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Renal lesions of diabetes mellitus

Robert Francis Glock
University of Nebraska Medical Center

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Robert F. Glock

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When insulin was discovered and proven to be of value in the control of diabetes, the medical profession and the people afflicted with the disease were optimistic that a drug had been developed which would conquer this disorder. Patients no longer needed to die of diabetic coma, infections and other complications; they could lead relatively normal lives and carry out a daily routine of living. However, as the years passed and diabetic patients lived with their disease for longer periods of time, new complications appeared in the place of the older, even in the presence of good diabetic control. The vascular system is the seat of the most serious of the present day complications of diabetes; irreversible damage to the blood vessels appears throughout the body in many of these people. It occurs so regularly that many investigators do not consider this vascular damage a complication of diabetes, but a part of the clinical picture of diabetes.

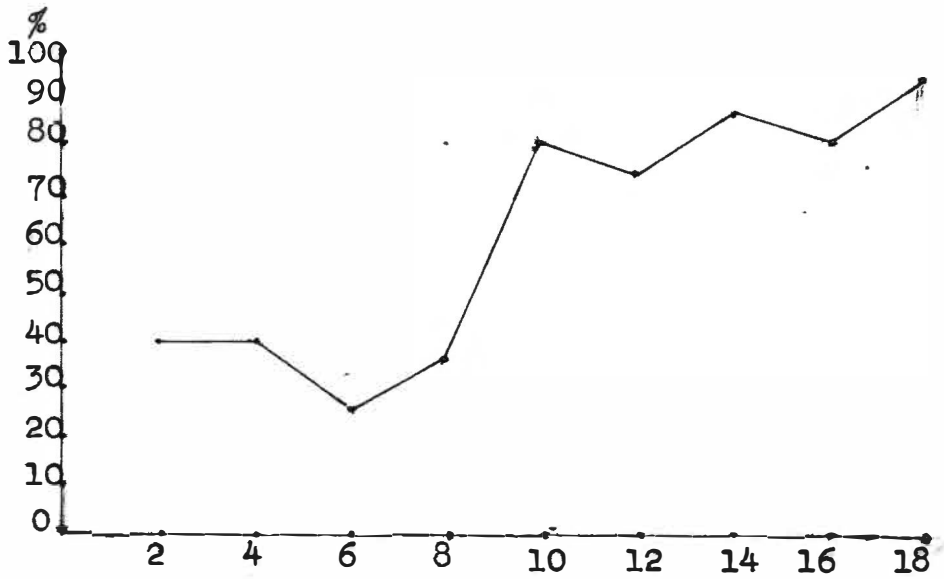
In 1936, Kimmelstiel and Wilson (1) reported on the pathological findings of eight diabetic patients who gave a clinical picture of diabetes, albuminuria, edema and hypertension. The kidneys showed striking and characteristic lesions of the glomeruli to which the two investigators gave the name intercapillary glomerular sclerosis. Others soon began reporting similar findings, and the syndrome became popularly known as Kimmelstiel-Wilson's disease.

There are three outstanding features of the condition: First, it is a serious vascular complication and common cause of death in

diabetes mellitus of long duration. Second, it is likely to exist whenever albuminuria, edema, hypertension and retinitis appear in a diabetic patient. Third, in its most advanced stages it is rarely seen except among diabetic patients, although a less characteristic and possibly earlier form of the disease is not uncommon in vascular and kidney disease in non-diabetics. (2)

There are no definite clinical features by which diabetes with intercapillary lesions can be distinguished from diabetes without glomerular alterations. Also, the clinical features are practically indistinguishable from those of glomerulo-nephritis or nephro-sclerosis. However, there are certain findings associated with intercapillary glomerular sclerosis which suggest its presence. Among these are diabetes of long standing, albuminuria, hypertension, retinopathy, edema, and hypoalbuminemia.

Almost all cases have been diabetic for a number of years before any other signs of intercapillary glomerular sclerosis appear. The duration of the diabetes is of more importance than the age of the patients; also, the duration of the diabetes is of more importance in the development of degenerative lesions than the control measures used. The following graph, devised by Goodof as a result of his studies, shows the relation of the duration of diabetes to the incidence of intercapillary glomerular sclerosis.



The Incidence of Intercapillary Glomerulosclerosis in Relation to The Duration of Diabetes Mellitus

It can be seen that the incidence of glomerular lesions increases rapidly in the group of patients who have had diabetes more than 6 years. The diabetes is usually of a comparatively mild character. The lesion may appear at any age beyond the second decade; it is most commonly observed between the ages of 40-60. Also, it is more frequently found in the patients who develop diabetes early in life than in the aged, possibly because the younger patients live with the disease longer, or possibly because of the greater severity of the disease in the young patient. This points to the importance of the duration of the disease rather than of age alone. Horn and Smetana (4) found that intercapillary glomerular sclerosis occurred to a mild degree in 10% of non-diabetic patients of an age group corresponding to a group of diabetic patients. Also, in 100 non diabetic patients with arteriolar

nephrosclerosis, eleven instances of intercapillary glomerular sclerosis were found; however, these were of such minimal degree as to not show up clinically or by laboratory methods. Advanced lesions are found only in diabetes mellitus as a rule. This would seem that the glomerular lesions are directly related to the diabetes, although additional factors may be required for its precipitation. Whether or not sex of the patient is an important factor in the development of the lesion has been a point of debate; however, most investigators feel that there is almost a 2:1 ratio of females over males afflicted with the disorder.

Albuminuria is the most common early sign of the disease; it usually appears before other signs. It seems to be roughly parallel to the severity of intracapillary glomerular sclerosis but lesser degrees of albuminuria may be due to cardiac or other renal involvement. The majority of advanced cases show from 2 plus to 4 plus test (5); it becomes progressively more severe as the condition advances. In Goodof's (3) series of 18 cases with advanced lesions 15 excreted large amounts of albumin.

In the final analysis of causes of albuminuria, the factors most probable are anoxia of the glomerular capillaries, and increased capillary pressure. Krogh and Landis (6) have shown experimentally that stasis, anoxia and distension of capillaries in which there is an increase of pressure will bring about an increase of permeability, even to proteins. About most diabetic lesions in the kidney one sees more or less dilatation of the

peripheral capillary loops. Occasionally the loops are engorged with red blood cells; the capillary basement membrane is stretched to a fine line. Protein may lie in the lumen and in Bowman's space. This is the picture of stasis and therefore probable anoxia and increased capillary pressure. This dilatation of capillaries is probably largely due to stenosis produced by the thickened hyalin mass of the associated diabetic lesion which projects into the lumen of the capillary. The narrowing of the efferent arterioles may contribute by tending to raise the intra-glom-erular pressure. In addition, possible damage to the capillary wall as a consequence of its participation in the process of glomerulosclerosis may be a factor. (7)

Although present in most of the cases, just as it is in patients with other forms of chronic renal disease, hypertension is not a necessary part of the clinical picture. Benign and moderate arterial hypertension are seen often; however, there are many cases of intercapillary glomerular sclerosis without hypertension. In the series of cases studied by Laipply et al (8), intercapillary glomerular sclerosis was present in 51 of 76 (67.1%) of diabetic patients with systolic and diastolic hypertension; systolic and diastolic hypertension were present in 51 of 79 cases (64.6%) of diabetic patients with intercapillary glomerular sclerosis. There was no demonstrable relation between the stage of the glomerular lesion and presence or absence of hypertension in these cases. There is nothing characteristic about the hypertension of intercapillary glomerular sclerosis.

When present it is probably associated with the arterial and arteriolar nephrosclerosis which is commonly present in diabetes mellitus. A close relation between intercapillary glomerular sclerosis and arteriolosclerosis of the kidneys has been obvious to all observers. Although arteriolosclerosis cannot be excluded as a contributing factor in the etiology of intercapillary glomerular sclerosis it cannot be regarded as the sole cause. In the age in which most cases of intercapillary glomerular sclerosis occur, a large per cent of patients reveal marked arteriosclerosis of the kidneys with or without glomerular lesions. Intercapillary glomerular sclerosis has been found at times without significant vascular changes (5). As said before, when hypertension occurs in intercapillary glomerulosclerosis it is more likely to be correlated with the accompanying arteriolosclerosis. However, hypertension is not observed as constantly as arteriolosclerosis in the disease. According to Bell (9), renal arteriolosclerosis occurs in 31.8% of patients under 50 years of age and in 77.9% of patients over 50 years of age. It occurs in frequency as blood pressure rises.

Retinopathy associated with this disorder almost always includes changes due to diabetes. It is found in over 2/3 of the cases of diabetic intercapillary glomerular sclerosis, and in less than $\frac{1}{4}$ of cases of diabetes without this complication. Purely hypertensical retinopathy is rare; the great majority of cases show a more complex type of retinopathy (5). The observations of Dolger (10) show that retinopathy often appears before the vascular lesions

and in some instances, before the intercapillary glomerular sclerosis itself. Using material obtained from the study of 200 diabetic patients whose diabetes began before the age of 50 he found that not one of the 200 escaped retinal hemorrhages regardless of the age of onset, severity of diabetes or type of treatment used. In well-controlled diabetic patients the average duration of diabetes was 13 years before onset of retinal lesions. By the time retinopathy had developed 50% of the patients showed definite hypertension and 30% had albuminuria. The appearance of retinal hemorrhage, however, often presaged the inevitable pattern of more generalized and progressive vascular degeneration. 27 of the 200 patients studied eventually became partially or totally blind. In these cases, control of glycosuria did not avert the complication. Eventually, all of these patients had albuminuria of varying severity; hypertension was found in 60%. Retinopathy is the most characteristic of all the clinical findings associated with interoapillary glomerular sclerosis; hemorrhages, exudates, retinal arteriosclerosis and retinitis are the most frequent of these findings. The hemorrhages are the punctate, macular hemorrhages so characteristic of diabetes. The waxy and cotton-wool exudates usually appear after the albuminuria, edema, and hypertension.

Edema and hypoalbuminemia are other findings in the clinical picture of interoapillary glomerular sclerosis. There is often a drop in the Albumin-Globulin ratio without much drop in total serum protein. Some clinicians have reported edema of severe degree

with total serum protein of 5.5 to 6.0. The albumin usually ranges from 2.5 to 3 gm.%. It has been suggested that this low serum albumin may be of value as a diagnostic aid (2). The edema is resistant to the usual therapeutic aids, such as high protein diet, digitalis, salt restriction and acid therapy, although the mercurial diuretics help. Fully developed nephrosis does not often participate in the complex syndrome associated with this disorder. Applying rigid criteria to identifying the nephrotic syndrome, it would probably appear in about 10% of cases (5). However, the nephrotic syndrome is not found in diabetes without intercapillary glomerular sclerosis.

The differences in incidence of intercapillary glomerular sclerosis as reported by various investigators seems to be due to variable pathological signs which are taken as criteria for diagnosis of the disease. Various observers have reported the incidence as 20%-64% of routine diabetic autopsies, depending upon the histologic criteria used for diagnosis of the lesion. Dolger (10) believes that the lesion exists with varying degrees of severity in every instance of diabetes mellitus of some duration.

The lesion consists of a hyalin-like mass in the central portion of the glomerular lobules, giving the impression of lying between the lobules. Bell (9), in a microscopic study of kidneys of 460 diabetic patients described the lesion as a sub-intimal deposit of hyalin substance in the afferent and efferent glomerular

arterioles. Hyalin masses between the capillaries are formed by thickening and splitting of the capillary basement membrane. There are no changes in the juxta-glomerular apparatus.

It is frequently necessary to differentiate intercapillary glomerular sclerosis from chronic glomerulonephritis; as stated before, the clinical features of the two diseases may be practically indistinguishable. Diabetic patients with albuminuria, edema, hypertension and renal insufficiency have often been diagnosed as diabetes complicated by independent glomerulonephritis. Cases of chronic glomerulonephritis are seen at post mortem in which the kidneys show occasional or even numerous glomeruli indistinguishable from advanced lesions of intercapillary glomerular sclerosis in the absence of diabetes. Henderson (11) et al made a study that revealed the following facts: cases of chronic glomerulo nephritis with or without intercapillary glomerular sclerosis show no significant clinical differences; patients with chronic glomerulonephritis with intercapillary glomerular sclerosis differ from diabetic patients with intercapillary glomerular sclerosis in spite of superficial resemblances. Both groups have in common hypertension of varying degrees, albuminuria, edema and retinopathy. Most of the differences are quantitative ones; only the retinopathy differs in quality, and this type of retinopathy is directly dependent upon the diabetes rather than upon the renal lesion. Allen (7), feels that the renal lesion in intercapillary glomerular sclerosis arises in the capillary basement membrane in a manner similar to

that of glomerulonephritis and that the only significant difference appears to be essentially quantitative, pertaining to the focal character and to the frequently greater length and characteristic arrangement of the fibers in the diabetic lesion.

Because of the close resemblance of symptoms, there is no reason to assume a difference in pathogenesis between diabetic intercapillary glomerular sclerosis and intercapillary glomerular sclerosis of chronic glomerulonephritis.

(5) Condition	Diabetes with Intercapillary Glomerular-sclerosis	Chronic Glomerular Nephritis with Intercapillary Glomerular-sclerosis.
Average age of patients	58 years	32 years
Edema	Less Prominent	More Prominent
Albuminuria	Less Intense	More Intense
Specific gravity	Higher	Lower
Urea Nitrogen	Lower	Higher
Anemia	Less severe	More severe
Retinopathy	Diabetic type	Hypertensive type
Duration of Terminal illness	Months to years	1-4 months
Cause of death	Varied	Usually cardiac, renal or infectious

Subacute glomerulonephritis complicated by the nephrotic syndrome is also often very difficult to differentiate from intercapillary glomerular sclerosis. There are two important features which favor the diagnosis of nephritis: (1) anemia is almost a universal finding in glomerulonephritis, whereas it is not an important feature of the other. (2) The nephrotic stage of subacute glomerulonephritis usually appears in patients under 50 years of age, whereas in the other the majority of patients are over 50 years. (12)

The question has been raised at times about the status of intercapillary glomerular sclerosis as a clinico-pathological entity. The question cannot be answered with finality. Even though rare, exceptions have been noted: cases in which diabetes is absent, although renal lesions are fully developed. Identical lesions do occur in chronic glomerulonephritis without diabetes in a few cases. However, a similar situation occurs in many other diseases in which a definite pattern of clinical signs and symptoms is correlated to distinct pathological findings, although the same histologic change may occur in a different set of circumstances and may result from different etiological factors, e.g. the same histologic changes in arterioles occur in malignant hypertension, periarteritis nodosa and lupus erythematosis. (5)

In the past, a clinician seeing the diabetic patient develop albuminuria, hypertension, edema, retinopathy, and decreased kidney function regarded the condition as coincidence or as the simultaneous

occurrence of two or three different disease processes. Now, however, he can predict with reasonable accuracy a pathological lesion in the kidney related to the basic metabolic disorder - the diabetes - merely constituting a variant of its manifestations. One can say that in a patient over 50 years of age with chronic diabetes and the above picture one can safely make the diagnosis of intercapillary glomerular sclerosis with approximately 100% accuracy. Chronic glomerulonephritis is rarely a problem in this age group. Repeated Addis counts will dispel any doubt if chronic glomerulonephritis is suspected.

Data concerning renal function in this condition are still not as complete as one would like. Although renal function is very much impaired in a large percentage of cases (probably about 2/3 of cases) as shown by significantly elevated urea nitrogen or non protein nitrogen, death is just as often due to cardiovascular disease and intercurrent infections. Death in uremia occurs in about 1/5 of cases. In the remaining cases cerebral accidents, cardiac failure, coronary occlusion and other cardiovascular lesions are the most common causes of death. (5) No definite statement can be given concerning prognosis, but death may usually be expected in two or three years after the syndrome is fully developed. Microcytic hypochromic anemia seems to parallel renal impairment.

The diagnosis of intercapillary glomerular sclerosis carries with it a grave prognosis because the treatment of the diabetes

will not influence the downward progress of the patient. The difficulty in recognizing earlier or less advanced lesions does not interfere with the concept of intercapillary glomerular sclerosis as a clinico-pathological entity. It should rather constitute a challenge to a search for better criteria for early diagnosis and for improved techniques, methods and standards of diabetic control that may help in preventing the progression of vascular damage in diabetes mellitus into the condition described in these pages.

Therapy with insulin has such a broad zone of safety that its use tends to encourage a complacent attitude on the part of the patient and the physician. Degenerative lesions often develop insidiously in patients who have been led to believe that the management of their disease has been adequate (13). This raises the question: "Is physiologic control of diabetes, as shown by freedom from hyperglycemia and glycosuria adequate control?"

Only when we have complete domination of the course of the disease and can prevent the complications can we speak truthfully about having adequate diabetic control. Banting and Best gave us a most valuable weapon with which to combat the immediate dangers of diabetes mellitus; insulin has been a lifesaving drug for over 25 years. Possibly the next 25 years will reveal a means of overcoming the more slowly developing dangers of the disease.

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