OBSERVATIONS

High Prevalence of Immunounreactive Albumin in Urine From Diabetic Patients With a Low Glomerular Filtration Rate and Normoalbuminuria

Diabetic patients have been shown to excrete increased quantities of albumin, which is undetectable by conventional albumin antibodies (immunounreactive) using high-performance liquid chromatography (HPLC) (1). Furthermore, the lead time for the development of microalbuminuria (albumin excretion rate [AER] >20 μg/min) measured by HPLC has been shown to occur 3.9 and 2.4 years earlier than that determined by radioimmunoassay (RIA) for type 1 and type 2 diabetic patients, respectively (2). This study not only identified that progression from normo- to microalbuminuria is associated with an increase in urinary immunounreactive albumin, but also raises the possibility that measurement of total albumin (immunoreactive plus immunounreactive) may allow earlier detection of progression to kidney disease.

The aim of this study was to determine whether a group of type 2 diabetic patients with a low glomerular filtration rate (GFR) of <60 ml · min^{-1} · 1.73 m^{-2}, as measured by a single-injection isotopic technique using ^{99m}Tc-DTPA (3), and normoalbuminuria, as measured by RIA, excrete increased quantities of immunounreactive albumin. Total albumin was measured by HPLC analysis (1,2), and immunoreactive albumin was measured by RIA on two to three consecutive urine samples collected from 38 type 2 diabetic patients attending the Austin & Repatriation Medical Centre, Victoria, Australia. Patients who had recurrent urinary tract infections or hematuria, known nondiabetic renal disease, or severe intercurrent illness, such as a malignancy or symptomatic cardiac failure, were excluded from the study.

The major finding of this study is that 24% (9 of 38) of patients had an AER >20 μg/min and 37% (14 of 38) of patients had an AER >15 μg/min, as measured by HPLC, in comparison with RIA analysis, which detected 0% (0 of 38) of patients with an AER >20 μg/min and 13% (5 of 38) of patients with an AER >15 μg/min. There was no significant difference between HPLC and RIA analysis of albumin in urine from nondiabetic subjects (1). These results identify that type 2 diabetic patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2}, and therefore presumably some form of kidney dysfunction, have an increased prevalence of urinary immunounreactive albumin. The possible pathogenesis of increased urinary immunounreactive albumin in these patients is limited given the absence of renal ultrastructural data. In fact, there is a paucity of information available regarding the renal morphology of normoalbuminuric patients with type 2 diabetes, regardless of their GFR. Nevertheless, the discrepancy between the HPLC and immunochemical assays demonstrates that conventional albumin assays may provide a relatively late diagnosis of incipient kidney disease at a threshold of 20 μg/min.

The combination of impaired renal function and normoalbuminuria in patients with diabetes was first highlighted by Lane et al. (4). For healthy nondiabetic individuals, the rate of decline in GFR with age has been reported to range from 0.6 to 1.0 ml · min^{-1} · 1.73 m^{-2} · year^{-1} (5). We have previously shown that the rate of decline in renal function for normoalbuminuric type 2 diabetic patients is -5.5 ± 1.0 ml · min^{-1} · 1.73 m^{-2} · year^{-1}, which is clearly greater than that related to aging alone (6). It should also be noted that the rate of decline in patients who had a GFR of <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was similar to that observed for micro- and macroalbuminuric patients (6).

In summary, this study demonstrates that urine from diabetic patients with a low GFR contains a high prevalence of immunounreactive albumin as measured by HPLC. This indicates that HPLC analysis of albumin components in the urine may provide a better indication of kidney dysfunction than the conventional immunoassays currently available.

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Understanding the Associations Between Statewide Diabetes Prevalence and Air Pollution Emissions

In a recent letter in *Diabetes Care*, Lockwood (1) presented a statistically significant correlation between statewide diabetes prevalence and statewide total air pollution emissions reported in the Environmental Protection Agency's (EPA) toxic release inventory (TRI) database

($r = 0.54$, $P < 0.0001$). Lockwood noted that such a correlation does not necessarily result from a causal relationship, but called for further research into understanding the association between air pollution and diabetes. In response, Nicolich (2) took issue with Lockwood's use of statewide data. To demonstrate that correlations based on statewide data may not show causal relationships, Nicolich presented four highly statistically significant correlations between statewide diabetes prevalence and factors that would not be expected to be causal factors in diabetes: latitude of the state capital, longitude of the state capital, state population, and numerical position of the state name on an alphabetized list. Nicolich stated that relationships should be based on individual-level data, rather than statewide data, and on the existence of a plausible mechanism. Lockwood's response (3) pointed out a previous association between Nicolich and ExxonMobil but did not address Nicolich's claim that statewide data are inherently prone to nonsensical correlations.

The highly significant correlations pointed out by both Lockwood and Nicolich are puzzling. There should be some explanation for these correlations, though as both authors note, this explanation need not be causal in nature. To investigate the issue further, the calculations of Lockwood and Nicholich were repeated using data available on the internet (http://www.epa.gov/tri, http://www.census.gov, and http://apps.nccd.cdc.gov/brfss). The Pearson correlation coefficient calculated between log diabetes prevalence and log TRI air emissions matched the value reported by Lockwood ($r = 0.54$, $P < 0.0001$). The correlation between log population and log diabetes prevalence ($r = 0.48$, $P < 0.001$) also closely matched the value reported by Nicolich. However, the correlation of diabetes prevalence and state alphabetic rank was nonsignificant ($r = -0.017$, $P = 0.904$), in contrast to the results reported by Nicolich ($r = 0.49$, $P < 0.001$). Log transformations of either or both variables did not produce a statistically significant result.

The potential role of confounding in producing these correlations was examined using a multivariate regression approach. Statewide diabetes prevalence was regressed on both state population and TRI emissions because these factors had been shown to be significant in the bivariate analysis. In addition, the proportions of the state population in each of three ethnic groups (African American, Latino, and white) were included in the regression because ethnicity is known to influence diabetes prevalence. All variables were log transformed since this was observed to produce roughly normally distributed residuals.

Table 1—*Linear regression coefficients*

Variable	Standardized coefficient	*t*	*P*
ln TRI emissions	0.235	1.297	0.201
ln population	0.079	0.387	0.701
ln percent white	−0.125	−0.919	0.363
ln percent African American	0.487	3.417	0.001
ln percent Latino	−0.142	−0.940	0.352

The natural logarithm of the state prevalence of diabetes is the dependent variable.

The results (Table 1) indicate that only the association between statewide diabetes prevalence and proportion of African-American population is statistically significant. The bivariate correlations noted by Lockwood and Nicolich appear to result from partial confounding with this factor. African Americans have historically migrated to large industrial states, such as New York, Michigan, Louisiana, and Texas, that would be expected to have both high populations and high TRI air emissions. In contrast, rural northern states, such as Vermont, North Dakota, and Idaho, have low populations, low TRI emissions, and low proportions of African Americans. The negative correlations with latitude and longitude reported by Nicolich appear to result from higher African-American populations in the southeastern states.

This does not rule out air pollution as a causal factor in diabetes. However, the analysis of state-level emissions data is unlikely to yield much insight into this issue given the lack of contaminant-specific exposure information, the small variation in the statewide prevalence that would be expected from environmental factors, and the many potentially confounding factors. Further research into the causes of diabetes is certainly desirable (1), and promising avenues of research (2) include individual-level and mechanistic studies (4–8).

Although the analysis of state-level data would not be expected to be a powerful tool to understand individual-level risk factors, it may be a worthwhile enterprise for other reasons. Understanding regional variations and their underlying causes may help to focus and prioritize efforts to improve health outcomes. In this particular case, the explanatory power of ethnicity is striking and may provide motivation to efforts to assist African Americans with both the prevention and treatment of diabetes.

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Intrinsic Motivation and Glycemic Control in Adolescents with Type 1 Diabetes

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Treatment for type 1 diabetes is often difficult for adolescents because of the multiple daily tasks required for successful management. Hence, adolescents who are more intrinsically motivated to manage their health might be more persistent with their diabetes care and consequently be in better glycemic control. We therefore examined the proportion of variance that intrinsic motivation contributed to HbA_{1c} in 43 adolescents diagnosed with type 1 diabetes relative to other disease-related and psychosocial factors that have been linked to glycemic control in cross-sectional research.

After receiving approval from the institutional review board, we recruited adolescents with a mean age of 14.14 ± 1.73 years from a university-affiliated diabetes clinic to participate in the study. All of the participants had been diagnosed with diabetes for a minimum of 1 year (M = 5.85 ± 4.53 years), and none were on an insulin pump. The sample consisted mostly of girls (65%); 74% were Caucasian, and 26% were African American. The mean family income was in the $30,000–45,000 range. The adolescents completed standardized measures of intrinsic/extrinsic motivation (Health Self-Determinism Index for Children), self-efficacy (Self-Efficacy for Diabetes Scale), family conflict (Family Environment Scale), diabetes-specific family behaviors (Diabetes Family Behavior Scale), and adherence to their diabetes regimen (Diabetes Regimen Adherence Questionnaire) while waiting for their medical appointment with the physician. Their parents completed a screening measure of behavioral adjustment on the adolescent (Pediatric Symptom Checklist) and a general demographic questionnaire.

Bivariate correlations revealed that adolescents who were more intrinsically motivated to manage their health were more likely to report adhering to their treatment ($r = 0.38$, $P < 0.05$) but were also more likely to be in poorer metabolic control, as measured by HbA_{1c}, at the time of testing ($r = 0.43$, $P < 0.05$). The relation between intrinsic motivation and poor glycemic control was unexpected, but is consistent with research (1) suggesting that adolescents who are primarily responsible for their diabetes care tend to be in poor metabolic control. Family conflict was also found to be related to poor adherence ($r = -0.38$, $P < 0.05$) and to being in poor glycemic control at the time of testing ($r = 0.35$, $P < 0.05$). But intrinsic motivation was the only psychosocial variable that was related to HbA_{1c} 4 months later ($r = 0.41$, $P < 0.05$). The proportion of variance that intrinsic motivation contributed to future glycemic control, however, was not significant after controlling for baseline HbA_{1c} in hierarchical regression analyses. Given that baseline HbA_{1c} was highly correlated with follow-up HbA_{1c} ($r = 0.78$, $P < 0.0001$), further research on intrinsic motivation is worth pursuing with larger samples.

Although we observed significant relations between intrinsic motivation and both adherence and HbA_{1c}, we did not observe a significant relation between adherence and HbA_{1c} at baseline ($r = -0.10$) or at follow-up ($r = -0.06$), which is similar to reports in the literature (2). The present findings suggest that adolescents who are intrinsically motivated could be at risk for poor glycemic control because they are more likely to rely on their own internal cues and judgment for managing their health. Adolescents may lack the experience and objectivity to make medically sound judgments. Thus, frequent consultation with parents and medical staff may be recommended instead of encouraging adolescents to assume more personal responsibility for their diabetes care. This recommendation contradicts the popular practice of encouraging adolescents to manage their diabetes care autonomously, but may be warranted until they can successfully manage their diabetes independently.

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The Metabolic Syndrome in Inuit

Inuit have been considered to have a lower prevalence of diabetes and age-adjusted mortality from cardiovascular disease than the general population (1,2). This observation has prompted investigation of both traditional and newer cardiovascular risk factors. A new risk cluster called the metabolic syndrome, defined as three or more of *1*) fasting glucose ≥6.1 mmol/l; *2*) blood pressure ≥130/85 mmHg; *3*) triglycerides ≥1.69 mmol/l; *4*) HDL cholesterol <1.04 mmol/l in men or <1.29 in women; and 5) waist circumference >102 cm in men or >88 cm in women (3), has not been evaluated in the Inuit. We thus determined the prevalence of the metabolic syndrome among 168 Inuit (48.2% women) and 53 Caucasian control subjects (38.5% women) who were residents in the arctic and had participated in a cardiovascular survey in 1989–1991 (2). Using the 2001 criteria, we found that Inuit had a lower prevalence of the metabolic syndrome (13.1%) compared with both regional Caucasian control subjects (20.8%) and Caucasian subjects from the contemporaneous 1988–1994 National Health and Nutrition Examination Survey (NHANES) III

(4) (23.8%, $P = 0.0013$). We next examined each of the metabolic syndrome components in Inuit and resident Caucasian control subjects. The frequencies of hypertriglyceridemia (7.1 vs. 24.5%, $P = 0.0005$) and of depressed HDL cholesterol (20.8 vs. 47.1%, $P = 0.0002$) were significantly lower in Inuit than in Caucasians. In contrast, the frequencies of high blood pressure (11.9 vs. 9.4%, P = NS), elevated fasting serum glucose (53.6 vs. 60.4%, P = NS), and increased waist circumference (28.6 vs. 18.9%, P = NS) were not different between Inuit and Caucasians. Furthermore, 32.1% of Inuit, compared with only 13.2% of Caucasians, were free of any positive metabolic syndrome variable ($P = 0.0072$).

Thus, Inuit studied in 1989–1991 had a lower prevalence of the metabolic syndrome compared with two independent Caucasian samples studied at the same time. Inuit had a favorable lipid profile, specifically lower triglycerides and higher HDL cholesterol, despite a trend to increased prevalence of higher waist circumference. Although genetic factors might have played a role, lower plasma triglycerides and higher plasma HDL cholesterol are both related to lifestyle factors, mainly activity level and diet. In this regard, it may be important that the consumption of marine-based fats by the Inuit study participants in 1989–1991 was high (2). Therefore, Inuit had a lower prevalence of the metabolic syndrome compared with Caucasians, which is consistent with the previous impression of lower cardiovascular disease and diabetes prevalence. Because lifestyle is changing dramatically in this "population in transition" (5), systematic reevaluation of the metabolic syndrome would be important in order to identify interval changes that could predict future increases in diabetes and cardiovascular disease (6).

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COMMENTS AND RESPONSES

The Association of NAD(P)H Oxidase p22phox With Diabetic Nephropathy Is Still Uncertain

Response to Hodgkinson, Millward, and Demaine

We believe that there are limitations in the study by Hodgkinson, Millward, and Demaine (1) about the association of the NAD(P)H oxidase p22phox polymorphisms with susceptibility to diabetic nephropathy. The case-control association studies on the polymorphisms in p22phox have been performed by a number of researchers, and their results are still in conflict, especially with regard to coronary artery disease. On the other hand, the allele frequencies of the C242T polymorphism have been found to be consistent in various Caucasian populations (2,3). The C242T allele frequencies in the control samples by Hodgkinson, Millward, and Demaine differ from those in previous reports, and the genotype frequencies also deviated significantly from Hardy-Weinberg equilibrium ($P = 0.025$), suggesting a nonrandom sampling or some technical error.

The estimation of haplotype frequencies in case-control association studies is often performed on the basis of a maximum-likelihood method with an expectation-maximization algorithm. It is usually impossible to determine whether an individual with the genotype Aa-Bb has haplotypes A-B and a-b or A-b and a-B. Moreover, the χ^2 test by contingency table is not appropriate for comparing the estimated haplotype frequencies. Hodgkinson, Millward, and Demaine did not describe how the haplotypes of their samples were determined. Tsai et al. (4) applied a proper method, referred to as permutation-based hypothesis testing, to evaluate the association between multilocus angiotensinogen gene polymorphisms and hypertension.

Although Hodgkinson, Millward, and Demaine reported a very low and striking P value, we believe the association of diabetic nephropathy with p22phox remains unsolved.

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The Association of NAD(P)H Oxidase p22phox With Diabetic Nephropathy Is Still Uncertain

Response to Doi, Noiri, and Tokunaga

We have noted the comments made by Doi, Noiri, and Tokunaga (1) in this issue of *Diabetes Care*. To our knowledge, our study (2) is the first to look at Caucasoid patients with type 1 diabetes. Previous studies have reported on type 2 diabetes. Unlike these previous studies, we have a unique group of patients with no microvascular disease after 20 years' duration of diabetes (mean duration of diabetes 32.7 years). In our study, this group of uncomplicated patients had a distribution of p22phox alleles and genotypes similar to that of the normal healthy control subjects. They were very different from those of the patients with nephropathy. Similarly, those with retinopathy but no proteinuria (mean duration of diabetes 29.8 years) had remarkably different p22phox distribution from those with nephropathy. The study by Cahilly et al. (3) only included patients, and the frequency of the C242T alleles were not dissimilar from those found in our study. The study by Gardemann et al. (4) included blood donors and patients without coronary artery disease and myocardial infarction, participants who may be subject to selection bias. Our normal control population consisted of sequential cord blood samples taken after normal obstetric delivery and had no selection bias.

The calculation of haplotype frequencies was based on gene counting. Because it is impossible to absolutely determine the haplotypes of the double heterozygotes, these were excluded from the analysis. It is entirely appropriate to use the χ^2 test and contingency tables to compare haplotype frequencies between these groups because the values relate to the actual numbers of chromosomes and are not estimates.

We must note that since the publication of our study, Matsunaga-Irie et al. (5) published a study of the association between p22phox C242T and diabetic nephropathy in Japanese patients with type 2 diabetes. Unfortunately, no normal control subjects were included in the study, although they report a lower frequency of the T242 allele than we found in our study.

Clearly, further studies are required to unravel the role of this polymorphism in susceptibility to diabetic nephropathy as well as macrovascular disease.

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Adiponectin in Youth

Response to Bacha et al.

Bacha et al. (1) studied the relationship of serum adiponectin concentrations with hepatic and peripheral insulin sensitivity, body fat distribution, and components of the metabolic syndrome in adolescents. In addition, they reported a negative association between fasting serum proinsulin and the fasting serum proinsulin-to-insulin ratio with adiponectin levels, which was independent of adiposity. They conclude that hypoadiponectinemia may be a marker of β-cell dysfunction.

These data are novel and appear to be suggestive of a primary role of adiponectin in β-cell function. We consider this hypothesis to be valid, especially since expression of adiponectin receptor 1 and 2 was recently detected in β-cells (2). In addition, administration of adiponectin to β-cells seems to inhibit palmitic acid–induced apoptosis (3). However, it is not readily obvious that the correlations of serum adiponectin with fasting serum proinsulin and serum proinsulin-to-insulin ratio indicate a direct effect of adiponectin on insulin secretory function in vivo. First, the proinsulin-to-insulin ratio was negatively associated with acute insulin response only in subjects with type 2 diabetes (4) but not in individuals without diabetes (5), indicating that this ratio can be used as a parameter for β-cell function

only when a more severe insulin secretory defect is present. Second, as discussed by Roder et al. (5), this ratio is associated with insulin sensitivity in a group of subjects covering a broad range of insulin resistance. Thus, because in the article by Bacha et al. the proinsulin-to-insulin ratio was adjusted for BMI but not for insulin sensitivity, it remains unclear whether the relationship with adiponectin simply reflects insulin sensitivity.

Based on the findings in the study by Bacha et al., we investigated whether plasma adiponectin is associated with parameters of insulin secretory function in our database from the Tübingen Family Study. A total of 685 normal glucose tolerant subjects (aged 36 ± 0.4 years [mean ± SE]) were included and underwent a 75-g oral glucose tolerance test (OGTT). We measured insulin and proinsulin and determined the fasting proinsulin-to-insulin ratio. The 30-min C-peptide plasma concentrations during the OGTT and the first-phase insulin secretory index (ISI) proposed by Stumvoll et al. (6) were used as an estimate of β-cell function. Insulin sensitivity was calculated as proposed by Matsuda et al. (7). In multiple linear regression models, neither proinsulin-to-insulin ratio ($r = 0.03$, $P = 0.46$) nor 30-min C-peptide plasma concentrations ($r = 0.01$, $P = 0.79$) or ISI ($r = 0.01$, $P = 0.80$) during the OGTT were associated with fasting plasma adiponectin concentrations after adjustment for age, sex, percentage body fat, and insulin sensitivity. These findings argue against an association of plasma adiponectin concentrations with β-cell function.

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Adiponectin in Youth

Response to Stefan et al.

We appreciate the comments of Stefan et al. (1) in this issue of *Diabetes Care* regarding adiponectin in youth. We are excited to have received the opinion of investigators in internal medicine, since traditionally pediatric investigations seldom cross the boundaries to adult medicine. The changing face of childhood diabetes might be playing a role (2). We offer the following responses.

1) Our study demonstrated associations and correlations between adiponectin and proinsulin and the proinsulin-to-insulin ratio. We never implied that a direct effect of adiponectin on insulin secretory function exists. However, as recommended by Stefan et al., we investigated the relationship between the proinsulin-to-insulin ratio and adiponectin after adjusting for insulin sensitivity per metabolically active fat-free mass. The partial correlation coefficient of adiponectin to the proinsulin-to-insulin ratio after controlling for insulin sensitivity was $r = -0.24$, two-tailed $P = 0.12$, and one-tailed $P = 0.06$. Furthermore, in a multiple regression analysis with proinsulin-to-insulin ratio as the dependent variable and adiponectin and insulin sensitivity as the independent variables, adiponectin ($P = 0.007$) and not insulin sensitivity ($P = 0.60$) was the significant independent correlate of the proinsulin-to-insulin ratio ($R^2 = 0.168$, $P = 0.02$ with adiponectin and insulin sensitivity in the formula; $R^2 = 0.162$, $P = 0.007$ with only adiponectin in the formula). Also, in an effort to determine if adiponectin is related to an index of glucose homeostasis, we evaluated the correlation of adiponectin with the glucose disposition index (product of insulin sensitivity × first-phase insulin secretion), which revealed that $r = 0.35$ and $P = 0.013$.

2) The observation by Roder et al. (3) that the association between the proinsulin-to-insulin ratio and acute insulin response was only present in diabetic adults and not in nondiabetic subjects is contrary to our findings in healthy adolescents. Extrapolating observations from 60-year-old subjects to adolescents may not be justified, especially taking into consideration the uniqueness of puberty-related changes in insulin sensitivity and secretion (2,4). Analysis of our unpublished data demonstrates that first-phase insulin secretion during a hyperglycemic clamp correlates positively with proinsulin ($r = 0.43$, $P = 0.04$) and the proinsulin-to-insulin ratio ($r = 0.50$, $P = 0.01$) in normal-weight adolescents ($n = 23$) with no correlations in obese adolescents ($n = 26$). Thus, in normal adolescents, the puberty-related increase in insulin secretion may also be accompanied by increased proinsulin secretion, whereas in obese adolescents, this relationship may disappear due to variable degrees of β-cell compensation.

In summary, despite the wealth of data in adults with respect to insulin sensitivity and secretion, gradually accumulating data in pediatrics would suggest that developmental differences in these parameters are distinguishing features of youth. At the moment, our data in pediatrics remain supportive of an important relationship between adiponectin and measures of β-cell function.

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Acknowledgments— This work was supported by U.S. Public Health Service Grants Ro1 HD27503, K24 HD01357, and MO1-RR00084, the General Clinical Research Center, and Eli-Lilly.

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Kidney Function During and After Withdrawal of Long-Term Irbesartan Treatment in Patients With Type 2 Diabetes and Microalbuminuria

Response to Andersen, Bröchner-Mortensen, and Parving

We read with great interest the article by Andersen, Bröchner-Mortensen, and Parving (1) about the effects of long-term treatment with irbesartan on kidney function in a subgroup of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA)-2 trial (2). In this population, the authors did not find a significant difference between irbesartan and placebo administration with respect to the change in the glomerular filtration rate (GFR). In the RESULTS section of the article, the authors report that a similar change in the GFR occurred in all study groups during the first 3 months (loss of GFR: 1.0 to 1.3 ml · min^{-1} · 1.73 m^{-2} · month^{-1}) as well as for the rest of the follow-up period (0.3 to 0.4 ml · min^{-1} · 1.73 m^{-2} · month^{-1}). However, in Fig. 2, the slope of GFR for placebo is exactly the same during the entire duration of the study, including the first 3 months, 0.3 ml · min^{-1} · 1.73 m^{-2} · month^{-1}, which is obviously contradictory to the aforementioned numbers in the RESULTS section of the article (1). Therefore, the loss of GFR may be more pronounced in patients treated with irbesartan than in those treated with placebo. In fact, when GFR values at the beginning of the study are compared with the final values at the end of the withdrawal period after 25 months (Fig. 2), there seems to be no loss of GFR in the placebo group at all, whereas GFR declined by about 10 and 6 ml/min in the 150- and 300-mg irbesartan groups, respectively.

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Kidney Function During and After Withdrawal of Long-Term Irbesartan Treatment in Patients With Type 2 Diabetes and Microalbuminuria

Response to Kaiser, Florack, and Sawicki

We thank Kaiser, Florack, and Sawicki (1) for their interest in our article (2). The glomerular filtration rate (GFR) values in Fig. 2 represent the mean values of measurements carried out at the specified visits. However, the rates of decline in GFR cannot be correctly estimated from Fig. 2, but are instead calculated from paired observations of changes in GFR and specified in the RESULTS section. GFR values at baseline were available from 42, 38, and 39 patients from the placebo, irbesartan 150-mg, and irbesartan 300-mg groups, respectively, whereas paired observations of changes in GFR during the initial 3 months of the study were accessible from 37, 37, and 34 patients in the placebo, irbesartan 150-mg, and irbesartan 300-mg groups, respectively. Rates of decline in GFR during the initial 3-month period were 1.3 ± 0.7, 1.2 ± 0.7, and 1.0 ± 0.8 ml · min^{-1} · month^{-1}, as specified in the RESULTS section.

According to Fig. 2, GFR was unchanged from baseline to the end of the study after withdrawal of antihypertensive medication (24 + 1 month) in the placebo group compared with a decline in GFR of 10 ml/min in the irbesartan 150-mg group and 5 ml/min in the irbesartan 300-mg group. However, changes in GFR from baseline to the end of the study cannot be precisely evaluated from Fig. 2 due to fewer patients at the end of the study. By paired comparisons of changes in GFR from baseline to the end of the study after withdrawal of antihypertensive medication (24 + 1 month), rates of decline in GFR were 0.3 ± 0.1, 0.5 ± 0.1, and 0.3 ± 0.1 ml · min^{-1} · month^{-1} in the placebo (23 patients), irbesartan 150-mg (17 patients), and

irbesartan 300-mg (19 patients) groups, respectively (P = NS).

In conclusion, rates of decline in GFR during the study were similar in the placebo and irbesartan-treated groups, as specified in the RESULTS section of our article (2).

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S.A. has received research funding from Merck. H.-H.P. holds stock in Novo Nordisk, has received honoraria and consulting fees from Merck and Sanofi-Synthelabo, and has received grants from Merck, Astra, and Sanofi-Synthelabo.

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