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Review

Abnormal Lipid Metabolism and Renal Disorders

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SAITO, T. *Abnormal Lipid Metabolism and Renal Disorders.* Tohoku J. Exp. Med., 1997, **181** (3), 321-337 —— Although renal diseases including nephrotic syndrome and chronic renal failure are associated with hyperlipidemia, significance of abnormal lipid metabolism has been thought to be limited in some inherited renal diseases. However, recent studies have postulated that glomerulosclerosis is induced by hyperlipidemia and is in common with atherosclerosis. This involvement is found in the progressive renal disorders, e.g., focal glomerular sclerosis, diabetic nephropathy and glycogen storage disease. Interaction between macrophages and mesangial cells may play an important role in such conditions. This evidence is supported by experimental models with hyperlipidemia. On the other hand, discovery of new hereditary metabolic disorders, such as type III hyperlipoproteinemia and lipoprotein glomerulopathy, shows that apolipoprotein (apo) E abnormalities are responsible for the glomerular lesions. Especially, lipoprotein glomerulopathy has specific features different from those of lipid-induced renal diseases. In this disease, apo E Sendai which results from new substitution (Arginine 145→Proline) may induce intraglomerular lipoprotein thrombi characteristic of lipoprotein glomerulopathy. ———— hyperlipidemia; focal glomerular sclerosis; diabetic nephropathy; type III hyperlipoproteinemia; lipoprotein glomerulopathy

It has been well-known that nephrotic syndrome and chronic renal failure are associated with lipid and lipoprotein abnormalities. For a long time, however, it has been thought that hyperlipidemia is a secondary and insignificant condition in these renal injuries and that abnormal lipid metabolism inducing renal lesions is found in limited inherited diseases, e.g., Fabry disease and glycogen storage disease. Meanwhile, Moorhead and the associates (1982) hypothesized that chronic progressive renal disease may be mediated by abnormalities of lipid metabolism. Furthermore, some works (Keane et al. 1988; Kees-Folts and Diamond 1993) showed that hyperlipidemia was closely related to deterioration of

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renal injuries in nephrotic syndrome. Recently, newly-discovered lipid-metabolic disorders, e.g., familial type III hyperlipoproteinemia (Amatruda et al. 1974; Suzaki et al. 1990; Ellis et al. 1995), Lecithin-cholesterol acyltransferase (LCAT) deficiency (Gjone 1981) and lipoprotein glomerulopathy (Saito et al. 1989; Watanabe et al. 1989), also showed unique renal lesions. Accordingly, in this decade, the relationship between abnormal lipid metabolism and renal injuries has become more obvious.

In the current review, several renal disorders based on lipid and lipoprotein abnormalities, which we have studied are described.

Focal glomerular sclerosis in human

Focal glomerular sclerosis (FGS) was first reported by Rich (1957). He investigated autopsy specimens derived from children who suffered from severe nephrotic syndrome. In his description, focal segmental lesions of sclerosis were found especially in the juxta-medullary glomerulus. In 1970s, the disease entity having these characteristics was recognized as one of the representative progressive and incurable glomerular diseases (Churg et al. 1970; Habib 1973). Recently, many studies have tried to clarify its pathogenesis. Owing to some of these works (Keane et al. 1988; Kees-Folts and Diamond 1993), the mesangial and endothelial degeneration induced by abnormal lipid metabolism is considered as one of the risk factors in the pathogenesis of FGS.

In the minimal change nephrotic syndrome (MCNS), hyperlipidemia is usually obvious. However, serum cholesterol level is easily normalized when complete remission is brought up by the steroid and/or other immunosuppressive therapies. On the other hand, FGS associated with nephrotic syndrome is poorly responsive to the therapies. In such a condition, extreme hyperlipidemia continues for a long time, and, histologically, vacuoles and foam cells develop around sclerotic changes in the glomerulus. Even in primary hyperlipidemia without nephrotic syndrome, as we reported previously (Saito et al. 1987a), FGS was occasionally developed and advanced. This evidence suggests that hyperlipidemia plays a causative role in the mechanism of FGS. As described later, FGS-like lesions found in the inherited lipid metabolism abnormalities, e.g., glycogen storage disease (Obara et al. 1993) and lipoprotein glomerulopathy (Saito et al. 1993b, 1995), may also support this concept.

Although the mechanism of renal lesions in which abnormal lipid metabolism is involved is still unclear, attention is paid to the analogies to atherosclerosis. In the process of atherosclerosis, Brown and Goldstein (1983) have clarified that an accumulation of macrophages beneath the endothelium takes oxidized low-density lipoprotein (LDL) into their cytoplasm through scavenger receptors and change themselves into foam cells. On the basis of these findings, Diamond and Karnovsky (1987) postulated that glomerulosclerosis, as found in FGS, is developed by the similar mechanism of atherosclerosis. Especially, the interaction

between macrophages and mesangial cells under increased LDL levels seems to be important in a series of the process (van Goor 1991; Schlondorff 1993). Coritsidis et al. (1991) demonstrated that scavenger receptors were expressed in the mesangium. Furthermore, Takemura et al. (1993) showed that LDL receptors and scavenger receptors in the mesangial cells and macrophages infiltrating in the glomerulus increase under several pathological conditions. On the other hand, we demonstrated that an increase of macrophages was associated with the formation of glomerulosclerosis in hyperlipidemic condition when we analyzed biopsy specimens derived from patients with FGS (Saito et al. 1993b), diabetic nephropathy (Furuta et al. 1993) and glycogen storage disease (Obara et al. 1993). These results show that the role of macrophages is common and important in the hyperlipidemia if the glomerulosclerosis is formed in any kind of glomerulopathies. Studies using experimental FGS also suggest this evidence as described below.

Experimental FGS

FGS-like lesions are found in hypercholesterolemic animals. French et al. (1967) showed that guinea pigs fed 1% cholesterol diet developed progressive glomerulosclerosis. Grond et al. (1984) also studied chronic puromycin-aminonucleoside (PAN) nephrosis in rats and mentioned that increased accumulation of macromolecular substances such as lipids in mesangial cells leads to overproduction of matrix and eventually sclerosis. Diamond and Karnovsky (1987) noted that 4% cholesterol and 1% cholic acid dietary supplement to rats with PAN nephrosis resulted in severe glomerulosclerosis with a prevalence of mesangial foam cells which was identified as macrophages by a mouse monoclonal antibody, ED-1. In the 5/6 renal ablation model, van Goor et al. (1991) clarified that the macrophage flux in the glomerulus correlated with plasma cholesterol level and was a major structural alteration associated with FGS.

We presented a model of progressive FGS in rats which was induced by repeated co-administrations of PAN and protamine sulfate (PS) (Saito et al. 1987b). In this model, extreme hypercholesterolemia was observed and simultaneously macrophages increased in the glomerulus in association with the development of sclerosis (Saito and Atkins 1990). Harris et al. (1990) showed that lovastatin, one of HMG-CoA reductase, reduced plasma cholesterol and triglyceride levels and sclerotic lesions in the same model without effect on albuminuria. These results also confirmed the relationship between hyperlipidemia and glomerulosclerosis. Moreover, co-administrations of PAN and PS in spontaneously hypertensive rats caused malignant arteriosclerosis including onion peel lesions and fibrinoid thrombi with sclerotic changes in the glomerulus (Saito et al. 1990). This means that the sclerosis in both arteries and glomeruli may develop on the basis of the common mechanism under the coexistence of hypertension and hyperlipidemia.

It is thought that triton WR1339 (TR), a nonionic detergent, suppresses lipoprotein lipase (LPL) and LCAT activities and induces extremely high levels of plasma triglyceride (TG) and very-low-density lipoprotein (VLDL). Although obvious renal injuries were not induced by TR alone, many foamy macrophages were involved in progressive glomerulosclerosis by continuous administrations of TR into rats with chronic PAN nephrosis (Obara et al. 1992). Therefore, the uptake of VLDL is as important as that of LDL when macrophages degenerate into foam cells in the development of glomerulosclerosis analogous to atherosclerosis.

Spontaneously hypercholesterolemic (SHC) rats originally derived from Sprague-Dawley rats show hyperlipidemia and proteinuria (Imai et al. 1977). Renal lesions mimic human FGS and, especially in males, develop into an end-stage renal disease (Yoshikawa and Yamasaki 1991). Recently, we administered an nonpeptide vasopressin V1 antagonist per os into this strain, and showed that hypertriglyceridemia and the following glomerulosclerosis were suppressed by this agent without amelioration of proteinuria (Kurihara et al. 1996). Since arginine vasopressin stimulates liver lipogenesis through V1 receptors (Jeannet et al. 1981), V1 antagonist may reduce plasma TG levels by preventing lipogenesis (Rossi and Scharrer 1993). Thus TR-induced hyperlipidemia in PAN nephrosis and V1 antagonist efficacy in SHC rats suggest that TG may play a deleterious role in glomerulosclerosis.

Diabetic nephropathy

Diabetes mellitus (DM) is frequently associated with abnormal lipid metabolism whether it is classified into insulin dependent type (IDDM) or not (NIDDM) (Howard 1987). In NIDDM, elevated levels of serum glucose and free fatty acid induce hepatic synthesis of triglyceride and VLDL. These results may lead to an increase of serum LDL and glycosilation of LDL. In IDDM, insulin-dependent lipoprotein lipase activity is reduced, and catabolism of VLDL is delayed. Accordingly, extreme hyperlipidemia with elevated chylomicron and TG in serum is frequently found. Such conditions in DM are important risk factors for diabetic glomerulosclerosis as well as for atherosclerosis. Actually, several diabetic cases with extreme hyperlipidemia have been reported to have prominent foam cells in the glomerular tufts. Reaven (1987) suggests that peritoneal macrophages bind and degrade VLDL from patients with NIDDM more easily than from normal subjects. On the other hand, Schlondorff (1993) mentioned that the apolipoprotein (apo) B of LDL undergoes nonenzymatic glycation in diabetes which may alter its affinity for the LDL receptor and that the non-uptaken modified LDL may be trapped in the mesangial matrix. Then, the interaction between mesangial cells and macrophages may play a key role in the development of glomerulosclerosis (Ellis et al. 1995). When biopsy specimens from diabetic patients were examined by a three-layer immunoperoxidase tech-

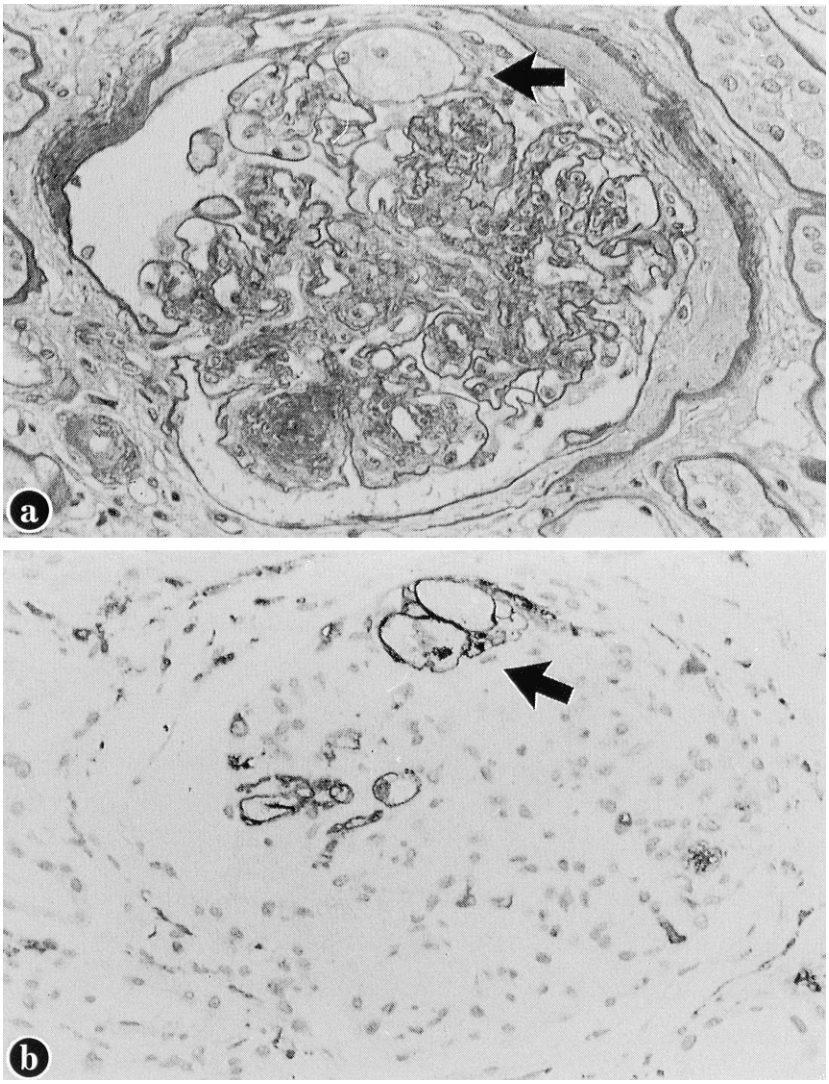

Fig. 1. Glomerulosclerosis in diabetic nephropathy and infiltration of macrophages.
(a) PAS staining preparation shows diffuse expansion and nodular lesions of the mesangium. Foam cells are seen around them (arrow). (b) In a serial section, macrophages ($CD68^+$) are demonstrated with the immunoperoxidase method, some of which are consistent with foam cells (arrow). (a & b, $\times 150$)

nique using monoclonal antibodies, we demonstrated that macrophages infiltrated into the glomeruli in the development of diabetic glomerulosclerosis and that some of them were transferred to foam cells (Furuta et al. 1993) (Fig. 1). Therefore, as mentioned previously, analogous mechanisms in atherosclerosis may contribute to irreversible structural damage in diabetic nephropathy.

Hereditary metabolic disorders

Hereditary metabolic disorders sometimes induce excess storage of lipids in systemic organs including the kidney. These are considered as the cases of primary lipidoses which clearly show the relationship between lipids and organ damage. Faraggiana and Churg (1987) reviewed primary lipidoses of the kidney,

TABLE 1. *Primary lipidoses associated with glomerulopathy*

Sphingolipidoses: Fabry disease, Gaucher disease, Niemann-Pick disease, Farber disease
Glycogen storage disease type 1 (von Gierke disease)
Familial lecithin-cholesterol acyltransferase deficiency
Refsum disease
I-cell disease
Wolman disease
Lipoprotein glomerulopathy
Type III hyperlipoproteinemia

and some of these diseases are included in *Renal Diseases: Classification and Atlas of Glomerular Diseases* published in collaboration with World Health Organization (Churg et al. 1995) (Table 1). Here, I would like to describe four representative lipidoses which we have studied.

Fabry disease. Most primary lipidoses belong to the category of sphingolipid storage diseases due to inborn deficiency of an enzyme (Faraggiana and Churg 1987). Sphingolipid is a ceramide, a complex of sphingosine and a fatty acid, and linked to various groups, e.g., saccharides and phosphorylcholine. In the process of metabolism, deficiency of an enzyme catalyzing the derivative induces storage of sphingolipid as a substrate in the organs. In this category, Fabry disease is comparatively common and sometimes found in male adults. The disorder is

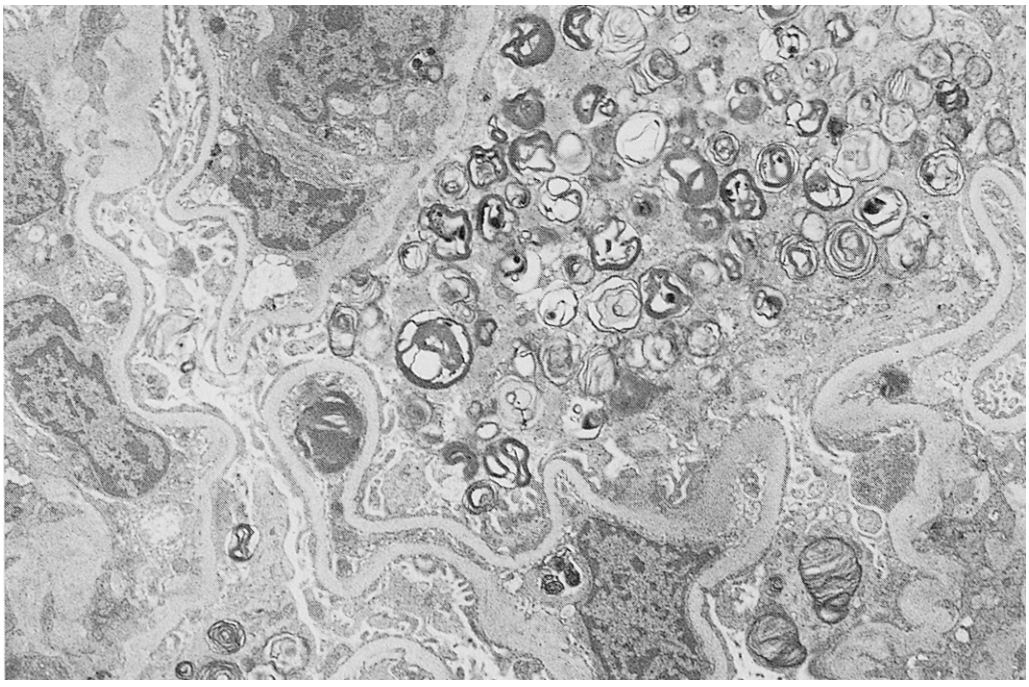

Fig. 2. Electron micrograph of the glomerulus in Fabry disease. Many lamellated bodies are seen in the epithelial cell (×4,000).

caused by deficient activity of α-galactosidase-A which is inherited as X-linked recessive manner. However, heterozygous females are known to occasionally show mild to severe clinical manifestations. Deficiency of α-galactosidase-A, which divides a galactose-galactose linkage, leads to the deposition of ceramide trihexoside in several organs including the kidney. In our four male cases (Matsubara et al. 1990), angiokeratoma of the skin and extremely reduced α-galactosidase-A activity in leukocytes were revealed. Renal histology showed severe swelling and vacuolation of the glomerular epithelium under light microscopy and myelin-like bodies under electron microscopy (Fig. 2). In the arteries, intimal thickening and degeneration of smooth muscle cells were marked. Two cases rapidly fell into renal failure associated with the development of accelerated hypertension at around 40 years of age. Accordingly, it is suggested that the advanced arterial changes in Fabry disease have a principal role in the rapid deterioration of renal function.

Glycogen storage disease type I (von Gierke disease). Glycogen storage disease type I causes the other form of lipid accumulation in the kidney. This disease is induced by an autosomal recessive pattern of abnormal inheritance and characterized by glycogen accumulation in several organs including the kidney. The main clinical manifestations are fasting hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia and hepatomegaly. However, renal enlargement is a common finding and was described in the first report by von Gierke (1929). Renal dysfunction has also been reported during the past few decades. Although the main findings at autopsy are interstitial fibrosis with tubular degeneration, recent biopsy specimens reveal glomerular lesions consistent with focal glomerular sclerosis (Chen et al. 1988; Baker et al. 1989; Obara et al. 1993). On the other hand, numerous lipid deposits in the glomerulus were observed in our patients (Obara et

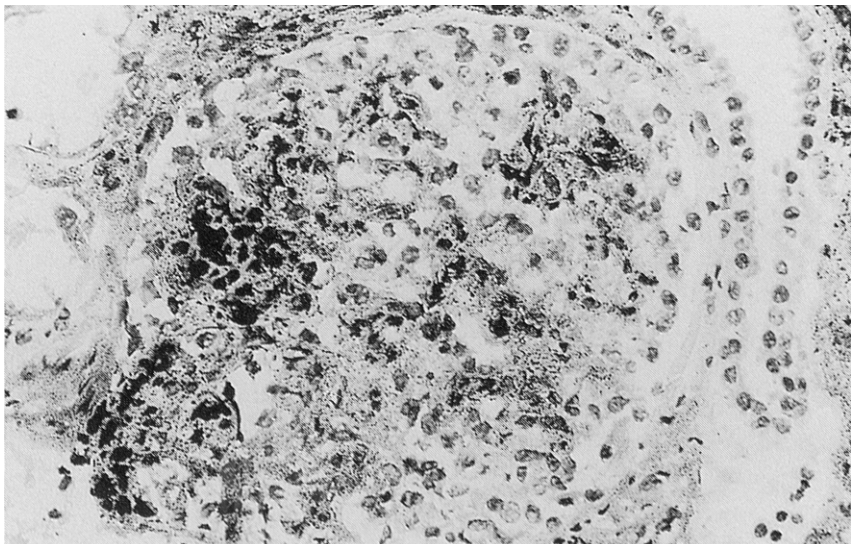

Fig. 3. Oil red O staining of the glomerulus in glycogen storage disease type I. Numerous lipid deposits are seen in the mesangium and sclerotic area ($\times 200$).

al. 1993) (Fig. 3). These deposits may be caused by hypertriglyceridemia which results from suppression of glyconeogenesis based on the deficiency of glucose-6-phosphatase. Glomerular sclerosis may be accelerated by lipid deposition subsequent to hyperlipidemia.

Lipoprotein glomerulopathy. Recently, curious glomerular injuries showing lipoprotein thrombi were presented (Saito et al. 1989; Watanabe et al. 1989) (Figs. 4 and 5). These changes were clinically associated with over two-fold elevation of serum apo E (Oikawa et al. 1991). We proposed that the pathological conditions were classified in a single disease entity termed as *lipoprotein glomerulopathy*.

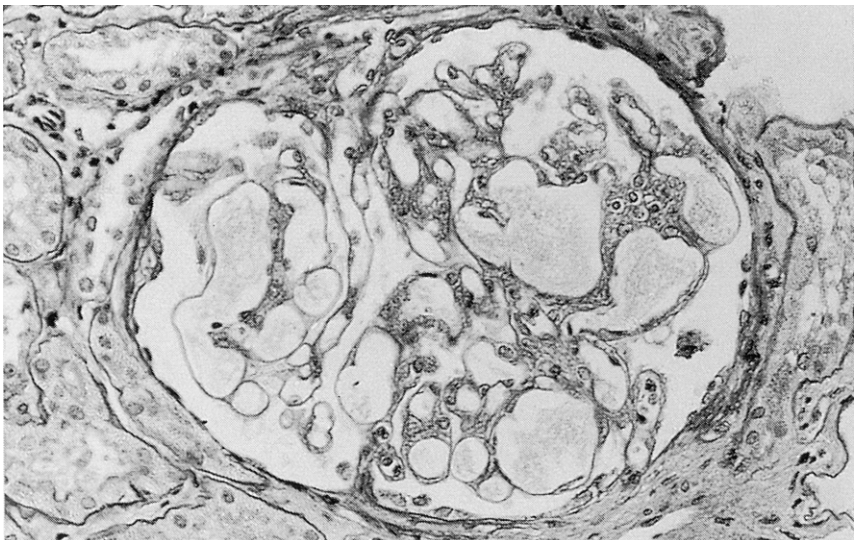

Fig. 4. Light micrograph of the glomerulus in lipoprotein glomerulopathy. Pale-stained lipoprotein thrombi are seen in the dilated capillary lumina. ($\times$200)

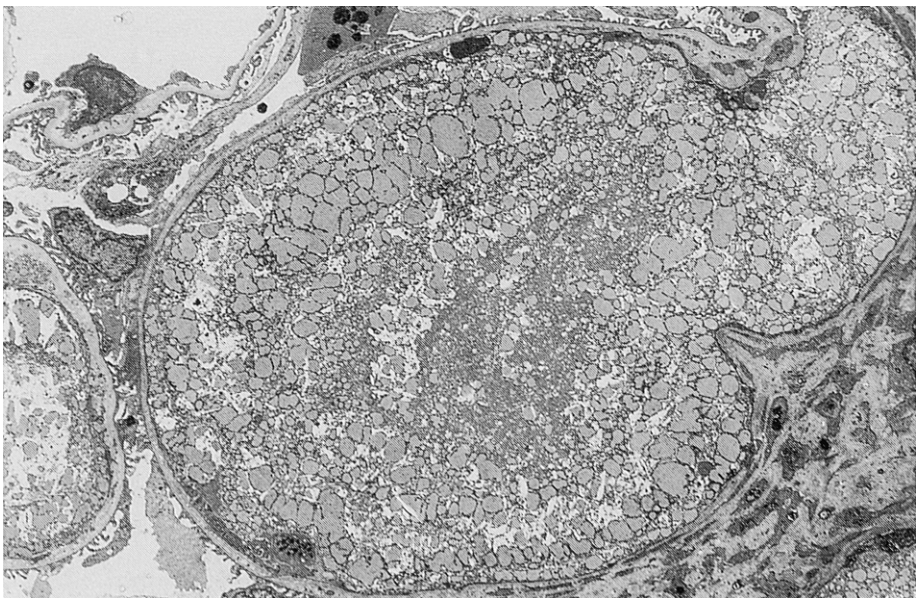

Fig. 5. Electron micrograph of the glomerulus in lipoprotein glomerulopathy. The capillary lumen is occluded with various sized granules. ($\times$2,000)

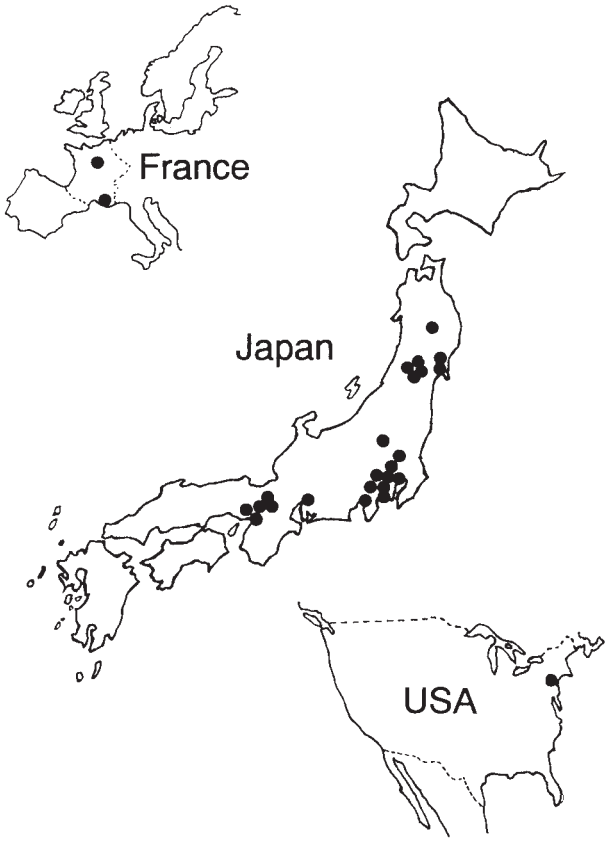

Fig. 6. Cases of lipoprotein glomerulopathy in the world.

This disease is now included in the second edition of *Renal Diseases: Classification and Atlas of Glomerular Diseases* published in collaboration with the World Health Organization (Churg et al. 1995). Moreover, it is elucidated by us that a new apo E2 variant may play a causative role in this disease as described later (Oikawa et al. 1997). To date, 23 patients have been reported in Japan (Saito et al. 1995) as well as 2 in France (Meyrier et al. 1995; Djamali et al. 1996) and one in the United States (Zhang et al. 1994) (Fig. 6). There were several cases showing familial occurrence (Saito et al. 1989; Koitabashi et al. 1990) (Fig. 7).

Although hyperlipidemia was not always observed clinically, our assay using ultra-centrifugation showed increase of cholesterol in VLDL and intermediate-density lipoprotein (IDL) fractions (Oikawa et al. 1991; Saito et al. 1993a). Accordingly, the lipoprotein pattern indicated type III hyperlipoproteinemia as defined by Hazzard et al. (1972) or Fredrickson et al. (1975). However, the apo E phenotype by isoelectric focusing was not the homozygous E2/2 essential to familial type III hyperlipoproteinemia but the heterozygous E2/3 or E2/4. On the other hand, in the examination of the apo E genotype by polymerase chain reaction and restriction fragment length polymorphisms (PCR-RFLP) analysis for genomic DNA, the cases with phenotypes of E2/3 and E2/4 showed $\varepsilon 3/3$ and $\varepsilon 3/4$, respectively (Oikawa et al. 1997). These discrepancies between genotype and phenotype imply that the apparent apo E2 isoprotein in lipoprotein glomerulopathy is not the true type which results from the substitution of cystein for

arginine at amino acid residue 158 of apo E (Arginine 158→Cystein).

Our further analysis for DNA sequencing of apo E found that the abnormal E2 isoprotein had a new substitution (Arginine 145→Proline), which was recognized in all examined cases including ones familially occurred (Fig. 7) and termed *apolipoprotein E Sendai* (Oikawa et al. 1997) (Fig. 8). Therefore, lipoprotein glomerulopathy may be induced by an inherited apo E Sendai. This hypothesis

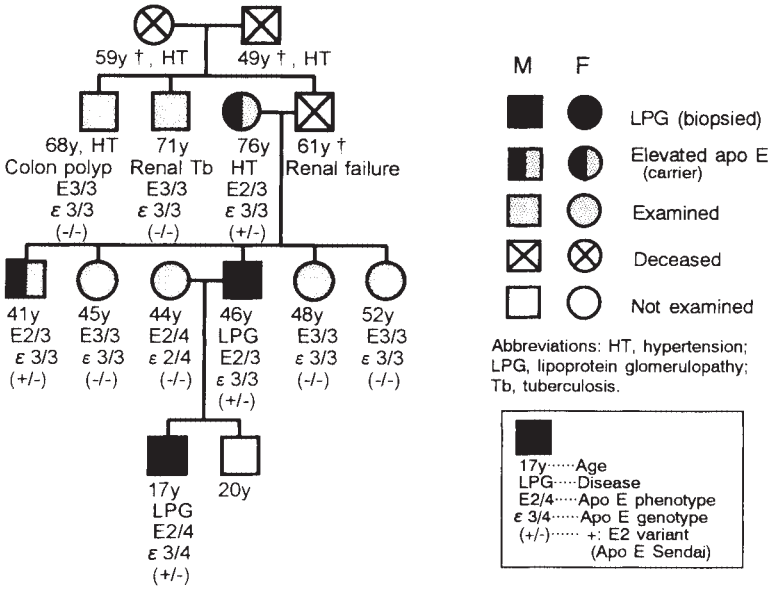

Fig. 7. Familial occurrence of lipoprotein glomerulopathy.

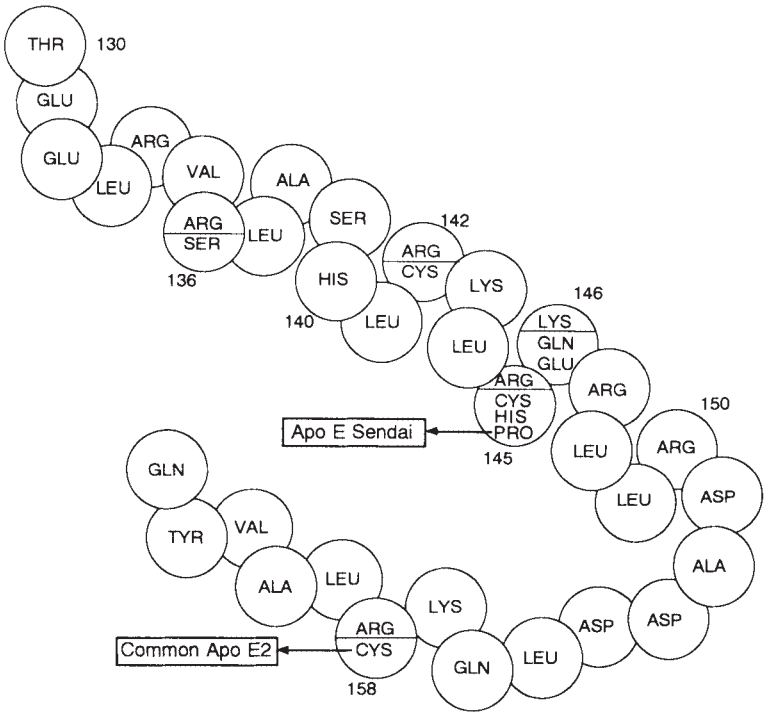

Fig. 8. Receptor-binding region of apolipoprotein E partly modified from the schema by Mahley (1988). Lower amino acids are the substitutions at residue 136, 142, 145, 146 and 158.

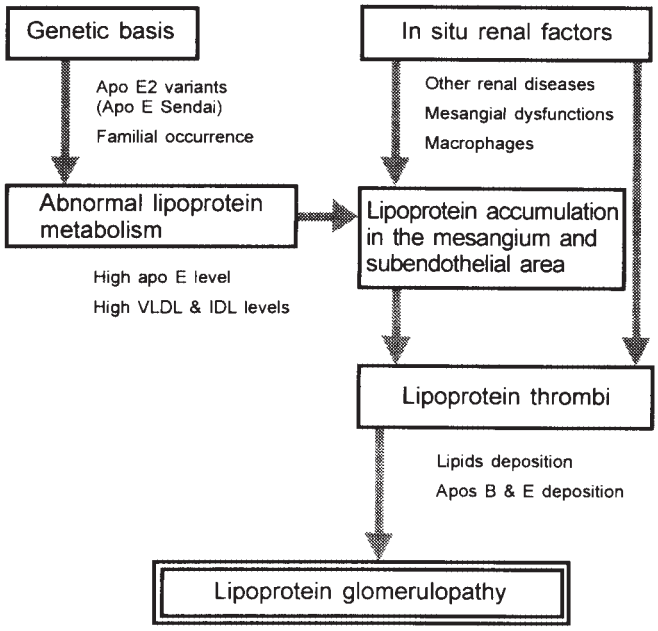

Fig. 9. Proposed mechanisms for the pathogenesis of lipoprotein glomerulopathy.

is supported by the evidence that lipoprotein glomerulopathy recurs in transplanted kidneys (Saito et al. 1993a; Djamali et al. 1996). Meanwhile, carriers who had apo E Sendai and elevated serum apo E without any symptoms were detected in some patients' families (Saito et al. 1996). Accordingly, it is likely that other factors cooperate with apo E Sendai in the development of lipoprotein glomerulopathy (Fig. 9).

Lipoprotein glomerulopathy shows features different from those of other lipid-induced renal diseases (Saito et al. 1995). Histologically, lipoprotein thrombi are essential but foam cells are not seen in the glomerulus (Figs. 4 and 5). Clinically, systemic manifestations characteristic of lipidoses, e.g., corneal arcus, xanthoma and Achilles tendon thickening, are not observed. Liver functions are usually within normal ranges. Hypertension is not accelerated even if recognized. However, other glomerulopathies such as IgA nephropathy, membranous nephropathy and lupus nephritis are associated in several cases, respectively. This evidence suggests that in situ factors in the glomerulus may contribute to lipoprotein glomerulopathy (Saito et al. 1997) (Fig. 9).

Nephropathy associated with type III hyperlipoproteinemia. Although true type III hyperlipoproteinemia has extreme hyperlipidemia and systemic manifestations, the cases associated with nephropathy have been rarely reported (Amatruda et al. 1974; Suzaki et al. 1990; Ellis et al. 1995). In these cases, renal histology shows glomerulosclerosis associated with massive foam cells, which are defined as $CD68^+$ macrophages by immunoperoxidase staining (Ellis et al. 1995) (Fig. 10). Moreover, it is reported that treatment with plasmapheresis or lipid-lowering drugs sometimes ameliorates the renal lesions (Suzaki et al. 1990; Amenomori et al. 1994). These studies suggest that the mechanisms of glomerular

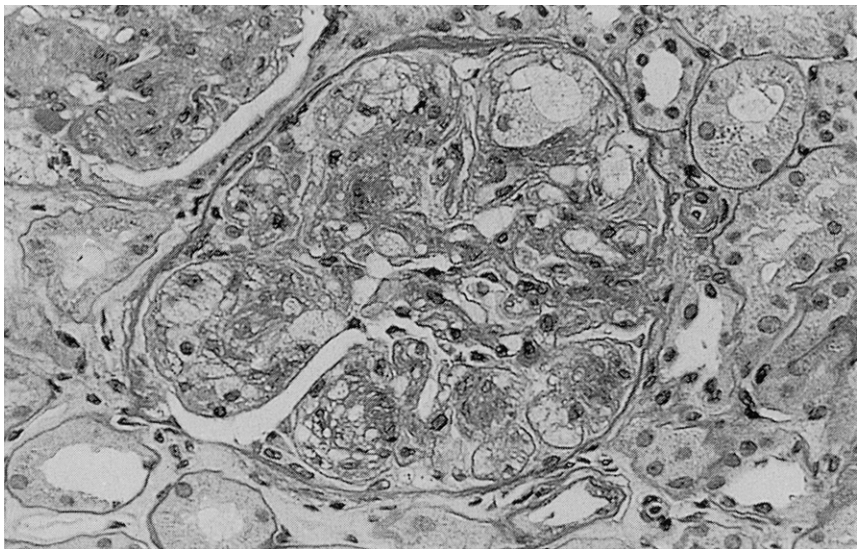

Fig. 10. Light micrograph of the sclerotic glomerulus in type III hyperlipoproteinemia. Foam cells are seen associated with expansion of the mesangial matrices. (PAS stain, ×200)

injuries in type III hyperlipoproteinemia are similar to those of FGS and diabetic glomerulosclerosis, and are analogous to atherosclerosis (Ellis et al. 1995). In type III hyperlipoproteinemia, however, plasma TG level is more markedly elevated than plasma cholesterol level. Accordingly, abnormal TG metabolism may play a key role in such resal lesions of type III hyperlipoproteinemia. As mentioned above, some of our experiments suggest that TG is responsible for aggravation of the glomerular injuries (Obara et al. 1992; Kurihara et al. 1996).

Comparison between type III hyperlipoproteinemia and lipoprotein glomerulopathy. True type III hyperlipoproteinemia is known to have homozygous apo E2/2 which may cause the defective binding to the lipoprotein receptors and delay the metabolic rate of lipoprotein (Mahley 1988). It is of interest that type III hyperlipoproteinemia has clinical features and renal histology different from those of lipoprotein glomerulopathy despite the similarity of lipoprotein profiles (Oikawa et al. 1991; Saito et al. 1995). This may be related in part to the different amino acid substitution between apo E2 (Arg158→Cys) in type III hyperlipoproteinemia and apo E Sendai (Arg145→Pro) in lipoprotein glomerulopathy (Fig. 8). In the apo E Sendai, the substitution of Arg145 to Pro may result in a severe structural change in the middle of α-helix and may alter the three-dimensional conformation of apo E (Oikawa et al. 1997). On the other hand, it is possible that apo E is synthesized in the kidney as well as in the liver and brain because apo E messenger RNA is detected there (Elshourbagy et al. 1985). Therefore, it is predicted that lipoproteins composed of apo E Sendai are generated in the kidney and aggregated in vivo in lipoprotein glomerulopathy. In our recent study on type III hyperlipoproteinemia, however, electron microscopy showed intraglomerular lipoprotein thrombi which are characteristics of

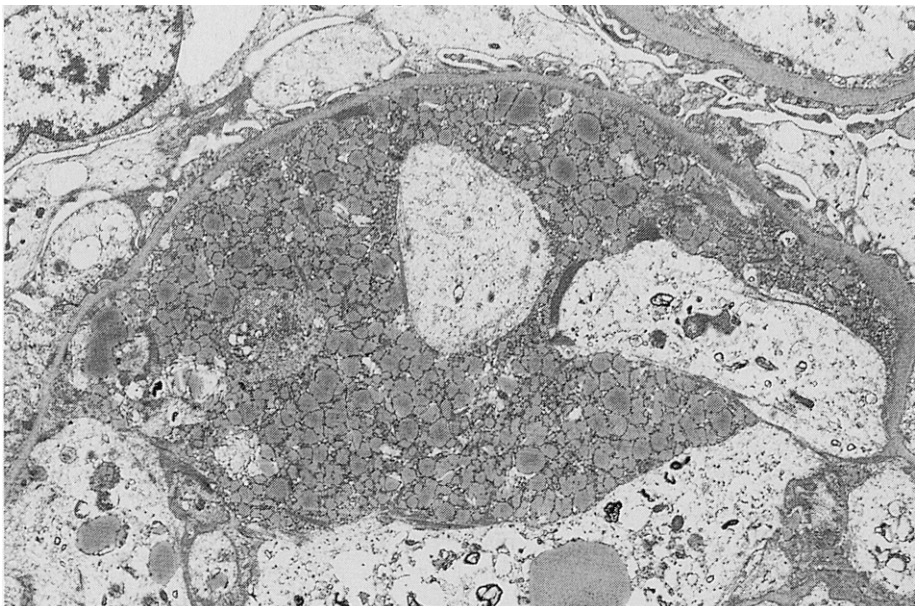

Fig. 11. Electron micrograph of the glomerulus in type III hyperlipoproteinemia. A mass of electron dense granules forms a structure similar to lipoprotein thrombus in lipoprotein glomerulopathy. A biopsy specimen was supplied by Dr. Y. Nakamura, Tokyo Metropolitan Tama Geriatric Center. ($\times$5,000)

lipoprotein glomerulopathy (Fig. 11). This finding suggests that both lipoprotein glomerulopathy and type III hyperlipoproteinemia occasionally have similar abnormalities in the glomerulus.

Conclusion

Recently, the relationship between lipid abnormalities and renal diseases is paid attention world-widely. There is a possibility that hyperlipidemia due to nephrotic syndrome and chronic renal failure induces cerebro-vascular injuries and cardio-vascular diseases. Besides, these secondary lipid abnormalities are

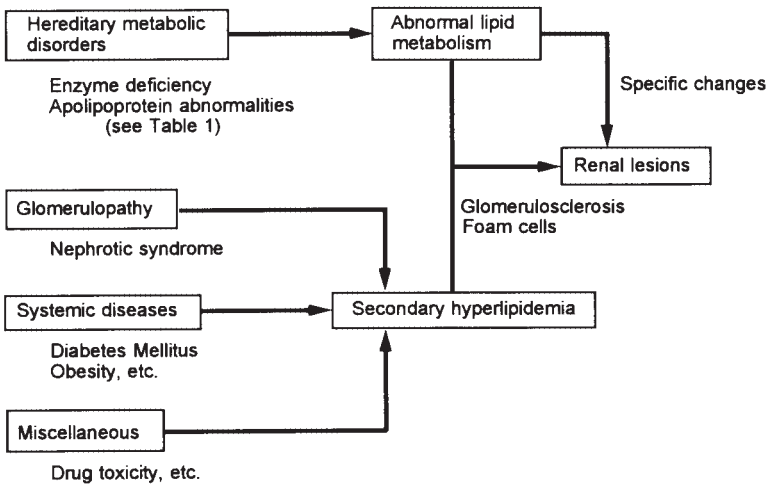

Fig. 12. Relationship between renal diseases and lipid abnormalities.

thought to contribute to the development of renal injuries as well as hereditary metabolic disorders. Thus the lipid metabolism participates in various aspects of the renal diseases (Fig. 12). In the near future, more detailed mechanisms in these conditions will be clarified by excellent studies particularly in the field of molecular biology.

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