Glomerular Hyperfiltration in Human Diabetes

CARL ERIK MOGENSEN, MD

The presence of the characteristic early glomerular hyperfiltration seen in diabetes was originally suggested long ago by Cambier (1), indeed a few years before the well-known studies by Kimmelstiel and Wilson (2) that documented the typical glomerular structural lesions in diabetic patients. Brenner (3,4), in his breakthrough glomerular hyperfiltration-hemodynamic theory, also used diabetes as an example and proposed that hyperfiltration was an important factor in the genesis of glomerular damage, and not only in the damage caused by diabetes. This means that the two classic findings (1,2) may well be closely connected, with the former causing the latter.

Diabetic renal disease remains one of the major complications observed with long-term diabetes (5), although the incidence may be declining now, at least in certain areas (6). However, even in the optimized treatment group in the recently completed Diabetes Control and Complications Trial (DCCT), a high proportion of the combined cohorts (~20%) developed microalbuminuria and thus, probably later, more advanced nephropathy (7). In insulin-dependent diabetes mellitus (IDDM), the eventual development of end-stage renal disease reflects a long process and is most usually seen after ~30 years of diabetes (8). In the U.S., diabetes is now the main underlying cause of end-stage renal failure (ESRF) in patients in renal supportive programs; both type I and type II diabetes contribute to ~35% of all new cases of uremia. In Europe, fewer new diabetic patients (~15%) are enrolled in these programs (5).

The development of renal changes can be divided into stages, which are now fairly well described (8). According to several follow-up studies, three characteristic phases are described. First, there is an initial stage with hyperfiltration, often lasting ~10 years. In the typical course, patients thereafter develop microalbuminuria, defined as urinary albumin excretion (UAE) rates of between 20 and 200 μg/min. At this stage, patients still have increased glomerular fitration rate (GFR), which suggests that renal function is still well preserved, although the exact UAE level where GFR tends to fall is not well defined (9). This fall probably occurs in the upper microalbuminuric range, and so far, reductions in GFR have mainly been observed with the development of overt proteinuria >200 μg/min (9–12). Thereafter, with progressive proteinuria, GFR tends to fall in a linear fashion, terminating with ESRF again after ~10 years, albeit with a great variability in progression rate, in part depending on blood pressure (BP). With optimized diabetes care and, in particular, intensified antihypertensive treatment, these stages may be protracted and ESRF thus postponed (8).

That microalbuminuria predicts overt renal disease is now well accepted, and even the excretion rate in the upper normal range seems to predict later microalbuminuria and renal disease (11). Poor metabolic control is an important factor in this context; accordingly, intervention programs have focused on patients with microalbuminuria (11). This stage seems to be an important one for intervention because there is usually not yet a pathological decline in GFR and, therefore, effective intervention measures that result in better preservation of renal function are anticipated. Preliminary results suggest this is true (12).

However, patients with microalbuminuria already exhibit morphological lesions (13), and new results show that the rate of this development is correlated to metabolic control (14). Because the disease process is already well advanced in patients with microalbuminuria, one has searched for markers that will predict development of microalbuminuria (or incipient renal disease) in normoalbuminuric individuals, and several studies suggest that hyperfiltration, i.e., abnormally elevated GFR, predicts renal disease. Two possible definitions of hyperfiltration in IDDM exist. Obviously, the level will depend on the GFR procedure used. Thus, the constant infusion technique, which is the classic procedure, seems to provide values 15–20% above the single-shot procedure (15). The most feasible, applicable definition of hyperfiltration would rely on follow-up studies, defining the level at which overt renal disease may consistently be predicted. With this approach, using the constant infusing technique, a GFR >150 ml · min^{-1} · 1.73 m^{-2} body surface obtained with this technique would be a relevant cut-off

From the Medical Department M, Endocrinology & Diabetes, Aarhus Kommunehospital, Aarhus, Denmark.

Address correspondence and reprint request to Carl Erik Mogensen, MD, Medical Department M, Endocrinology & Diabetes, Aarhus Kommunehospital, DK–8000 Aarhus C, Denmark.

Received for publication 7 March 1994 and accepted 10 March 1994.

DCCT, Diabetes Control and Complications Trial; IDDM, insulin-dependent diabetes mellitus; ESRF, end-stage renal failure; UAE, urinary albumin excretion; GFR, glomerular fitration rate; BP, blood pressure; ARI, aldose reductase inhibitor; NIDDM, non-insulin-dependent diabetes mellitus.

Table 1—*Studies relating early hyperfiltration to late nephropathy*

Study	Initial *n*	Entrance criteria (IDDM)	Main outcome measure	Significant early factors for outcome
Mogensen et al. (16) 1985 (retrospective)	31	Age at onset: <20 years DD: 3–20 years Follow-up: >7 years UAE: <70 μg/min	Increasing UAE (6 progressors)	Hyperfiltration + UAE (multiple regression analysis)
Lervang et al. (17) 1988 (retrospective)	37	Age at onset: <40 years DD: <10 years No clinical proteinuria	High UAE (8 progressors)	Not identified Hyperfiltration not significant
Jones et al. (18) 1991 (letter) (prospective)	52	Normoalbuminuria. Hyperfiltration versus normofiltration (26 + 26)	Undefined microalbuminuria only seen in 2 patients	Sufficient endpoints not reached
Rudberg et al. (19) 1992 (prospective)	64	Young patients DD: >8 years No proteinuria	Increasing UAE (5 developed proteinuria)	Hyperfiltration + UAE (multiple regression analysis)
Rossing et al. (20) 1993 (prospective)	519	Normoalbuminuria age: ≥18 years DD: >5 years No antihypertension treatment	Increasing UAE: →91 microalb. →24 macroalb.	High normoalbuminuria High HbA_{1c} Smoking Hyperfiltration? (low serum creatinine)

DD, diabetes duration.

level (16). This level also complies very well with the other approach, which uses the upper 90 or 95 percentile of normal values in young individuals. With the constant infusion technique, the mean value of GFR is ~116 ml · min^{-1} · 1.73 m^{-2} body surface for normal subjects <45 years of age, at least according to Scandinavian studies (9). The standard deviation is ~15, suggesting that a level at ≥150 would be highly unusual in normal individuals. The usual mean of GFR using the constant infusion technique in IDDM patients with normal UAE is ~135 ml/min (9).

Table 1 reviews the longitudinal follow-up data in studies (16–20) indicating an association between early renal function changes, that is, hyperfiltration, and late diabetic renal disease. Data from three Scandinavian centers suggest that hyperfiltration predicts overt renal disease, including the strongest study with a prospective design from the Karolinska Institute in Stockholm (19). This study, with continuous follow-up, documented hyperfiltration as an early risk marker, but not all patients with hyperfiltration after 8 years of follow-up have developed abnormal albuminuria. Thus, not surprisingly, other factors also seem to be involved in the genesis of diabetic renal disease, although a longer follow-up than 8 years may be required (19).

The design and the conclusions of certain negative studies cause some concern. In one study (17), initial data were collected in some patients at the clinical diagnosis of diabetes, before insulin treatment, where GFR may be extremely high because of poor metabolic control (16). This GFR elevation at the time of diagnosis has been shown not to predict renal disease in other studies (21), probably because GFR is partially normalized with the start of ordinary diabetes and insulin treatment. In another study (18), with only 5 years of follow-up, patients did not significantly reach end points, and therefore, documentation is insufficient. Thus, it can be concluded that the most meticulous studies in this area associate early hyperfiltration with late diabetic renal disease. Obviously, hyperfiltration may be an innocent bystander, only indirectly related to the pathogenesis of renal disease. The real culprit may be other factors related to poor control. Hyperfiltration appears to be predictive very early in the course of diabetes (22), as are microalbuminuria and marginally elevated BP (23). Data from these studies were evaluated by multiple regression analysis (16). Finally, animal studies strongly suggest an independent role of hyperfiltration in the genesis of diabetic renal damage (24).

Poor metabolic control is of importance, and usually there is an association between hyperfiltration and glycemic control, which is most convincingly documented in studies carried out before and during insulin treatment at the clinical diagnosis (25). Also, in cross-sectional studies, there may be an association, but it may not be uniform (9). In studies with repeated GFR measurement, it appeared that the intra-individual variability in GFR was related, in part, to metabolic control (26) and also to the level of antinatriuretic peptide, a phenomenon also compatible with animal studies (24).

Table 1—*Continued*

Mean follow-up (years)	GFR determination	Role of BP	Missing information and main confounding factors	% follow-up
12	Constant infusion technique	Microalbuminuria predicts BP elevation	HbA_{1c} missing so metabolic control not clearly defined	100
18	Single-shot technique	Diastolic BP did not increase at follow-up	Initial UAE missing. GFR measured before insulin treatment in seven patients. HbA_{1c} missing initially	78
5	Single-shot technique	Not defined	Degree of microalbuminuria at follow-up not documented. Regression toward the mean a factor in hyperfilters (GFR 147→121)	96
8	Single-shot technique	Increases after microalbuminuria	HbA_{1c} technique changed during the study	86
7	Index based on serum creatinine	Normal initially	GFR not done	97

In this respect, the two studies in this issue of the journal are of interest (M. Pecis et al., p. 665–672; and K.S. Nair et al., 711–715) because they highlight the role of dietary factors. Clearly, ingestion of a protein-rich meal and generally a protein-rich diet induces hyperfiltration (this issue, K.S. Nair et al., p. 711–715). A characteristic of the diabetic diet is that it is usually rich in protein (30–32). Therefore, part of the hyperfiltration in diabetes could, in theory, be explained by the high-protein diet. Several surveys document that the calories derived from protein in diets of diabetic individuals may exceed that of the background population by 20–40% (31,32). Therefore, it cannot be excluded that this iatrogenic factor may be of importance for the development of hyperfiltration and, thus, renal disease. Normalization of protein in the diet also results in normalization of GFR (30). In a cross-sectional study (33) in nonproteinuric IDDM patients, there was no correlation between protein intake and degree of hyperfiltration nor between protein intake and albuminuria. However, in smokers with hyperfiltration, protein intake correlated to albuminuria (33). Importantly, in patients with microalbuminuria and overt renal disease, reduction of protein content in the diet seems to have a renal protective effect with the reduction of microalbuminuria (34) and the fall rate of GFR (35,36), although a concomitant effect related to BP reductions is difficult to exclude (36). Many studies show that BP reduction is the most important interventive measure in reducing abnormal albuminuria and fall rate of GFR (37,38).

The study by Pecis et al. (this issue, p. 665–672) is interesting because it suggests that the source of dietary protein may be important. The chicken and fish diet (white meat) seems to reduce hyperfiltration compared with a usual diet with unselected protein sources. The mechanism(s) remains unexplored, and further studies are required before changing dietary policy in diabetes.

The exact pathogenesis of early hyperfiltration remains elusive, but it is clearly related to poor metabolic control (25) and possibly increased protein content in the diet (30). Other factors may also be involved, such as ketone bodies (39), although this is controversial because, in one study, no effect of administration of ketone bodies was seen in normal individuals (40). Mechanisms related to the polyol pathway may also be involved. Diabetic hyperfiltration in normoalbuminuric patients can be reduced by one aldose reductase inhibitor (ARI) (41,42), but not with all agents (43). An extremely surprising result was obtained recently in Napoli: considerable hyperfiltration was seen with overt proteinuria and a continuous fall was seen from ARI over 6 months (44).

Clearly, hyperfiltration is associated with hypertrophy of the kidney (45) documented at the clinical diagnosis and is reversible with treatment (46,47). When GFR is expressed per gram, normal kidney values are found in diabetic patients during conventional insulin treatment (48). Extensive studies have been conducted on the mechanisms of the early hypertrophy in experimental diabetes (49).

Several studies have been carried out to assess whether hyperfiltration can be reduced with improved glycemic control (8,50) as well as with normalization of dietary protein (30). As mentioned,

ARI may be important, but, so far, no long-term clinical trials have been published. Administration of octreotide also reduces hyperfiltration (51,52) as well as ameliorating renal hypertrophy (52), but long-term studies with these agents are still lacking. A study in this issue confirms in small numbers of patients that somatostatin infusion reduces the hyperfiltration induced by amino acids (K.S. Nair et al., p. 711–715). Glucagon infusion appeared to have no effect on GFR in contrast to other situations (53,54). The renal response to somatostatin was in another study related to changes in serum glucagon (51), and so controversy still exists in this area.

Early intervention with angiotensin-converting enzyme inhibitors in normoalbuminuric IDDM patients does not reduce an elevated GFR (55), but the filtration fraction is reduced, and albuminuria in the normal range also seems to be reduced, which suggests that filtration pressure may be normalized by early intervention with these agents. Thus, an important perspective is prevention of microalbuminuria and, later, overt renal disease with angiotensin-converting enzyme inhibitors. One way would be to treat all IDDM patients, but another, more realistic possibility would be to select individuals at high risk characterized by high normal UAE rate (10–12 μg/min), poor metabolic control, and hyperfiltration. This would be the most radical approach in preventing diabetic renal disease. Because ~25% of individuals develop this complication, however, intervention in all individuals could, arguably, be considered reasonable.

Of considerable interest is the situation in non-insulin-dependent diabetes mellitus (NIDDM) patients. In these individuals, hyperfiltration is also observed (56), but in the typical elderly NIDDM patient in Europe and elsewhere in the Western world, hyperfiltration is less marked, although controversy exists (57). However, in young individuals with type II diabetes, a similar or even more pronounced degree of hyperfiltration is observed, and obviously these individuals are at high risk for overt renal disease (58; R. Bruce, M. Rutland, T. Cundy, unpublished observations).

Hyperfiltration may not be detrimental in all situations. Renal disease is not observed in acromegaly (60), and indeed, pregnancy-induced hyperfiltration does not seem to predict renal disease in nondiabetic individuals, e.g., after multiple pregnancies. Also, individuals with one kidney, congenitally or after uninephrectomy, appear to have a good prognosis (61). Thus, hyperfiltration alone may not be sufficient, but when orchestrated by the several metabolic characteristics of diabetes, hyperfiltration is likely to be detrimental in a large proportion of diabetic individuals. Additionally, recent evidence suggests that hyperfiltration is associated with early target organ damage in essential hypertension (62,63).

Measurement of microalbuminuria is well accepted as a screening procedure for predicting (and thereafter potentially preventing) overt renal disease (64,65). It could also be proposed to include exact measurement of GFR in screening patients. However, this is, at the present time, not clinically feasible, because exact GFR measurements are laborious and, therefore, usually not suitable for ordinary clinical practice. Thus, the fundamental screening procedure for early diabetic renal disease remains microalbuminuria, whereas GFR is used as a research tool. In our outpatient clinic, diabetic patients are screened with HbA_{1c} and for microalbuminuria at each visit (albumin/creatinine ratio in an early morning urine) every 3 months.

Obviously, further studies are needed in this area to further document the initial association between early hyperfiltration and late nephropathy and to clarify the mechanisms involved. Important information will probably appear from the DCCT (7). This study documented that the development of microalbuminuria is clearly related to poor metabolic control (7). It probably also has a sufficiently long follow-up to further document the role of hyperfiltration in the genesis of clinically relevant diabetic renal disease, but longer follow-up may be necessary.

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