periods. U_{NAG}/U_{cr} was significantly elevated ($P < 0.05$) over control values for both exercise periods.

Since age, metabolic control, and duration of disease have been implicated as affecting albumin excretion during exercise, patients and controls were divided into two subgroups: age ≤11 yr and >11 yr, which is about the age at which others found differences in albumin excretion with exercise;[15] hemoglobin A_{1c} ≤11% and >11%; and duration ≤1 yr and >1 yr. For all subgroups, U_{NAG}/U_{cr} ratios were significantly elevated in the diabetic subjects versus controls (Table 3), whereas U_{alb}/U_{cr} ratios were not significantly different (Table 4). There were no significant differences between pre- and postexercise periods for any of the subdivisions for U_{NAG}/U_{cr} or U_{alb}/U_{cr} except for the diabetic subjects <11 yr old in the first exercise period, in which U_{alb}/U_{cr} increased significantly after exercise. There was a trend for U_{NAG} activity to decrease after exercise in the controls but rise in the diabetic subjects for both exercise periods, whereas albuminuria rose or remained the same in both groups. Thus an attempt was made to determine if the percent change of U_{NAG}/U_{cr} and U_{alb}/U_{cr} was different between the two groups before and after exercise.

TABLE 3
Comparison of U_{NAG}/U_{cr} according to age, hemoglobin A_{1c}, and duration of diabetes

	Controls age (yr)		Diabetic subjects age (yr)	
Period 1				
	≤11 (N = 10)	>11 (N = 17)	≤11 (N = 7)	>11 (N = 21)
Pre	3.4 ± 0.43	2.6 ± 0.35	5.7 ± 0.9	7.8 ± 0.9*
Post	3.3 ± 0.56	2.2 ± 0.28	8.4 ± 2.5	9.7 ± 2.1
			A_{1c} (%)	
			≤11% (N = 9)	>11% (N = 9)
			5.3 ± 1.2	4.6 ± 1.3
			6.4 ± 1.3	5.4 ± 1.4
Duration (yr)				
			≤1 yr (N = 14)	>1 yr (N = 14)
			7.4 ± 1.1	7.2 ± 0.87
			9.6 ± 1.4	10.3 ± 2.5
Period 2				
	≤11 (N = 10)	>11 (N = 17)	≤11 (N = 7)	>11 (N = 21)
Pre	3.7 ± 0.55	3.1 ± 0.51	5.3 ± 1.8	7.5 ± 1.3*
Post	2.8 ± 0.58	2.6 ± 0.30	7.2 ± 2.4	10.2 ± 2.6
			A_{1c} (%)	
			≤11% (N = 9)	>11% (N = 9)
			4.6 ± 1.3	8.6 ± 1.5
			5.4 ± 1.4	12.3 ± 2.6
Duration (yr)				
			≤1 (N = 14)	>1 (N = 14)
			5.0 ± 0.8	9.4 ± 2.0
			7.4 ± 1.9	12.1 ± 3.1

*$P < 0.05$ controls versus diabetic subjects for both age groups pre- and post-exercise.

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TABLE 4
Comparison of U_{alb}/U_{cr} divided according to age, hemoglobin A_{1c}, and duration of diabetes

	Controls age (yr)		Diabetic subjects age (yr)	
Period 1				
	≤11 (N = 10)	>11 (N = 17)	≤11 (N = 7)	>11 (N = 21)
Pre	0.017 ± 0.004	0.016 ± 0.003	0.008 ± 0.002*	0.024 ± 0.006
Post	0.049 ± 0.015	0.034 ± 0.008	0.015 ± 0.003	0.031 ± 0.013
			A_{1c} (%)	
			≤11% (N = 9)	>11% (N = 9)
			0.013 ± 0.001	0.021 ± 0.009
			0.021 ± 0.04	0.032 ± 0.021
Duration (yr)				
			≤1 (N = 14)	>1 (N = 14)
			0.025 ± 0.009	0.015 ± 0.004
			0.020 ± 0.004	0.033 ± 0.019
Period 2				
	≤11 (N = 10)	>11 (N = 17)	≤11 (N = 7)	>11 (N = 21)
Pre	0.029 ± 0.015	0.015 ± 0.005	0.030 ± 0.023	0.046 ± 0.016
Post	0.028 ± 0.009	0.025 ± 0.007	0.050 ± 0.015	0.031 ± 0.019
			A_{1c} (%)	
			≤11% (N = 9)	>11% (N = 9)
			0.076 ± 0.029	0.015 ± 0.003
			0.057 ± 0.016	0.030 ± 0.011
Duration (yr)				
			≤1 (N = 14)	>1 (N = 14)
			0.054 ± 0.025	0.032 ± 0.013
			0.064 ± 0.012	0.022 ± 0.009

*$P < 0.05$ pre- versus post-exercise.

The study as structured could be analyzed as a classical, repeated measured experiment if the error variance structure from the diabetic subjects to the controls is homogeneous. This however is not the case, as seen by the disparity of the subject by time on test interactions (Table 5). Thus, the nonparametric Wilcoxon rank sum test was performed to detect any differences between the diabetic and control groups in relation to the percent change from pre- to postexercise (Table 6). From these data it is clear that albumin excretion increased about the same in the diabetic subjects and the controls. However, changes in U_{NAG} activity are clearly different in the diabetic subjects and controls, with the diabetic subjects showing increased and the controls decreased U_{NAG} activity.

DISCUSSION

Exercise testing has been used as a provocative test of glomerulopathy in patients with diabetes.[10,13–18] Mogensen and Vittinghus[13] found that young (age 21–38 yr) diabetic men showed a significant increase in U_{alb} excretion with bicycle exercise at 600 kpm/min for 20 min; however, exercising at 450 kpm/min produced no significant rise in microalbuminuria. Viberti and co-workers[14] confirmed these studies and concluded that the elevated U_{alb} excretion was due to increased transglomerular passage of albumin. Mogensen et al.[15] noted a difference in albumin excretion depending on the duration of diabetes, greater excretion for those patients of 16–20 yr duration than for those of 2–16 yr, and normal excretion for those <1 yr. Since our longest duration was 8 yr, we could not evaluate the effect of exercise on longer duration. Since these authors showed normal excretion rates with disease duration <1 yr, we divided our patients at this time also. Viberti and associates[10] further found that improved blood sugar control, with continuous subcutaneous insulin infusion, also lessened albumin excretion during exercise. Although our patients generally showed poor control, we arbitrarily compared those above and below the mean of the hemoglobin A_{1c} (11%).

Similar studies in children have not provided such consistent results. All previous studies again used bicycle exercise testing. Poortsman and colleagues[23] in a pilot study and in a more extensive follow-up investigation[17] found no significant increase in U_{alb} excretion after 30 min of exercise on a cycloergometer with 25-W increases in workload until exhaustion, although there was a significant increase in albuminuria at rest. Hermansson and Ludvigsson,[16] testing children between ages 8 and 20.5 yr with a bicycle ergometer until a maximal pulse rate of 170 bpm, found the same basal rate of excretion of albumin in both diabetic subjects and controls. In those children <10 yr of age, no increase in albumin excretion with exercise was noted. However, children age 16–20 yr did show an increase ($P < 0.05$) in albuminuria; duration of disease did not affect results. In contrast to these

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TABLE 5
Error variance magnitudes (subject × time on test)

	N	Subject × Time	P*
U_{alb}/U_{cr}			
Period 1			
Diabetic subject	28	0.00749	0.0001
Control	27	0.00054	
Period 2			
Diabetic subject	28	0.00137	0.0022
Control	27	0.00035	
U_{NAG}/U_{cr}			
Period 1			
Diabetic subject	28	20.56	0.0001
Control	27	0.55	
Period 2			
Diabetic subject	28	12.12	0.0001
Control	27	0.57	

*Significance level for treatment versus control by the F-test.

studies, Huttunen and associates,[18] also using a bicycle ergometer for an exercise period of 16 min to attain a heart rate of 170–200 bpm, found a significant increase in albuminuria after exercise that was significantly higher than the controls ($P < 0.02$), although pre-exercise values were similar. Furthermore, there was a significant correlation between hemoglobin A_{1c} and albuminuria at rest ($P < 0.02$) and during exercise ($P < 0.001$).

The current study, although not using a bicycle ergometer, is comparable with the previous studies in children. The duration of our first exercise period (12.6 min in the diabetic and 14.5 min in the control) is similar to that of the study conducted by Huttunen et al.,[18] whereas the second exercise period may be more comparable with the studies of Poortmans et al.[17] The degree of work as measured by the heart rate is certainly comparable with the other studies, even though the treadmill was used instead of the bicycle ergometer. As did Hermansson and Ludvigsson[16] and Huttunen et al.,[18] we found no statistically significant increase in resting albuminuria, regardless of age or metabolic control, as measured by hemoglobin A_{1c}. Although the former investigators found significant increases in older adolescents (ages 16–20 yr), we had only two patients in this age range.

Our results additionally confirm the results of Poortmans et al.[16] and Hermansson and Ludvigsson[16] in that significant increases in albuminuria do not occur in children who exercise to exhaustion or to a lesser degree for a longer period of time. Even in the study of Huttunen et al.,[18] who showed a significant change with exercise, the authors noted that 31% of the diabetic subjects showed a decrease in albuminuria with exercise. The difference between the studies in adults and children may be due to the degree of exercise. In adults, 600 kpm/min for 20 min appears to be a critical workload to induce proteinuria. Studies of children usually proceed until exhaustion for a somewhat shorter period of time; however, even at submaximal heart rate for 30 min, no significant increase occurred. The study of Hermansson and Ludvigsson[16] found significant increases in abluminuria only in older adolescents.

In addition to metabolic control, duration of disease, and age, another influence on the expression of exercise-induced albuminuria is blood pressure. Christensen and Mogensen[24] have shown exercise-induced albuminuria in patients with incipient diabetic nephropathy to be positively and significantly correlated with systolic blood pressure. Furthermore, these patients had significantly higher baseline diastolic and mean blood pressures; thus, increased blood pressure may have an adverse effect on renal function. None of our patients were hypertensive. Additionally, both Christensen and Mogensen[24] and Mogensen et al.[15] have suggested that reduced physical fitness is not responsible for the increased albuminuria seen in their subjects. Thus, if the shorter period of exercise for our diabetic subjects represented reduced fitness, it is unlikely that the results would have changed even if they had continued to exercise for a time equal to that of the controls.

In evaluating the U_{NAG} activity response to exercise, the diabetic subjects showed a consistent and significantly different response to exercise when compared with the controls. U_{NAG} activity represents renal output of this hydrolase to various stimuli,[2,25–27] including hyperglycemia with and without diabetic nephropathy.[6,8] As in our previous studies,[6] U_{NAG} activity was significantly elevated in the diabetic subjects compared with the controls, regardless of age. We did not find a positive correlation with A_{1c} as previously noted or with pre- or post-blood glucose levels. In previous studies with diabetic subjects using the artificial pancreas, U_{NAG}/U_{cr} decreased markedly in 24 h with decreases in blood sugars.[28] Thus, U_{NAG} activity can fluctuate more rapidly than glycosylated hemoglobin. The previously studied patients were somewhat more stable than the current group, many of whom

TABLE 6
Mean percent change from before to after exercise

	N	Mean % change from pre to post	Mean rank order	P*
Albumin				
Period 1				
Diabetic subject	28	58	24.28	0.9260
Control	27	13	24.70	
Period 2				
Diabetic subject	28	22	18.94	0.8015
Control	27	18	19.91	
NAG				
Period 1				
Diabetic subject	28	27	29.17	0.0466
Control	27	−6	21.00	
Period 2				
Diabetic subject	28	36	28.16	0.0015
Control	27	−8	16.00	

*Significance level for treatment versus control by the Wilcoxon two-sample test.

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were referred for improvement in metabolic control and were having frequent insulin adjustments made. Tables 2 and 3 show that pre-exercise U_{NAG}/U_{cr} did tend to fluctuate somewhat. In normal subjects Lockwood and Bosmann[22] demonstrated no diurnal variation in NAG excretion but occasional unexplained elevations did occur. Given the fact that U_{NAG}/U_{cr} varies with blood sugar and may do so within 24 h,[28] it is possible that variations could have occurred between the times of the exercise periods. In animal studies designed to evaluate the precise time course of rise of U_{NAG} activity, we have found that at least 2 h or constant hyperglycemia is necessary to increase U_{NAG}/U_{cr} (Brouhard, B. H., unpublished observations). Thus, the fluctuations seen from pre- to postexercise would not likely be explained by the variations in blood sugar that were noted during the 12–30 min of exercise. Furthermore, during exercise, blood glucose in the diabetic subjects decreased while U_{NAG}/U_{cr} increased, the opposite of what would be expected if blood glucose were the dominant factor in determining this change in U_{NAG}/U_{cr}.

A tubular enzyme showing distinctive changes during exercise may be somewhat surprising; however, support from the previously mentioned studies in children can be found, since B_2 microglobulin has also been considered to reflect tubular function. In the studies of Poortmans et al.,[16] B_2 microglobulin was significantly elevated in the diabetic subjects over the control patients' values before and after exercise; although it did tend to increase with exercise, it did not do so significantly. In the investigation of Huttunen et al.,[17] diabetic subjects with sporadic proteinuria showed a significant increase in this microglobulin with exercise above nondiabetic values (118.0 versus 28.5 ng/min/m^2). Hermansson and Ludvigsson[15] found significantly increased B_2 microglobulin at rest in diabetic subjects age 8–16 yr. As the albumin excretion response to exercise appears to differ between adults and children, these data may again underscore the difference between children and adults since studies investigating diabetic adults show no differences in basal or exercise-induced B_2 microglobulin excretion.

Using treadmill exercise, the present study confirms the results of previous studies, namely, that albuminuria does not increase significantly in children with insulin-dependent diabetes compared with controls. Furthermore, age, duration of disease, and metabolic control do not appear to influence the results. However, U_{NAG} activity responded significantly differently to both shorter and longer duration exercise in the diabetic subjects compared with controls. As previously noted, U_{NAG} activity may vary with fluctuations in blood sugar levels over a few hours; furthermore, differences in elevations of U_{NAG}/U_{cr} that reflect transient elevations in blood glucose versus those that represent nephropathy have not been defined. Thus, whether this response will be useful in predicting early nephropathy or selecting those patients at risk for nephropathy will require further study.

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