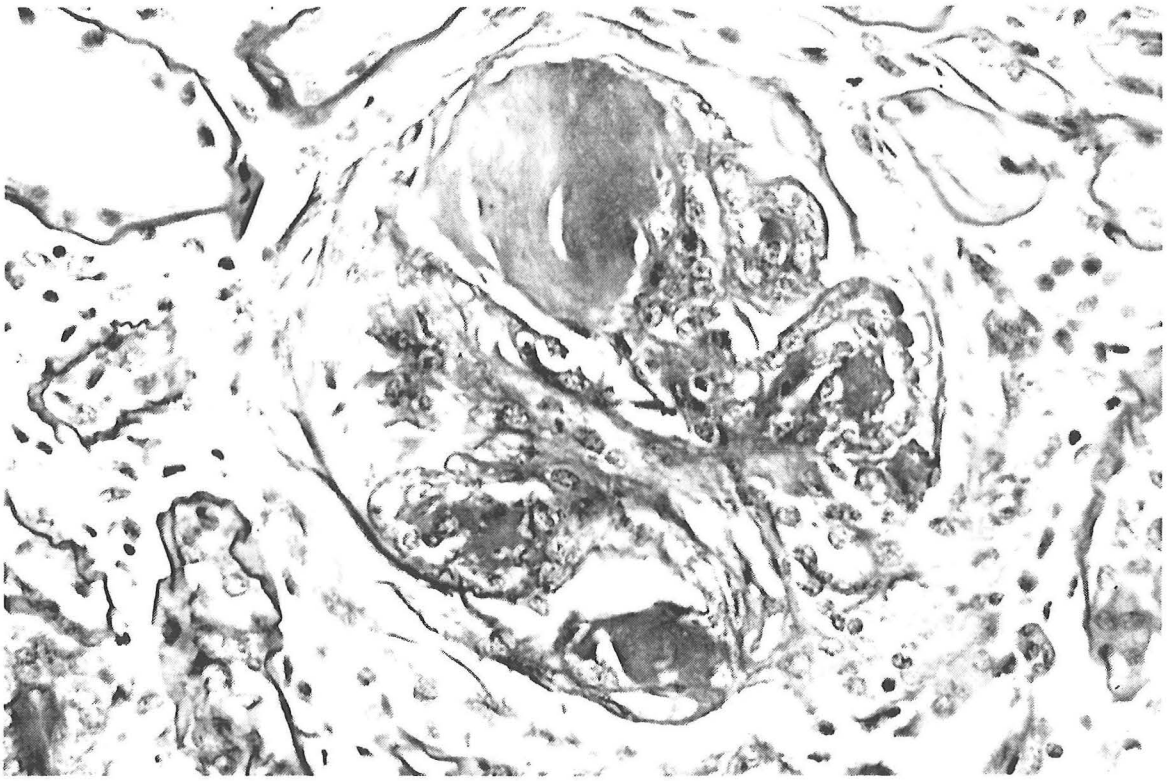
INTERNAL MEDICINE GRAND ROUNDS

May 3, 2001

Role of Lipids and Lipotoxicity in Diabetic Renal Disease

Moshe Levi, M.D.



Disclosure: This is to acknowledge that Moshe Levi, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Levi will be discussing "off-label" uses in his presentation

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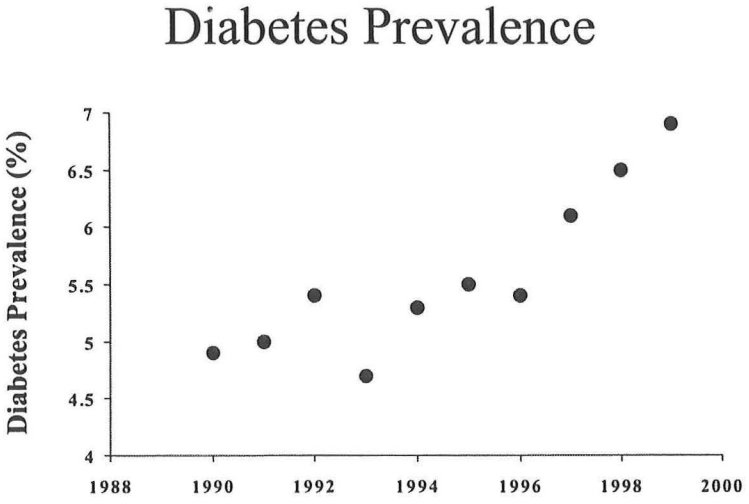
His research interests include 1) the role of lipids and lipid rafts in regulation of renal phosphate transport, 2) the role of lipids in regulation of diabetic and age-related renal disease, 3) application of near infrared spectroscopy for early diagnosis of peripheral vascular disease, 4) application of multi-photon microscopy for the study of lipid and protein dynamics.

Dr. Levi's research is funded by grants from the Department of Veterans Affairs, NIH, JDF and AHA Texas.

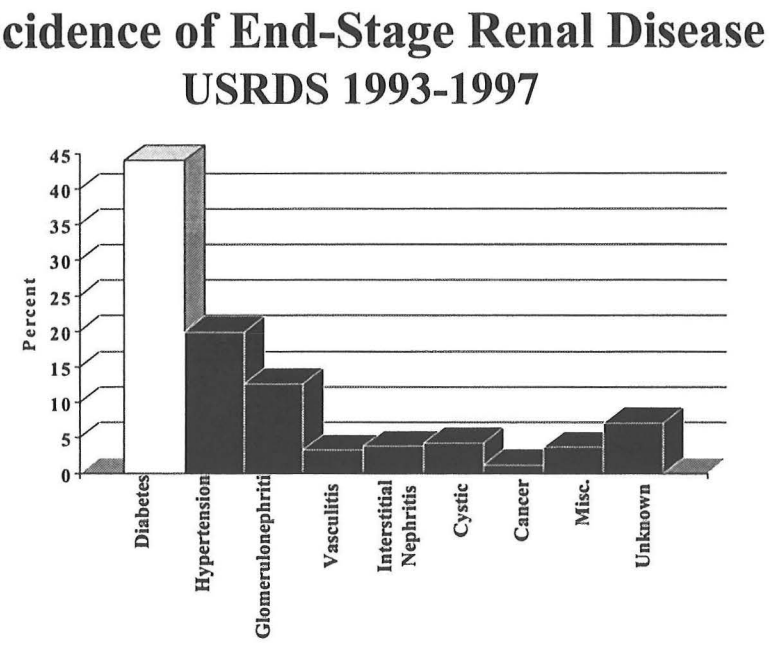
Introduction



Diabetes mellitus has become the leading cause of cardiovascular and renal disease in this country. This is especially worrisome since the prevalence of diabetes is increasing in this country mainly due to increasing incidence of obesity and the closely associated metabolic syndrome.

According to recent USRDS data diabetes accounts for over 50% of the 80,000 new patients who develop end stage renal disease each year (National Institute of Diabetes and Digestive and Kidney Diseases, USRDS Annual Data Report 1998). Hypertension, which is quite common in diabetic patients, is the primary cause of renal disease in the other 25% of the patients who develop end stage renal disease. Diabetes and hypertension, therefore, account for more than 75% of the patients with ESRDS who require dialysis or transplantation for the maintenance of life.

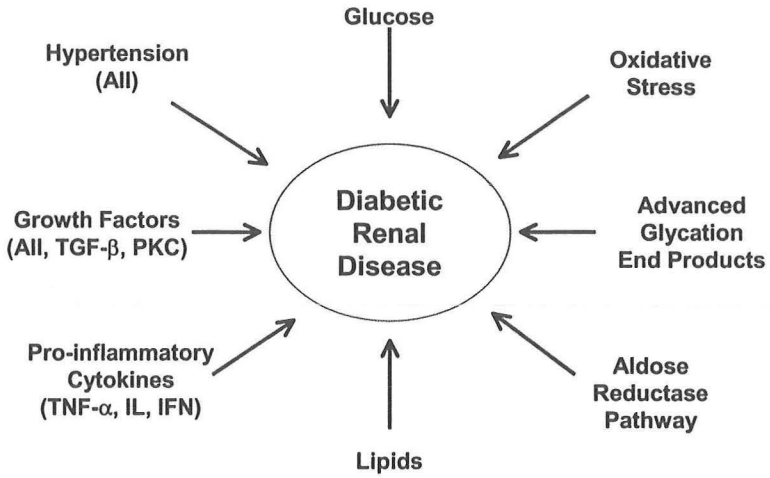
Diabetic patients do poorly on dialysis, with high rates of morbidity and mortality (greater than 25% annual mortality rate) due to cardiovascular disease (in excess of 50%), infection, and vascular access failure. Of all the long-term complications of diabetes, renal disease (diabetic nephropathy) imposes the highest costs, both in dollars and in terms of human suffering. Measures to identify the pathogenesis of diabetic renal and cardiovascular disease and interventions to prevent or at least slow down the progression of renal and cardiovascular disease are greatly needed.



Mediators of diabetic renal disease

Studies in recent years have identified a number of factors that play a role in the pathogenesis of diabetic renal disease or nephropathy: **a)** Enhanced intrarenal angiotensin II activity, resulting in glomerular hypertension, hyperfiltration, hypertrophy as well as regulation of plasminogen activator inhibitor-1 (PAI-1) and matrix proteins [1-5]. **b)** Activation of intrarenal pro-inflammatory cytokines, including tumor necrosis factor alpha (TNFα) and interleukins (IL-1 and IL-6), that regulate cell growth, matrix proteins and possibly lipid metabolism [6-12]. **c)** Increased activity of growth factors, including transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), that regulates cell

growth and matrix proteins [13-29]. **d)** Increased diacylglycerol (DAG) and protein kinase C (PKC) activity [30-35], as well as increased MAP kinase activity [36-39]. **e)** Activation of pathways for glucose metabolism, including the aldose reductase-dependent polyol pathway (increased sorbitol), pentose phosphate shunt (increased UDP-glucose), and altered glycosphingolipid metabolism (increased ceramide and glucosylceramide) [40-44]. **f)** Non-enzymatic glycation of circulating or matrix proteins, including Amadori-modified glucose adducts and advanced glycosylation end products (AGEs) [45-57]. **g)** Increased levels of reactive oxygen species, resulting in oxidative stress and in oxidation of proteins and lipids [58-61]. **h)** Increased deposition and/or accumulation of lipids.



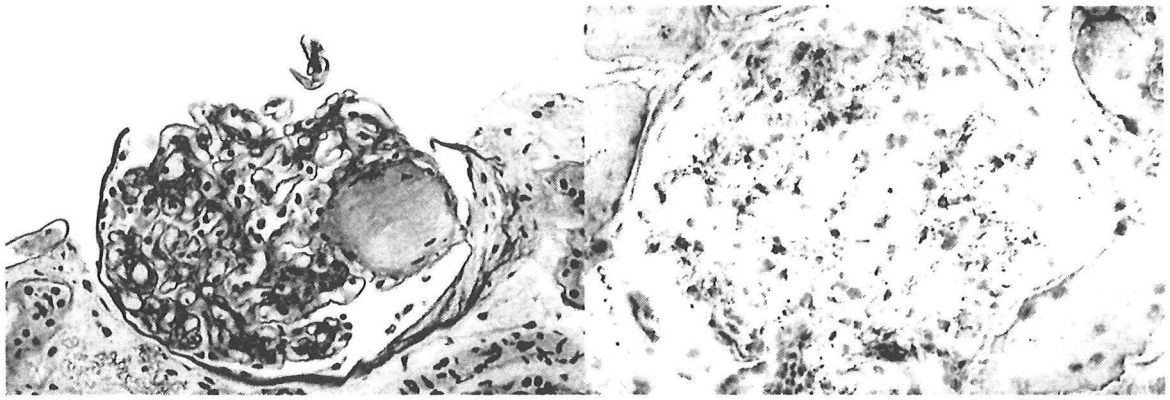
Historically, the association between lipids and renal disease was first suggested by Virchow in his lecture in 1858 titled "a more precise account of fatty metamorphosis" when he described successive stages of fatty metamorphosis and fatty detritus in the renal epithelium in Bright's disease (62). In 1916 Munk observed similar lipid deposits in the kidneys of young patients with nephritic syndrome and used the term lipoid nephrosis to indicate the association between systemic lipid abnormalities and the pathogenesis of renal disease in patients with nephrotic syndrome (63).

In their classical paper in 1936 describing the pathological sign of nodular sclerosis Kimmelstiel and Wilson also demonstrated the presence of lipid deposits in the kidneys of diabetic patients and they suggested that these lipids play an important role in the pathogenesis of renal disease (64). Newburger and Peters also demonstrated the presence of lipid deposits in 1939 (65) and Wilens and Elans in 1951 suggested that the hyperlipidemia and elevated glomerular pressure were the major mediators of diabetic nephropathy (66).

The two clinical cases that I will present today also illustrate the presence of lipid deposits in the kidneys of patients with type I diabetes and type II diabetes.

The first patient is a 46 year old white male with 17 year history of type I diabetes mellitus, hypertension, increased alcohol and tobacco use, who first experienced gross painless hematuria 8 months prior to presentation. Urology evaluation, including cyctoscopy, IVP and bladder washings, was normal. Renal ultrasound showed 12.7 cm right kidney, 13 cm left kidney, with normal echogenicity and no masses. 24 hr urine showed total protein of 902 mg per 24 hr and creatinine clearance of 60 ml/min. Serologies were negative. Patient had poor glycemic control with hemoglobin A1C of 9.5%. Serum lipids including Triglyceride 103, Cholesterol 190, LDL Cholesterol 82 were normal. HDL Cholesterol was 87.

Renal biopsy showed evidence of diabetic glomerulosclerosis with presence of lipids in the glomerulus as determined by positive oil-red-o staining.

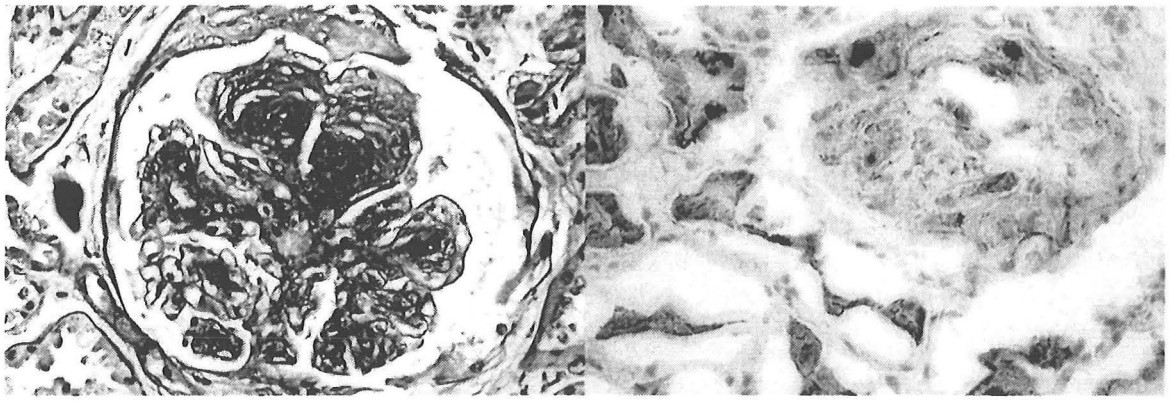


The second patient is a 67-year old Hispanic male with 25 year hx of type II diabetes treated with a sulfonylurea, 1 year hx of hyperlipidemia treated with simvastatin and 1 year hx of hypertension treated with diltiazem, who presented with severe lower extremity edema, dyspnea and was admitted for treatment of new onset volume overload/CHF.

On admission glucose 130, BUN 28, Cr 1.3, Hgb A1C 5.2 %, cholesterol 168, triglyceride 254, HDL 35, LDL 82, VLDL 51, U/A protein greater than 1000.

Further evaluation revealed normal renal ultrasound, urine protein / creatinine ratio of 7.8 and essentially negative serologies.

Renal biopsy showed the classical lesion of diabetic nephropathy with nodular sclerosis and oil-red-o stain showed marked presence of lipid accumulation in the glomeruli and tubulointerstitial cells.



Renal Involvement in Primary Disorders of Lipid and Carbohydrate Metabolism

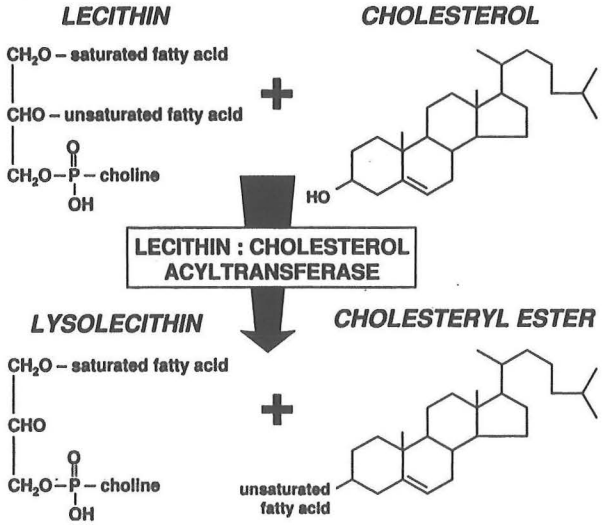
Before I further discuss the role of lipids in diabetic renal disease I will briefly discuss the role of lipids in the pathogenesis of renal disease in inherited disorders of lipid and carbohydrate metabolism, including Lecithin Cholesterol Acyltransferase (LCAT) Deficiency, α-galactosidase deficiency (Fabry's Disease) and type I glycogen storage disease (von Gierke's disease). These diseases will illustrate the potential role of cholesterol, glycosphingolipids and triglycerides in mediating renal disease, as their potential role will also become apparent when I further discuss the role of lipids in diabetic renal disease.

Primary Lipodoses Associated with Glomerulopathy

- Familial Lecithin cholesterol acyltransferase deficiency
- Sphingolipidoses:
  - Fabry disease
  - Gaucher disease
  - Neiman-Pick disease
  - Farber disease
- Glycogen storage disease type I (von Gierke disease)
- Refsum disease
- I-cell disease
- Wolman disease
- Lipoprotein Glomerulopathy
- Type III hyperlipoproteinemia

Lecithin Cholesterol Acyltransferase (LCAT) Deficiency

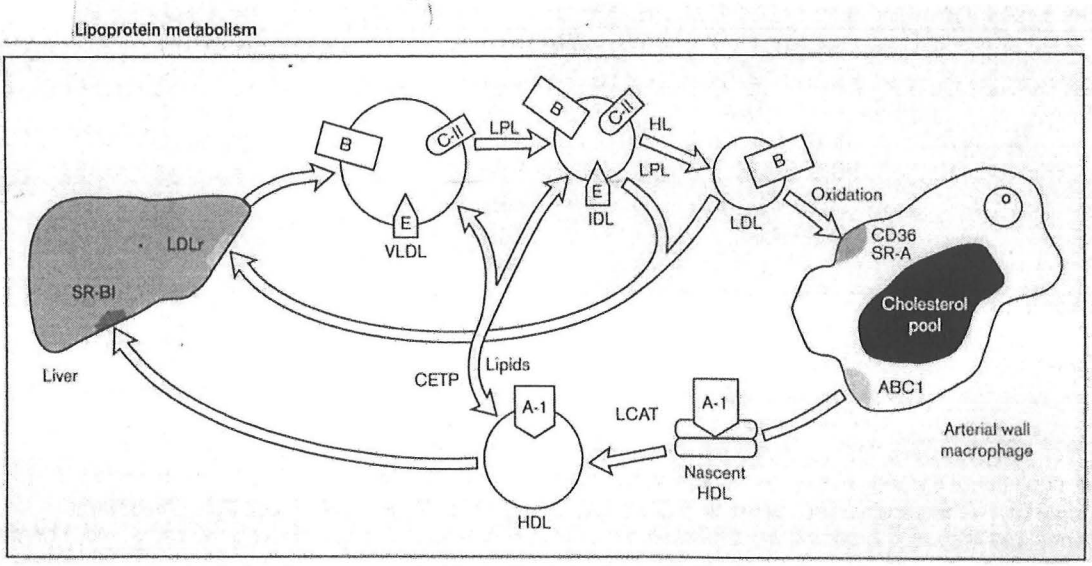
LCAT mediates the esterification of plasma cholesterol by a mechanism that involves the transfer of fatty acids from phosphatidylcholine to free cholesterol, generating cholesteryl esters and lysophosphatidylcholine.



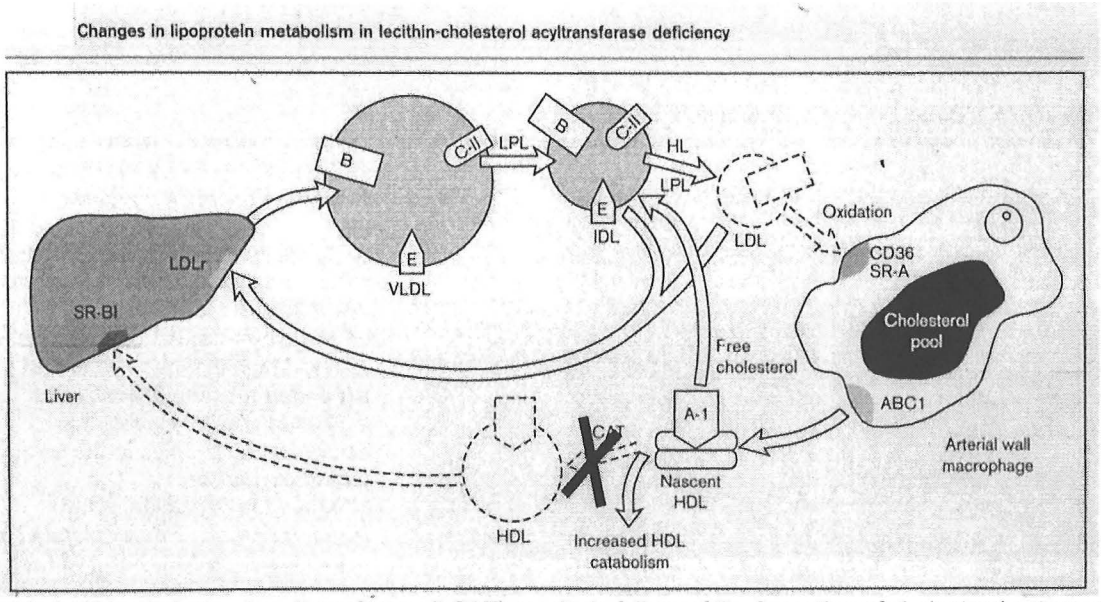
The plasma lecithin cholesterol acyltransferase reaction.

Reprinted from:
S. Santamarina-Fojo, et al, Lecithin cholesterol acyltransferase deficiency and Fish eye disease. In: The Metabolic & Molecular Bases of Inherited Disease, Vol II, 8th ed., Eds: Scriver, Beaudet, Valle, Sly, pp 2817-2833, 2001

LCAT plays an important role in reverse cholesterol transport, a process by which cholesterol from peripheral cells is transferred to the liver for catabolism. Cellular free cholesterol is taken up by high-density lipoprotein where it is esterified by LCAT. The newly generated cholesteryl esters are packaged in the core of the lipoprotein, resulting in the maturation of discoidal pre-β-HDL to spherical α-HDL. The cholesteryl ester may then be exchanged for VLDL-triglycerides by the cholesteryl ester transfer protein (CETP) for transport to the liver. Alternatively, the cholesteryl ester may be taken up directly by the liver or steriodogenic tissues.



The pathway of triglyceride-rich chylomicrons secreted from the intestine with the formation of remnants after triglyceride hydrolysis by LDL, is illustrated. Chylomicron remnants are taken up by the liver primarily by the LDL receptor related protein receptor. Triglyceride-rich VLDL are secreted from the liver and are converted initially to IDL, and finally to LDL. LDL removed from the plasma by the LDL receptor or under-oxidation are taken up by the scavenger receptors scavenger receptor class A or CD36 on the macrophages. Nascent HDL removes excess cholesterol from cells after interaction with ATP-binding cassette transporter-1 (ABC1). The pivotal role of lecithin-cholesterol acyltransferase (LCAT) in the esterification of cholesterol and the maturation of disc-shaped nascent pre-β HDL into spherical α-HDL particle is illustrated. Cholesterol is transported back to the liver directly by HDL or following transfer to the apoB containing lipoproteins by cholesteryl ester transfer protein (CETP). The cholesteryl ester (CE) in HDL is selectively removed by the hepatic scavenger receptor class B type I (SR-BI) receptor. *Reprinted from: S Santamarina-Fojo et al, Curr Op Lipid 11:267-275, 2000.*



The deficiency in lecithin-cholesterol acyltransferase (LCAT) results in failure of the formation of cholesteryl esters and the maturation of the nascent HDL particles. The poorly lapidated HDL particles undergo rapid catabolism resulting in low plasma HDL levels. The apoB containing lipoproteins, which are increased in concentration, also undergo rapid catabolism. In addition, there is decreased conversion of IDL to LDL resulting in low plasma LDL levels in LCAT deficiency. Abnormal multilaminar lipoprotein particles resembling lipoprotein X (LpX) may also be present in VLDL, IDL, and LDL in LCAT deficiency. *Reprinted from: S Santamarina-Fojo et al, Curr Op Lipid 11:267-275, 2000.*

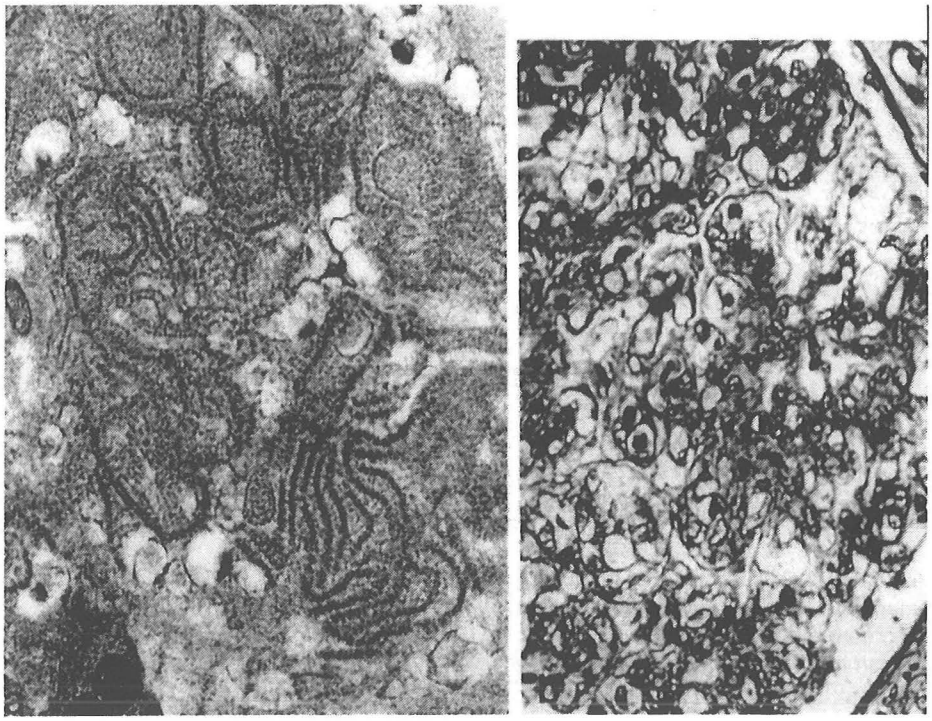
Familial LCAT deficiency is inherited as an autosomal recessive trait and is associated with increases in plasma free cholesterol, triglyceride and phospholipid levels, decreases in cholesteryl esters and lysophosphatidylcholine and undetectable HDL level. An abnormal lipoprotein, lipoprotein-X is also present.

Plasma Lipid Profile, LCAT Activity, and LCAT Concentration in Patients with FLD and FED

	FLD	FED	Controls
TC (mg/dl)	172 (89-185)	215 (185-253)	163 ± 24
TG (mg/dl)	723 (110-723)	149 (60-408)	65 ± 18
HDL-C (mg/dl	8 (0-12)	8 (0-7)	65 ± 17
Apo A-1 (mg/dl)	39 (36-48)	42 (29-45)	145 ± 24
Apo A-II (mg/dl)	6 (4-8)	12 (10-15)	34 ± 6
CE/TC	6 (6-49)	46 (57-65)	69 ± 2
LCAT activity (nmol/ml/h)	1.5 (0)	0.9 (0-14)	99 ± 5
CER (nmol/ml/h)	0 (0-16)	51 (25-74)	59 ± 11
LCAT concentration (μg/ml)	0.2 (0-0.3)	4.0 (0-4)	5.2 ± 0.7
Reference	(173, 168)	(185, 188)	(188)

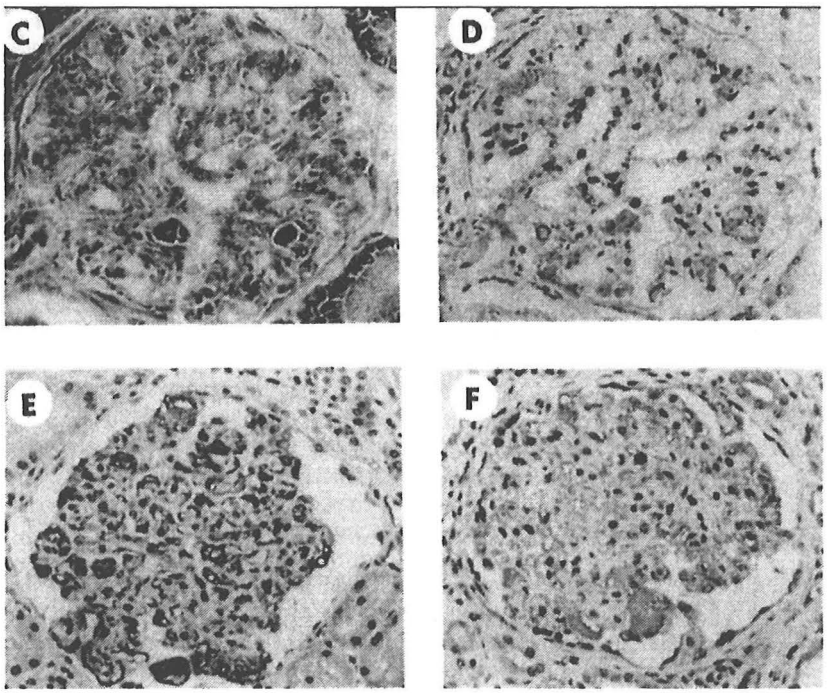
TC = total cholesterol; TG = triglycerides; CE/TC = cholesteryl ester/total cholesterol; LCAT = lecithin cholesteryl acyltransferase; CER = cholesteryl esterification rate. FLD and FED data for individual patients are shown (range in parenthesis). Control data (n = 7) are expressed as mean ± SEM. *Reprinted from SS Fojo et al, Lecithin Cholesterol Acyltransferase Deficiency and Fish Eye Disease, In: The Metabolic & Molecular Bases of Inherited Disease, 8th ed, Volume II, eds: CR Scriver, AL Beaudet, WS Sly, D Valle, The McGraw Hill Co Inc, pp 2817-2833, 2001.*

These patients usually develop corneal opacities, anemia and proteinuria with renal dysfunction. Renal disease is the major cause of morbidity and mortality in these patients. Renal symptoms begin as proteinuria and microscopic hematuria and sometimes progress to end stage renal disease after a prolonged cause. Histologically there is accumulation of foam cells in the glomeruli, as well as collections of dark irregular particles that may be abnormal lipids in the subendothelial spaces and mesangium. There is progressive expansion of the mesangium with accumulation of matrix and eventual sclerosis of glomeruli (67-77).



Lecithin-cholesterol acyltransferase deficiency. **a:** Electron micrograph illustrating an additional feature of the glomerular deposits of complex lipids. Note the serpiginous pattern of the lamellar structures. (Original magnification, X38,000.)
b: Histologic aspect of a glomerulus in late-stage disease. Note the expanded mesangial areas and thickened capillary walls, due to accumulation of lipids in the sub-endothelial areas.
(Original magnification, X 640.)
Reprinted from: T Faraggiana et al, Hum Pathol 18:662-679, 1987.

Lipid analysis of isolated glomeruli shows marked increases in free cholesterol and phospholipid levels. A recent study also showed marked elevation in oxidized phosphatidylcholine (oxPC)-modified LDL in the plasma and glomeruli of these patients, which may play an important role in the mediation of the renal disease (78).

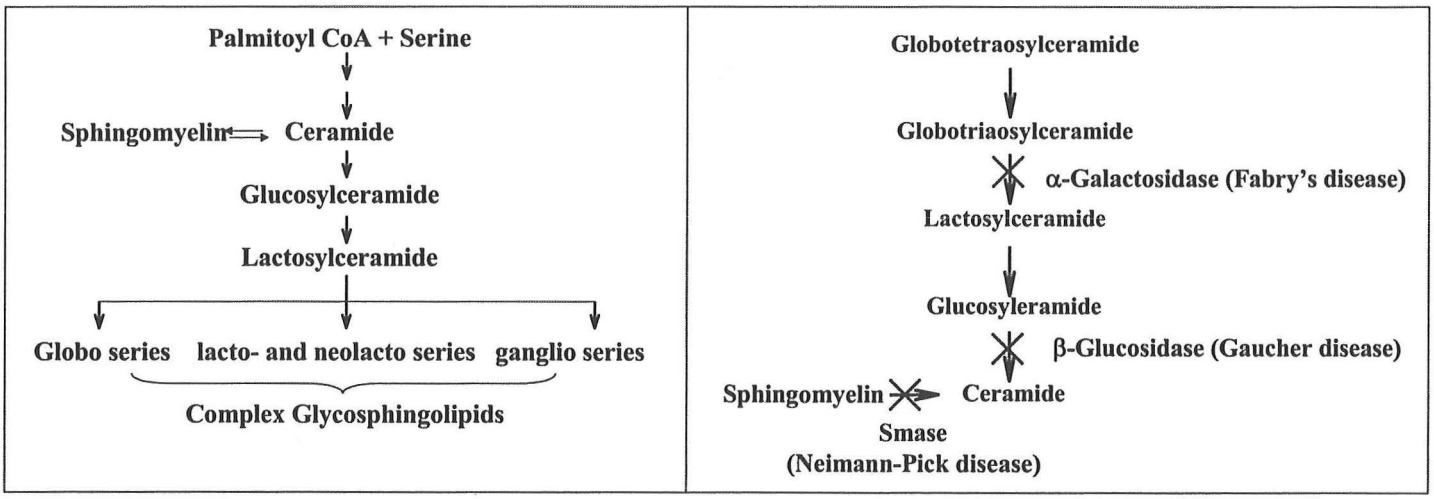


Characteristics of accumulated materials in glomeruli in a patient with LCAT deficiency. Acid-hematin-positive materials (phospholipids, C) and DLH3-positive materials (oxPC, D) are diffusely deposited in the mesangium with a fluffy appearance and show a similar distribution pattern. Apo B(E) and E (F) are greatly accumulated in expanded loops and along the subendothelium in the glomerulus; however, the expanded mesangium is only weakly positive for both. (Magnification X 140). *Reprinted from: S Jimi et al, Arterioscler Thromb Vasc Biol 19:794-801, 1999.*

α-Galactosidase A Deficiency (Fabry Disease)

Fabry disease is an X-linked recessive inborn error of glycosphingolipid catabolism resulting from deficient activity of the lysosomal hydrolase α-galactosidase A in tissues and fluids of affected hemizygous males. Most heterozygous females carriers of the gene have an intermediate level of enzymatic activity.

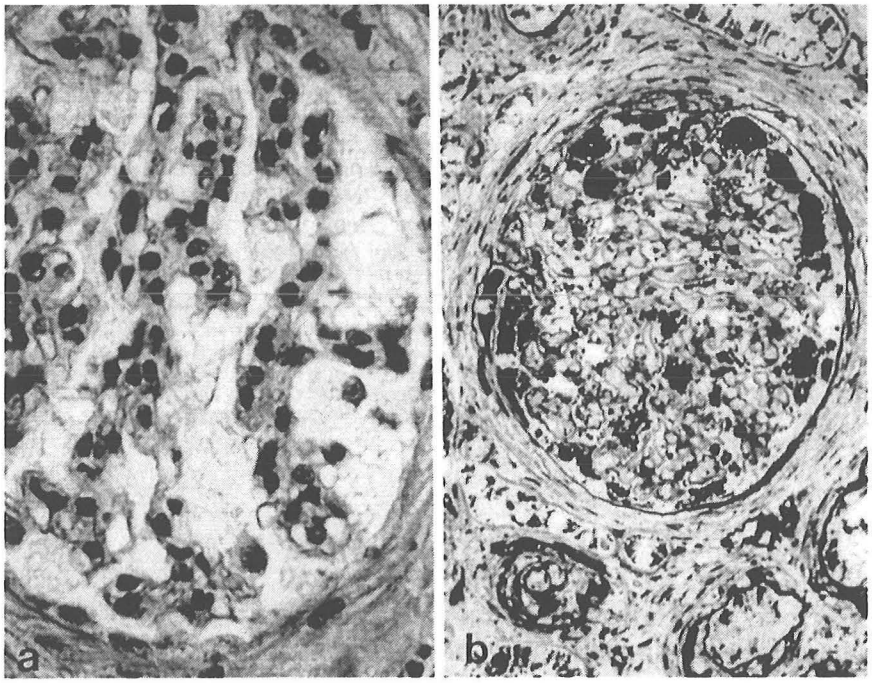
The enzymatic defect leads to the systemic deposition of predominantly globotriaosylceramide and to a lesser extent galabiosylceramide and the blood group B glycosphingolipids.



Almost every tissue is involved in Fabry's disease with predominant involvement of kidneys, eyes, nervous tissue, and endothelial cells throughout the body. Clinically most patients present with parasthesias, pain the extremities and angiokeratomas.

The kidney is the major target organ in Fabry disease. Progressive accumulation of glycosphingolipids in the kidney is associated with proteinuria and a progressive decline in renal function, resulting in end stage renal disease usually in the third to fifth decades of life. Glomeruli show severe ballooning of the podocytes

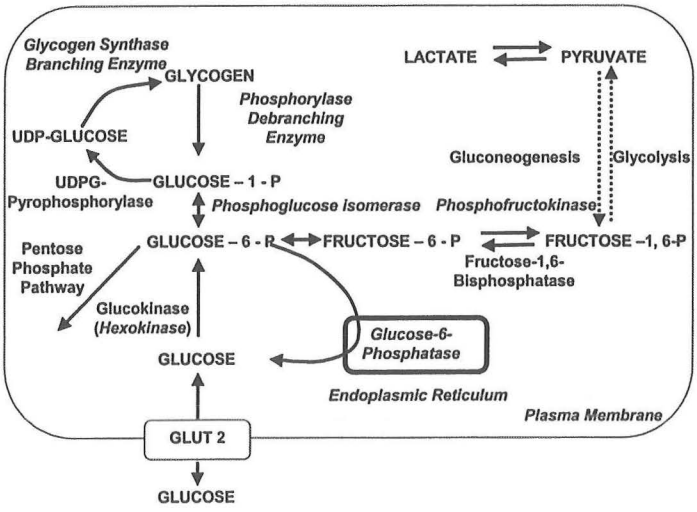
and the glycosphingolipid accumulates in the podocytes, mesangial cells and endothelial cells. The tubules are also affected, the distal tubules usually more severely affected than the proximal tubules. Lipid-laden distal tubular epithelial cells desquamate and may be seen in the urinary sediment. There is also marked involvement of the renal vasculature with severe vacuolization of the endothelial and vascular smooth muscle cells and severe luminal narrowing (79-94).



Fabry disease, a: The glomerulus shows considerable vacuolization of podocytes. The appearance is common to several lipidoses and therefore is not pathognomonic. The stored lipids have been extracted during processing, leaving clear, empty vacuoles. (Formalin fixation, paraffin embedding, periodic acid-Shiff stain. Original magnification, X640.) b: Histologic appearance of the kidney after osmium fixation. A glomerulus similar to the one seen in figure 1a shows strongly stained vacuoles in podocytes. Note periodic acid-Schiff-positive droplets also in arterioles, tubules, and interstitial cells. With this type of fixation, paraffin embedding would give similar results due to the insolubility of lipids after osmium fix ation. (Formalin fixation, osmium post-fixation, methacrylate embedding, periodic acid-Schiff stain. Original magnification, X400.) *Reprinted from: T Faraggiana et al, Hum Pathol 18:662-679, 1987.*

Type Ia glycogen storage disease: von Gierke disease

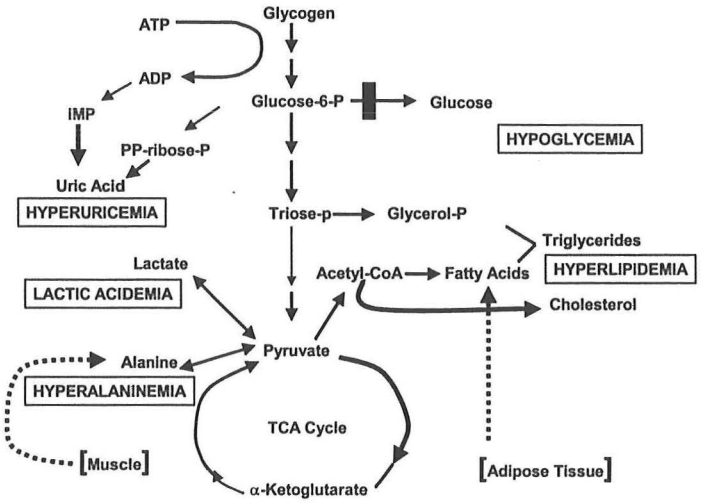
Type Ia glycogen storage disease is an autosomal recessive disorder caused by a deficiency of glucose-6-phosphatase activity in the liver, kidney and intestinal mucosa with extensive accumulation of glycogen in these organs. The clinical manifestations are growth retardation, hepatomegaly, hypoglycemia, lactic acidosis, hyperuricemia and hyperlipidemia.



Major pathways of synthesis and breakdown of glycogen in liver. The broken line indicates that severalenzymes have been omitted between pyruvate and fructose-1,6-P2.

GLUT = glucose transport protein;
UDP = uridine diphosphate;
UDPG = uridine diphosphate-glucose.

Reprinted from Glycogen Storage Diseases, YT Chen, In: The Metabolic & Molecular Bases of Inherited Disease. Eds: Scriver, Beaudet, Valle, Sly, 8th Ed., Vol I., pp 1521-1551, 2001



Metabolic consequences of the type I glycogen storage d

Acetyl-CoA = acetyl coenzyme A;
IMP = inosine-5'-monophosphate;
TCA = tricarboxylic acid.

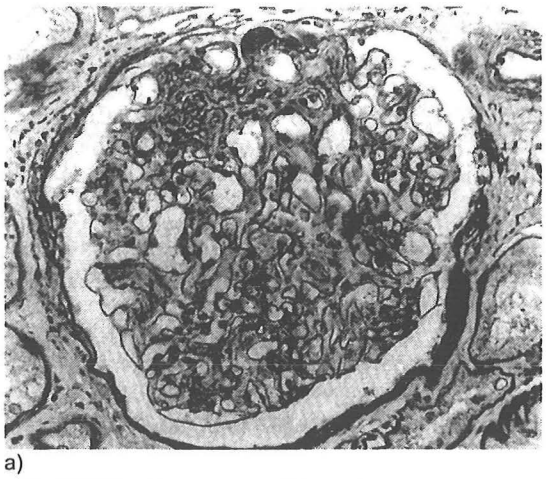
Reprinted from Glycogen Storage Diseases, YT Chen, In: The Metabolic & Molecular Bases of Inherited Disease. Eds: Scriver, Beaudet, Valle, Sly, 8th Ed., Vol I., pp 1521-1551, 2001

The kidney is one of the main targets in this disease. The characteristic renal lesions include focal glomerular sclerosis, interstitial fibrosis, tubular atrophy or vacuolization and prominent arteriosclerosis. In addition, there is marked glomerular hypertrophy with numerous lipid deposits in the glomerular mesangium, tubular epithelial cells and interstitium. The lipid deposits may be caused by hypertriglyceridemia, which results from suppression of glyconeogenesis based on the deficiency of glucose 6-phosphatase (95-99).

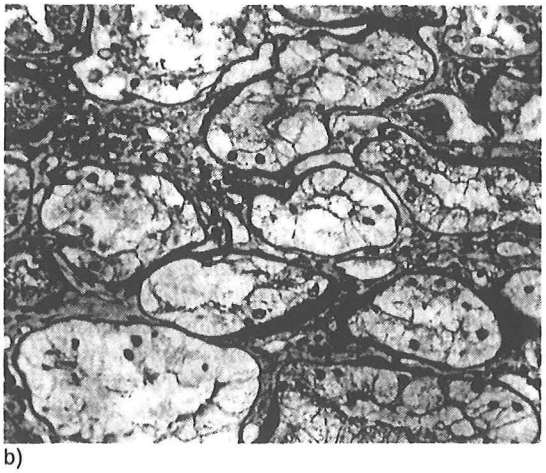
Clinical Data at Renal Biopsy

	Patient 1	Patient 2
Age (years)	37	28
Body height (cm)	156.0	158.0
Body weight (kg)	53.5	53.5
Blood pressure (mmHg)	230/100	132/60
Urinalysis		
Protein (g/day)	3.0	3.1
Glucose	negative	negative
Red cell (/HPF)	0-1	0-1
White cell (/HPF)	0-1	0-1
Hyaline cast (/LPF)	1-2	2-3
Blood urea nitrogen (mg/dl)	55	19
Serum uric acid (mg/dl)	9.3	8.0
Serum creatinine (mg/dl)	2.5	0.8
Creatinine clearance (ml/min)	18	78
Serum total cholesterol (mg/dl)	339	321
Serum triglyceride (mg/dl)	814	1269

Reprinted from K. Obara, et al, Renal histology in two adult patients with type I glycogen storage disease. Clinical Nephrology 39 (2):59-64, 1993.

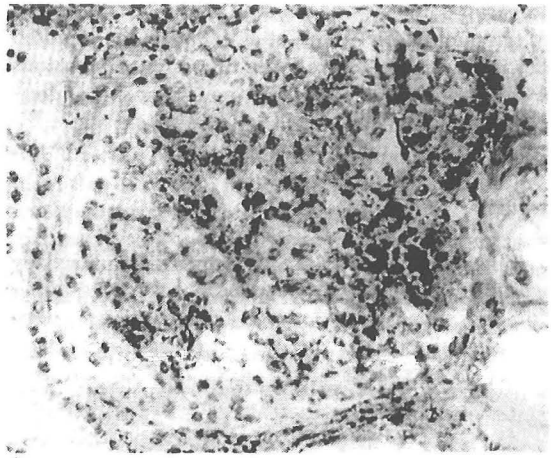


a)

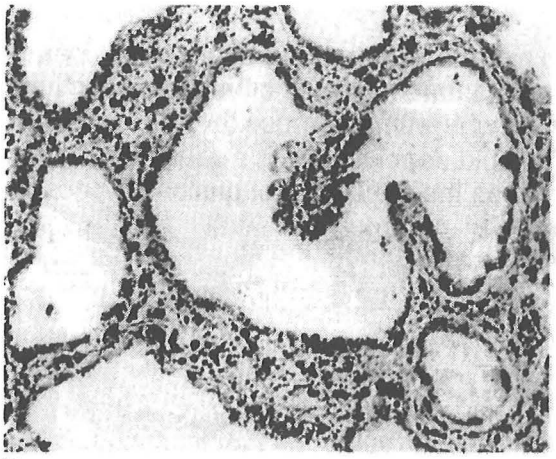


b)

Light micrograph of the kidney from patient 2, showing segmental sclerosis and hyalinosis with mesangial matrix expansion in the glomeruli (a: PAS, original magnification X 220). The tubular epithelial cells are degenerated with clear cytoplasm (b: PAS, X220).



a)



b)

Oil Red O staining of the kidney from patient 1, showing numerous lipid deposits in the glomerular mesangium and sclerotic area (a: original magnification X200), in the tubular epithelial cells, and in the interestitium (b: X200).

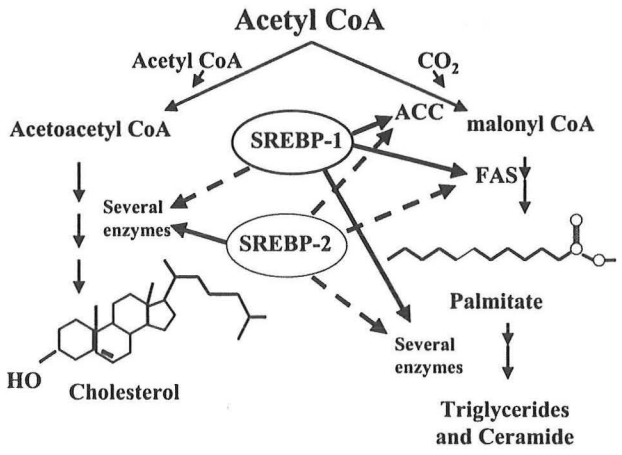
Reprinted from: K Obara et al, Renal histology In two adult patients with type I glycogen storage disease. Clinical Nephrology 39:59-64, 1993.

Role of lipids in diabetic renal disease

Several studies in human subjects and in experimental animals with diabetes have shown a correlation between serum lipids, renal lipids and proteinuria and progressive decline in renal function (100-113). Cell culture studies have shown direct effects of LDL and VLDL in regulation of mesangial cell expression of growth factors, pro-inflammatory cytokines and matrix protein deposition (114-122). In addition, several but not all studies in diabetic patients or animals have shown beneficial effects of low fat diets or diets enriched in unsaturated fats (123-128) as well as pharmacological inhibition of cholesterol and/or triglyceride synthesis (129-137) in decreasing proteinuria and slowing the decline in renal function.

Potential role of SREBPs in regulation of renal lipid metabolism in diabetes

Sterol regulatory element binding proteins (**SREBPs**) belong to the basic-helix-loop-helix-leucine zipper family of transcription factors (138-139). SREBPs regulate the transcription of the LDL receptor and multiple enzymes required for the biosynthesis of cholesterol and fatty acids.



Pathway selective gene activation by SREBI and –2. Thick lines and dotted lines identify proposed major (thick lines) and minor (dasl lines) sites of action for SREBP-1 and SREE respectively. ACC, acetyl-CoA carboxylase. *Reprinted from: TF Osborne, J Biol Chem, 276(42):32379-32382, 2001.*

To date three SREBP isoforms have been identified and characterized, SREBP-1a, SREBP-1b, and SREBP-2. Studies in transgenic mice overexpressing each of the three SREBP isoforms in the liver have indicated that SREP-1a and –1c isoforms play a greater role in fatty acid synthesis compared to cholesterol synthesis, whereas SREBP-2 plays a greater role in cholesterol synthesis compared to fatty acid synthesis (140-142). Indeed in the SREBP-1 knockout mice there is a significant decrease in fatty acid synthesis (143). SREBP-1, or ADD-1/SREBP-1, and SREBP-2 has also been shown to regulate PPAR-γ expression in adipocytes and hepatic cells, indicating multiple mechanisms for SREBPs in regulating lipid metabolism (144).

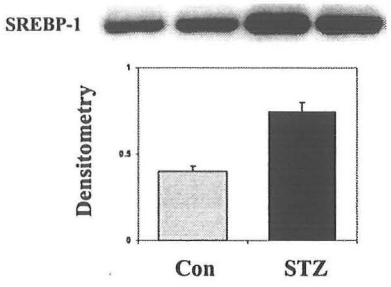
Recent studies indicate that insulin and glucose are important regulators of SREBP-1 activation in the liver. Both insulin and glucose cause increases in SREBP-1 expression in the liver cells by MAPK and protein kinase B/ cAkt dependent signaling pathways (145). In ob/ob mouse and in Zucker Diabetic Fatty rat models of type II diabetes, SREBP-1 and SREBP-2 are upregulated in the liver and the adipocytes (151-152). In contrast, in rats with STZ-induced diabetes, there is an acute and rapid decrease in SREBP-1c mRNA in the liver and administration of insulin normalizes SREBP-1c mRNA level (153).

In contrast to the liver, the regulation of SREBPs in the diabetic kidney has not been studied. Preliminary studies in our laboratory indicate that SREBP-1a, SREBP-1c and SREBP-2 are expressed in the kidney.

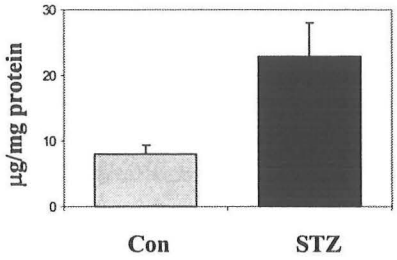
In studies in our laboratory using animal models of type I diabetes, streptozotocin-induced diabetes in the rat and/or mice and in the NOD mice we have found that the glomerulosclerosis and the proteinuria (diabetic nephropathy) are associated with increased lipid accumulation as determined by presence of oil-red-o deposits and increased triglyceride content.

The increase in triglyceride content is associated with increased expression of the transcriptional factor SREBP-1 and increased mRNA of FAS, the enzyme that mediates increased fatty acid synthesis, resulting in increased triglyceride and ceramide accumulation.

SREBP-1 Protein is Increased in STZ Rats

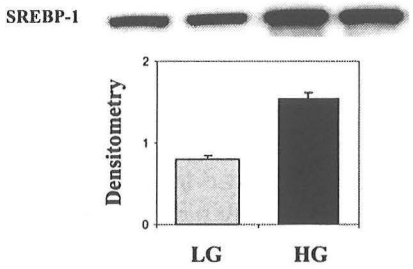


Renal Triglyceride Content is Increased in STZ Rats

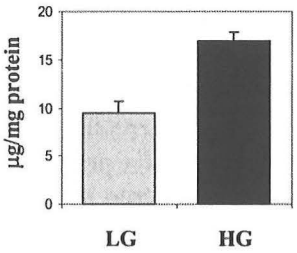


The increase in SREBP-1 seems to be mediated by a direct stimulatory effect of glucose as in proximal tubular cells incubated in the presence of a high glucose medium there is direct stimulation of SREBP-1a and SREBP-1c resulting in increased mRNA for FAS and increased accumulation of triglyceride.

Glucose Induces SREBP-1 Upregulation in MCT Cells



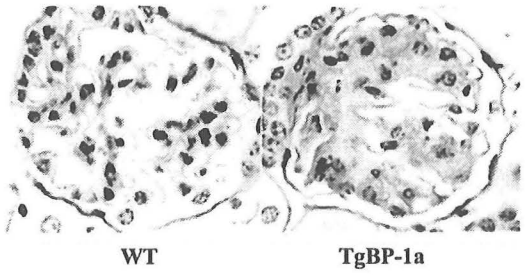
Glucose Causes Increased Triglyceride Accumulation in MCT Cells



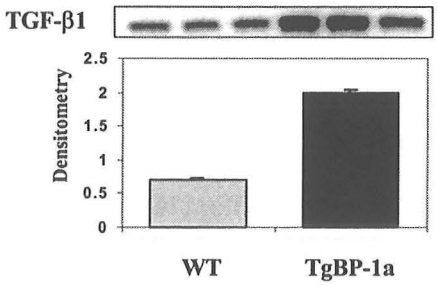
To determine whether increased renal expression of SREBP-1 per se mediate the diabetic nephropathy we have used SREBP-1a transgenic mice and we have found that induction of SREBP-1 gene in the kidney results in increased mRNA of two enzymes that mediate fatty acid synthesis, resulting in increase triglyceride accumulation.

The increased renal expression of SREBP-1a and accumulation of triglycerides also results in glomerulosclerosis and increased expression of the fibrosis inducing growth factor TGF-β and extracellular matrix proteins, well-established cellular markers of diabetic nephropathy.

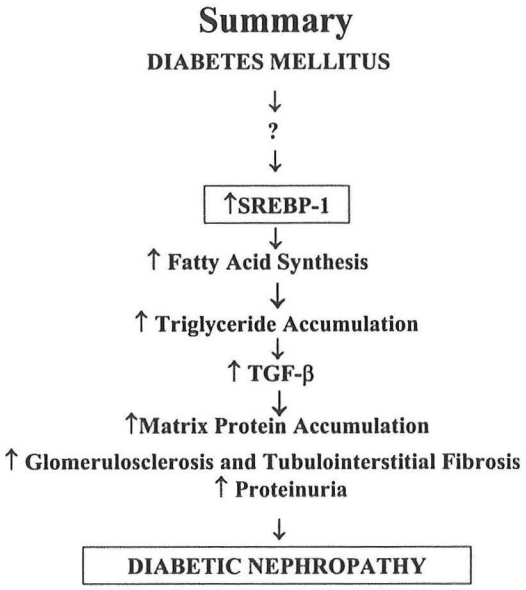
PAS Staining is Increased in SREBP-1a Transgenic mice



TGF-β1 Expression is Increased in SREBP-1a Transgenic Mice



Our preliminary data therefore indicates that alterations in the renal expression of SREBP-1 plays an important role in regulation of renal lipid metabolism and suggest that SREBP-1 plays an important role in diabetic nephropathy.

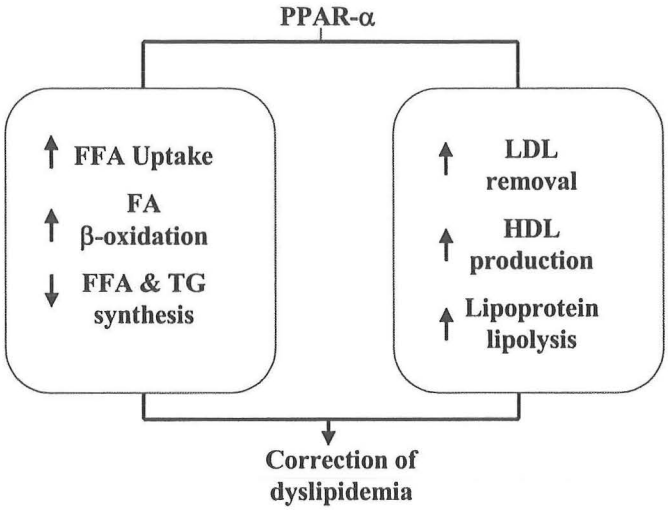


Potential role of PPARs in regulation of renal lipid metabolism in diabetes

Peroxisome proliferator-activated receptors (**PPARs**) are ligand-inducible transcription factors that belong to the nuclear hormone receptor superfamily, together with the receptors for thyroid hormone, retinoids, steroid hormones, and vitamin D. They occur in 3 different isotypes, α, β/δ, and γ that have been described in various species including human and rodents. Each of them has a specific pattern of expression (154-158).

PPAR-α is mostly expressed in brown adipose tissue, liver, kidney, duodenum, heart and skeletal muscle. PPAR-γ expression is mainly found in brown and white adipose tissues, and also the retina, kidney and vascular cells. PPAR-δ is the most ubiquitously expressed isotype and is found in higher amounts than α and γ in almost all tissues examined, except for adipose tissue.

PPARs play a key role in lipid, glucose and energy homeostasis (159-166). **PPAR-α** mediates the hypolipidemic action of fibrates by transcriptional modulation of genes involved in lipid and lipoprotein metabolism. PPAR-α activators also improve glucose homeostasis and influence body weight and energy homeostasis (167-172). These actions of PPAR-α activators on lipid, glucose and energy metabolism are, at least in part, mediated by increased hepatic fatty acid β-oxidation, resulting in enhanced fatty acid flux and degradation in the liver (173-177).



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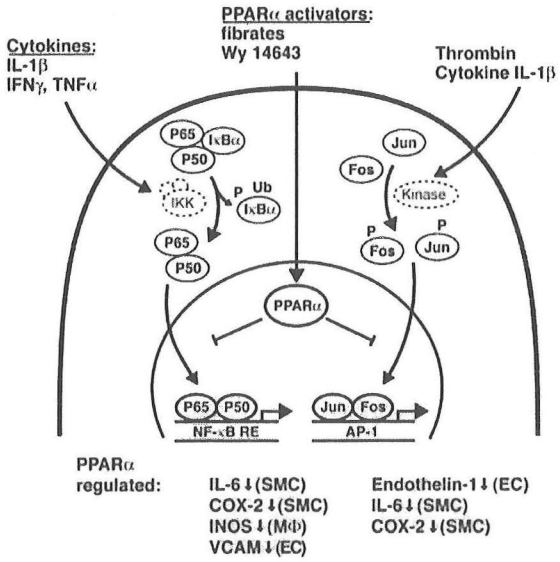
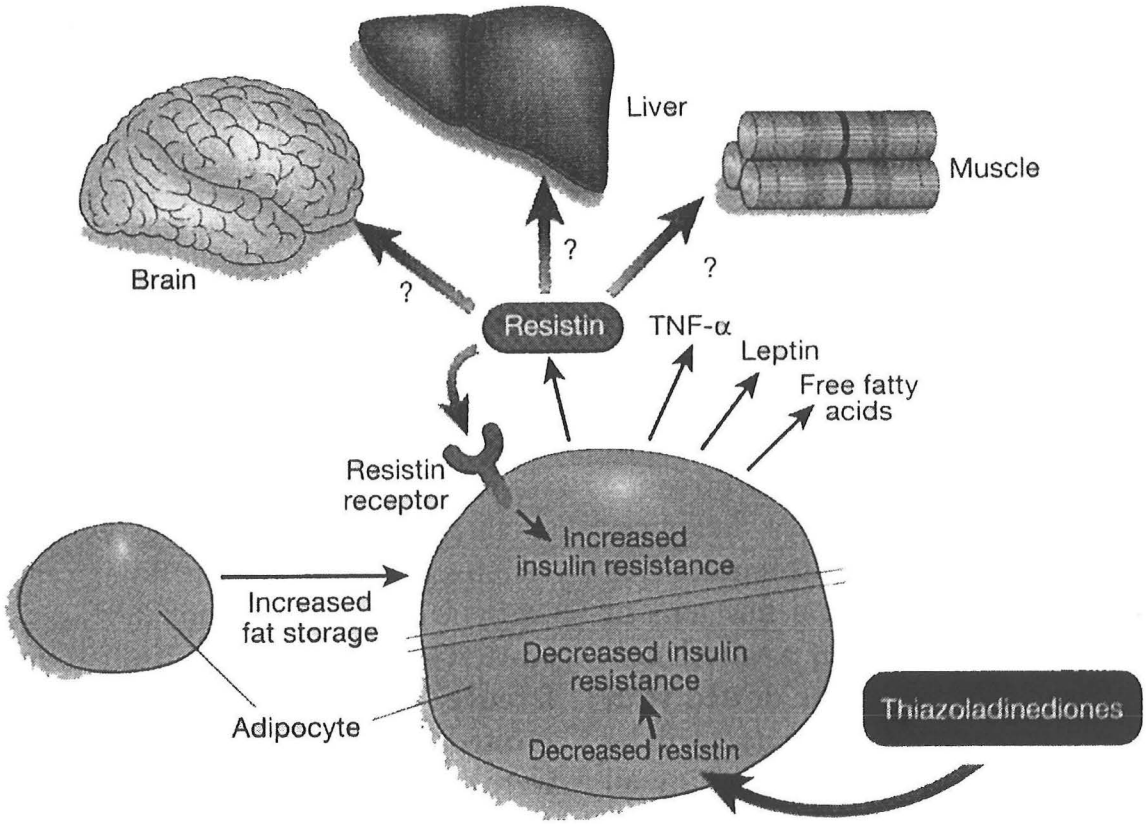


Reprinted from Refs. 160 and 161

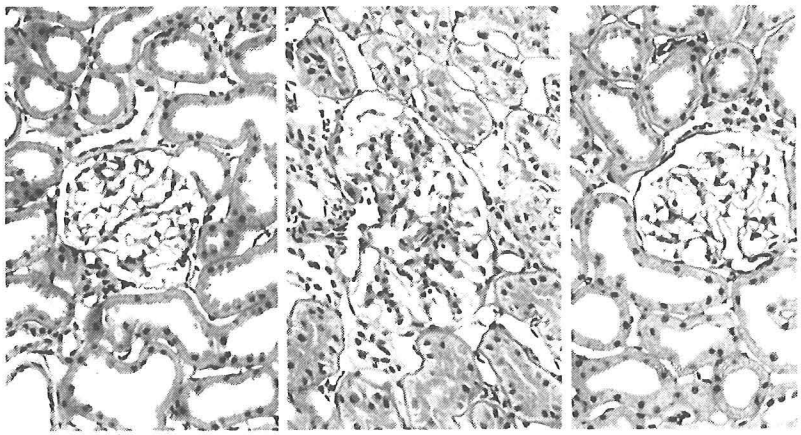
In contrast, **PPAR-γ** triggers cellular differentiation and regulates adipogenesis and insulin action (144-147, 175-176, 178-182). PPAR-γ is the functional receptor for the thiazolidinedione class of insulin-sensitizing drugs (183-184).



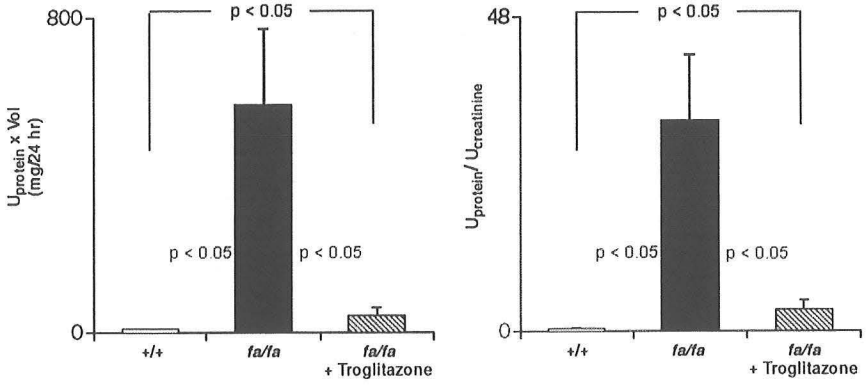
Obesity causes certain tissues in the body (such as muscle and liver) to be less sensitive to insulin. Such insulin resistance is one of the main features of type II diabetes. From left, as fat cells (adipocytes) store more fat molecules and enlarge, they release several products that can modify the body's sensitivity to insulin. Free fatty acids and tumour necrosis factor-α (TNF-α) cause insulin resistance, and leptin, which regulates energy balance, probably causes insulin sensitivity. Steppan et al have identified a new protein, resistin, that is secreted by adipocytes. Resistin causes insulin resistance through its effects on adipocytes and perhaps other tissues. Thiazoladinedione drugs reduce insulin resistance and are used to treat type II diabetes. These drugs suppress the expression of resistin by adipocytes, and their antidiabetes effects may, at least in part, be achieved through this mechanism. *Reprinted from: JS Flier, Nature 409:292-293, 2001.*

Recent studies indicate that PPARs also plays an important role in regulation of cell growth, angiogenesis, inflammation and atherosclerosis. PPAR-α and PPAR-γ agonists have been shown to reduce inflammatory cytokine (TNFα, IL-1 and IL-6) production by inhibiting the activity of pro-inflammatory transcription factors such as AP-1, STAT and NF-κB (185-194).

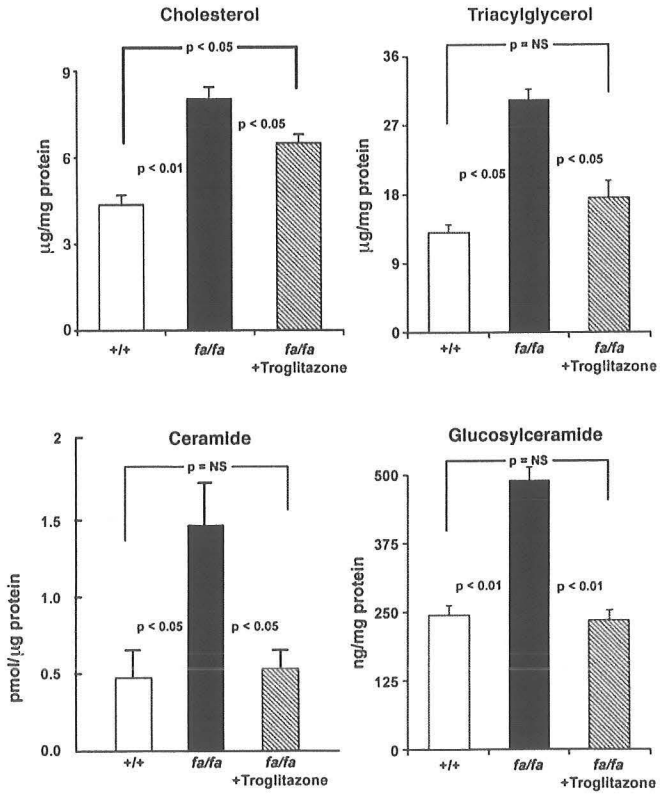
Both PPAR-α and PPAR-γ are expressed in the kidney (195-199). In preliminary studies we have found that PPAR-α and PPAR-γ expression are decreased in a model of type II diabetes in the rat, the Zucker Diabetic Fatty (ZDF) rats, and it correlates with decreased expression of enzymes that mediate fatty acid oxidation and increased expression of enzymes that mediate fatty acid synthesis, resulting in increased triglyceride content in the kidney. Treatment of these animals with a PPAR-γ agonist reverses most of the lipid defects and prevents the development of glomerulosclerosis.



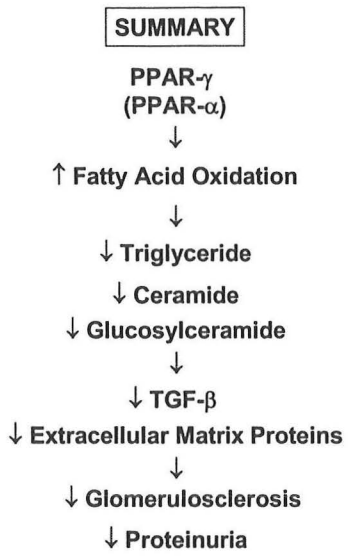
Effect of treatment with Troglitazone on renal pathology as determined by PAS (Periodic Acid Schiff) staining in **a)** control, **b)** ZDF and **c)** ZDF rats treated with Troglitazone. In ZDF rats there is increased PAS staining and evidence of glomerulosclerosis and treatment with Troglitazone prevents the development of glomerulosclerosis.



Effects of treatment with Troglitazone on **a)** 24-hr urinary protein excretion and **b)** Urine protein/Urine creatinine ratio. ZDF rats have significantly higher urinary protein excretion and treatment with Troglitazone markedly reduces the proteinuria.

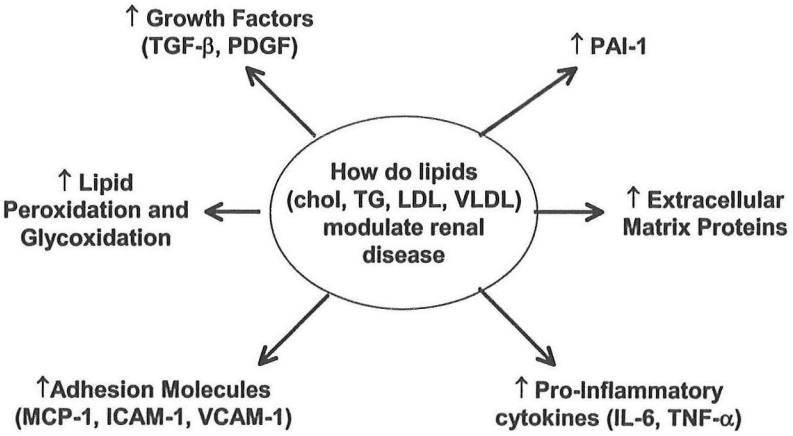


Renal **i)** cholesterol, **ii)** triglyceride, **iii)** ceramide and **iv)** glucosylceramide content in **a)** control (+/+) rats, **b)** ZDF (fa/fa) rats and **c)** ZDF (fa/fa) rats treated with Troglitazone. Renal cholesterol, triglyceride, ceramide and glucosylceramide content are significantly increased in ZDF rats and treatment with Troglitazone causes a marked decrease in the renal content of these lipids.

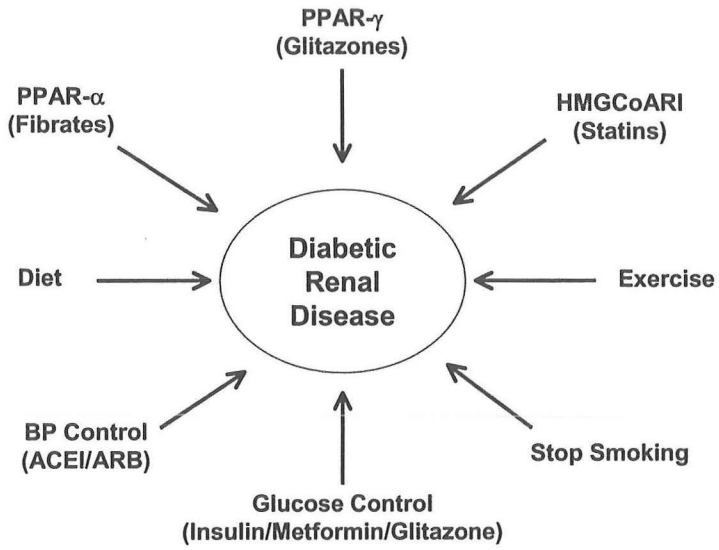


Potential mechanisms of lipid-induced renal disease:

In vivo studies in hypercholesterolemic or hypertriglyceridemic animals and cell culture studies using mesangial cells grown in the presence of LDL or VLDL indicate that lipids have multiple effects in the kidney including **a)** stimulation of TGF-β and PDGF (114-122), **b)** increased transcriptional activation of plasminogen activator inhibitor-1 (PAI-1) (200-206), **c)** increased synthesis and secretion of extracellular matrix proteins including collagen, fibronectin and laminin (114-122), **d)** enhanced secretion of pro-inflammatory cytokines IL-6 and TNF-α (207-218), **e)** increased expression of monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (207-218), and **f)** enhanced lipid peroxidation and glycoxidation (219-233).



Strategies to treat and prevent diabetic renal disease:



Acknowledgements

I thank Teresa Autrey for preparing this protocol; Teresa Autrey, Lijun Sun and the Medical Media Department for the illustrations; and the Library Service for the literature search.

I also thank my many collaborators including Dr. Thomas Rogers for the ongoing pathological examination of the kidney samples, Dr. Roger Unger and Dr. Yang-Tin Zhou for their inspiration and for making ZDF rats and other important reagents available, Dr. Jay Horton, Dr. Iishiro Shimomura, Dr. Michael Brown and Dr. Joseph Goldstein for making the many probes and the SREBP transgenic mice available to us.

Finally, I thank my most valuable research associates including Lijun Sun, Ph.D., Nabil Halaihel, Ph.D., Weiping Zhang, M.D., Hubert Zajicek, M.D. and Paul Wilson, B.S. for performing all the studies mentioned in this Grand Rounds.

REFERENCES

1. Anderson S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockade in type I diabetic patients with diabetic nephropathy. Kidney Int 57:601-606, 2000.
2. Hebert LA, Falkenhain ME, Nahman Jr NS, Cosio FG, O'Dorisio TM. Combination ACE inhibitor and angiotensin II receptor antagonist therapy in diabetic nephropathy, Am J Nephrol 19:1-6, 1999.
3. Kato S, Luyckx VA, Ots M, Lee KW, Ziai F, Troy JL, Brenner BM, MacKenzie HS. Renin-angiotensin blockade lowers MCP-1 expression in diabetic rats. Kidney Int 56:1037-1048, 1999.
4. Kelly DJ, Skinner SL, Gilbert RE, Cox AJ, Cooper ME, Wilkinson-Berka JL. Effects of endothelin or angiotensin II receptor blockade on diabetes in the transgenic (mRen-2)27 rat. Kidney Int 57:1882-1894, 2000.
5. Sharma K, Eltayeb BO, McGowan TA, Dunn SSR, Alzahabi B, Rohde R, Ziyadeh FN, Lewis EJ. Captopril-induced reduction of serum levels of transforming growth factor-β1 correlates with long-term renoprotection in insulin-dependent diabetic patients. Am J Kid Dis 34:818-823, 1999.
6. Amrani A, Verdaguer J, Thiessen S, Bou S, Santamaria P. IL-1α, IL-1β, and IFN-γ mark β cells for Fas-dependent destruction by diabetogenic CD4(+) T lymphocytes. J Clin Invest 105:459-468, 2000.
7. Clausell N, Kalil P, Biolo A, Molossi S, Azevedo M. Increased expression of tumor necrosis factor-α in diabetic macrovasculopathy. Cardiovasc Pathol 8:145-151, 1999.
8. Green EA, Flavell RA. The temporal importance of TNFα expression in the development of diabetes. Immunity 12:459-469, 2000.
9. Nicoletti F, Zaccone P, Conget I, Gomis R, Moller C, Meroni PL, Bendtzen K, Trepicchio W, Sandler S. Early prophylaxis with recombinant human interleukin-11 prevents spontaneous diabetes in NOD mice. Diabetes 48:2333-2339, 1999.
10. Sekine N, Ishikawa T, Okazaki T, Hayashi M, Wollheim CB, Fujita T. Synergistic activation of NF-κb and inducible isoform of nitric oxide synthase induction by interferon-γ and tumor necrosis factor-alpha in INS-1 cells. J Cell Physiol 184:46-57, 2000.
11. Shikano M, Sobajima H, Yoshikawa H, Toba T, Kushimoto H, Katsumata H, Tomita M, Kawashima S. Usefulness of a highly sensitive urinary and serum IL-6 assay in patients with diabetic nephropathy. Nephron 85:81-85, 2000.
12. Sigrist S, Bedoucha M, Boelsterli UA. Down-regulation by troglitazone of hepatic tumor necrosis factor-α and interleukin-6 mRNA expression in a murine model of non-insulin-dependent diabetes. Biochem Pharmacol 60:67-75, 2000.
13. Border WA, Okuda S, Languino LR, Sporn MB, Ruoslahti E. Suppression of experimental glomerulonephritis by antiserum against transforming growth factor β 1. Nature 346:371-374, 1990.
14. Han DC, Isono M, Hoffman BB, Ziyadeh FN. High glucose stimulates proliferation and collagen type I synthesis in renal cortical fibroblasts: mediation by autocrine activation of TGF-β. J Am Soc Nephrol 10: 1891-1899, 1999
15. Han DC, Hoffman BB, Hong SW, Guo J, Ziyadeh FN. Therapy with antisense TGF-β1 oligodeoxynucleotides reduces kidney weight and matrix mRNAs in diabetic mice. Am J Physiol Renal Physiol 278:F628-F634, 2000.
16. Pankewycz OG, Guan J-X, Bolton WK, Gomez A, Benedict JF. Renal TGF-β regulation in spontaneously diabetic NOD mice with correlations in mesangial cells. Kidney Int 46:748-758, 1994.
17. Peters H, Noble NA, Border WA. Transforming growth factor-β in human glomerular injury. Curr Opin Nephrol Hypertension 6:389-393, 1997.
18. Pfeiffer A, Middelberg-Bisping K, Drewes C, Schatz H. Elevated plasma levels of transforming growth factor-β1 in NIDDM. Diabetes Care 19:1113-1117, 1996.
19. Shankland SJ, Scholey JW. Expression of transforming growth factor-β1 during diabetic renal hypertrophy. Kidney Int 46:430-442, 1994.
20. Sharma K, Ziyadeh FN. Renal hypertrophy is associated with upregulation of TGF-β1 gene expression in diabetic BB rat and NOD mouse. Am. J. Physiol 267:F1094-F1101, 1994
21. Sharma K, Ziyadeh FN. Hyperglycemia and diabetic kidney disease: The case for transforming growth factor-β as a key mediator. Diabetes 44:1139-1146, 1995

22. Sharma K, Jin Y, Guo J, Ziyadeh FN. Neutralization of TGF-β by anti TGF-β antibody attenuates kidney hypertrophy and the enhanced extracellular matrix gene expression in STZ-induced diabetic mice. Diabetes 45:522-530, 1996.
23. Sharma K, Ziyadeh FN, Alzahabi B, McGowan TA, Kapoor S, Kurnik RC, Kurnik PB, Weisberg LS. Increased renal production of transforming growth factor-β1 in patients with type II diabetes. Diabetes 46:854-859, 1997.
24. Yamamoto T, Noble NA, Cohen AH, Nast CC, Hishida A, Gold LI, Border WA. Expression of transforming growth factor-β isoforms in human glomerular diseases. Kidney Int 49:461-469, 1996.
25. Yang C-W, Hattori M, Vlassara H, he C-J, Carome MA, Yamamoto E, Elliot S, Striker GE, Striker LJ. Overexpression of transforming growth factor-β1 mRNA is associated with up-regulation of glomerular tenascin and laminin gene expression in nonobese diabetic mice. J Am Soc Nephrol 5:1610-1617, 1995.
26. Ziyadeh FN, Sharma K, Ericksen M, Wof G. Stimulation of collagen gene expression and protein synthesis in murine mesangial cells by high glucose is mediated by autocrine activation of transforming growth factor-β. J Clin Invest 93:536-542, 1994.
27. Ziyadeh FN, Hoffman BB, Chan DC, Iglesias-de la Cruz MC, Hong SW, Isono M, Chen S, McGowan TA, Sharma K. Long-term prevention of renal insufficiency, excess matrix gene expression, and glomerular mesangial matrix expansion by treatment with monoclonal antitransforming growth factor-β antibody in db/db diabetic mice. Proc Natl Acad Sci USA 97:8015-8020, 2000.
28. Abboud HE. Role of platelet-derived growth factor in renal injury. Annu. Rev. Physiol. 57:297-309, 1995.
29. Floege J, Eng E, Young BA, Alpers CE, Barrett TB, Bowen-Pope DF, Johnson RJ. Infusion of platelet-derived growth factor or basic fibroblast growth factor induces selective glomerular mesangial cell proliferation and matrix accumulation in rats. J Clin Invest 92:2952-2962, 1993.
30. DeRubertis FR, Craven PA. Activation of protein kinase C in glomerular cell in diabetes: Mechanisms and potential links to the pathogenesis of diabetic glomerulopathy. Diabetes 43:1-8, 1994.
31. Kang N, Alexander G, Park JK, Maasch C, Buchwalow I, Luft FC, Haller H. Differential expression of protein kinase C isoforms in streptozotocin-induced diabetic rats. Kid Int 56:1737-1750, 1999.
32. Koya D, Jirousek MR, Lin Y-W, Ishii H, Kuboki K, King GL. Characterization of protein kinase C β isoform activation on the gene expression of transforming growth factor-β, extracellular matrix components, and prostanoids in the glomeruli of diabetic rats. J Clin Invest 100:115-126, 1997.
33. Koya D, Haneda M, Nakagawa H, Isshiki K, Sato H, Maeda S, Sugmioto T, Yasuda H, Kashiwagi A, Ways DK, King GL, Kikkawa R. Amelioration of accelerated diabetic mesangial expansion by treatment with a PKCβ inhibitor in diabetic db/db mice, a rodent model for type 2 diabetes. FASEB J 14:439-447, 2000.
34. Weiss RH, Ramirez A. TGF-β- and angiotensin-II-induced mesangial matrix protein secretion is mediated by protein kinase C. Nephrol Dial Transpl 13:2804-2813, 1998
35. Xia P, Inoguchi T, Kern TS, Engerman RL, Oates PJ, King GL. Characterization of the mechanism for the chronic activation of diacylglycerol-protein kinase C pathway in diabetes and hypergalactosemia. Diabetes 43:1122-1129, 1994.
36. Haneda M, Araki S-I, Togawa M, Sugimoto T, Isono M, Kikkawa R. Mitogen-activated protein kinase cascade is activated in glomeruli of diabetic rats under glomerular mesangial cells cultured under high glucose conditions. Diabetes 46:847-853, 1997.
37. Igarashi M, Wakasaki H, Takahara N, Ishii H, Jiang Z-Y, Yamauchi T, Kuboki K, Meier M, Rhodes CJ, King GL. Glucose or diabetes activates p38 mitogen-activated protein kinase via different pathways. J Clin Invest 103:185-195, 1999
38. Ingram AJ, Ly H, Thai K, Kang M-J, Scholey JW. Mesangial cell signaling cascades in response to mechanical strain and glucose. Kid Int 56:1721-1728, 1999
39. Kang MJ, Wu X, Ly H, Thai K, Scholey JW. Effect of glucose on stress-activated protein kinase activity in mesangial cells and diabetic glomeruli. Kidney Int 55:2203-2214, 1999.
40. El-Khatib M, Radin NS, Shayman JA. Glycosphingolipid synthesis and proliferation in renal cell line grown in high glucose. Am J Physiol 270:F476-F484, 1996.
41. Jacobs LS, Kester M. Sphingolipids as mediators of effects of platelet-derived growth factor in vascular smooth muscle cells. Am J Physiol 265:C740-C747, 1993.

42. Merrill Jr AH, Schmelz E-M, Dillehay DL, Speigel S, Shayman JA, Schoreder JJ, Riley RT, Voss KA, Wang E. Sphingolipids – The enigmatic lipid class: Biochemistry, Physiology, and Pathophysiology. Toxicol Appl Pharmacol 142:208-225, 1997.
43. Shayman JA, Deshmukh GD, Mahdiyoun S, Thomas TP, Wu D, Barcelon FS, Radin NS. Modulation of renal epithelial cell growth by glucosylceramide: association with protein kinase C, sphingosine, and diacylglycerol. J Biol Chem 266:22968-22974, 1991.
44. Zador IZ, Deshmukh GD, Kunkel R, Johnson K, Radin NS, Shayman JA. A role for glycosphingolipid accumulation in the renal hypertrophy of streptozotocin-induced diabetes mellitus. J Clin Invest 91:797-803, 1993.
45. Giardino I, Fard AK, Hatchell DL, Brownlee M. Aminoguanidine inhibits reactive oxygen species formation, lipid peroxidation, and oxidant-induced apoptosis. Diabetes 47:1114-1120, 1998.
46. Hammes HP, Brownlee M, Lin J, Schleicher E, Bretzel RG. Diabetic retinopathy risk correlates with intracellular concentrations of the glycoxidation product Nepsilon-(carboxymethyl) lysine independently of glycohaemoglobin concentrations. Diabetologia 42:603-607, 1999.
47. Hammes HP, Alt A, Niwa T, Clausen JT, Bretzel RG, Brownlee M, Schleicher ED. Differential accumulation of advanced glycation end products in the course of diabetic retinopathy. Diabetologia 42:728-736, 1999.
48. Stitt AW, Li YM, Gardiner TA, Bucala R, Archer DB, Vlassara H. Advanced glycation end products (AGEs) co-localize with AGE receptors in the retinal vasculature of diabetic and of AGE-infused rats. Am J Pathol 150:523-531, 1997.
49. Pugliese G, Pricci F, Romeo G, Pugliese F, Mene P, Giannini S, Cresci B, Galli G, Rotella CM, Vlassara H, Di Mario U. Upregulation of mesangial growth factor and extracellular matrix synthesis by advanced glycation end products via a receptor-mediated mechanism. Diabetes 46:1881-1887, 1997.
50. Stitt AW, He C, Vlassara H. Characterization of the advanced glycation end-product receptor complex in human vascular endothelial cells. Biochem Biophys Res Commun 256:549-556, 1999.
51. He C, Sabol J, Mitsuhashi T, Vlassara H. Dietary glycotoxins: inhibition of reactive products by aminoguanidine facilitates renal clearance and reduces tissue sequestration. Diabetes 48:1308-1315, 1999.
52. Osicak TM, Yu Y, Panagiotropoulos S, Clavant SP, Kiriazis Z, Pike RN, Pratt LM, Russo LM, Kemp BE, Comper WD, Jerums G. Prevention of albuminuria by aminoguanidine or ramipril in streptozotocin-induced diabetic rats is associated with the normalization of glomerular protein kinase C. Diabetes 49:87-93, 2000
53. Raj D, Choudhury D, Welbourne TC, Levi M. Advanced glycation end products: A nephrologist's perspective. Am J Kid Dis 35:365-380, 2000.
54. Tsuchida K, Makita Z, Yamagishi S, Atsumi T, Miyoshi H, Obara S, Ishida M, Ishikawa S, Yasumura K, Koike T. Suppression of transforming growth factor β and vascular endothelial growth factor in diabetic nephropathy in rats by a novel advance glycation end product inhibitor, OPB-9195. Diabetologia 42:579-588, 1999
55. Yang C-W, Vlassara H, Striker GE, Striker LJ. Administration of AGEs in vivo induces genes implicated in diabetic glomerulosclerosis. Kidney Int 47:S55-S58, 1995.
56. Ziyadeh FN, Cohen MP, Guo J, Jin Y. RAGE mRNA expression in the diabetic mouse kidney. Mol Cell Biochem F170:147-152, 1997.
57. Ziyadeh FN, Mogyorosi A, Kalluri R. Early and advanced non-enzymatic glycation products in the pathogenesis of diabetic kidney disease. Exp. Nephrol 5:2-9, 1997.
58. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 48:1-9, 1999.
59. Guha M, Bai W, Nadler JL, Natarajan R. Molecular mechanisms of tumor necrosis factor α gene expression in monocytic cells via hyperglycemia-induced oxidant stress-dependent and independent pathways. J Biol Chem 275:17728-17739, 2000.
60. Nishikawa T, Edelstein D, Du XL, Yamagishi S-I, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes H-P, Giardino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 404:787-790, 2000
61. Scivittaro V, Ganz MB, Weiss MF. AGEs induce oxidative stress and activate protein kinase C-β_{II} in neonatal mesangial cells. Am J Physiol Renal Physiol 278:F676-F683, 2000.

62. Virchow R. A more precise account of fatty metamorphosis. In cellular pathology, as based upon physiological and pathological histology, 2nd ed. pp 383-408. RM Dewittt, NY. 1860
63. Munk F. Berichte Uber Krankheitsfalle, Behand lungs Verfahren. Med Klin 12: 1019-1076, 1916
64. Kimmelstiel P, Wilson C: Intercapillary lesions in the glomeruli of the kidney. Am J Pathol 12:83-98, 1936
65. Newburger RA, Peters JP: Intercapillary glomerulosclerosis: A syndrome of diabetes, hypertension and albuminuria. Arch Int Med 64:1252-1264, 1939.
66. Wilens SL, Elster SK: The role of lipid deposition in renal arteriolar sclerosis. Am J Med Sci 219:183-196,1951.
67. Borysiewicz LK, Soutar AK, Evans DJ, Thompson GR, Rees AJ: Renal failure in familial lecithin: cholesterol acyltransferase deficiency. Qtr J Med New Series LI (204): 411-426, 1982
68. Chevet D, Ramee MP, Pogamp PL, Thomas R, Garre M, Alcindor LG: Hereditary lecithin cholesterol acyltransferase deficiency. Nephron 20:212-219, 1978
69. Frohlich J, Godolphin WJ, Reeve CE, Evelyn KA: Familial LCAT deficiency: Report of two patients from a Canadian family of Italian and Swedish descent. Scand J Clin Lab Invest 38 (Suppl 150): 156-161, 1978.
70. Gjone E: Familial lecithin: cholesterol acyltransferase deficiency: A clinical survey. Scand J Clin Lab Invest 33 (Suppl 137): 73-82, 1974.
71. Hovig T, Gjone E: Familial lecithin: Cholesterol acyltransferase deficiency: Ultrastructural aspects of new syndrome with particular reference to lesions in the kidneys and the spleen. Acta Pathol Microbiol Scand 81:681-697, 1973.
72. Hovig T, Gjone E: Familial lecithin: Cholesterol acyltransferase deficiency: Ultrastructural studies on lipid deposition and tissue reactions. Scand J Clin Lab Invest 33 (Suppl 137): 135-146, 1974.
73. Imabasciati E, Paties C, Scarpioni L, Mihatsch MJ: Renal lesions in familial lecithin-cholesterol acyltransferase deficiency. Am J Nephrol 6:66-70,1986
74. Karmin O, Ly M, Fang DZ, Frohlich J, Choy PC. Effect of lipoprotein-X on lipid metabolism in rat kidney. Mol Cell Biochem 173:17-24, 1997
75. Lynn EG, Choy PC, Magil A, O K: Uptake and metabolism of lipoprotein-X in mesangial cells. Mol Cell Biochem; 175(1-2): 187-94. 1997.
76. Magil A, Chase W, Frohlich J: Unusual renal biopsy findings in a patient with familial lecithin: Cholesterol acyltransferase deficiency. Hum Pathol 13:283-285, 1982.
77. Stokke KT, Bjerve KS, Blomhoff JP, Oystese B, Flatmark A, Norum KR, et al.: Familial lecithin:cholesterol acyltransferase deficiency. Studies on lipid composition and morphology of tissues. Scand J Clin Lab Invest 33: (Suppl 137): 93-100 1974.
78. Jimi S, Uesugi N, Saku K, Itabe H, Zhang B, Arakawa K, Takebayashi S: Possible induction of renal dysfunction in patients with lecithin: Cholesterol acyltransferase deficiency by oxidized phosphatidylcholine in glomeruli. Arterioscler Thromb Vasc Biol 19:794-801, 1999
79. Banks DE, Milutinovic J, Desnick RJ, Grabowski GA, Lapp NL, Boehlecke BA: Silicon nephropathy mimicking Fabry's disease. Am J Nephrol. 3(5): 279-84. 1983.
80. Burkholder PM, Updike SJ, Ware RA, Reese OG: Clinicopathologic, enzymatic, and genetic features in a case of Fabry's disease. Arch Pathol Lab Med 104:17-25, 1980
81. Colombi A, Kostyal A, Bracher R, Gloor F, Mazzi R, Tholen H: Angiokeratoma corporis diffusum – Fabry's disease. Helv Med Acta 34:67- 83, 1976.
82. Franceschetti AT, Philippart M, Franceschetti A: A study of Fabry's disease. I. Clinical examination of a family with cornea verticillata. Dermatologica. 138(4): 209-21 1969
83. Desnick RJ, Astrin KH, Bishop DF: Fabry disease: molecular genetics of the inherited nephropathy. Adv Nephrol Necker Hosp.18: 113-27 1989.
84. Faraggiana T, Churg J, Grishman E, Srauss L, Prado A, Bishop DF, Schuchman E, Desnick RJ. Light- and electron-microscopic histochemistry of Fabry's disease. Am J Pathol 103:247-262,1981
85. Gahl WA, Adamson M, Kaiser-Kupfer I, Ludwig IH, O'Connell HJ, Cohen W, et al.: Biochemical phenotyping of a single sibship with both cystinosis and Fabry disease. J Inherit Metab Dis. 8(3): 127-31, 1985
86. Kawamura O, Sakuraba H, Itoh K, Suzuki Y, Doi M, Kuwabara H, et al.: Subclinical Fabry's disease occurring in the context of IgA nephropathy. Clin Nephrol. 47(2): 71-5. 1997.

87. Krivit W, Bernlohr RW, Desnick RJ: Enzyme replacement in genetic disease. Prospectus. Birth Defects Orig Artic Ser;9(2):232-3. 1973.
88. Meroni M, Sessa A, Battini G, Tazzari S, Torri Tarelli L: Kidney involvement in Anderson-Fabry disease. Contrib Nephrol;122:178-84 1997.
89. Mosnier JF, Degott C, Bedrossian J, Molas G, Degos F, Pruna A, Potet F: Recurrence of Fabry's disease in a renal allograft eleven years after successful renal transplantation. Transplantation 51(4): 759-762, 1991
90. Pabico RC, Atanacio BC, McKenna BA, Pamurcoglu T, Yodaiken R: Renal pathologic lesions and functional alterations in a man with Fabrys disease. Am J Med 55:415-425, 1973.
91. Peters PC, Leeber D, Hull AR, Philippart M: Renal transplantation in Fabry's disease. Trans Am Assoc Genitourin Surg;64:36-8 1972.
92. Philippart M: Fabry disease: kidney transplantation as an enzyme replacement technic. Birth Defects Orig Artic Ser;9(2):81-7. 1973.
93. Sheth KJ, Roth DA, Adams MB: Early renal failure in Fabry's disease. Am J Kidney Dis;2(6):651-4. 1983.
94. Simon M, Frey H, Gruler H, Bultmann B: Glycolipid storage material in Fabry's Disease: A study by electron microscopy, freeze-fracture, and digital image analysis. J Struct Biol 103:40-47,1990
95. Baker L, Dahlem S, Goldfarb S, Kern EFO, Stanley CA, Egler J, Olshan JS, Heyman S. Hyperfiltration and renal disease in glycogen storage disease, type I. Kidney Int 35:1345-1350, 1989.
96. Chen YT, Coleman RA, Scheinman JL, Kolbeck PC, Sidbury JB. Renal disease in type I glycogen storage disease. N Engl J Med 318:7-11, 1988.
97. Faraggiana T, Churg J: Renal lipidoses: a review. Hum Pathol;18(7):661-79. 1987.
Obara K, Saito T, Sato H, Ogawa M, Igarashi Y, Yoshinaga K. Renal histology in two adult patients with type I glycogen storage disease. Clin Nephrol 39:59-64, 1993.
98. Saito T: Abnormal lipid metabolism and renal disorders. Tohoku J Exp Med;181(3):321-37. 1997.
99. Wolfsdorf JI, Laffel LM, Crigler JF Jr. Metabolic control and renal dysfunction in type I glycogen storage disease. J Inherit Metab Dis 20:559-68, 1997.
100. Lee HS, Lee JS, Koh HI, Ko KW: Intraglomerular lipid deposition in routine biopsies. Clinical Nephrology 36: 67-75, 1991
101. Kamanna VS, Roh DD, Kirschenbaum MA: Hyperlipidemia and kidney disease: concepts derived from histopathology and cell biology of the glomerulus. Histol Histopathology 13: 169-179, 1998
102. Magil AB: Interstitial foam cells and oxidized lipoprotein in human glomerular disease. Mod Pathol 12: 33-40, 1999
103. Wilens SL, Elster SK. The role of lipid deposition in renal arteriolar sclerosis. Am J Med Sci 219:183-196, 1951.
104. Hasslacher C, Bostedt-Kiesel A, Kempe HP, Wahl P. Effect of metabolic factors and blood pressure on kidney function in proteinuric type 2 (non-insulin-dependent) diabetic patients. Diabetologia 36:1051-1056, 1993.
105. Krolewski AS, Warram JH, Christlieb AR. Hypercholesterolemia: A determinant of renal function loss and death in IDDM patients with nephropathy. Kidney Int 45(suppl 45):S125-S131, 1994.
106. Gröne JH, Hohbach J, Gröne EF. Modulation of glomerulosclerosis and interstitial fibrosis by native and modified lipoprotein. Kidney Int 49(suppl 54):S18-S22, 1996.
107. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. BMJ 314:783-788, 1997.
108. Gröne HJ, Walli AK, Gröne EF. The role of oxidatively modified lipoproteins in lipid nephropathy. Contrib Nephrol 120:160-175, 1997.
109. Smulders YM, Rakic M, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J. Determinants of progression of microalbuminuria in patients with NIDDM. A prospective study. Diabetes Care 20:999-1005, 1997.
110. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. Arch Intern Med 158:998-1004, 1998.

111. Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: Insights from experimental data and clinical studies. Diabetes & Metabolism (Paris) 26:254-264, 2000.
112. Gin H, Rigalleau V, Aparicio M. Lipids, protein intake, and diabetic nephropathy. Diabetes & Metabolism (Paris) 26:45-53, 2000.
113. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: The atherosclerosis risk in communities study. Kidney Intl 58:293-301, 2000.
114. Kamanna VS, Pai R, Roh DD, Kirschenbaum MA. Oxidative modification of low-density lipoprotein enhances the murine mesangial cell cytokines associated with monocyte migration, differentiation, and proliferation. Lab Invest 74:1067-1079, 1996.
115. Lee HS, Kim BC, Kim YS, Choi KH, Chung HK. Involvement of oxidation in LDL-induced collagen gene regulation in mesangial cells. Kidney Intl 50:1582-1590, 1996.
116. Pczek L, Teschner M, Schaefer RM, Lao M, Gradowska L, Heidland A. Low-density lipoprotein suppresses cathepsins B and L activity in rat mesangial cells. Miner Electrolyte Metab 22;51-53, 1996.
117. Studer RK, Craven PA, DeRubertis F. Low-density lipoprotein stimulation of mesangial cell fibronectin synthesis: Role of protein kinase C and transforming growth factor-β. J Lab Clin Med 125:86-95, 1995
118. Ha H, Roh DD, Kirschenbaum MA, Kamanna VS. Atherogenic lipoproteins enhance mesangial cell expression of platelet-derived growth factor: Role of protein tyrosine kinase and cyclic AMP-dependent protein kinase A. J Lab Clin Med 131:456-465, 1998.
119. Roh DD, Kamanna VS, Kirschenbaum MA. Oxidative modification of low-density lipoprotein enhances mesangial cell protein synthesis and gene expression of extracellular matrix proteins. Am J Nephrol 18:344-350, 1998.
120. Lee HS. Oxidized LDL, glomerular mesangial cells and collagen. Diabetes Res Clin Pract 45:117-122, 1999.
121. Nishida Y, Oda H, Yorioka N. Effect of lipoproteins on mesangial cell profiferation. Kidney Intl 56(suppl 71):S51-S53, 1999.
122. Lynn EG, Siow YL, O K. Very low-density lipoprotein stimulates the expression of monocyte chemoattractant protein-1 in mesangial cells. Kidney Intl 57:1472-1483, 2000.
123. Shimamura T. Relationship of dietary intake to the development of glomerulosclerosis in obese Zucker rats. Exper Molec Pathol 36:423-434, 1982.
124. Gröne H-J, Walli A, Gröne E, Niedmann P, Thiery J, Seidel D, Helmchen U. Induction of glomerulosclerosis by dietary lipids: A functional and morphological study in the rat. Lab Invest 60:433-446, 1989.
125. Barcelli UO, Weiss M, Beach D, Motz A, Thompson B. High linoleic acid diets ameliorate diabetic nephropathy in rats. Am J Kid Dis 16:244-251, 1990.
126. Kasiske BL, O'Donnell MP, Lee H, Kim Y, Keane WF. Impact of dietary fatty acid supplementation on renal injury in obese Zucker rats. Kidney Intl 39:1125-1134, 1991.
127. Dumler F, Schmidt R, Vera G, Cortes P, Bernstein J. Effect of diet composition on renal morphology in diabetic rats. Miner Electrolyte Metab 18:120-122, 1992.
128. Logan JL. Studies on the impact of dietary fat composition on proteinuria in diabetic rats. Diabetes Res Clin Pract 33:21-29, 1996.
129. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF. Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. Kidney Intl 33:667-672, 1988.
130. Kasiske BL, O'Donnell MP, Garvis WJ, Keane WF. Pharmacologic treatment of hyperlipidemia reduces glomerular injury in rat 5/6 nephrectomy model of chronic renal failure. Circ Res 62:367-374, 1988.
131. Sasaki T, Kurata H, Nomura K, Utsunomiya K, Ikeda Y. Amelioration of proteinuria with pravastatin in hypercholesterolemic patients with diabetes mellitus. Jpn J Med 29:156-163, 1990.
132a. Shoji T, Nishizawa Y, Toyokawa A, Kawagishi T, Okuno Y, Moril H. Decreased albuminuria by pravastatin in hyperlipidemic diabetics. Nephron 59:664-665, 1991.
132b. Guijarro C, Keane WF. Effects of lipids on the pathogenesis of progressive renal failure: Role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in the prevention of glomerulosclerosis. Miner Electrolyte Metab 22:147-152, 1996.
133. Michel O, Heudes D, Lamarre I, Masurier C, Lavau M, Bariety J, Chevalier J, Belair M-F, Mandet C. Reduction of insulin and triglycerides delays glomerulosclerosis in obese Zucker rats. Kidney Intl 52:1532-1542, 1997.

134. Smulders YM, van Eeden AE, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J. Can reduction in hypertriglyceridaemia slow progression of microalbuminuria in patients with non-insulin-dependent diabetes mellitus? Eur J Clin Invest 27:997-1002, 1997.
135. Tonolo G, Ciccarese M, Brizzi P, Puddu L, Secchi G, Calvia P, Atzeni MM, Melis MG, Maioli M. Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. Diabetes Care 20:1891-1895, 1997.
136. Inman SR, Stowe NT, Cressman MD, Brouhard BH, Nally JV Jr, Satoh S, Satodate R, Vidt DG. Lovastatin preserves renal function in experimental diabetes. Am J Med Sci 317:215-221, 1999.
137. Kim SI, Han DC, Lee HB. Lovastatin inhibits transforming growth factor-beta1 expression in diabetic rat glomeruli and cultured rat mesangial cells. J Am Soc Nephrol 11:80-87, 2000.
138. Brown MS, Goldstein JL: A proteolytic pathway that controls the cholesterol content of membranes, cells, and blood. Proc Natl Acad Sci USA 96: 11041-11048, 1999
139. Horton JD, Shimomura I. Sterol regulatory element-binding proteins: Activators of cholesterol and fatty acid biosynthesis. Curr Opinion Lipidology 10:143-150, 1999.
140. Shimano H, Horton JD, Hammer RE, Shimomura I, Brown MS, Goldstein JL. Overproduction of cholesterol and fatty acids causes massive liver enlargement in transgenic mice expressing truncated SREBP-1a. J Clin Invest 98:1575-1584, 1996.
141. Shimano H, Horton JD, Shimomura I, Hammer RE, Brown MS, Goldstein JL. Isoform 1c of sterol regulatory element binding protein is less active than isoform 1a in livers of transgenic mice and in cultured cells. J Clin Ivest 99:846-854, 1997.
142. Horton JD, Shimomura I, Brown MS, Hammer RE, Goldstein JL, Shimano H. Activation of cholesterol synthesis in preference to fatty acid synthesis in liver and adipose tissue of transgenic mice overproducing sterol regulatory element-binding protein-2. J Clin Invest 101:2331-2339, 1998.
143. Shimano H, Shimomura I, Hammer RE, Herz J, Goldstein JL, Brown MS, Horton JD. Elevated levels of SREBP-2 and cholesterol synthesis in livers of mice homozygous for a targeted disruption of the SREBP-1 gene. J Clin Invest 100:2115-2124, 1997.
144. Fajas L, Schoonjans K, Gelman L, Kim JB, Najib J, Martin G, Fruchart JC, Briggs M, Spiegelman BM, Auwerx J. Regulation of peroxisome proliferator-activated receptor γ expression by adipocyte differentiation and determination factor 1/sterol regulatory element binding protein 1: implications for adipocyte differentiation and metabolism. Mol Cell Biol 19:5495-5503, 1999.
145. Fleischmann M, Iynedjian PB. Regulation of sterol regulatory-element binding protein 1 gene expression in liver: Role of insulin and protein kinase B/cAkt. Biochem J 349:13-17, 2000.
146. Foretz M, Guichard C, Ferre P, Foufelle F. Sterol regulatory element binding protein-1c is a major mediator of insulin action on the hepatic expression of glucokinase and lipogenesis-related genes. Proc Natl Acad Sci USA 96:12737-12742, 1999.
147. Foretz M, Pacot C, Dugail I, Lemarchand P, Guichard C, Liepvre XL, Berthelier-Lubrano C, Spiegelman B, Kim JB, Ferre P, Foufelle F. ADD1/SREBP-1c is required in the activation of hepatic lipogenic gene expression by glucose. Molecular Cell Biol 19:3760-3768, 1999
148. Hasty AH, Shimano H, Yahagi N, Amemiya-Kudo M, Perrey S, Yoshikawa T, Osuga J-I, Okazaki H, Tamura Y, Iizuka Y, Shionoiri F, Ohashi K, Harada K, Gotoda T, Nagai R, Ishibashi S, Yamada N. Sterol regulatory element-binding protein-1 is regulated by glucose at the transcriptional level. J Biol Chem, 275:31069-31077, 2000.
149. Kotzka J, Muller-Wieland D, Roth G, Kremer L, Munck M, Schurmann S, Knebel B, Krone W. Sterol regulatory element binding proteins (SREBP)-1a and SREBP-2 are linked to the MAP-kinase cascade. J Lipid Res 41:99-108, 2000.
150. Osborne TF. Sterol regulatory element binding proteins (SREBPs): Key regulators of nutritional homeostasis and insulin action. J Biol Chem 275:32379-32382, 2000.
151. Boizard M, Le Liepvre X, Lemarchand P, Foufelle F, Ferre P, Dugail I. Obesity-related overexpression of fatty-acid synthase gene in adipose tissue involves sterol regulatory element-binding protein transcription factors. J Biol Chem 273:29164-29171, 1998.
152. Shimomura I, Bashkamov Y, Horton JD: Increased levels of nuclear SREBP-1c associated with fatty livers in two mouse models of diabetes mellitus. J Biol Chem 274: 30028-30032, 1999.

153. Shimomura I, Bashmakov Y, Ikemoto S, Horton JD, Brown MS, Goldstein JL. Insulin selectively increases SREBP-1c mRNA in the livers of rats with streptozotocin-induced diabetes. Proc Natl Acad Sci USA 96:13656-13661, 1999.
154. Bertger J, Leibowitz MD, Doebber TW, Elbrecht A, Zhang B, Zhou G, Biswas C, Culinan CA, Hayes NS, Li Y, Tanen M, Ventre J, Wu MS, Berger GD, Mosley R, Marquis R, Santini C, Sahoo SP, Tolman RL, Smith RG, Moller DE. Novel peroxisome proliferator-activated receptor (PPAR)γ and PPARδ ligands produce distinct biological effects. J Biol Chem 274:6718-6725, 1999.
155. Braissant O, Foufelle F, Scotto C, Dauca M, Wahli W. Differential expression of peroxisome proliferator-activated receptors (PPARs): Tissue distribution of PPAR-α, -β, -γ in the adult rat. Endocrinology 137:354-366, 1996
156. Kersten S, Desvergne B, Wahli W: Roles of PPARs in health and disease. Nature 405: 421-424, 2000
157. Michalik L, Wahli W. Peroxisome proliferator-activated receptors: Three isotypes for a multitude of functions. Curr Opin Biotech 10: 564-570, 1999
158. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: From orphan receptors to drug discovery. J Med Chem 43: 527-550, 2000
159. Clark SD, Thuillier P, Baillie RA, Sha X. Peroxisome proliferator-activated receptors: A family of lipid-activated transcription factors. Am J Clin Nutr 70:566-571, 1999.
160. Fruchart J-C, Duriez P, Staels B. Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. Curr Opin Lipidol 10:245-257, 1999
161. Gelman L, Fruchart J-C, Auwers J. An update on the mechanisms of action of the peroxisome proliferator-activated receptors (PPARs) and their roles in inflammation and cancer. Cell Mol Life Sci 55:932-943, 1999.
162. Medh JD. Peroxisome proliferator-activated receptors in atherosclerosis. Curr Opin Lipidol 10:69-71, 1999
163. Ricote M, Huang JT, Welch JS, Glass CK. The peroxisome proliferator-activated receptorγ (PPARγ) as a regulator of monocyte/macrophage function. J Leukoc Biol 66:733-739, 1999
164. Rocchi S, Auwerx J. Peroxisome proliferator-activated receptor-γ: a versatile metabolic regulator. Ann Meds 31:342-351, 1999
165. Vanden Heuvel JP. Symposium: Steroid hormone receptor and nutrient interactions: Implications for cancer prevention. Peroxisome proliferator-activated receptors: A critical link among fatty acids, gene expression and carcinogenesis. J Nutr 129:575S-580S, 1999.
166. Wu Z, Puigserve P, Spiegelman BM. Transcriptional activation of adipogenesis. Curr Opin Cell Biol 11:689-694, 1999
167. Anderson Y, Majd Z, Lefebvre AM. Martin G, Sechkin AV, Kosykh V, Fruchart JC, Najib J, Staels B. Developmental and pharmacological regulation of apolipoprotein C-II gene expression: Comparison with Apo C-I and Apo C-III gene regulation. Arterioscler Thromb Vasc Biol 19:115-121, 1999.
168. Butow RA, Bahassi EM. Adaptive thermogenesis: Orchestrating mitochondrial biogenesis. Curr Biol 9:R767-R769, 1999
169. Costet P, Legendre C, More J, Edgar A, Galtier P, Pineau T. Peroxisome proliferator-activated receptor α-isoform deficiency leads to progressive dyslipidemia with sexually dimorphic obesity and steatosis. J Biol Chem 273:29577-29585, 1998.
170. Kockx M, Gervois PP, Poulain P, Derudas B, Peters JM, Gonzalez FJ, Princen HM, Kooistra T, Staels B. Fibrates suppress fibrinogen gene expression in rodents via activation of the peroxisome proliferator-activated receptor α. Blood 93:2991-2998, 1999.
171. Peters JM, Hennuyer N, Staels B, Fruchart J-C, Fievet C, Gonzalez JF, Auwerx J. Alterations in lipoprotein metabolism in peroxisome proliferator-activated receptor α-deficient mice. J Biol Chem 272:27307-27312, 1997.
172. Pineda Torra I, Gervois P, Staels B. Peroxisome proliferator-activated receptor α in metabolic disease, inflammation, atherosclerosis and aging. Curr Opin Lipidol 10:151-159, 1999
173. Cabrero A, Llaverias G, Roglans N, Alegret M, Sanchez R, Adzet T, Laguna JC, Vazquez M. Uncoupling protein-3 mRNA levels are increased in white adipose tissue and skeletal muscle of bezafibrate-treated rats. Biochem and Biophys Res Commun 260:547-556, 1999

174. Kelly LJ, Vicario PP, Thompson GM, Candelore MR, Doebber TW, Ventre J, Wu MS, Meurer R, Forrest MJ, Conner MW, Cascieri MA, Moller DE. Peroxisome proliferator-activated receptors γ and α mediate in vivo regulation of uncoupling protein (UCP-1, UCP-2, UCP-3) gene expression. Endocrinology 139:4920-4927, 1998
175. Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J. Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARα and PPARγ activators. J Biol Chem 272:28210-28217, 1997.
176. Motojima K, Passilly P, Peters JM, Gonzalez FJ, Latruffe N. Expression of putative fatty acid transporter genes are regulated by peroxisome proliferator-activated receptor α and γ activators in a tissue- and inducer-specific manner. J Biol Chem 273:16710-16714, 1998.
177. Nagase I, Yoshida S, Canas X, Irie Y, Kimura K, Yoshida T, Saito M. Up-regulation of uncoupling protein 3 by thyroid hormone, peroxisome proliferator-activated receptor ligands and 9-cis retinoic acid in L6 myotubes. FEBS Lett 46:319-322, 1999
178. King FJ, Hu E, Harris DF, Sarraf P, Spiegelman BM, Roberts TM. DEF-1, a novel Src SH3 binding protein that promotes adipogenesis in fibroblastic cell lines. Molec Cell Biol 19:2330-2337, 1999
179. Lee W-NP, Lim S, Bassilian S, Bergner EA, Edmond J. Fatty acid cycling in human hepatoma cells and the effects of troglitazone. J Biol Chem 273:20929-20934, 1998
180. Matsuda J, Hosoda K, Itoh H, Son C, Doi K, Hanaoka I, Inoue G, Nishimura H, Yoshimasa Y, Yamori Y, Odaka H, Nakao K. Increased adipose expression of the uncoupling protein-3 gene by thiazolidinediones in Wistar fatty rats and in cultured adipocytes. Diabetes 47:1809-1814, 1998
181. Rosen ED, Sarraf P, Troy AE, Bradwin G, Moore K, Milstone DS, Spiegelman BM, Mortensen RM. PPARγ is required for the differentiation of adipose tissue in vivo and in vitro. Molec Cell 4:611-617, 1999
182. Wu Z, Rosen ED, Brun R, Hauser S, Adelmant G, Troy AE, McKeon C, Darlington GJ, Speigelman BM. Cross-regulation of C/EBPα and PPARγ controls the transcriptional pathway of adipogenesis and insulin sensitivity. Molec Cell 3:151-158, 1999
183. Makherjee R, Davies PJA, Crombie DL, Bischoff ED, Cesario RM, Jow L, Hamann LG, Boehm MF, Mondon CE, Nadzan AM, Paterniti Jr JR, Heyman RA. Sensitization of diabetic and obese mice to insulin by retinoid X receptor agonists. Nature 386:407-410, 1997
184. Spiegelman BM. Perspectives in Diabetes. PPAR-γ: Adipogenic regulator and thiazolidinedione receptor. Diabetes 47:507-514, 1998
185. Chinetti G, Fruchard J-C, Staels B. Peroxisome proliferator-activated receptors (PPARs): Nuclear receptors at the crossroads between lipid metabolism and inflammation. Inflamm Res 49:497-505, 2000.
186. Poynter ME, Daynes RA. Peroxisome proliferator-activated receptor α activation modulates cellular redox status, represses nuclear factor-κB signaling, and reduces inflammatory cytokine production in aging. J Biol Chem 273:32833-32841, 1998.
187. Poynter ME, Daynes RA. Age-associated alterations in splenic iNOS regulation: influence of constitutively expressed IFN-γ and correction following supplementation with PPARα activators or vitamin E. Cell Immunol 195:127-136, 1999.
188. Marx N, Mach F, Sauty A, Leung JH, Sarafi MN, Ransohoff RM, Libby P, Plutzky J, Luster AD. Peroxisome proliferator-activated receptor-γ activators inhibit IFN-γ-induced expression of the T cell-active CXC chemokines IP-10, Mig, and I-TAC in human endothelial cells. J Immunol 164:6503-6508, 2000.
189. Pasceri V, Wu HD, Willerson JT, Yeh ETH. Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator-activated receptor-γ activators. Circulation 101:235-238, 2000.
190. Delerive P, DeBosscher K, Besnard S, Berghe WV, Peters JM, Gonzalez FJ, Fruchart J-C, Tedgui A, Haegeman G, Staels B. Peroxisome proliferator-activated receptor α negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF-κB and AP-1. J Biol Chem 274:32048-32054, 1999.
191. Su CG, Wen X, Bailey ST, Jiang W, Rangwala SM, Keilbaugh SA, Flanigan A, Murthy S, Lazar MA, Wu GD. A novel therapy for colitis utilizing PPAR-γ ligands to inhibit the epithelial inflammatory response. J Clin Invest 104:383-389, 1999.
192. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature 391:79-82, 1998.

193. Devchand PR, Keller J, Peters JM, Vazquez M, Gonzalez FJ, Wahli W. The PPARα-leukotriene B_4 pathway to inflammation control. Nature 384:39-43, 1996.
194. Nawa T, Nawa MT, Cai Y, Zhang C, Uchimura I, Narumi S, Numano F, Kitajima S. Repression of TNF-α-induced E-selectin expression by PPAR activators: involvement of transcriptional repressor LRF-1/ATF3. Biochem Biophys Res Commun 275:406-411, 2000.
195. Kintscher U, Goetze S, Wakino S, Kin S, Nagpal S, Chandraratna RAS, Graf K, Fleck E, Hsueh WA, Law RE. Peroxisome proliferator-activated receptor and retinoid X receptor ligands inhibit monocyte chemotactic protein-1-directed migration of monocytes. Eur J Pharmacol 401:259-270, 2000.
196. Guan Y, Zhang Y, Davis L, Breyer MD. Expression of peroxisome proliferator-activated receptors in urinary tract of rabbits and humans. Am J Physiol 273:F1013-F1022, 1997.
197. Mukherjee R, Jow L, Croston GE, Paterniti Jr JR. Identification, characterization, and tissue distribution of human peroxisome proliferator-activated receptor (PPAR) isoforms, PPARγ2 versus PPARγ1 and activation with retinoid X receptor agonists and antagonists. J Biol Chem 272:8071-8076, 1997
198. Portilla D, Dai G, Peters JM, Gonzalez FJ, Crew MD, Proia A. Etomoxir-induced PPARα-modulated enzymes protect during acute renal failure. Am J Physiol Renal Physiol 278:F667-F675, 2000.
199. Yang T, Michelle DE, Park J, Smart AM, Lin Z, Brosius III FC, Schnermann JB, Briggs JP. Expression of peroxisomal proliferator-activated receptors and retinoid X receptors in the kidney. Am J Physiol 277:F966-F973, 1999.
200. Yamamoto T, Nakamura T, Noble NA, Ruoslahti E, Border WA. Expression of transforming growth factor-β is elevated in human and experimental diabetic nephropathy. Proc Natl Acad Sci USA 90:1814-1818, 1993.
201. Kolm-Litty V, Sauer U, Nerlich A, Lehmann R, Schleicher ED. High glucose-induced transforming growth factor beta 1 production is mediated by the hexosamine pathway in porcine glomerular mesangial cells. J Clin Invest 101:160-169, 1998.
202. Chen Y, Billadello JJ, Schneider DJ. Identification and localization of a fatty acid response region in the human plasminogen activator inhibitor-1 gene. Arterioscler Thromb Vasc Biol 20:2696-2701, 2000.
203. Dichtl W, Ares MPS, Stollenwerk M, Giachelli CM, Scatena M, Hamsten A, Eriksson P, Nilsson J. In vivo stimulation of vascular plasminogen activator inhibitor-1 production by very low-density lipoprotein involves transcription factor binding to a VLDL-responsive element. Thromb Heamost 84:706-711, 2000.
204. Goldberg HJ, Scholey J, Fantus IG. Glucosamine activates the plasminogen activator inhibitor 1 gene promoter through Sp1 DNA binding sites in glomerular mesangial cells. Diabetes 49:863-871, 2000.
205. James LR, Fantus IG, Goldberg H, Ly H, Scholey JW. Overexpression of GFAT activates PAI-1 promoter in mesangial cells. Am J Physiol Renal Physiol 279:F718-F727, 2000.
206. Rerolle J-P, Hertig A, Nguyen G, Sraer J-D, Rondeau EP. Plasminogen activator inhibitor type 1 is a potential target in renal fibrogenesis. Kidney Intl 58:1841-1850, 2000.
207. Hasegawa G, Nakano K, Sawada M, Uno K, Shibayama Y, Ienaga K, Kondo M. Possible role of tumor necrosis factor and interleukin-1 in the development of diabetic nephropathy. Kidney Intl 40:1007-1012, 1991.
208. Sterzel RB, Schuze-Lohoff E, Marx M. Cytokines and mesangial cells. Kidney Intl 43(Suppl 39):S26-S31, 1993.
209. Sekizuka K, Tomino Y, Sei C, Kurusu A, Tashiro K, Yamaguchi Y, Kodera S, Hishiki T, Shirato I, Koide H. Detection of serum IL-6 in patients with diabetic nephropathy. Nephron 68:284-285, 1994.
210. Suzuki D, Miyazaki M, Naka R, Koji T, Yagame M, Jinde K, Endoh M, Nomoto Y, Sakai H. In situ hybridization of interleukin 6 in diabetic nephropathy. Diabetes 44:1233-1238, 1995.
211. Loughrey BV, Maxwell AP, Fogarty DG, Middleton D, Harron JC, Patterson CC, Darke C, Savage DA. An interleukin 1B allele, which correlates with a high secretor phenotype, is associated with diabetic nephropathy. Cytokine 10:984-988, 1998.
212. Ina K, Kitamura H, Okeda T, Nagai K, Liu ZY, Matsuda M, Fujikura Y. Vascular cell adhesion molecule-1 expression in the renal interstitium of diabetic KKAy mice. Diabetes Res Clin Pract 44:1-8, 1999.
213. Kato S, Luyckx VA, Ots M, Lee K-W, Ziai F, Troy JL, Brenner BM, Mackenzie HS. Renin-angiotensin blockade lowers MCP-1 expression in diabetic rats. Kidney Intl 56:1037-1048, 1999.

214. Navarro JF, Mora C, Rivero A, Gallego E, Chahin J, Macia M, Mendez ML, Garcia J. Urinary protein excretion and serum tumor necrosis factor in diabetic patients with advanced renal failure: effects of pentoxifylline administration. Am J Kid Dis 33:458-463, 1999.
215. Sugimoto H, Shikata K, Wada J, Horiuchi S, Makino H. Advanced glycation end products-cytokine-nitric oxide sequence pathway in the development of diabetic nephropathy: aminoguanidine ameliorates the overexpression of tumour necrosis factor-α and inducible nitric oxide synthase in diabetic rat glomeruli. Diabetologia 42:878-886, 1999.
216. Banba N, Nakamura T, Matsumura M, Kuroda H, Hattor Y, Kasai K. Possible relationship of monocyte chemoattractant protein-1 with diabetic nephropathy. Kidney Intl 58:684-690, 2000.
217. Panousis CG, Zuckerman SH. Regulation of cholesterol distribution in macrophage-derived foam cells by interferon-γ. J Lipid Res 41:75-83, 2000.
218. Shikano M, Sobajima H, Yoshikawa H, Toba T, Kushimoto H, Katsumata H, Tomita M, Kawashima S. Usefulness of a highly sensitive urinary and serum IL-6 assay in patients with diabetic nephropathy. Nephron 85:81-85, 2000.
219. Horie K, Miyata T, Maeda K, Miyata S, Sugiyama S, Sakai H, van Ypersele de Strihou C, Monnier VM, Witztum JL, Kurokawa K. Immunohistochemical colocalization of glycoxidation products and lipid peroxidation products in diabetic renal glomerular lesions. J Clin Invest 100:2995-3004, 1997.
220. Schleicher ED, Wagner E, Nerlich AG. Increased accumulation of the glycoxidation product N-carboxymethyl lysine in human tissues in diabetes and aging. J Clin Invest 99:457-468, 1997.
221. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 48:1-9, 1999.
222. Ishiyama A, Atarashi K, Minami M, Takagi M, Kimura K, Goto A, Omata M. Role of free radicals in the pathogenesis of lipid-induced glomerulosclerosis in rats. Kidney Intl 55:1348-1358, 1999.
223. Baynes JW, Thorpe SR. Glycoxidation and lipoxidation in atherogenesis. Free Radical Biol Med 28:1708-1716, 2000.
224. Du X-L, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. Proc Natl Acad Sci (USA) 97:12222-12226, 2000.
225. Evans M, Anderson RA, Graham J, Ellis GR, Morris K, Davies S, Jackson SK, Lewis MJ, Frenneaux MP, Rees A. Ciprofibrate therapy improves endothelial function and reduces postprandial lipemia and oxidative stress in type 2 diabetes mellitus. Circulation 101:1773-1779, 2000.
226. Guha M, Bai W, Nadler JL, Natarajan R. Molecular mechanisms of tumor necrosis factor α gene expression in monocytic cells via hyperglycemia-induced oxidant stress-dependent and –independent pathways. J Biol Chem 25:17728-17739, 2000.
227. Lal MA, Körner A, Matsuo Y, Zelenin S, Cheng SXJ, Jaremko G, DiBona GF, Eklöf A-C, Aperia A. Combined antioxidant and COMT inhibitor treatment reverses renal abnormalities in diabetic rats. Diabetes 49:1381-1389, 2000.
228. Leonarduzzi G, Arkan MC, Basaa H, Chiarpotto E, Sevanian A, Poli G. Lipid oxidation products in cell signaling. Free Radical Biol Med 28:1370-1378, 2000.
229. Montero A, Munger KA, Zhan RZ, Valdivielso JM, Morrow JD, Guasach A, Ziyadeh FN, Badr KF. F_2-isoprostanes mediate high glucose-induced TGF-β synthesis and glomerular proteinuria in experimental type I diabetes. Kidney Intl 58:1963-1972, 2000.
230. Nishikawa T, Edelstein D, Du XL, Yamagishi S-I, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes H-P, Giardino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 404:787-790, 2000.
231. Poirier B, Lannaud-Bournoville M, Conti M, Bazin R, Michel O, Bariety J, Chevalier J, Myara I. Oxidative stress occurs in absence of hyperglycaemia and inflammation in the onset of kidney lesions in normotensive obese rats. Nephrol Dial Transplant 15:467-476, 2000.
232. Scivittaro V, Ganz MB, Weiss MF. AGEs induce oxidative stress and activate protein kinase C-β_{II} in neonatal mesangial cells. Am J Physiol Renal Physiol 278:F676-F683, 2000.

233. Tanji N, Markowitz GS, Fu C, Kislinger T, Taguchi A, Pischetsrieder M, Stern D, Schmidt AM, D'Agati VD. Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. J Am Soc Nephrol 11:1656-1666, 2000.