20

Metabolic Syndrome Associated Kidney Damage

Hequn Zou[1], Yuxin Wang[2], Guimian Zou[3] and Jianxin Wan[4]
[1]*Institute of Nephrology and Urology,*
The 3rd Affiliated Hospital of Southern Medical University, Guangzhou,
[2]*Department of Nephrology, The No. 2 Hospital of Xiamen,*
Fu Jian Medical University, Xiamen,
[3]*Nephrology Department of Guilin 181 Hospital &*
Guangxi Provincial Key Laboratory of Metabolic Disease Research, Guilin,
[4]*Department of Nephrology, The No. 1 Hospital of Fu Jian Medical University,Fuzhou*
China

1. Introduction

We evaluated the incidences of metabolic syndrome (MS) and its components in the urban residents of southern China, analyzed their relationship to insulin resistance (IR), meanwhile compared the different of MS diagnostic criteria between Chinese Diabetes Society (CDS) and International Diabetes Federation (IDF) in clinic practice in the southern urban residents of China. The total incidence of MS was 8.7% according to the diagnostic criteria of CDS, but up to 19.8% according to the diagnostic criteria of IDF. The total incidences of hypertension, abdominal obesity and diabetes were 22.1%, 39.2% and 6.7%, respectively. The incidence of IR was 5.0% according the value of HOMA-IR. By means of binary logistic regression analysis, impaired fasting glucose, diabetes, obesity, abdominal obesity, elevated triglyceride and high sensitivity C reactive protein were independent risks of insulin resistance, but gender, hypertension, elevated low density lipoprotein and total cholesterol were not independent risks of insulin resistance. It is suggested by the data of our present screening in the residents of southern China that the incidence of MS according to the diagnostic criteria of CDS was lower than that according to the diagnostic criteria of IDF. Some residents with MS main presentation of abdominal obesity would be missed diagnosis by the criteria base on BMI. In the components of MS, hypertension, abdominal obesity and lower high density lipoprotein were more common than others. IR was associated to most of the components of MS and may be one of the main pathogenic factors.

By means of cross-section epidemiological analysis, we investigated the relationship of glycometabolic disorder and IR with chronic kidney diseases (CKD). The prevalence of CKD was 12.6% in the community population, with 11.2% in the youth group, 19.4% in the middle age group and 17.7% in the elder group. And there were a significantly difference between the three age groups ($P<0.01$). The awareness rates and treatment rates of CKD were very low in all of the three groups. In the whole screened population there was a higher CKD prevalence in IR residents when compared to non-IR residents, 36.9% versus 12.6% ($P<0.01$). Among population with only impair FBG but not diabetes, CKD prevalence in those residents with IR was higher than those without IR, 33.3% versus 16.0% ($P<0.05$).

Even among population with normal FBG, CKD prevalence in those residents with IR was higher than whose without IR, 39.1% versus 12.0% (P<0.01). It was observed in different age group that the prevalence of albuminuria and the mean albuminuria level were higher in the residents with IR when compared to the residents without IR. No difference existed between either the prevalence of decreasing eGFR or the mean level of eGFR in residents with IR and without IR in the middle age group and the old group, but not in the youth group in which. The mean level of eGFR was significantly higher in the residents with IR when compared to the residents without IR (P<0.01). It is indicated in our data that CKD is common and the awareness rate and treatment rate are very low in this investigated community population. IR might be associated with the increasing prevalence of CKD, especially with the increased prevalence of microalbuminuria, even in the population with normal FBG. Furthermore IR might also be associated with elevated eGFR in population at the early stage of diabetes but without CKD, while associated with decreased eGFR in those with CKD. It is suggested that IR might be a risk factor of CKD and also a prevention and treatment target of CKD in community residents.

We also explored the incidences of hyperuricemia (HUA) in the urban residents and the related risk factors. The total incidence of HUA was 23.5% in the cohort residents, and was 28.4% in the males and 19.7% in the females (P<0.01). The serum uric acid level was positively related to body weight (or BMI), waist circumference and the age (for females) when controling with serum creatinine (P<0.01). Alcohol consumption and smoke influences significantly on the serum uric acid level, and highest uric acid levels were in the residents frequently drunk and smoked in the past. More common prevalence of HUA was in the patients with chronic kidney disease and hypertension, and the serum uric acid levels were similar in these patients. There was no significant difference of the incidences of HUA between the patients with diabetes and non diabetes. It is suggested by our present investigation that the incidence of HUA is increasing in the residents of inland city of China, and that the change of their lifestyle with lose weight, prevention of obesity, avoid smoke and restriction of alcohol would be the most effective measures to change the high prevalence of HUA.

2. Pathogenesis of metabolic syndrome associated kidney damage

2.1 Insulin resistance and pathogenesis of metabolic syndrome-associated kidney damage

Insulin resistance and metabolic renal damage is closely related. So the metabolic syndrome were screened for kidney damage, assessment is very necessary. Regarding to the pathogenesis of insulin resistance and to improve the treatment based on will also be a metabolic control of renal damage in a new direction for the future.

2.1.1 Insulin resistance leads to kidney damage

The metabolic syndrome (MS) was defined as the presence of 3 or more of the following risk factors: elevated blood pressure, insulin resistance, low high-density lipoprotein cholesterol level, high triglyceride level, elevated glucose level, and abdominal obesity. MS disease risk factors in order to gather more focus is characterized by heart, kidney blood vessels and other target organs. The impact is clear. Now the increasing number of researches show that compared with simple hypertension, metabolic syndrome is more easily lead to kidney damage. Some studies further confirmed that the large vessels and kidney of metabolic syndrome patients damaged obvious. MS can cause kidney damage, and the kidney disease affects MS as well. This shows the relationship between MS and kidney disease is very close.

So people consensus that MS is started for obesity as the common factor. And insulin resistance is the central link of MS. This can be inferred that the relationship between insulin resistance and metabolic renal damage is close.

Insulin resistance refers to the uptake of insulin to promote peripheral tissue, the use of glucose output and inhibit the biological effects of glycogen decreased, with the changes in the compensatory ability of the body showed hyperinsulinemia and (or) high blood sugar status. The kidney damage mechanisms caused by high blood sugar is including that: ① polyol pathway activation; ② protein non-enzymatic glycation (advanced glycation end products formation); ③ activation of protein kinase C. The renal injury is caused by these lesions and GBM thickening. In addition, the recent study found, MS appears hyperinsulinemia is also often high viremia of amylin, amylin is a high-fiber protein, mainly deposited in the glomerular mesangial area widened, K-W nodules, blood vessel walls and renal interstitial, which become one of the causes of injury about glomerular and interstitial. In vitro experiments showed that amylin may be higher in mesangial cells through induction of apoptosis and increased permeability in endothelial cells kidney damage, but the exact mechanism is still not very clear.[1, 2]

Now that insulin resistance occurs most often in patients with metabolic syndrome, is the central link in the pathogenesis and pathogenic basis. It not only prompts a new-onset diabetes mellitus, cardiovascular events and all-cause mortality in high-risk, but also the renal damage and failure are independent risk factors.[3-6] The primary kidney disease before there is often severely impaired renal function also showed insulin resistance.[4] Therefore, insulin resistance and renal damage can reinforce each other, so to clear the relationship between insulin resistance and metabolic renal damage is useful that in the prevention and treatment of kidney disease is especially prominent role in the process. This article is the review on the causes of pathogenesis why insulin resistance leads to metabolic kidney damage.

2.1.2 Insulin resistance and pathogenesis of metabolic syndrome-associated kidney damage

Insulin resistance is the central link of metabolic syndrome. The U.S. NHANES III data shows that the prevalence of metabolic syndrome has reached 23.7% for the adults who over 20 years 'old.[3] The study showed that In type 2 diabetes, more severe insulin resistance is independently associated with microalbuminuria.[5, 6] Animal experiments confirmed that clinical diabetes mellitus in the event of hyperinsulinemia stage before changes of structure and function in kidney have been.[7] Such early renal damage has its own characteristics and pathogenesis, which are different from diabetic nephropathy. Insulin resistance mechanisms lead to kidney damage mainly in the following areas.

Insulin-like growth factor (IGF) axis is involved in diabetic renal disease

Insulin-like growth factor I (IGF-I) is a potent mitogenic polypeptide under the regulation of growth hormone (GH). Evidence of significant involvement of the GH/IGF system in diabetic nephropathy and other nephropathies has been provided by several studies. Kidney tissue expresses receptors not only for IGF-I but also for GH, which suggests that although most of the biologic effects of GH are mediated by IGF-I, GH may also act independently of IGF-I. IGF-I may have pathogenic roles in diabetic nephropathy and other nephropathies. Serum IGF-I levels are reduced in hyperglycemic diabetic subjects, despite elevated GH levels. This phenomenon has been explained by inhibition of hepatic IGF-I synthesis, resulting from decreases in hepatic GHR expression and binding. The metabolic consequences of these

alterations produce a "vicious cycle," wherein the hyperglycemia/insulinopenia induce decreases in serum IGF-I levels, which in turn induce GH hypersecretion, making optimal metabolic control more difficult to achieve.[8] People speculate that the mechanism underlying the renal effects of this GHR antagonist involves renal GHR inhibition of renal IGF-I (and IGFBP-1) protein accumulation. They also speculate that the mechanism underlying the renal effects of this GHR antagonist involves renal GHR inhibition of renal IGF-I (and IGFBP-1) protein accumulation. This study demonstrates that the GH/IGF axis plays a central role in the pathogenesis of early diabetic renal changes, and it suggests specific GHR blockade as a new concept in the treatment of diabetic kidney disease.[9]

Insulin resistance increase renal damage through the rennin-angiotensin system

Angiotensin II (Ang II) and insulin are implicated in the mesangial cell hypertrophy and excessive accumulation of mesangial matrix seen in glomerulosclerosis. Therefore, the effects of Ang II with and without insulin on mRNA levels of several important extracellular matrix genes and transforming growth factor beta-1 (TGF-beta 1) were examined. The results of the studies suggest that insulin, itself, significantly increases TGF-beta 1 and extracellular matrix gene expression in rat mesangial cells. Ang II alone has modest effects, while Ang II and insulin have additive effects. To explain the mechanism of these additive effects, we investigated the action of Ang II on insulin signaling and the effect of insulin on Ang II AT1 receptor mRNA expression. Ang II did not enhance insulin-induced insulin receptor substrate-1 (IRS-1) phosphorylation or phosphatidylinositol 3 (PI-3) kinase activity, but did enhance insulin-induced mitogen activated protein (MAP) kinase activity.[10] Insulin increased message levels of AT1 receptor by twofold. These results suggest that enhancement of MAP kinase activity and AT1 receptor regulation by insulin may contribute to the additive effects of insulin and Ang II in mesangial cells.

The direct impact of insulin resistance on kidney

Insulin major role in the tubules, but the specific sites of action are not yet entirely clear.It has a strong role in preserving sodium and dose dependent, while the presence of insulin to counter, this is still Paul sodium. Therefore, insulin resistance and hyperinsulinemia that occurs when the sodium sensitivity of blood pressure increase in glomerular pressure increased, resulting in microalbuminuria. A study was performed by Vedovato M to measure the effect of Na+ intake on blood pressure and albuminuria, in relation with insulin sensitivity and kidney haemodynamics, in Type 2 diabetic patients with and without microalbuminuria. They found that high salt intake increases blood pressure and albuminuria in Type 2 diabetic patients with microalbuminuria. These responses are associated with insulin resistance and increased glomerular pressure. Insulin resistance could contribute to greater salt sensitivity, increased glomerular pressure and albuminuria.[11]

Insulin resistance increase the renal damage by the plasminogen activator inhibitor 1

The insulin resistance syndrome typically features glucose intolerance and elevated fasting insulin and triglyceride levels. Elevated levels of PAI-1 and tPA antigens associated with glucose intolerance, hyperinsulinemia, and hypertriglyceridemia support inclusion of impaired fibrinolysis as an additional feature of the insulin resistance syndrome. Elevated fibrinolytic factors are also correlated with elevated markers of inflammation and endothelial dysfunction, which has been hypothesized to cause insulin resistance and thereby be the common pathogenic mechanism underlying atherosclerosis, insulin resistance, and glucose intolerance.[12] Hagiwara H's study proved that renal PAI-1 gene

expression is up-regulated in both type 1 and type 2 diabetic rats, and changes in gene expressions of fibrinolytic factors may play important roles in the development and pathogenesis of diabetic nephropathy.[13] In addition, TGF-β, angiotensin Π and thrombin could stimulate the synthesis of PAI-1, the process by inhibiting fibrinolysis and plasmin-mediated matrix metalloproteinase activity, so that less matrix degradation, resulting in renal fibrosis.

Insulin resistance increases the rates of renal damage by endothelin (ET) -1

Endothelin-1, released from the vascular endothelium after cleavage from big endothelin-1, is a potent paracrine vasoconstrictor peptide. Small studies suggest that the circulating level of endothelin-1 is elevated in subjects with cardiovascular risk factors. High endothelin-1 level may better reflect endothelin-1 generation. It is indicated by studies that endothelin-1 level is not related to blood pressure, but higher in healthy young men with insulin resistance and obesity.[14] It was discovered in a diabetic mouse model treated with A-type ET receptor antagonist that glomerular TGF-β and collagen I, II, IV production were decreased.

Insulin resistance increase the renal damage through oxidative stress

Insulin-stimulated (or inhibited) pathways retain normal sensitivity to the hormone, hyperinsulinemia could, by its effects on antioxidative enzymes and on free radical generators, enhance oxidative stress. Other effects of insulin involve the inhibition of proteasome and the stimulation of polyunsaturated fatty acid (PUFA) synthesis and of nitric oxide (NO).[15] Prabhakar SS attempted to review the existing literature, discuss the controversies, and reach some general conclusions as to the role of NO production in the diabetic kidney. He found that genetic polymorphisms of the NOS enzyme also may play a role in the NO abnormalities that contribute to the development and progression of diabetic nephropathy.[16]

Insulin resistance increases renal damage through nitric oxide

The results of study performed by Steinberg HO argued that insulin effect on the endothelium is mediated by its own receptor and insulin signaling pathways, resulting in the increased release of nitric oxide. The vascular actions of insulin are impaired in insulin-resistant conditions such as obesity, Type II (non-insulin-dependent) diabetes mellitus and hypertension, which could contribute to the excessive rate of cardiovascular disease in these groups. Insulin-resistant state in obesity and Type II diabetes shows a multitude of metabolic abnormalities that could cause vascular dysfunction. Non-esterified fatty acid level increased long before hyperglycaemia becomes present.[17] Under the circumstance of insulin resistance, endothelial dysfunction leads to vascular complications in the central link, which results in microalbuminuria.

2.2 Hypertension and pathogenesis of metabolic syndrome-associated nephropathy

The abnormality of kidney structure and function caused by hypertension is called hypertensive renal damage. Arteriolar nephrosclerosis is the most characteristic pattern in hypertensive renal damage, including benign arteriolar nephrosclerosis and malignant arteriolar nephrosclerosis. The former caused by benign hypertension, the latter caused by malignant hypertension. Sustained hypertension can cause renal arteriolosclerosis for 5-10 years (tunica intimal thickening of arcuate artery and interlobular arteries, hyaline of afferent artery), wall thickening, lumens narrowing, and secondary ischemic renal

parenchyma ischemic lesions, including glomerular ischemic shrinkage, sclerosis, tubular atrophy, interstitial infiltration of inflammatory cells and fibrosis, which lead to benign arteriolar nephrosclerosis. Malignant arteriolar nephrosclerosis is an accelerated hypertension or malignant hypertension-induced renal damage.

2.2.1 Pathogenesis of benign arteriolar nephrosclerosis

Factor of hemodynamics

Due to normal autoregulatory mechanism of renal vessels, renal blood flow (RBF) can be kept relatively stable, which can protect the kidney from blood pressure fluctuation. Renal arteriolar constrictive response occurs in the presence of hypertension, which increase renal vascular resistance and decrease renal blood flow (RBF). The degree of contraction of efferent arteries is more significant than afferent arteries in early stage. Glomerular filtration rate (GFR) can still be maintained within the normal range. With the progress of hypertension, there is renal arteriosclerosis, compliance decreasing, arterial wall thickening, lumens stenosis, and RBF further decline, GFR falling, which lead to ischemic renal lesions. Impairment of kidney tubules secondary to ischemia is more sensitive than glomeruli. Furthermore, renal tubular load does not reduce for maintaining normal GFR, thus more likely to increase renal tubular injury secondary to glomerular hyperperfusion.[18] However, benign arteriolar nephrosclerosis has obvious individual differences. There is not observed renal arteriolar sclerosis in some glomerulosclerosis secondary to hypertension. Hypertensive renal injury is not completely ischemic lesions. In addition to ischemic hypoperfusion nephron, the recent view is that most hypertensive renal damage is characterized by hypertransfusion compensatory nephron. The existence of glomerular hyperperfusion, high pressure and high filtration promote renal parenchyma lesions, especially is the major pathogenesis of glomerulosclerosis.[19].

Under hypertension state, renal vascular sensitivity to Ang II was significantly enhanced. Renal vascular resistance increased in the patients with hypertension who are injected low dose Ang II, and did not significantly change in normal people. The mechanism of proteinuria occurence is currently considered that increased RAS activity lead to podocyte fracture membrane damage and basilar membrane permeability increasing. High intra-glomerular pressure and high shear stress-induced endothelial cell injury and dysfunction, activated local lesions, increased Ang II and aldosterone, induced renal vascular remodeling and renal arteriosclerosis.[20]

Non-hemodynamic factors

In hypertension state, vascular endothelium bear high pressure and shear stress, cause endothelial cell injury, injured endothelial cell can lease cytokines, such as transforming growth factor β (TGF-β), plasminogen activator inhibitor (PAI).[21] Hypertension can directly cause renin-angiotensin-aldosterone system activation and oxidative stress. These factors can cause together kidney damage, matrixfibrosis and tissue hardening.[22, 23]

Clinically nephroangiosclcrosis may occur before significant elevation of blood pressure, such as unilateral nephrectomy or early type 1 diabetes mellitus (TIDM). Glomerular capillary blood flow is still significantly increased. Therefore, the renal capillary pressure overload, it can lead to nephrosclerosis. high pressure and high shear in glomerular cause endothelial cell dysfunction, which could lead to increase in some active factors such as angiotensin II (Ang II), endothelin-1(ET-1), thromboxane A2 (TXA2), TGF-β2 and platelet-

derived growth factor (PDGF) factors, leading to vasoconstriction, mesangial cell proliferation and collagen deposition, promoting ECM synthesis and secretion. The high pressure in glomeruli can also lead to glomerular visceral epithelial cell injury, increasing permeability of the basement membrane, causing proteinuria, eventually leading to glomerulosclerosis, nephron loss. Therefore, the patients with essential hypertension have low perfusion of ischemic nephron and high perfusion nephron, the latter is more characteristic pattern.

In addition, reactive oxygen species, salt intake, lithium-sodium counter-transport abnormalities, racial and genetic backgrounds, metabolic disorders, age, gender, body mass index, smoking is also influencing factors.

In summary, hypertensive renal damage is secondary to vascular lesions caused by high arterial pressure. The main mechanism of hypertensive renal damage is hemodynamics abnormalities in glomerular, and cytokines, vasoactive substances and the ECM are involved in the disease process.

2.2.2 Pathogenesis of malignant arteriolar nephrosclerosis

The direct vascular injury of elevated blood pressure

When blood pressure is significant elevated, renal artery and glomerular capillary stress and shear stress can be changed, which induce endothelial cells to secrete varied adhesion molecules, promoting inflammatory cell adhesion to endothelial cells, leading to endothelial cell damage.[24] Vascular endothelial cell damage lead to increased permeability, plasma protein and fibrinogen deposition in the vessel wall, induce vascular fibrinoid necrosis and tunica intimal damage. Finally, it appears vascular lumen narrowed and renal ischemia. But some patients with severe and persistent hypertension, whose vascular injury can not become malignant state. It indicates that in addition to intravascular pressure, there are other factors involved in vascular damage.

Activation of renin-angiotensin-aldosterone system (RAAS) and endothelin

Malignant hypertension often accompanied with activation of RAAS, It should be noted that the activation of RAAS may be primary or secondary. Activation of RAAS can promote intermittent vasoconstriction, activate platelets, release thromboxane and platelet derived growth factor (PDGF), stimulate myointimal cell migration and proliferation, cause vascular lumen narrowed, increased level of blood pressure and renal ischemia. When the systolic pressure is over 180-190mmHg critical level, it can occur naturally natriuretic and diuretic phenomenon, the decline in blood volume can further activate the RAAS.[25] In addition, elevated angiotensin can promote inflammatory cells adhesion to endothelial cell, induce apoptosis of endothelial cells, damage the integrity of blood vessels, induce fibrinoid necrosis of arteriole by "vascular toxicity".[26] Endothelin is of powerful vasoconstrictor function, it can cause sustained elevation of blood pressure. Animal model of malignant hypertension has been confirmed to plasma endothelin and endothelin-mRNA expression in renal tissue increased.[27]

Microvascular coagulation and thrombosis

Hypertension damage vascular endothelial, which active directly coagulation system, lead to platelet aggregation and fibrin deposition in vascular lumen. When red blood cells pass through the damaged vascular lumen, it prone to result in damage and lead to microvascular coagulation. Meanwhile, both platelet aggregation and adhesion of

leukocytes on vessel wall lead to turbulence, promoting to form platelet micro-thrombus.[28]

Genetic factors

It is reported that HLAB15, DR3, BW35 and CW4 are significantly associated with the incidence of malignant hypertension.[29, 30]

2.3 Lipid metabolic disorders and pathogenesis of metabolic syndrome-associated nephropathy

Lipid metabolism and kidney disease are closely related. As early as 1982, Moorhead[31] proposed that lipid accumulation can lead to chronic renal injury, it is not only a lot of primary or secondary renal diseases with common clinical manifestations, but also the progress of the diseases.[32] Hyperlipidemia, in addition to proteinuria and hypertension, promotes CKD progression outside the third most important factor. In polycystic kidney disease, obesity, diabetes and hypertension in animal models, hypercholesterolemia were found to accelerate the progress of kidney diseases, and high-fat diet can induce kidney macrophages and foam cell formation leaching, resulting in glomerular sclerosis.[33] In obese Zucker rats, lowering serum triglycerides improves glomerular sclerosis.[34] These results suggest that lipid metabolism is closely related with renal dysfunction, and a series of clinical studies have also been to the same conclusion. Samuelsson et al[35] found triglyceride-rich lipoproteins containing Apo-B in patients with CKD are closely related to the progress of the disease; Muntner et al[36] found in 12 728 subjects with normal renal function that low HDL cholesterol and hypertriglyceridemia in individuals with impaired renal function appeared more dangerous.

2.3.1 Mesangial cell function

Regulation of glomerular filtration of mesangial cells to produce matrix components, involved in the development of many glomerular diseases. Mesangial cell surface LDL, oxidized HDL and very low density lipoprotein act through receptor pathway and the corresponding lipoproteins. LDL can bind to mesangial cells and mesangial cell function can offset.[37] LDL stimulates mesangial cells and had a "phase effect", ie, low concentration of LDL stimulates cell proliferation, and high concentrations inhibits cell proliferation as toxic cells effect. The effect of LDL promoting mesangial cell proliferation may be related to arachidonic acid metabolism. Mesangial cells cytochrome P450 monooxygenase system produces epoxide metabolic pathways, it can promote cell proliferation, LDL oxidation and the formation of more toxic OX-LDL in a dose dependent manner, which can further increase mesangial cell injury. The mesangial cells and macrophages form foam cells and release cytokines and growth factors, such as transforming growth factor β, tumor necrosis factor, platelet derived growth factor and interleukin-1 and so on. These cytokines can stimulate the LDL receptor gene transcription and expression of epithelial cells, mesangial cells and macrophages, and promote the deposition of lipid in kidney cells and induced renal injury.[38] Mesangial cells themselves can be oxidized by LDL. OX-LDL can induce apoptosis of mesangial cells.

2.3.2 Mesangial matrix

Glomerular mesangial matrix includes type IV collagen, fibronectin and laminin. LDL and LDL oxidation in vitro can stimulate the increase of extracellular matrix components. LDL

can be activated in mesangial cells by LDL protein kinase C, which promotes transforming growth factor-β synthesis in the cells, and TGF-β can stimulate the cells to produce tissue inhibitor of matrix metalloproteinases, inhibiting matrix degradation and leading to the increase of mesangial matrix.[39] It has been confirmed by in vitro experiments that lipids increased the expression of TGF-β mRNA in mesangial cells and epithelial cells.

2.3.3 Endothelial cells

Endothelial cells with LDL receptor, VLDL receptor and LDL receptor related protein. Lipoprotein receptors and related, or non-receptor pathway, causing cell proliferation, lipoprotein lipase and lipoprotein receptors can enhance and strengthen its effect in promoting cell proliferation. OX-LDL and Lp of endothelial dysfunction caused mainly by interfering with the vasodilators nitric oxide synthesis and direct inactivation; and increased thromboxane A2 and endothelin production, damage vascular endothelial NO dependent relaxation response, cause renal ball efferent arteries, increasing the pressure in the glomerular endothelial cells to further damage, the release of cytokines, to promote cell proliferation, glomerular sclerosis. In addition, the lipoprotein receptor pathway through the endothelial cells directly mediated endothelial cell injury, while activation of coagulation and fibrinolytic system activation and inhibition of platelet function, leading to fibrin deposition and thrombosis, increased glomerular injury.

2.3.4 Glomerular epithelial cells

Glomerular epithelial cell surface LDL, VLDL receptor and lipoprotein receptor related protein, which contains both apoB and apoE, respectively, with the lipoproteins, the annexation of the metabolism of cells. apoE with high affinity receptors, the degree of cellular cholesterol esterification increased, and inhibition of cholesterol synthesis, therefore, glomerular epithelial cellsith more and VLDL, thus not explain the clinical hypercholesterolemia, only lipoprotein formed an exception. Can also cause the deposition of lipids in the glomeruli, glomerulosclerosis occurring phenomenon.

2.3.5 Tubulo-interstitium

Tubular injury showed increased tubulointerstitial matrix proteins and fibrosis. Proximal tubular epithelial cells present LDL, very low density lipoprotein receptor, hyperlipidemia lipid deposition in the renal tubules, tubular epithelial cells by phagocytosis, the formation of foam cells, while LDL, OX-LDL for the expression and FN mRNA secretion, further stimulate tubulointerstitial synthesis, promoting fibrosis.

2.3.6 OX-LDL renal toxicity

OX-LDL can promote renal cell proliferation, apoptosis and phenotypic transformation, involved in the glomerulosclerosis process from cell to cell is too small too many states the state of the process of cell loss.[40] OX-LDL also has the monocyte chemotactic activity of macrophages can express clear the OX-LDL receptor, OX-LDL uptake by macrophages stimulated macrophages after the synthesis of growth factors, cytokines and other related matrix protein synthesis in the media. Extraordinary receptor exists in glomerular mesangial cells and epithelial cells. In the case of lipid metabolism, the oxidation of LDL can be modified first intake, OX-LDL accumulation in the kidney and stimulate the kidney cells to secrete TGF-β1 and other cytokines to promote renal fibrosis, leading to monocyte-

macrophage in the local infiltration. Moreover, the activation of macrophages and can promote LDL oxidation, secretion of TGF-β and PDGF-AD, caused by extracellular matrix and mesangial expansion, creating a vicious cycle.[41] Focal segmental glomerulosclerosis in animal models and human glomerular diseases, a number of chronic renal biopsy tissues were detected by OX-LDL deposition, and the extent of OX-LDL deposition and renal dysfunction and protein was positively correlated with urine.

2.4 Hyperuricemia and pathogenesis of metabolic syndrome-associated nephropathy

Hyperuricemia is highly prevalent in MS patients. A few studies showed that hyperuricemia was associated closely with progression of kidney disease.[42] About 20% to 60% of patients with gout have mild or moderate renal failure. The histological lesion named "gouty nephropathy" includes glomerulosclerosis, interstitial fibrosis, and renal arteriolosclerosis, often with focal interstitial urate crystal deposition.

The precipitation of uric acid in the renal medulla with formation of characteristic tophi was believed to activate an inflammatory response resulting in renal interstitial fibrosis, a loss of nephrons, and ultimately to irreversible chronic renal failure. When pH<5.5 in vivo or dehydration, urate can deposit in the renal tubules and interstitium which cause urate nephropathy. It also can form kidney stone in distal tubule and collecting duct and induce obstruction. Emmerson[43] found that some interstitial deposits of urate and uric acid in the kidney derived from intra-tubular deposits which react with the tubular epithelium and pass into the interstitium; loss of tubular integrity may not be a prerequisite for crystal migration. Toblli[44] confirmed that urate crystals deposit in renal tubular cells, evoke complement, platelet, inflammatory cell and macrophages by classical pathway or alternative pathway, induce the expression of cytokine and transforming growth factor beta increased; stimulate fibroblast to be fibrocyte, activate cross linkage of collagen and ultimately lead to renal fibrosis or renal failure.

However, it is difficult to ascribe the generalized renal damage in gout to the deposition of urate crystals, for they are often only focally present.

Recent studies have reported that mild hyperuricemia in normal rats induced by the uricase inhibitor, oxonic acid (OA), results in systemic hypertension, renal vasoconstriction, glomerular hypertension and hypertrophy, and tubulointerstitial injury independent of intra-renal crystal formation.[45-47] It has also been found that hyperuricemia can accelerate renal disease in the remnant kidney model and accelerate experimental cyclosporine nephropathy.[48,49] The main pathophysiological mechanism by which uric acid causes these conditions involves the inhibition of endothelial nitric oxide bioavailability and direct actions on endothelial cells and vascular smooth muscle cells.[50,51] The importance of these pathways is suggested by a recent prospective study in which lowering uric acid in individuals with hyperuricemia and renal dysfunction was associated with improved BP control and slower progression of renal disease.[52]

There are a lot of clinical evidences that hyperuricemia may induce endothelial dysfunction, as lowering uric acid with allopurinol can improve endothelial function as measured by brachial artery vasodilatation.[53] Interestingly, while both uric acid and nitric oxide (NO) exhibit circadian variation, serum uric acid peaks around 6 a.m. when the level of NO is lowest.[54] This relationship can be accounted for by the finding that uric acid also inhibits endothelial cell dependent vasodilatation of rat aortic rings[55] and NO production in endothelial cells.[56] Furthermore, uric acid blunts endothelial cell proliferation in response to serum. [56] The mechanism by which uric acid inhibits NO levels is complex. It may involve scavenging by

oxidants, which can be induced by NADPH oxidase under hyperuricemia.[57] A reduced NO bioavailability could also be due in part to inhibition secondary to CRP production.[56]
In addition, the activation of RAS plays an important role in the exacerbation of renal injury caused by uric acid, which has been shown to be an important mediator of progression of renal disease, not only by its hemodynamic effects to increase systemic and glomerular pressure, but also by its direct fibrogenic effect in kidney and vessels. The increase of renin expression is observed in hyperuricemic rats. The relationship between serum uric acid and plasma renin activity has been described in humans.[58] Blocking the renin angiotensin system can ameliorate hypertension and renal injury in hyperuricemic rats.[45] Furthermore, studies in humans suggest that uric acid acts on blood pressure and renal injury in part via the renin angiotensin system.[59] All of above discoveries suggest that the roles of uric acid may also be mediated by the activation of the renin angiotensin system.
Hyperuricemia also alters glomerular hemodynamics.[47] Hyperuricemia induces cortical renal vasoconstriction in rats as evidenced by a significant increase of afferent and efferent arteriolar resistances. A decrease in glomerular plasma flow and the ultrafiltration coefficient resulted in a 35% decrease in single nephron GFR whereas glomerular pressure was increased. These changes were restored by allopurinol treatment. Aberrant renal autoregulation appears to be responsible for the glomerular hypertension observed with experimental hyperuricemia. Under normal conditions, an increase in mean systemic arterial pressure causes a reflex vasoconstriction of the afferent arteriole, thus preventing the transmission of the increased pressure to the glomerular circulation. However, in the event that the afferent arteriolar vasoconstriction is insufficient, the transmission of increased pressure to the glomeruli results in glomerular hypertension.[47] While renal vasoconstriction occurs in experimental hyperuricemia, it may be insufficient for the degree of systemic hypertension, therefore glomerular pressures are increased. This may be due to the disease of the afferent arteriole that occurs in the hyperuricemic rats, as evidenced by an increase in the media to lumen ratio. Again, the observation that allopurinol was able to prevent arteriolar hypertrophy leading to a normal renal autoregulatory response indicates a potential role of uric acid on this process.[47]

2.5 Obesity and pathogenesis of metabolic syndrome-associated nephropathy

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure.[60] Abdominal obesity is the form of obesity most strongly associated with metabolic syndrome. Obesity and metabolic syndrome has been found to be independent risk factors for CKD.[3, 61, 62] Treating obesity might stabilize renal function or reverse early hemodynamic abnormalities and glomerular dysfunction.[63, 64] Since the first description of an association between massive obesity and nephrotic proteinuria in 1974, a specific histopathologic pattern characterized by glomerulomegaly, in many cases accompanied by focal segmental glomerulosclerosis, has been described repeatedly in obese patients without any other defined primary or secondary glomerular diseases (including diabetic nephropathy, hypertensive nephrosclerosis, and secondary focal segmental glomerulosclerosis) and now is referred to as "obesity-related glomerulopathy".[65, 66] Overweight, obesity, and the metabolic syndrome have recently emerged as strong independent risk factors for chronic kidney disease (CKD) and ESRD. The multivariate analysis made by Chen et al[3] showed that the risk for being affected by CKD was more than twice as high in patients with an increased waist circumference than in those without, suggesting that obesity may be an independent risk factor for CKD.

Obesity with the features of the metabolic syndrome causes renal dysfunction,[67] increase glomerular filtration rate (GFR), renal blood flow (RBF), and filtration fraction (FF) in experimental and clinical observations.[64, 68, 69] Obesity also increases the risk factor for diabetes and hypertension. Iseki[70] indicate that obesity, including metabolic syndrome, is a potential treatable cause of CKD and ESRD. In a large cohort of >320,000 patients who were followed at Kaiser Permanente, Hsu et al[62, 71] found that a higher BMI was a strong independent risk factor for ESRD even after adjustment for other major risk factors that are associated with ESRD, including smoking, baseline hypertension, and diabetes.

Hyperlipidemia, hyperinsulinemia, hyperleptinemia, hyperuricemia and hypercoagulability, together in obese patients may directly or indirectly affect renal structure and function, caused kidney damage.

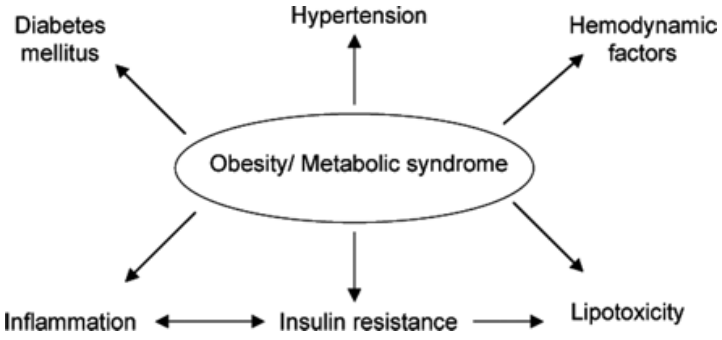
The pathogenesis of ORG may be implicated:

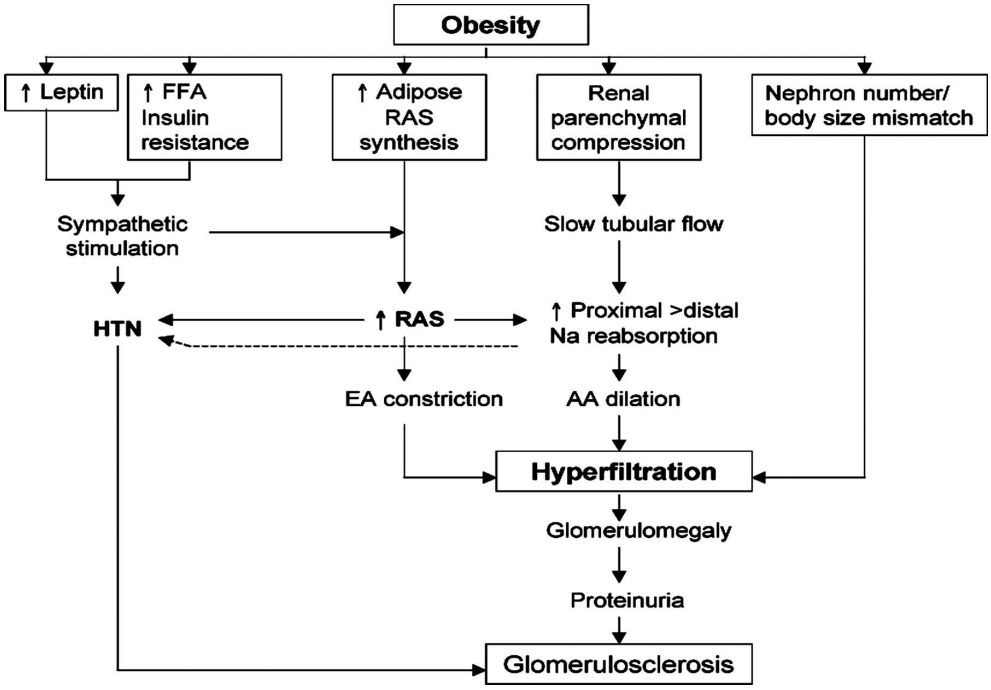
1. Renal hemodynamic alterations: Studies in animals and in humans have shown that obesity is associated with elevated GFR and increased renal blood flow.[68, 71] This likely occurs because of afferent arteriolar dilation as a result of proximal salt reabsorption, coupled with efferent renal arteriolar vasoconstriction as a result of elevated Ang II. In addition, Ang II may have a role in the regulation of adipokine production in adipose tissue and may increase insulin resistance in the setting of obesity.[72, 73]
2. Sympathetic stimulation: Obesity-related there is widespread increased sympathetic nerve activity, its causes and obese patients with baroreceptor dysfunction and vasomotor centers less on the incoming inhibitory signals.[74]
3. Leptin: Wolf[75] studies have shown that Leptin levels in obese patients was significantly higher, it was upregulated in glomerular endothelial cells and mesangial cells. Increased TGF-β1 and its receptor mRNA expression promote glomerular endothelial cells and mesangial cell proliferation.
4. Inflammation: The results of several studies have suggested that adipose tissue, especially visceral adipose tissue, is a major source of cytokine secretion in the metabolic syndrome, and that inflammatory cells, especially mature bone marrow–derived macrophages, invade adipose tissue early in obesity.[76, 77] Inflammation was linked to obesity and the metabolic syndrome in patients with CKD. Ramkumar et al[78] found a strong association between inflammation as defined by a CRP level >3 mg/dl and a high BMI in patients with CKD.
5. Changes in fatty acid composition in kidney, causing kidney reduced the release of vasoactive substances, increased the pressure of glomerular capillary. Hall et al[79] show that the mechanisms responsible for increased sodium reabsorption and altered pressure natriuresis in obesity include activation of the renin-angiotension and sympathetic nervous systems, and physical compression of the kidneys due to accumulation of intra-renal fat and extracellular matrix.

2.6 Diabetes and pathogenesis of metabolic syndrome-associated nephropathy

Diabetic nephropathy is the most important long-term complication of diabetes mellitus and a major cause of end-stage renal disease. The condition is associated with excess cardiovascular morbidity and mortality, as well as other diabetic microvascular complications.[80] The etiopathogenesis of diabetic nephropathy appears to involve both genetic and environmental factors leading to disease in a subgroup of patients. Improved knowledge of the natural history and pathophysiology of the condition have enabled

therapeutic strategies to be employed that have improved the outlook for patients with nephropathy.[81]





2.6.1 Historical background

DN has the characteristic of obvious family accumulation, but the incidence of the disease in different races is very different. Diabetic nephropathy is a serious problem resulted from microvascular complications of diabetes mellitus. Thus, genetic factors determining susceptibility plays an important role in DN, which was shown by studies about angiotensinogen (AGT) gene, angiotensin converting enzyme (ACE) gene, aloes reeducates (AR) gene, Glut21 gene, endothelial cells Nitric oxide synthase (eNOS) gene, cell receptor β-

chain of fixed area (TCRβ) genes. Correlation between gene polymorphism and the occurrence and development of DN has also been discovered.[82]

2.6.2 Chronic hyperglycemia

Hyperglycemia can activate intracellular key catalytic glucose into sorbitol AR. With high glucose increased AR activity, polyol metabolism in kidney is active, so that excessive accumulation of sorbitol and fructose. Sorbitol polarity is strong, thus can not freely through the membrane, while fructose has little further metabolism. It results in fructose accumulation and the increase of intracellular osmotic pressure and therefore cell edema. While the level of intracellular inositol is decreased, glutathione, NADH / NAD + ratio increased, Na2K2ATP activity decreased, which results in tissue hypoxia and endothelial cell damage, contributing to the occurrence and development of DN.[83] Some studies suggest that AR gene polymorphism is related to AR mRNA levels in peripheral blood mononuclear cells and diabetic micro-vascular complications. High glucose can lead to non-enzymatic glycosylation reaction, formation of advanced glycation end products (AGEs) in many organs. AGEs bind the AGE receptor (RAGE) of vascular endothelial cells, macrophages, vascular smooth muscle cells, mesangial cells and other cells. RAGE, as a signal transduction receptor, activates mitogen-activated protein kinase pathway (MAPK) and nuclear factor (NF) -κB signaling pathway (cell proliferation and inflammatory response), Ras pathway (stress and apoptosis), Rac/Cdc-42 pathway (cell growth and movement), Jak / Stat pathway (regulation of gene expression), raising the expression of a variety of growth factors, such as platelet derived growth factor and transforming growth factor, basic fibroblast growth factor, and adhesion molecules, such as intercellular adhesion molecules-1 and vascular cell adhesion molecule.[84]

Reactive oxygen species (ROS), including superoxide radicals, hydrogen peroxide, hydroxyl radicals, and lipid peroxidation, are of in vivo biological activity of inducing aerobic metabolism. Studies demonstrated that increased oxidative stress existed in diabetes. High glucose increased the generation of ROS by inhibiting the activity of the three glycerol phosphate dehydrogenase, leading to the development of microvascular complications mediated by diabetes-related signaling pathways, such as PKC pathway, polyol pathway, hexosamine pathway and AGEs formation. High glucose can also increase the the gene transcription of adhesion molecules and inflammatory NF-κB. Increased levels of ROS can also increase peroxynitrite synthesis and nitrotyrosine formation, leading to DNA damage, prompting the development of diabetic microvascular complications.[85]

PKC activation in diabetes is a common pathway of vascular injury. PKC family, has more than ten isozymes and plays, mainly PKC-β, a role in vascular injury in diabetes. PKC can be activated through a variety of ways. Hyperglycemia within the tissue cells can increase PKC activation, increase NADH / NAD + ratio, increase oxidative stress.[86] PKC inhibited endothelial nitric oxide synthase (eNOS) activity, decreasing NO level and NO-mediated inhibition of cyclic guanosine monophosphate (cGMP) generation, leading to vasomotor dysfunction.[87] PKC stimulated platelet aggregation and increased the content and activity of PAI-1, promoting the hypercoagulability of patients with diabetes. PKC promoted vascular endothelial growth factor (VEGF) expression, promoting angiogenesis, increasing vascular permeability.[88] PKC regulated the expression of transforming growth factor (TGF)-β and increased the expression of fibronectin and collagen type IV, leading to extracellular matrix expansion. Researches had shown that TGF-β promoted local extracellular matrix deposition.

2.6.3 Microvascular disorders

Homodynamic changes in early diabetic micro-vascular disorders characterized by increased pressure, is generally reversible. High glucose increased the plasma osmolality, increasing blood volume and renal blood flow. Diabetes changed the ratio between the resistance of glomerular arterioles, resulting in glomerular capillary hyperperfusion and high pressure, the mesangial matrix expansion and basement membrane thickening, and therefore leading to focal glomerular sclerosis.[89] Meanwhile, the capillary endothelial cell was damaged, the normal filtration barrier was damaged, protein filtration was increased, which result in the loss of glomerular function.

Microvascular disorders in DN is the pathological basis of clinical manifestations, the most prominent is the basement membrane thickening and the damage of glomerular filtration barrier function. The pathogenesis includes continuing glomerular hyperperfusion and hyperfiltration, increased collagen synthesis. Sustained high glucose leads to the non-enzymatic glycation of basement membrane protein components. Another major pathological feature of DN is increased mesangial matrix. Mesangial expansion is mainly resulted from the following factors: glomerular hemodynamic abnormalities, increased capillary pressure. High filtration can stimulate the increase of mesangial matrix, the damage of glomerular filtration barrier. The leakage and accumulation of macromolecules in the membrane system stimulate mesangial cell proliferation and promote matrix production. High blood glucose activates protein kinase C in mesangial cell and the increase in mesangial matrix protein synthesis. Cellular growth factors are the important factors playing roles in increasing mesangial matrix. The most important of which is TGF-β. High blood glucose, glomerular capillary pressure and angiotensin (Ang) - II can promote the synthesis of extracellular matrix of mesangial and tubular epithelial cell. In addition endothelin (ET) also stimulate the proliferation of mesangial cells and the secretion of matrix. NO had inhibitory effect on mesangial cells. NO level is increased in early stage of diabetic nephropathy, which results in glomerular hyperperfusion and hyperfiltration. And it is reduced in the late stage due to endothelial cell damage, which leds to the increasing of mesangial matrix, playing a role in accelerating glomerular injury.[90]

In diabetes, blood flow slows down and micro-thrombosis is easy to form, mainly due to abnormal endothelial cell and platelet function. The increase in serum of von Willebrand factor (vWF) is considered a sign of vascular endothelial cell injury. vWF is synthesized by endothelial cells, mediates platelet adhesion to endothelium, promote thrombosis. Overseas studies suggest that vWF is an independent risk factor for microvascular disease in diabetes.[91] In addition endothelial dysfunction is also reflected by the decreased activity of tissue plasminogen activator (t-PA) or the incresed activity of plasminogen activator inhibitor (PAI) which result in decreased fibrinolytic activity. Decreased prostacyclin-2 (PGI-2) synthesis reduced platelet inhibition. Increased release of ET can promote platelet aggregation. Plasma β platelet globulin (β-TG) and platelet factor 4 (PF4) levels reflect platelet activation. Increased thromboxane (TXA) -2 synthesis promote platelet aggregation and thrombosis. Many studies shown that increased platelet aggregation plays a very important role in the development of microangiopathy in type-2 diabetes mellitus, in addition to long-term hyperglycaemia.

2.7 Metabolic syndrome in pathogenesis of allograft renal damage

The metabolic syndrome (MS) is a cluster of interrelated common clinical entities, which include obesity, insulin resistance, glucose intolerance, hypertension and dyslipidaemia. Insulin resistance is their common pathophysiological basis. Metabolic syndrome

significantly increases the risk for cardiovascular disease and chronic kidney disease.[92] Recently it has been found that MS is also common in renal transplant recipients. How is kidney transplantation complicated with metabolic syndrome?

2.7.1 Immunosuppressive therapies

Immunosuppressive therapies induce post-transplantation diabetes

Post-transplantation diabetes is believed to be multi-factorial, probably involving β-cell toxicity and increased insulin resistance. In addition to other risk factors, studies suggest that immunosuppressive regimens may account for a large degree of the increased risk for the development of post-transplantation diabetes.

Corticosteroids and Calmodulin inhibitors (cyclosporine and tacrolimus) are widely used in kidney transplant recipients. They have long been recognized to potently affect glucose tolerance by a prevalent increase of peripheral insulin resistance.

Increasing daily prednisolone dose was independently associated with insulin resistance as glucocorticoids promote gluconeogenesis in the liver, inhibit glucose uptake, diminish glycogen synthesis in skeletal muscle cells and also may attenuate insulin secretion from pancreatic beta-cells. Several mechanisms displayed in vitro studies on murine β-cell or human cell lines incubated with dexamethasone, have been proposed: insulin secretion inhibition by increased expression of a2-adrenergic receptors, decreased cAMP levels, decreased Glut2 protein at the β-cell plasma membrane, down regulation of glucokinase mRNA, increased voltage-gated K+channel activity, β-cell apoptosis through the activation of the calcineurin phosphatase and the corticosteroid receptor.[93-96]

Calcineurin inhibitors, tacrolimus and cyclosporine cause reversible toxicity to islet cells and may directly affect the transcriptional regulation of insulin expression. Furthermore, both calcineurin inhibitors impair insulin gene transcription regulation through the inhibition of calcineurin signalisation. Other mechanisms have been proposed: closing of the ATP-sensitive potassium channel, interference with mitochondrial function of pancreatic β-cell, impairment of glucose-stimulated insulin secretion downstream of the rise in intracellular Ca2+ at insulin exocytosis, reduced ATP production and glycolysis derived from reduced glucokinase activity, decreased islet cell viability by a down regulation of anti-apoptotic factors and accumulation of pro-apoptotic mediators in cultures of freshly isolated human islets. Tacrolimus is more diabetogenic than cyclosporine.[97-99] At the first, it can be due to the steroid mimetic effect of tacrolimus. Tacrolimus binds to FK506-binding protein (FKBP), predominantly FKBP-12. Another immunophilin, FKBP-52 is associated with the cytoplasmic glucocorticoid (GC) receptor complex. When cells are exposed to glucocorticoids, the steroid binds to the GC receptor and liberates it from the complex. By binding to FKBP-52 in the GC receptor complex, tacrolimus may alter the affinity of interactions and either cause a release of the GC receptor at lower steroid concentrations, a steroid-sparing effect, or it may free the GC receptor I absence of steroids . Second, tacrolimus increases the bioavailability of steroids.

Immunosuppressive therapies induce obesity

Prednisone can induce overweight or obesity in transplant recipients, espically abdominal obesity, the abdominal fat which is sensitive to catecholamine can induce insulin resistance through elevating the level of low density lipoprotein and very low density lipoprotein, inhibiting the activity of phosphofructokinase, blocking glycolysis and glucose uptake.

2.7.2 Virus infection

Cytomegalovirus is one of the most important pathogenic microorganism after renal transplantation, Cytomegalovirus infection can infect insulin secretion, induce insulin resistance and impair the function of pancreatic β-cell, and it is independent infector of post-transplant diabetes mellitus（PTDM).[100] Cytomegalovirus infection increases the activity of tumor necrosis factor(TNF), TNF can affect the function of islet B cell and decrease the organism's sensitivity to insulin, that will promote insulin resistance in renal transplant recipients.

Patients with HCV infection were found to have a 8.3-fold higher risk of appearing PTDM compared with HCV(-) patient.[101] Patients with HCV disease have increased peripheral insulin resistance and are hyperinsulinemic, similar to those with type 2 DM. It also is postulated that patients with HCV have decreased β-cell responsiveness, possibly caused by direct viral effects. Other explanations include an autoimmune pathogenesis because HCV has been associated with several autoimmune diseases, including cryoglobulinemia, Hashimoto's thyroiditis, and Sjogren's syndrome. This would suggest antibody-mediated destruction of pancreatic β-cells. A potential role of viruses in the cause of type 1 DM has been suggested, as well as a role for enteroviruses. A greater prevalence of PTDM in patients with HCV therefore likely is caused by a combination of increased peripheral insulin resistance and either a direct viral- or immune-mediated effect of HCV on pancreatic β-cells that results in relative insulin deficiency.

2.7.3 Polycystic kidney disease

Insulin resistance with compensatory hyperinsulinaemia has been reported in adult polycystic kidney disease patients. It is reported that post-transplant diabetes mellitus (PTDM) occured in 10 adult polycystic kidney disease (APKD) patients and four controls (34.6% vs 15.3%; $P<0.005$).[102] It has been shown that increased membrane fluidity and abnormal erythrocyte Na/Li counter-transport, both abnormalities associated with insulin resistance, are present in APKD patient.[103, 104]

3. Diagnosis

Till now there is no formal denomination of metabolic syndrome associated kidney diseases which are often diagnosed as obesity-associated glomerulonephropathy, diabetic nephropathy, hypertension-associated kidney damage, lipid disorder associated kidney damage and hyperuricemia-associated kidney damage.

The diagnosis of metabolic syndrome associated renal disease is generally two levels criterion (Table 3-1). The first level is for large sample epidemiological screening, which is base on the diagnosis of MS and CKD, and often including MS complicated with CKD or CKD complicated with MS. The second is for clinical evaluation and treatment, which base on the diagnosis of MS and the clinical presentation and renal pathology of obesity-associated glomerulonephropathy, diabetic nephropathy, hypertension related renal damage lipid disorder associated kidney damage and hyperuricemia-associated kidney damage. Renal biopsy might be necessary for the investigation and clinical diagnosis of metabolic syndrome associated kidney diseases under some circumstances, and the pathological evaluation should be made with not only light microscope, but also immunofluorescence and electron microscope. The definite diagnosis of metabolic syndrome associated kidney diseases should exclude other primary or secondary kidney diseases. In clinical practice, metabolic syndrome

associated kidney diseases are often accompanied with other primary or secondary kidney diseases. Post-transplant metabolic syndrome associated kidney diseases are often complicated with acute or chronic rejection in renal allograft.

Level 1 Metabolic syndrome complicated with chronic kidney disease

1. Consistent with the diagnosis criterion of metabolic syndrome (necessary).
2. Consistent with the chronic kidney disease (necessary).

Level 2 Metabolic syndrome associated kidney disease

1. Consistent with the diagnosis criterion of metabolic syndrome (necessary).
2. One of the following diagnosis criterions.
    i. The obesity patient with the renal pathological character of obesity- associated glomerulonephropathy.
    ii. The diabetes patient with the renal pathological character of diabetic nephropathy.
    iii. The hypertension patient with the renal pathological character of hypertension related renal damage.
    iv. The patients with hyperuricemian and the renal pathological character of uric acid nephropathy

Table 3.1. The diagnosis of metabolic syndrome associated renal disease: two levels of criterion

3.1 Diagnosis of MS

A diagnosis of metabolic syndrome associated kidney diseases must be based on the diagnosis of metabolic syndrome which is not only composed of central obesity, diabetes or prediabetes, hypertension, lipid metabolic disorder, etc., but also insulin resistance as its critical pathophysiological basis. the American Heart Association (AHA) along with the National Heart, Lung and Blood Institute issued an up-to-date version on the diagnosis of the metabolic syndrome.[105] The International Diabetes Federation (IDF) also provided a working definition for the syndrome (Table 3-2).[106]

Clinical diagnosis criteria	**Categorical cut points**
Insulin resistance	None
Body weight	Increased WC (population specific) plus any 2 of the following
Lipid	TG ≥150 mg/dL (1.7 mmol/L)or on TG Rx HDL-C <40 mg/dL (1.03 mmol/L)in men or <50 mg/dL (1.3 mmol/L) in women or on HDL-C Rx
Blood pressure	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	≥100 mg/dL(5.6 mmol/L), includes diabetes

Table 3.2. Criteria for Clinical Diagnosis of Metabolic Syndrome (IDF, 2005)

The present AHA/NHLBI statement, in contrast to IDF, maintains the ATP III criteria except for minor modifications (Table 3-3).

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	**Categorical cut points**
Elevated waist circumference	≥102 cm (≥40 inches) in men, ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) Or On drug treatment for elevated triglycerides
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men<50 mg/dL (1.3 mmol/L) in women Or On drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mm Hg systolic blood pressure, Or ≥85 mm Hg diastolic blood pressure Or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL (5.6 mmol/L) or On drug treatment for elevated glucose

Table 3.3. Criteria for Clinical Diagnosis of Metabolic Syndrome (AHA/NHLBI)

It is suggested by the data of our recent community-based screening that the incidence of MS according to the diagnostic criteria of CDS was lower than that according to the diagnostic criteria of IDF. Some residents with MS mainly presentation of abdominal obesity would be missed diagnosis by the criteria base on BMI. In the components of MS, hypertension, abdominal obesity and lower high density lipoprotein were more common than others.

3.2 Diagnosis of CKD

The early evidences of metabolic syndrome associated kidney diseases might exist before the occurrence of clinical diabetes or hypertension, and it should include elevated or decreased GFR, microalbuminuria or even smaller proteins occurring in the urine before microalbuminuria, the presentation of renal pathological disorders existing before the clinical manifestation.

According the K/DOQI definition and classification, CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens. GFR can be estimated from calibrated serum creatinine and estimating equations.[107]

There are many methods to determine GFR have been used, such as measuring GFR using exogenous markers, or endogenous markers, using exogenous marker is extremely inconvenience and is not used in clinical and epidemic practice. The often used endogenous markers are serum creatinine (SCr), usually calculated as creatinine clearance (CCr), and serum cystatin C. Most studies have shown that serum cystatin C levels correlate better with GFR than does serum creatinine alone, especially at higher levels of GFR. In practice, combining use of multiple indexes, such as SCr, age gender and race to evaluate GFR will be more accurate. So there many equations have been used to estimate GFR. The two most commonly used equations to estimate GFR are serum creatinine based: Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) equations. A recent study involving a pooled analysis of individuals with chronic kidney disease proposed an

estimation equation that included serum cystatin C in addition to serum creatinine, age, sex, and race. Studies concluded this equation provided the most accurate estimates.
The CG equation is as follows:

$$CCr(ml/min) = \{[140 - Age(yr)] \times Weight(kg)\}/SCr(mg/dl) \times 72 \times (0.85, \text{if female})$$

The six variable MDRD equation is as follows:

$$GFR = 170 \times (SCr)^{-0.999} \times (Age)^{-0.176} \times 0.762(\text{if female}) \times 1.18(\text{if black}) \times (BUN)^{-0.170} \times (Alb)^{0.318}$$

where BUN is blood urea nitrogen and Alb is albumin.
The abbreviated version or four variable version of the MDRD equation (ml/min per 1.73 m2) is as follows:

$$GFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times 0.742(\text{if female}) \times 1.212(\text{if black})$$

The equation base on SCr and serum CysC is as follow:

$$eGFR = 177.6 \times (SCr)^{-0.65} \times (CysC)^{-0.57} \times (Age)^{-0.20} \times 0.82(\text{if female}) \times 1.11 (\text{if black})$$

3.3 Renal pathological changes in metabolic syndrome

There is a small sample retrospective design.[108] The histopathologic presentation of patients with metabolic syndrome compared with controls had a greater prevalence of tubular atrophy, interstitial fibrosis, and arterial sclerosis, suggesting microvascular disease. Patients with metabolic syndrome had greater global and segmental glomerulosclerosis. Glomerular volume and cross-sectional surface area were not different. The combined end point of tubular atrophy greater than 5%, interstitial fibrosis greater than 5%, and presence of arterial sclerosis was more prevalent in patients with metabolic syndrome than controls.

4. Prevention and treatment

Aggressive multitargeted management of the metabolic syndrome can also improve cardio vascular and renal outcomes and is highly recommended by the American Heart Association. Although no study has evaluated whether multiple interventions can reduce the incidence or progression of CKD in patients with the metabolic syndrome.[109]

4.1 Lifestyle changes

Lifestyle interventions are the first line therapies recommended for treatment of the metabolic syndrome. The essential and important measurements include weight reduction, regular exercise, and a low-calorie, low-fat diet. Yet few data are available to indicate that such lifestyle interventions can prevent or reverse renal damage.[109]

4.2 Medication treatment

If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated. Such as medicine for treatment of diabetes, hypertension, lipid disorder and hyperuricemia.

4.2.1 Treatment of elevated blood glucose

In metabolic syndrome patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset of type 2 diabetes mellitus.

Intensive glucose control to lower the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.

Oral Antihyperglycemic Agents:[110] Metformin, thiazolidinediones and acarbose will lower risk for type 2 diabetes mellitus in people with IFG or IGT. The nonsulfonylurea insulin secretagogues repaglinide and nateglinide can be used in renal failure without dose adjustments. Metformin is contraindicated in renal failure because of the associated risk for lactic acidosis. It can be used at low dosages up to a creatinine clearance of 30 to 60 ml/min and should be avoided with clearances<30 ml/min. Although the metabolism of thiazolidinediones is unaffected by renal failure, they must be used with caution in this context because of their volume retaining effect with a risk for heart failure. The sulfonylureas (glyburide, gliclazide, glipizide, glibenclamide, tolbutamide, and chlorpropamide) have increased potency to prolong sulfonylurea induced hypoglycemia as the renal function decreases and are contraindicated in severe renal failure. α-Glucosidase inhibitors (acarbose and miglitol) are also contraindicated in renal failure.

Insulin therapy: Insulin therapy maybe benefits in glycaemic control, but not improves insulin resistance and metabolic syndrome. Insulin analogues, whose main objective is to stimulate physiologic insulin secretion, has opened new therapeutic possibilities in diabetic CRF patients.[111] Although only a few studies have evaluated the clinical efficacy and safety profile of insulin analogues in CRF patients, preliminary results appear hopeful. There is another concern of insulin injection for long term might be unfavourable, as ectogenous insulin may inhibit endogenous insulin secretion and results in the lack of the co-secretion of other beneficial substances such as C-peptide which is just now known to be potential in the treatment of diabetic nephropathy.[112]

4.2.2 Treatment of elevated blood pressure

In the presence of diabetes or chronic kidney disease, the blood pressure goal is <130/80 mm Hg. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in the metabolic syndrome, especially when either type 2 diabetes mellitus or chronic renal disease is present. ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors.

4.2.3 Treatment of dyslipidemia

According to ATP III, as long as LDL-C remains above goal level, LDL-C is the primary target of therapy even in the metabolic syndrome. Other lipid risk factors are secondary. The LDL-C goals depend on estimates of absolute risk.

The main effects of Statin therapy are reduction of LDL-cholesterol, triglyceride and systemic inflammation, possible improvement of endothelial function and inhibition of renal endothelin 1-mediated proteinuria. The goal level of LDL-cholesterol: <1.80 mmol/l in very high-risk patients and <2.60 mmol/l in high-risk patients.[109]

Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. The main effects of fibrates therapy are decrease of triglycerides, increase of HDL, increase of insulin sensitivity, anti-inflammatory and antihypertensive action, and also reduction of mesangium-induced glomerular matrix deposition.[109]

4.3 New treatment

Islets transplantation or stem cell transplantation has shown very exciting future in more effectively controlling blood glucose and preventing and treating diabetes-associated organ damage. More early intervention and prevention targets have been found for metabolic syndrome associated kidney diseases.

4.3.1 Islets transplantation

Pancreas or Islets transplantation is indicated to treatment of type 1 diabetes which insulin is insufficient for normal glucose metabolism. After long term (more than five years) of normoglycemia, diabetic nephropathy will be reversed.[81] It is not clear that pancreas or Islets transplantation will be benefit to improve of type 2 diabetes. In fact, insulin resistance will be more serious after transplantation due to the use of immunosuppressive agent.[113] Our small sample of patients with type 2 diabetes and ESRD receive combined transplantation of islets and kidney shown reversion of the peripheral nerves and vascular diseases, and maybe a protection of renal graft from damage of hyperglycosemia.

Islet transplantation is an effective therapy for insulin-dependent diabetes mellitus, based on the research data which indicated that islet transplantation could not only retrieve the glycometabolism disorders but also prevent and reverse diabetes-associated microangiopathy. According to the registration data of the International Organ Transplantation Center, there had been up to 1300 patients received islet transplantation by the end of 2006. More than 40 institutes have developed islet transplantation for totally 550 cases of diabetic patients, since the Edmonton Islet Transplantation Protocol was available in 2000. The growth rate increased markedly compared to the era before 2000.

The islets isolated from donor's pancreatic tissue, by means of enzyme digestion and centrifugal purification, are injected into recipients' liver through portal vein. The transplanted islets locate in hepatic sinus, adjusting the synthesis of hepatic glycogen and reversing the disorders of glycometabolism through secreting insulin. Autogeneic islet transplantation is limited in patients received entire or partial resection of pancreas due to chronic pancreatitis and tumor. Allogeneic islet transplantation needs immunosuppressants and therefore is mainly suit for kidney transplant recipients with type I diabetes-associated renal failure. Along with the development of new immunosuppressants, the indications of islet transplantation are increasing. In recent years islet transplantation along has been applied in patients with "friable" type I diabetes with refractory severe hypoglycemia while without renal failure, and considered for patients with type II diabetes and complete lost of islets' function.

A four year cooperative study was carried out in 9 islet transplantation centers of USA, Canada and Europe and 36 cases of type I diabetes received islet transplantation according to coincident Edmondon Protocol. It was shown by the data that 16 cases were insulin-independent one year after transplantation (16/36, 44%) and, among them, 5 cases were still insulin-independent after 2 years follow-up (5/16, 31%). The study proved the efficacy of Edmondon Protocol in significantly increasing the success rate of islet transplantation. Besides, it is indicated by the success of Edmondon islet transplantation protocol that islet transplantation along is also fit to patients with type I diabetes while it is not always needed to be performed together with renal transplantation. In recent years some islet transplant recipients without renal failure were only administered short-term of immunosuppressive treatment (Daclizum administered on day 1 and day 3) and good efficacy achieved, which suggests that islet transplantation along may be do not need long-term immunosuppression therapy.

The surgical operation of islet transplantation is simple, but the isolation and the purification of islets belong to high-tech range. The skill and experience of operators are extremely important. Different operators have markedly different isolation results even they use the same pancreas from the same donor and apply the same isolation procedure. How to get enough functional islets from donor's pancreas is the key technique for islet transplantation. Islet transplantation is a program needs multi-department and multi-subject cooperation. A cooperation network should include endocrinologists, surgeons, transplantation center, net-serving staff, official administrators, transplant immunologists, transportation department. In addition, the qualities of a lot of procedures during transplantation can influence the result of islet transplantation, including patient selection, tissue matching, reservation and transportation, islet isolation and purification, islet implantation, blood glucose controlling during islet transplantation, immunosuppressant administration, and function evaluation after transplantation. The determination of islet cell auto-antibodies in recipients' blood after transplantation is important for the prognosis of long-term islet transplantation efficacy. We should further investigate the relationship between the production of islet cell auto-antibodies and the survival of transplanted islets, and make sure if the auto-antibodies is the main factor resulting in the damage of transplanted islets. Islet cell auto-antigens can be produced with gene recombination and immune absorption column can be prepare with the auto-antigens and used to in time eliminate the auto-antibodies in patients' blood, reducing islet damage induced by the antibodies and increase the long-term survival of transplanted islets.

4.3.2 Stem cell transplantation

Stem cell transplantation has shown effective in treatment of type 1 diabetes shown beta cell function increased,[114] and also in treatment of type 2 diabetes with significant increase of serum adiponectin and glucose tolerance.[115] Data from studies of NOD/SCID mice with diabetes shown that mesenchymal stem cells (MSCs) administration can prevent and treat diabetic nephropathy, prevent the pathological changes in the glomeruli and enhances their regeneration resulting in improved kidney function in diabetic animals.[116]

5. References

[1] Lim H. S., Patel J. V., Lip G. Y. Metabolic syndrome: a definition in progress. Circulation 2004, 110(4): e35; author reply e35.

[2] Lee H. B., Ha H., Kim S. I., et al. Diabetic kidney disease research: where do we stand at the turn of the century? Kidney Int Suppl 2000, 77S1-2.

[3] Chen J., Muntner P., Hamm L. L., et al. The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med 2004, 140(3): 167-174.

[4] Fliser D., Kielstein J. T., Menne J. Insulin resistance and renal disease. Contrib Nephrol 2006, 151203-211.

[5] Parvanova A. I., Trevisan R., Iliev I. P., et al. Insulin resistance and microalbuminuria: a cross-sectional, case-control study of 158 patients with type 2 diabetes and different degrees of urinary albumin excretion. Diabetes 2006, 55(5): 1456-1462.

[6] Chen J., Muntner P., Hamm L. L., et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol 2003, 14(2): 469-477.

[7] Cusumano A. M., Bodkin N. L., Hansen B. C., et al. Glomerular hypertrophy is associated with hyperinsulinemia and precedes overt diabetes in aging rhesus monkeys. Am J Kidney Dis 2002, 40(5): 1075-1085.
[8] Segev Y., Landau D., Rasch R., et al. Growth hormone receptor antagonism prevents early renal changes in nonobese diabetic mice. J Am Soc Nephrol 1999, 10(11): 2374-2381.
[9] Wang S., Denichilo M., Brubaker C., et al. Connective tissue growth factor in tubulointerstitial injury of diabetic nephropathy. Kidney Int 2001, 60(1): 96-105.
[10] Anderson P. W., Zhang X. Y., Tian J., et al. Insulin and angiotensin II are additive in stimulating TGF-beta 1 and matrix mRNAs in mesangial cells. Kidney Int 1996, 50(3): 745-753.
[11] Vedovato M., Lepore G., Coracina A., et al. Effect of sodium intake on blood pressure and albuminuria in Type 2 diabetic patients: the role of insulin resistance. Diabetologia 2004, 47(2): 300-303.
[12] Meigs J. B., Mittleman M. A., Nathan D. M., et al. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. JAMA 2000, 283(2): 221-228.
[13] Hagiwara H., Kaizu K., Uriu K., et al. Expression of type-1 plasminogen activator inhibitor in the kidney of diabetic rat models. Thromb Res 2003, 111(4-5): 301-309.
[14] Irving R. J., Noon J. P., Watt G. C., et al. Activation of the endothelin system in insulin resistance. QJM 2001, 94(6): 321-326.
[15] Facchini F. S., Hua N. W., Reaven G. M., et al. Hyperinsulinemia: the missing link among oxidative stress and age-related diseases? Free Radic Biol Med 2000, 29(12): 1302-1306.
[16] Prabhakar S. S. Role of nitric oxide in diabetic nephropathy. Semin Nephrol 2004, 24(4): 333-344.
[17] Steinberg H. O., Baron A. D. Vascular function, insulin resistance and fatty acids. Diabetologia 2002, 45(5): 623-634.
[18] Cowley A. W., Jr., Mattson D. L., Lu S., et al. The renal medulla and hypertension. Hypertension 1995, 25(4 Pt 2): 663-673.
[19] Sealey J. E., Blumenfeld J. D., Bell G. M., et al. On the renal basis for essential hypertension: nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction-volume relationship. J Hypertens 1988, 6(10): 763-777.
[20] Larochelle P. Glomerular capillary pressure and hypertension. Am Heart J 1991, 122(4 Pt 2): 1228-1231.
[21] Perticone F., Ceravolo R., Pujia A., et al. Prognostic significance of endothelial dysfunction in hypertensive patients. Circulation 2001, 104(2): 191-196.
[22] Koo J. R., Vaziri N. D. Effects of diabetes, insulin and antioxidants on NO synthase abundance and NO interaction with reactive oxygen species. Kidney Int 2003, 63(1): 195-201.
[23] Rodriguez-Iturbe B., Quiroz Y., Herrera-Acosta J., et al. The role of immune cells infiltrating the kidney in the pathogenesis of salt-sensitive hypertension. J Hypertens Suppl 2002, 20(3): S9-14.

[24] Piqueras L., Kubes P., Alvarez A., et al. Angiotensin II induces leukocyte-endothelial cell interactions in vivo via AT(1) and AT(2) receptor-mediated P-selectin upregulation. Circulation 2000, 102(17): 2118-2123.
[25] Mohring J., Mohring B., Petri M., et al. Studies on the pathogenesis of the malignant course of renal hypertension in rats. Kidney Int Suppl 1975, S174-180.
[26] Kumar D., Robertson S., Burns K. D. Evidence of apoptosis in human diabetic kidney. Mol Cell Biochem 2004, 259(1-2): 67-70.
[27] Jesmin S., Sakuma I., Togashi H., et al. Altered expression of endothelin and its receptors in the brain of SHR-SP at malignant hypertensive stage. J Cardiovasc Pharmacol 2004, 44 Suppl 1S11-15.
[28] Khanna A., McCullough P. A. Malignant hypertension presenting as hemolysis, thrombocytopenia, and renal failure. Rev Cardiovasc Med 2003, 4(4): 255-259.
[29] Gerbase-DeLima M., Paiva R. L., Bortolotto L. A., et al. Human leukocyte antigens and malignant essential hypertension. Am J Hypertens 1998, 11(6 Pt 1): 729-731.
[30] Forsberg B., Low B. Malignant hypertension and HLA antigens. Tissue Antigens 1983, 22(2): 155-159.
[31] Moorhead J. F., Chan M. K., El-Nahas M., et al. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet 1982, 2(8311): 1309-1311.
[32] Abrass C. K. Lipid metabolism and renal disease. Contrib Nephrol 2006, 151106-121.
[33] Hattori M., Nikolic-Paterson D. J., Miyazaki K., et al. Mechanisms of glomerular macrophage infiltration in lipid-induced renal injury. Kidney Int Suppl 1999, 71S47-50.
[34] Maddox D. A., Alavi F. K., Santella R. N., et al. Prevention of obesity-linked renal disease: age-dependent effects of dietary food restriction. Kidney Int 2002, 62(1): 208-219.
[35] Samuelsson O., Attman P. O., Knight-Gibson C., et al. Complex apolipoprotein B-containing lipoprotein particles are associated with a higher rate of progression of human chronic renal insufficiency. J Am Soc Nephrol 1998, 9(8): 1482-1488.
[36] Muntner P., Coresh J., Smith J. C., et al. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int 2000, 58(1): 293-301.
[37] Joles J. A., Kunter U., Janssen U., et al. Early mechanisms of renal injury in hypercholesterolemic or hypertriglyceridemic rats. J Am Soc Nephrol 2000, 11(4): 669-683.
[38] Sohn M., Tan Y., Klein R. L., et al. Evidence for low-density lipoprotein-induced expression of connective tissue growth factor in mesangial cells. Kidney Int 2005, 67(4): 1286-1296.
[39] Abrass C. K. Cellular lipid metabolism and the role of lipids in progressive renal disease. Am J Nephrol 2004, 24(1): 46-53.
[40] Bussolati B., Deregibus M. C., Fonsato V., et al. Statins prevent oxidized LDL-induced injury of glomerular podocytes by activating the phosphatidylinositol 3-kinase/AKT-signaling pathway. J Am Soc Nephrol 2005, 16(7): 1936-1947.

[41] Sugimoto K., Isobe K., Kawakami Y., et al. The relationship between non-HDL cholesterol and other lipid parameters in Japanese subjects. J Atheroscler Thromb 2005, 12(2): 107-110.
[42] Chonchol M., Shlipak M. G., Katz R., et al. Relationship of uric acid with progression of kidney disease. Am J Kidney Dis 2007, 50(2): 239-247.
[43] Emmerson B. T., Cross M., Osborne J. M., et al. Ultrastructural studies of the reaction of urate crystals with a cultured renal tubular cell line. Nephron 1991, 59(3): 403-408.
[44] Toblli J. E., DeRosa G., Lago N., et al. Potassium citrate administration ameliorates tubulointerstitial lesions in rats with uric acid nephropathy. Clin Nephrol 2001, 55(1): 59-68.
[45] Mazzali M., Hughes J., Kim Y. G., et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001, 38(5): 1101-1106.
[46] Nakagawa T., Mazzali M., Kang D. H., et al. Hyperuricemia causes glomerular hypertrophy in the rat. Am J Nephrol 2003, 23(1): 2-7.
[47] Sanchez-Lozada L. G., Tapia E., Santamaria J., et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int 2005, 67(1): 237-247.
[48] Kang D. H., Nakagawa T., Feng L., et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002, 13(12): 2888-2897.
[49] Mazzali M., Kim Y. G., Suga S., et al. Hyperuricemia exacerbates chronic cyclosporine nephropathy. Transplantation 2001, 71(7): 900-905.
[50] Khosla U. M., Zharikov S., Finch J. L., et al. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005, 67(5): 1739-1742.
[51] Kang D. H., Park S. K., Lee I. K., et al. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol 2005, 16(12): 3553-3562.
[52] Siu Y. P., Leung K. T., Tong M. K., et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006, 47(1): 51-59.
[53] Zoccali C., Maio R., Mallamaci F., et al. Uric acid and endothelial dysfunction in essential hypertension. J Am Soc Nephrol 2006, 17(5): 1466-1471.
[54] Kanabrocki E. L., Third J. L., Ryan M. D., et al. Circadian relationship of serum uric acid and nitric oxide. JAMA 2000, 283(17): 2240-2241.
[55] Nakagawa T., Tuttle K. R., Short R. A., et al. Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome. Nat Clin Pract Nephrol 2005, 1(2): 80-86.
[56] Sautin Y. Y., Nakagawa T., Zharikov S., et al. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol 2007, 293(2): C584-596.
[57] Feig D. I., Nakagawa T., Karumanchi S. A., et al. Hypothesis: Uric acid, nephron number, and the pathogenesis of essential hypertension. Kidney Int 2004, 66(1): 281-287.
[58] Saito I., Saruta T., Kondo K., et al. Serum uric acid and the renin-angiotensin system in hypertension. J Am Geriatr Soc 1978, 26(6): 241-247.

[59] Talaat K. M., el-Sheikh A. R. The effect of mild hyperuricemia on urinary transforming growth factor beta and the progression of chronic kidney disease. Am J Nephrol 2007, 27(5): 435-440.
[60] Sone H., Tanaka S., Ishibashi S., et al. The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions: additional analysis from the Japan Diabetes Complications Study. Diabetes Care 2006, 29(1): 145-147.
[61] Kurella M., Lo J. C., Chertow G. M. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 2005, 16(7): 2134-2140.
[62] Hsu C. Y., McCulloch C. E., Iribarren C., et al. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006, 144(1): 21-28.
[63] Agnani S., Vachharajani V. T., Gupta R., et al. Does treating obesity stabilize chronic kidney disease? BMC Nephrol 2005, 67.
[64] Chagnac A., Weinstein T., Herman M., et al. The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol 2003, 14(6): 1480-1486.
[65] Weisinger J. R., Kempson R. L., Eldridge F. L., et al. The nephrotic syndrome: a complication of massive obesity. Ann Intern Med 1974, 81(4): 440-447.
[66] Kambham N., Markowitz G. S., Valeri A. M., et al. Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 2001, 59(4): 1498-1509.
[67] Hall J. E., Kuo J. J., da Silva A. A., et al. Obesity-associated hypertension and kidney disease. Curr Opin Nephrol Hypertens 2003, 12(2): 195-200.
[68] Henegar J. R., Bigler S. A., Henegar L. K., et al. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 2001, 12(6): 1211-1217.
[69] Bosma R. J., van der Heide J. J., Oosterop E. J., et al. Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects. Kidney Int 2004, 65(1): 259-265.
[70] Iseki K. Body mass index and the risk of chronic renal failure: the Asian experience. Contrib Nephrol 2006, 15142-56.
[71] Chagnac A., Weinstein T., Korzets A., et al. Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 2000, 278(5): F817-822.
[72] Engeli S., Schling P., Gorzelniak K., et al. The adipose-tissue renin-angiotensin-aldosterone system: role in the metabolic syndrome? Int J Biochem Cell Biol 2003, 35(6): 807-825.
[73] Goossens G. H., Blaak E. E., van Baak M. A. Possible involvement of the adipose tissue renin-angiotensin system in the pathophysiology of obesity and obesity-related disorders. Obes Rev 2003, 4(1): 43-55.
[74] Grisk O., Rettig R. Interactions between the sympathetic nervous system and the kidneys in arterial hypertension. Cardiovasc Res 2004, 61(2): 238-246.
[75] Wolf G., Ziyadeh F. N. Leptin and renal fibrosis. Contrib Nephrol 2006, 151175-183.
[76] Xu H., Barnes G. T., Yang Q., et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003, 112(12): 1821-1830.
[77] Weisberg S. P., McCann D., Desai M., et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003, 112(12): 1796-1808.

[78] Ramkumar N., Cheung A. K., Pappas L. M., et al. Association of obesity with inflammation in chronic kidney disease: a cross-sectional study. J Ren Nutr 2004, 14(4): 201-207.
[79] Hall J. E., Brands M. W., Henegar J. R. Mechanisms of hypertension and kidney disease in obesity. Ann N Y Acad Sci 1999, 89291-107.
[80] Kikkawa R., Koya D., Haneda M. Progression of diabetic nephropathy. Am J Kidney Dis 2003, 41(3 Suppl 1): S19-21.
[81] Fioretto P., Steffes M. W., Sutherland D. E., et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 1998, 339(2): 69-75.
[82] Abdel-Wahab N., Weston B. S., Roberts T., et al. Connective tissue growth factor and regulation of the mesangial cell cycle: role in cellular hypertrophy. J Am Soc Nephrol 2002, 13(10): 2437-2445.
[83] Hudson B. I., Schmidt A. M. RAGE: a novel target for drug intervention in diabetic vascular disease. Pharm Res 2004, 21(7): 1079-1086.
[84] Boyd-White J., Williams J. C., Jr. Effect of cross-linking on matrix permeability. A model for AGE-modified basement membranes. Diabetes 1996, 45(3): 348-353.
[85] Ceriello A. New insights on oxidative stress and diabetic complications may lead to a "causal" antioxidant therapy. Diabetes Care 2003, 26(5): 1589-1596.
[86] Inoguchi T., Yu H. Y., Imamura M., et al. Altered gap junction activity in cardiovascular tissues of diabetes. Med Electron Microsc 2001, 34(2): 86-91.
[87] Prabhakar S. S. Pathogenic role of nitric oxide alterations in diabetic nephropathy. Curr Diab Rep 2005, 5(6): 449-454.
[88] Scivittaro V., Ganz M. B., Weiss M. F. AGEs induce oxidative stress and activate protein kinase C-beta(II) in neonatal mesangial cells. Am J Physiol Renal Physiol 2000, 278(4): F676-683.
[89] Maxfield E. K., Cameron N. E., Cotter M. A. Effects of diabetes on reactivity of sciatic vasa nervorum in rats. J Diabetes Complications 1997, 11(1): 47-55.
[90] Michimata T., Murakami M., Iriuchijima T. Nitric oxide-dependent soluble guanylate cyclase activity is decreased in platelets from male NIDDM patients. Life Sci 1996, 59(17): 1463-1471.
[91] Karamanos B., Porta M., Songini M., et al. Different risk factors of microangiopathy in patients with type I diabetes mellitus of short versus long duration. The EURODIAB IDDM Complications Study. Diabetologia 2000, 43(3): 348-355.
[92] Vykoukal D., Davies M. G. Metabolic syndrome and outcomes after renal intervention. Cardiol Res Pract 2010, 2011781035.
[93] Davani B., Portwood N., Bryzgalova G., et al. Aged transgenic mice with increased glucocorticoid sensitivity in pancreatic beta-cells develop diabetes. Diabetes 2004, 53 Suppl 1S51-59.
[94] Hamamdzic D., Duzic E., Sherlock J. D., et al. Regulation of alpha 2-adrenergic receptor expression and signaling in pancreatic beta-cells. Am J Physiol 1995, 269(1 Pt 1): E162-171.
[95] Ullrich S., Berchtold S., Ranta F., et al. Serum- and glucocorticoid-inducible kinase 1 (SGK1) mediates glucocorticoid-induced inhibition of insulin secretion. Diabetes 2005, 54(4): 1090-1099.

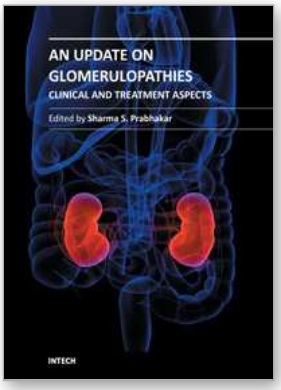
[96] Ranta F., Avram D., Berchtold S., et al. Dexamethasone induces cell death in insulin-secreting cells, an effect reversed by exendin-4. Diabetes 2006, 55(5): 1380-1390.
[97] Vincenti F., Friman S., Scheuermann E., et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant 2007, 7(6): 1506-1514.
[98] Duclos A., Flechner L. M., Faiman C., et al. Post-transplant diabetes mellitus: risk reduction strategies in the elderly. Drugs Aging 2006, 23(10): 781-793.
[99] Hoitsma A. J., Hilbrands L. B. Relative risk of new-onset diabetes during the first year after renal transplantation in patients receiving tacrolimus or cyclosporine immunosuppression. Clin Transplant 2006, 20(5): 659-664.
[100] Hjelmesaeth J., Asberg A., Muller F., et al. New-onset posttransplantation diabetes mellitus: insulin resistance or insulinopenia? Impact of immunosuppressive drugs, cytomegalovirus and hepatitis C virus infection. Curr Diabetes Rev 2005, 1(1): 1-10.
[101] Sun W, Zhang L, Tang Y W, et al. Role of C hepatitis on the morbidity of posttransplant diabetes mellitus in renal transplant recipients. Journal of Clinical Rehabilitative Tissue Engineering Research 2007, 11(38): 7529-7532.
[102] Ducloux D., Motte G., Vautrin P., et al. Polycystic kidney disease as a risk factor for post-transplant diabetes mellitus. Nephrol Dial Transplant 1999, 14(5): 1244-1246.
[103] Vareesangthip K., Thomas T. H., Tong P., et al. Erythrocyte membrane fluidity in adult polycystic kidney disease: difference between intact cells and ghost membranes. Eur J Clin Invest 1996, 26(2): 171-173.
[104] Vareesangthip K., Thomas T. H., Wilkinson R. Abnormal effect of thiol groups on erythrocyte Na/Li countertransport kinetics in adult polycystic kidney disease. Nephrol Dial Transplant 1995, 10(12): 2219-2223.
[105] Grundy S. M., Cleeman J. I., Daniels S. R., et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005, 112(17): 2735-2752.
[106] Alberti K. G., Zimmet P., Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006, 23(5): 469-480.
[107] Levey A. S., Eckardt K. U., Tsukamoto Y., et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005, 67(6): 2089-2100.
[108] Alexander M. P., Patel T. V., Farag Y. M., et al. Kidney pathological changes in metabolic syndrome: a cross-sectional study. Am J Kidney Dis 2009, 53(5): 751-759.
[109] Agrawal V., Shah A., Rice C., et al. Impact of treating the metabolic syndrome on chronic kidney disease. Nat Rev Nephrol 2009, 5(9): 520-528.
[110] Yale J. F. Oral antihyperglycemic agents and renal disease: new agents, new concepts. J Am Soc Nephrol 2005, 16 Suppl 1S7-10.
[111] Iglesias P., Diez J. J. Insulin therapy in renal disease. Diabetes Obes Metab 2008, 10(10): 811-823.
[112] Rebsomen L., Khammar A., Raccah D., et al. C-Peptide effects on renal physiology and diabetes. Exp Diabetes Res 2008, 2008281536.

[113] Sui W., Zou H., Zou G., et al. Clinical study of the risk factors of insulin resistance and metabolic syndrome after kidney transplantation. Transpl Immunol 2008, 20(1-2): 95-98.

[114] Voltarelli J. C., Couri C. E., Stracieri A. B., et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. JAMA 2007, 297(14): 1568-1576.

[115] Abraham N. G., Li M., Vanella L., et al. Bone marrow stem cell transplant into intra-bone cavity prevents type 2 diabetes: role of heme oxygenase-adiponectin. J Autoimmun 2008, 30(3): 128-135.

[116] Volarevic V., Arsenijevic N., Lukic M. L., et al. Mesenchymal stem cell treatment of complications of diabetes mellitus. Stem Cells 2010.



An Update on Glomerulopathies - Clinical and Treatment Aspects
Edited by Prof. Sharma Prabhakar

ISBN 978-953-307-673-7
Hard cover, 468 pages
Publisher InTech
Published online 02, November, 2011
Published in print edition November, 2011

An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Hequn Zou, Yuxin Wang, Guimian Zou and Jianxin Wan (2011). Metabolic Syndrome Associated Kidney Damage, An Update on Glomerulopathies - Clinical and Treatment Aspects, Prof. Sharma Prabhakar (Ed.), ISBN: 978-953-307-673-7, InTech, Available from: http://www.intechopen.com/books/an-update-on-glomerulopathies-clinical-and-treatment-aspects/metabolic-syndrome-associated-kidney-damage

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821