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HYPERTENSION AND NEPHROPATHY IN TYPE II DIABETES*

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Nephropathy in type II diabetes has recently become the single most important challenge to the nephrologist on epidemiological as well as on clinical grounds. Why is this topic now of such great interest? As recently as 1982, Fabre from Geneva reported in this journal on 510 patients with type II diabetes mellitus.[1] He stated that he did not find a single case where GFR decreased more than expected for age except in one patient who entered end stage renal failure—and this one patient suffered from superimposed glomerulonephritis. In retrospect this statement appears to be at odds with our current knowledge of diabetes mellitus.

In 1859 Griesinger stated 'Renal involvement complicates diabetes (by necessity of type II) in a decisive fashion. If glycosuria disappears in a diabetic patient with heavy proteinuria, M. Brightii [Bright's disease or, as we would say today uremia] will take its known fatal course with generalized hydrops etc.'.[2]

It is apparent to most physicians now that type II diabetes poses a threat to renal function. How large is this risk? We have examined this by performing a study in which we compared patients with type II and type I diabetes who were attending the Heidelberg diabetes clinic. Cumulative prevalence of proteinuria was similar in patients with type I and with type II diabetes who had survived up to 20 years after the diagnosis of diabetes had been made. Furthermore, once patients had developed proteinuria, a similar cumulative prevalence of renal failure was noted at different times after onset of proteinuria in both groups. The incidence of proteinuria and renal failure in type I and type II diabetes was virtually superimposable.

There appears to be, at present, an increase of almost epidemic proportions of patients with type II diabetes going into terminal renal failure.

Two decades ago an incredibly high prevalence of renal failure in diabetic patients was reported from the USA.[3,4] There was initially some scepticism amongst European nephrologists regarding these data but this is no longer so. In 1993 according to the US Renal Data System,[5] the incidence of dialysis-dependent renal failure overall in the white population was 150 per million inhabitants per year and that of diabetic patients 46,[7] accounting for 31 per cent of all patients entering renal replacement therapy.

This contrasts with the UK, where the overall incidence of terminal renal failure was only 60 per million per year. In London, the part of the UK where the incidence of renal failure is highest, the incidence of renal failure in diabetic patients is 34 per million per year, 57 per cent of whom have type II diabetes, according to the late Professor Raine's figures from Bart's Hospital.[6] This striking contrast between the US and the UK brings to mind the cynical statement of G. B. Shaw of the two nations separated by a common language.

However data are also different from other parts of Europe. In Germany, in

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the lower Neckar region surrounding Heidelberg, the overall incidence of end stage renal failure is 125 per million per year[7] (similar to that reported in US whites), and the incidence in diabetic patients is 52 per million per year against 46 in the US. In contrast in Northern Italy the incidence of renal failure in diabetic patients is substantially lower, i.e. 10 diabetic patients per million per year[8]. Italians and Germans report the same incidence of type I diabetic patients reaching terminal renal failure. The overall difference between these two countries must be accounted for entirely by patients with type II diabetes.

In an analysis by Cordonnier,[9] the prevalence of diabetes in the dialysis population was substantially lower in mainland France, 6.9%, compared to 23% in the overseas territories, particularly in the south Pacific. The difference again is accounted for by different prevalences in patients with type II diabetes. Whilst it would be some consolation to all those concerned about the quality of their lives, if French cuisine and lifestyle turned out to be protective against diabetic nephropathy, racial differences cannot be ruled out. From the above one could also draw the conclusion that in Europe the Germans are the ones who have been most successful in Americanising their lifestyle.

It is important to try and find out why such differences exist, since this may lead to the identification of pathogenetic factors important in the development of diabetic nephropathy.

Why has there been such an apparent dramatic recent increase in end stage renal failure in patients with type II diabetes in some countries?

The prevalence of type II diabetes in the general population is increasing as people live longer, since the incidence of type II diabetes increases dramatically with age. Probably the most important factor is that today nephropathic patients with type II diabetes live long enough to develop renal failure. In the past, attrition from cardiovascular death had been so high that few patients were exposed to the long-term risk of developing diabetic nephropathy. Finally, the recent increase in admission rates for patients with diabetes onto dialysis programmes may also play a role.

In former Communist East Germany, in the city of Erfurt, 45 per cent of patients were dead four years after diagnosis of type II diabetes in an era when antihypertensive treatment or access to coronary care was available only to the privileged few.[10] Contrast this with the recent decrease in mortality, even in the worst risk population, i.e. patients with type II diabetes and proteinuria. In the Heidelberg clinic, the 5-year mortality in this group of patients decreased from 65 to 25% in two consecutive decades.[11]

Undoubtedly in the past elderly patients with type II diabetes and renal failure were also not consistently referred to specialist renal units. This was clearly illustrated by a study from Thieler[12] which showed that the admission rate of diabetic patients onto renal replacement therapy tripled within the three years after the Berlin wall came down and our compatriots in the East had been exposed to the horrors of capitalism.

An interesting observation is the fact that one out of every 5 patients with type II diabetes entering dialysis programmes suffers from non-diabetic primary renal disease.[13] This proportion is much higher than would be expected by chance. It will be an interesting scientific problem to resolve whether in a patient with pre-existing renal disease the superimposition of diabetes accelerates the rate of progression of renal failure due to the non-diabetic renal disease. In terms of

patient survival, interestingly enough, there is apparently no difference between the patient who is uremic because of diabetic glomerulosclerosis and the one who has primary renal disease.

Based on renal biopsy studies in patients who had been referred for evaluation of heavy proteinuria, American and Danish authors stated that 20% of diabetic patients suffered from primary glomerulonephritis.[14,15] Does diabetes provide a more favourable milieu for the development of glomerulonephritis? Unfortunately, we could not confirm this hypothesis in 210 consecutive diabetic patients coming to autopsy. Evidence of glomerulonephritis, by immunohistology, was, if anything, less than in the general population.[16]

Are the renal lesions in type I and type II diabetes similar? Several studies, including that by Gambara from Bergamo,[17] showed that the typical lesions of Kimmelstiel Wilson's glomerulosclerosis were present in only 19 patients with type II diabetes and renal impairment, while 16 patients had non-specific, largely ischemic, lesions. It appears then, that in type II diabetes, renal lesions may be more heterogeneous with non-specific lesions of ischemic origins being common.

Is glomerular geometry a factor predisposing to diabetic nephropathy? There is indeed some evidence[18] that the risk of a diabetic developing glomerulosclerosis is related to glomerular size. Large glomeruli are more susceptible to glomerulosclerosis. Why may this be so?

Brenner proposed the interesting hypothesis that glomerulomegaly is an adaptive response to a low number of glomeruli at birth.[19] Individuals with low numbers of glomeruli are thought to be more susceptible to glomerulosclerosis because less nephrons have to perform more 'work'. According to an old trade union statement, work kills.

Other investigators have postulated that large glomeruli are subject to greater wall stress at any given level of intracapillary pressure, as one may predict from the Laplace relationship $T = R \times P$; where T = wall tension, R = radius, P = pressure. Still others have postulated that when growth of the glomerulus is stimulated by growth factors, a milieu is created which is more conducive to cell proliferation and extracellular matrix synthesis, crucial processes in the development of glomerulosclerosis.[20] One of the most convincing explanations has been offered by Rennke.[21] He showed that following glomerular enlargement the outer surface of the capillary was no longer completely covered by podocytes. Podocytes are postmitotic so that their number cannot increase during glomerular growth. As a consequence, focal areas of the capillary wall will be denuded of covering cells, creating areas of high hydraulic permeability and by this token initiating local scarring.

In support of this, it has been thought that diabetes induces nephromegaly and glomerulomegaly and, in accordance with the above theory, this would predispose to glomerulosclerosis.

It is of note, however, that those Pima Indians who ultimately develop diabetic glomerulosclerosis, indeed have larger glomeruli than those who do not—but the large glomeruli are apparent even before the onset of diabetes and no further increase of glomerular volume is seen when proteinuria develops.[18] The relationship between diabetes and renal damage appears, therefore, to be rather complex.

Which other factors are related to the risk of developing diabetic nephropathy? There can be little doubt that glycemic control is of major importance,

(but this remains to be proven, for type II diabetes) but there is also recent evidence that genetic factors are involved as well. Seaquist *et al*,[22] examined patients with type I diabetes and noted that the presence of a diabetic sibling with nephropathy increased the risk of a propositus developing nephropathy as well by a factor of 4. The same is true in a genetically unique Indian tribe, the Pima Indians, where familial clustering of diabetic nephropathy has also been noted.[23] These observations provide strong but not definite, evidence of genetic predisposition.

Recently Marre[24] and collaborators reported on abnormal allele frequencies for a polymorphism in the ACE gene in patients with diabetic nephropathy. Studying 702 diabetic patients in Germany and Poland, we have also looked into the genetics of diabetic nephropathy but did not find different genotypes in diabetic patients of either type I or type II with or without nephropathy.[25]

This finding brings to one's mind the sarcastic comment of Aldous Huxley 'The most tragic event in science is the slaying of a beautiful hypothesis by an ugly fact'.

While the original observation of Marre has not definitely been substantiated, it is of interest, though, that in an unpublished observation, Parving (personal communication) found a more rapid decrease of GFR in patients with type I diabetes who were homozygous for the DD allele compared to heterozygous ID individuals and homozygous II individuals and this has been confirmed in principle in the UK Prospective Diabetes Study.[26]

In a sample of 92 patients with type II diabetes of short duration we found a strong interaction between the effects of glycemic control and genetic factors.[27] The risk of developing microalbuminuria was strongly predicted by a history of cardiovascular events in first degree relatives, confirming the results of Viberti in patients with type I diabetes.[28] Individuals who had a negative family history and good glycemic control did not have microalbuminuria.

Those with a positive family history of cardiovascular events or poor glycemic control had a 5% frequency of microalbuminuria, while individuals with a positive family history plus poor glycemic control had a frequency of 60%. It is known that microalbuminuria is associated with both glomerular and cardiovascular disease in patients with type II diabetes. Because diabetologists are so much concerned with microalbuminuria, cynical American nephrologists recently began to refer to diabetologists as 'micronephrologists'.

One method to investigate the pathogenesis of diabetic nephropathy is to examine individuals early on in the disease when many factors confounding the analysis in later stages have not yet supervened. We had recently the opportunity to examine 92 consecutive patients with type II diabetes who were admitted to a self-control training program soon after the diagnosis of diabetes had been made.

In parallel with the notion that there is no risk of nephropathy in type II diabetes, it has been stated that hyperfiltration and hyperperfusion do not occur in early type II diabetes. We and others have documented hyperfiltration in type II diabetes, [29,30] particularly when corrections are made for lean body mass. In the above cohort irrespective of whether patients had normoalbuminuria or microalbuminuria, glomerular filtration and particularly renal plasma flow were substantially higher than in body mass-matched non-diabetic controls. By multiple linear regression analysis, plasma flow was found to be related to age (being lower at higher age), to albumin excretion and to fasting plasma glucose

(more tightly to the latter than to HbA1 concentration). We interpret this to indicate that when plasma glucose concentration (and thus by implication, filtered glucose presented the proximal tubular sodium glucose cotransporter) is high, the sodium concentration in the distal tubule at the site of the macula densa will be reduced. This will subsequently cause reduction in the vasoconstrictor tone of the afferent arteriole via tubuloglomerular feedback, and by this token, renal vasodilation will occur.

Microalbuminuria and macroalbuminuria were found in 16% of the patients in our cohort. However, in South West Germany we have found microalbuminuria also in approximately 5% of the age matched general population, similar to what had been reported by the UK-PDS Study on Type II Diabetes.[31]

We found the following factors correlated with the presence of microalbuminuria. By logistic regression analysis HbA1, smoking and night-time hypertension, and by multiple linear regression analysis renal plasma flow, current smoking and HbA1 were all related to the presence of microalbuminuria.

The effect of smoking is of particular interest. In essential hypertension both Mimran in Montpellier[32] and ourselves[33] found that smoking was strongly correlated to urinary albumin excretion rate. In type I diabetes smoking is strongly related to the risk of development of microalbuminuria and albuminuria.[34] Once nephropathy has developed, smokers have been shown to have a two fold higher rate of progression to renal failure in type I diabetes.[35] In an ongoing study we have provided preliminary evidence that patients with IgA glomerulonephritis and polycystic kidney disease who smoke have a greater risk of renal failure than non-smokers. Therefore the kidney apparently does not like smoking. Is there similar evidence in type II diabetes?

In one Danish study, at the time of diagnosis of diabetes smoking was positively correlated to the presence of microalbuminuria,[36] as in our own study.[27] In a cross-sectional study in Denver smoking was strongly correlated to albumin excretion[37] and in patients with type II diabetes and renal failure Biesenbach found two fold higher rates of progression in smokers.[35]

It appears therefore that smoking increases the risk of nephropathy in diabetes. This finding has obvious implications for patient management.

How about blood pressure in these patients? In our cohort[27] we measured ambulatory blood pressure. Normal pressure was defined according to the recommendations of the German Blood Pressure League, as 130/80 mm Hg, which is approximately the 95th percentile in the normal population. According to this definition 60% of our type II diabetic patients were hypertensive, and 61% had an attenuated nocturnal decrease in blood pressure (i.e. blood pressure decrease by less than 15%). The presence of either high ambulatory blood pressure or an attenuated nocturnal decline was found in 79% of the cohort. Consequently only 21% were strictly normotensive. Only 18% of the hypertensive patients had microalbuminuria. This is in marked contrast to type I diabetes where hypertension is tightly linked to nephropathy.[38]

Why may high blood pressure be injurious to kidneys of the diabetic patient, while it is better tolerated by the kidneys of the non-diabetic patient with hypertension?

Transmission of aortic pressure into the glomerulus is prevented under normal circumstances and in essential hypertension by high pre-glomerular resistance. This protects the glomerular vascular bed against elevations of systemic blood

pressure. In diabetes with renal vasodilatation, pre-glomerular resistance is low and a greater proportion of aortic pressure will be transmitted to the glomerulus thus causing glomerular hypertension. It is therefore not surprising that even a modest elevation of blood pressure is indeed a risk factor for diabetic nephropathy. In Pima Indians, Nelson found that even prediabetic blood pressure was an important determinant of albuminuria and subsequent risk of diabetic nephropathy.[39] Individuals in the lowest tertile of prediabetic blood pressure had the lowest incidence, 9%, and those in the highest tertile had the highest, 23% incidence, of microalbuminuria. This could not be documented in our patient sample, but one must be aware of the limited sensitivity of our study because of its relatively small size.

Nevertheless, based on the observation of Nelson it would make sense to rigorously treat hypertension in patients with a metabolic syndrome in the hope that the renal risk will be diminished when diabetes ultimately develops. This consideration, unfortunately, is currently not supported by any evidence.

Blood pressure measured before a type II diabetic patient develops persistent proteinuria is also consistently higher than in those matched diabetic patients who fail to develop persistent proteinuria. In our study[40] systolic blood pressure prior to the appearance of overt nephropathy was 164 vs 149 mm Hg in those who did not develop proteinuria, and the prevalence of hypertension 70 vs 43%.

A large number of progression promoters have been identified, i.e. factors that accelerate the progression of diabetic nephropathy; these include albuminuria, glycemic control, smoking, possibly dietary protein intake and hyperlipidemia.

There has been much focus on hypertension and its control because of its practical importance.

What is the effect of ACE inhibitors on diabetic nephropathy?

Animal studies have suggested that ACE inhibitors have a nephroprotective action, i.e. they reduce the risk of glomerulosclerosis more than can be accounted for by the lowering of blood pressure.[41] This has been an extremely stimulating hypothesis, if measured by the number of studies that have been carried out to test it in man. Currently it is not clear whether the apparent beneficial effect of these drugs may not be simply explained by more effective lowering of blood pressure around the clock, since in a study using telemetric monitoring of blood pressure, a tight relationship was found between time averaged blood pressure and degree of glomerulosclerosis.[42] Nevertheless, these drugs could also exert independent effects on blood pressure e.g. by altering glomerular charge selectivity. An electrical barrier function is conferred on the glomerular basement membrane by polysulfated glucosaminoglycans. Because of their negative charge glycosaminoglycans repel polyanionic albumin and prevent albuminuria. There is also evidence for an effect of angiotensin II, and conversely of ACE inhibitors, on glomerular synthesis of glycosaminoglycans and glomerular size selectivity.[43] A number of experimental studies have shown that ACE inhibitors have a beneficial effect on intraglomerular pressure by selectively lowering efferent arteriolar resistance.[41] Finally there is evidence that angiotensin II promotes glomerular growth by acting as a co-mitogen. Orth has shown that physiological concentrations of angiotensin II increase cell counts in human adult mesangial cell cultures.[44] There is also relevant *in vivo* evidence. Amann showed that treatment of subtotally nephrectomized rats with enalapril had a beneficial effect on the development of glomerulosclerosis[45] possibly because the enalapril-treated animals had smaller

glomeruli, and fewer mesangial cells than non-treated controls. As already discussed these may be the key players in the genesis of glomerulosclerosis.

What information is available on patients with type II diabetes?

Prospective controlled trials have shown that ACE inhibitors reduce albuminuria more effectively than atenolol in patients with type II diabetes.[46] Furthermore, Ravid in Israel showed that patients with type II diabetes experienced a smaller increment of albuminuria when treated with enalapril than with placebo.[47] However the really clinical important issue of whether ACE inhibitors have a beneficial effect on the loss of glomerular filtration is currently unresolved.

Together with Dr Lewis we are currently performing an international multicentre controlled trial on the effect of the angiotensin II receptor antagonist Irbesartan in patients with type II diabetes and nephropathy. There are investigators who claim that ACE inhibitors are superior to other methods of treating hypertension and those who find no difference in the reduction of proteinuria. A meta analysis of data has shown that if blood pressure is not lowered ACE inhibitors reduce albumin excretion by approximately 20%.[48] With aggressive lowering of blood pressure the additional benefit of ACE inhibitors on urinary protein excretion becomes less, so that with lowering of pressure by 25% the difference between ACE inhibitors and other antihypertensive agents is virtually obliterated.

How about calcium channel blockers? Experimental data on the effects of calcium channel blockers on glomerulosclerosis are much less consistent than those on ACE inhibitors. In some studies, for instance those of Mimran[49] and ourselves,[50] dihydropyridine type calcium channel blockers acutely increased albumin excretion.

An Australian study showed no difference between the ACE inhibitor perindopril and the calcium channel blocker nifedipine in reducing microalbuminuria.[51] However, in this study a large proportion of patients normalized their rate of albumin excretion at low blood pressures which would have made any difference between therapies harder to detect.

In two controlled trials[52,53] nifedipine was less effective than enalapril in reducing proteinuria. Nevertheless, calcium channel blockers are able to reduce albumin excretion, as documented for nifedipine monotherapy.[54]

It appears at present calcium channel blockers are effective, but less effective than ACE inhibitors with respect to reducing proteinuria in diabetic nephropathy.

Is there a rationale to combine ACE inhibitors and calcium channel blockers?

If we are convinced that angiotensin II is involved in the progression of diabetic renal disease, there would be logic in blocking the generation of angiotensin II by ACE inhibitors and in concurrently blocking the effect of angiotensin II on effector organs by administering calcium channel blockers.

In a recent study we have found evidence that the combination of the ACE inhibitor ramipril and the calcium channel blocker nifedipine caused less development of glomerulosclerosis in subtotally nephrectomized rats than the respective monotherapies,[55] although in the absence of telemetric monitoring in such studies, it remains extremely difficult to be sure that blood pressure in the two groups was exactly the same.

A clinical study of patients with type II diabetes and proteinuria, given lisinopril or verapamil as monotherapy or a combination of the two titrated to yield similar substantial lowering of mean arterial blood pressure, showed that

the effect of the combination on reduction of proteinuria was much more striking than that of either monotherapy.[56]

In conclusion there are many clues as to the development and the progression of nephropathy in the patient with type II diabetes, but more needs to be done to fully understand the condition.

The development of diabetic nephropathy is a turning point in the life of a type II diabetic patient which dramatically increases the risk of death from renal failure and from cardiovascular causes. This is not too surprising given the fact that the kidney is an organ of overriding importance. Ancient wisdom as stated by Talmud Berochot (*c.* 300 AD) held that 'the organs of the body were created to perform ten functions, amongst which it is the function of the kidney to furnish the human being with thought'. This view, although extremely flattering to the clinical nephrologist, may not be completely true. Nevertheless we concur with the Rabbis that the function of the kidney is crucial, particularly in type II diabetes.

However, even better than preventing the onset and progression of diabetic nephropathy would be an effort to prevent type II diabetes *per se* by changing the Western life style of relative caloric excess and physical inactivity.

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