

Insulin in Renal Diseases

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Insulin, a polypeptide product is significant in its history of evolution in form of very little change in architecture. Starting from its first appearance for activity at present, insulin molecule and to a lesser extent proinsulin displays considerable species variation in the C-peptide. Those regions of the primary sequence of the insulin A and B chains conserve in most species correspond to regions involved in (a) the folding of the molecule into its secondary structure, i.e. disulfide bond formation, (b) the association monomers and dimers to form the hexamer or of hexamers to pack into the crystal form and (c) correct structure, conformation and presentation of the regions thought to be involved in receptor binding and thus bioactivity. The practical benefit is in use of animal insulin for therapy.

Insulin biosynthesis is regulated by glucose at the level of either transcription or translation. Although the insulin gene may be regulated far upstream from transcription start site, smaller highly conserved regions of ~400 base pairs contain the major glucose control elements. The enhancer elements that seem particularly important include E1, A2-C1, A4-A3 and E2. Transcription factors that are relatively cell-specific are BETA 2 and PDX-1 and PDX-1 especially important for control by glucose. Insulin release is regulated by metabolic (i.e. glucose); hormonal (i.e. glucagon) and neural (i.e. acetylcholine) and at cellular level by ATP sensitive potassium channel, protein kinases with addition of calcium. The degradation of insulin occurred primarily in liver and kidney. That's why, patient of liver or renal failure have decreased requirement of insulin; having therapeutic importance.

Insulin has multifactorial bioactivity ranging from promoting genetic transcription to synthesis and degradation of specific proteins and mRNAs then to cell grown differentiation in addition to its metabolic effect on glucose and amino acids. Its actions to promote cell growth in certain cells and ability to halt process of apoptosis have regained a new insight regarding promotion of insulin as first choice of management of any form of diabetes instead of oral hypoglycemic agents. The effect on cell growth is promoted by IGF-I and IGF-II, polypeptide having major structural homologies with insulin, but little or no immunologic cross-reactivity with the hormone. Generally IGFs through IGF-1 receptor have more potent effects on cell growth than does insulin acting through the insulin receptors.

Recent research to identify the pathophysiology of complication of diabetes shifted the focus from insulin to insulin growth

factor (IGF) and IGFBP (insulin growth factor binding proteins and their receptor. IGF-I and IGF-II (~70 amino acids) are structurally related to proinsulin function described for IGF till date are effect on development starting from prenatal to postnatal stage and later in development of cancer as well. Even IGF receptors have structural homology to insulin receptor.

ROLE OF INSULIN IN MICROANGIOPATHY AND RENAL DISORDER

Since the discovery of insulin in 1921, it has been possible to ameliorate the hyperglycemia of diabetes, but even the most sophisticated treatment for the disease have not been able to abolish the threat of tissue damage that leads to chronic diabetes complications. Although the clinical manifestations are very diverse, their syndromes shares certain common pathophysiological characteristics. Much of the impact of chronic diabetes falls on the microcirculation. Mechanisms of hyperglycemia induced damage are based on four major hypothesis which are increased flux of glucose and other sugars through the polyol pathways, intracellular formation of advanced glycation end-products (AGEs), activation of protein kinase C (PKC) isoforms and overactivity of hexosamine pathways (Figs. 1 and 2).

The kidney clears insulin via two distinct routes. One route involves the diffusion of insulin from peritubular capillaries and the binding of insulin to the contralateral membrane of tubular cells. The second route is via luminal reabsorption of the glomerular filtrated insulin by proximal tubular cells. This insulin delivered to the proximal tubular cells is degraded to oligopeptide and amino acids by enzymatic pathways. The products of insulin degradation are reabsorbed in to the peritubular capillaries. Poor renal clearance prolongs the half-life of circulating insulin. Thus renal failure is associated with the risk of hypoglycemia. In relation to insulin resistance in renal failure, is increased due to tissue insensitivity to insulin. G Biesenbach et al¹ showed that the reduction in insulin requirement in renal insufficiency is similar in type I and insulin treated type 2 diabetic patients. In subjects with type 2 diabetes, the residual insulin secretion had no impact on the reduction in insulin requirement dependent on GFR.

NON-GLYCEMIC ROLE OF INSULIN IN RENAL METABOLISM

Maaten et al², in the study of effects of insulin and atrial natriuretic peptide on renal tubular insulin handling in sickle cell disease concluded that insulin and low dose atrial

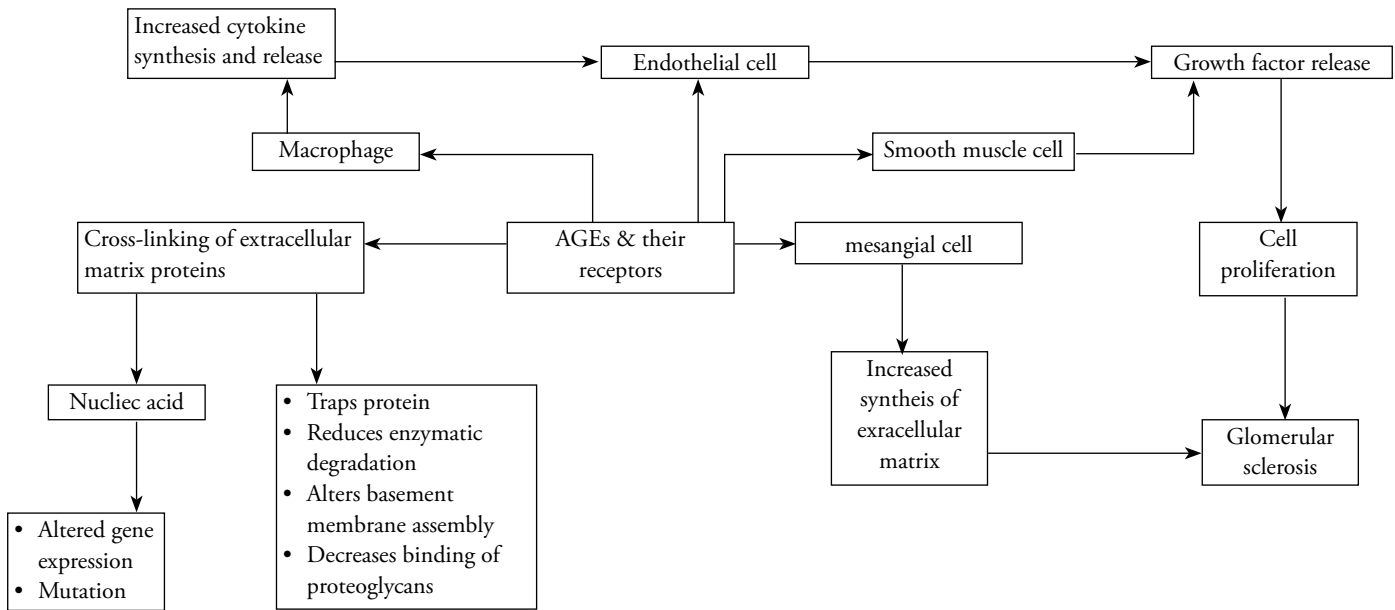


Fig. 1 : Schematic representation of the possible mechanisms by which advanced glycation end-product (AGEs) and their receptors may contribute to the pathogenesis of diabetic nephropathy.

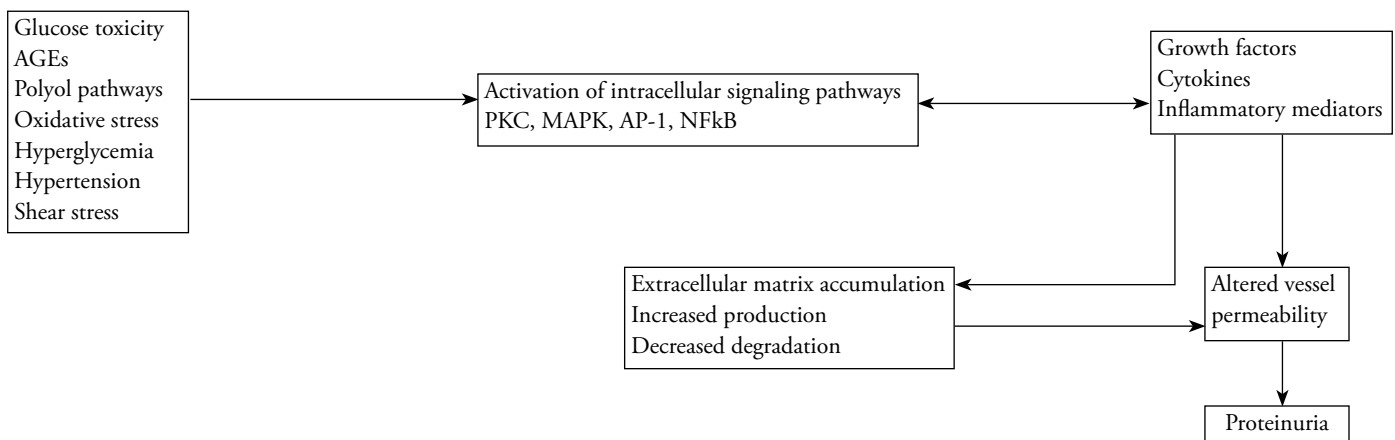


Fig. 2 : Mechanisms involved in the pathogenesis of diabetic nephropathy [AGEs (advanced glycation end-products), AP-1 (Activator protein-1 transcription factor), MAPK (Mitogen activated protein kinase), NFκB (Nuclear factor κB), PKC (protein kinase C)]

natriuretic peptide affect renal sodium handling in different parts of distal nephron. Insulin exerts an antinatriuretic effect in later segments of the distal nephron whereas low dose atrial natriuretic peptide exerts its natriuretic effect probably in the earlier part of the distal nephron i.e. along the loop of Henle. In addition insulin's antinatriuretic effect able to compensate for an increased sodium delivery in the more distal nephron during concomitant atrial natriuretic peptide infusion in normal subjects. It can be speculated that an impaired balance between both hormonal actions may contribute to abnormal sodium retention and blood pressure elevation in the long term.

Other important point is change in requirement of insulin in chronic renal failure due to inability of kidney to degrade insulin and also uremia inhibits degradation of insulin by liver. Thus sometimes patient ceases to have any requirement of insulin. After the institution of dialysis therapy, a complex situation arises

as insulin sensitivity increases and also degradation comes back to normal; it is difficult to predict what will happen to insulin requirement.

One of the most prominent renal effects of exogenously administered insulin is sodium reabsorption, whereas, at the same time, proximal tubular sodium reabsorption decreases.^{2,3} It is not yet clear, however, whether insulin increases distal tubular sodium reabsorption along the loop of Henle or a more distal tubular site. The authors demonstrated that retention of water in insulin treated membrane may also be a clue to increase in hydraulic permeability.⁴

Segar *Y et al* showed that renal hypertrophy in non-obese diabetic mice is associated with persistent accumulation of renal IGF-1 and IGFBP-1. These changes were partially reversed with insulin therapy which did not correct the hyperglycemia, suggesting an important role for insulin deficiency in mediating these

changes in the IGF system. These findings suggest that the IGF system may play a potential role in the development of diabetic nephropathy.

POST-TRANSPLANTATION DIABETES AND INSULIN

Post-transplantation diabetes is a complication of solid organ transplantation. Estimates of the frequency of post-transplantation diabetes ranges from 2 to 50%. *Montori et al* in their study showed decreased incidence of post-transplantation diabetes due to change in concept of immunosuppression. The risk factor identified were patient's age, non-White ethnicity, glucocorticoid treatment for rejection and immunosuppression with high dose cyclosporine and tacrolimus. *Montori et al* advised modification of immunosuppressive regimens to decrease the risk of post-transplantation diabetes in high risk transplant recipient.

Regarding PTD (post-transplantation diabetes), *Ducloux et al* in their study showed that adult polycystic kidney disease confers an increased risk. But this result is yet to show reproducibility and it is a retrospective study. In this study confabulation factor excluded are age, renal function, immunosuppressive regimen, number of acute rejection, cumulative dose of steroids and hemodialysis duration before transplantation. *Gentil MA et al*⁷ in their study showed a greater incidence of post-renal transplant insulin requiring diabetes in association with HCV infection. But this finding requires further confirmation, so follow up period would need to be extended.

THERAPEUTIC STRATEGIES

In recent years, focus of treatment modalities shifted from control of glucose to understanding the pathogenesis of various macrovascular, microvascular and structural complication involving various organ systems of the body. In kidney alone, it is evident in form of arteriosclerosis, arteriolosclerosis, glomerulosclerosis, basement membrane thickening, tubulointerstitial changes and non-diabetic renal diseases like pyelonephritis, glomerulonephritis and others. The result of these changes range from earliest microalbuminuria to nephrotic range proteinuria to renal failure to end-stage renal disease and its complications like anemia/uremia.

One of the landmark developments is use of recombinant human insulin growth factor-1 (rhIGF-1), which is tested in diabetes in an attempt to overcome the severe insulin resistance. Subcutaneous injection of rhIGF-1 reduces the requirement for insulin administration in both type 1 and type 2 diabetic patients and is associated with enhanced insulin-induced disposal of glucose, inhibition of hepatic glucose output, and improvement in metabolic status of these patients. Other potential uses include treatment of diabetic neuropathy; wound healing, osteoporosis etc. Its usefulness may be enhanced by the co-administration of IGFBP-3 and yet to be confirmed are its potential long term side effects, including enhanced mitogenesis and tumor growths.

Intensive diabetes therapy^{6,7} reduces the risk of transition from normo- to macroalbuminuria⁸⁻¹¹ by approximately 35% but doesn't abolish it. Excess glucose can directly exert toxic effects by activating intracellular signaling pathways and inducing a number of cytokines injurious to kidney. In kidney, in mesangial cells high glucose levels induce the transcription and secretion

of TGF β 1 are the most pro-sclerotic cytokines and induce cell hypertrophy,¹¹ increases gene expression and protein secretion of extracellular matrix components such as collagen, laminin and fibronectin and similarly type I and IV collagen mRNA levels are enhanced in tubular epithelial cells exposed to high glucose. Thus the question is how to achieve and maintain good glycemic control and $HbA_{1c} < 7.0\%$. The benefit of good glycemic control is proved in other way by demonstrating reversal of renal disease after transplantation of kidneys with established diabetic nephropathy into non-diabetic patient and also by combined pancreatic and renal transplantation in diabetic patient with advanced renal disease. Recent recommendation is to start intensive insulin therapy as early as before or during the phase of microalbuminuria (30-300 mg/day).

End-stage renal disease¹² can lead to abnormalities of glucose metabolism and hyperinsulinemia which may contribute to the atherosclerotic complication in these patients. *Sechi LA et al* in their study investigated the stage of renal disease in which abnormalities of glucose metabolism develop and whether these abnormalities were associated with an increased prevalence of cardiovascular events in patients with early renal failure. The result showed then patients with hypertensive nephrosclerosis and early impairment of glomerular filtration, alterations of glucose metabolism become evident only when creatinine clearance in $< 50 \text{ ml/min/1.73m}^2$ BSA and are not related to microalbuminuria and cardiovascular complications.

It is also emphasized that puberty accelerates microvascular complications of diabetes mellitus including nephropathy and factors involved are increased blood pressure, activation of growth hormone-insulin like growth factor-I axis and production of sex steroids which through several systems ultimately control TGF production including the renin-angiotensin system, cellular redox systems, polyol pathway and protein kinase C.

MANAGEMENT

In UKPDS study⁷ 18% of the patients had micro- and/or macroalbuminuria (UK prospective diabetes study 1998 during this study, 33% of the patients developed albuminuria of more than 50 mg/dl and 6.6% of more than 300 mg/dl while 2.0% developed renal failure. During a 10 year period, the cumulative risk for renal failure in type 2 diabetic patients with proteinuria has been shown to be at least 11%, other metabolic factors like hypertension dyslipidemia also had role in development of renal complication.¹³ *Ole Torffvit et al*^{14,15} in their study showed that poor metabolic control particularly HbA_{1c} , SBP but not DBP is associated with development and high BP with progression of nephropathy in type 2 diabetic patients.

Now-a-days there is integrated treatment approach for diabetes.¹⁶ For instance *Sawicki* reported that self-adjusted blood pressure therapy for 5 years reduced the risk for death or need of dialysis from 41% to 11% the risk of progression of renal disease decreased from 59% to 27%. *Rachmani et al* found that patient participation in the treatment for 4 years reduced the number of cardiovascular events from 55% to 36% and decrease in glomerular filtration rate diminished from 3.5 to 2.25 ml/min/year.

Although GFR usually remains elevated throughout the phase of microalbuminuria some patients may demonstrate an incipient

decline. In a biopsy series of young IDDM patients, it was found that patients with a decline in GFR above 5 ml/year had the thickest basement membranes and the most marked matrix expansion.¹¹

Regarding management the main factors are glycemic control and control of blood pressure. For glycemic control, various, insulin preparation available are, short acting insulin i.e. insulin aspart or lispro, regular insulin, intermediate acting insulin and long acting insulin preparation e.g. glargine, NPH, ultralente. The need of insulin is individualized.¹⁷ Each insulin has its particular property in controlled and maintaining prandial upsurge. So, insulin should be prescribed according to individual body system to maintain perfect control of blood sugar. Ohkubo Y et al⁶ showed that intensive glycemic control by multiple insulin injection therapy can delay the onset and the progression of diabetic retinopathy, nephropathy and neuropathy in Japanese patients with NIDDM. From this study, the glycemic threshold to prevent the onset and the progression of diabetic microangiopathy is indicated as follows; HbA_{1c} <6.5%, FBG <110mg/dl and 2 hrs post-prandial blood glucose concentration <180 mg/dl.

In the UKPDS⁷ tight control of blood pressure (achieved mean 144/82 mmHg) compared to less tight control (achieved mean 154/87 mmHg) resulted in a 29% reduction in risk of microalbuminuria over 6 years. There is no blood pressure level below which risk rises again i.e. no 'J' shape. In the subset of normoalbuminuric diabetic patients in the HOPE study treatment with ramipril also reduces the risk of developing proteinuria. In diabetic patient with established nephropathy the goal of antihypertensive treatment is <130/75 mmHg and drugs that inhibit the rennin-angiotensin system should be chosen as first-line antihypertensive therapy.¹⁸ In patients with proteinuria, inhibitors of the rennin-angiotensin system^{10,19} do offer specific benefits in renal disease, independent of systemic blood pressure effects. In Indo-Asian patients, calcium channel blockade,²⁰ blockade,²¹ diuretics and α blockade²² are all efficacious.

Lipid reduction and prophylactic use of low dose aspirin should be prescribed for secondary prevention of cardiovascular events and microvascular complication.

Candidates for future use, in addition to new agents which reduce blood glucose and blood pressure, include agents that affect various parts of the advanced glycation pathway, protein kinase C inhibitors, glycosaminoglycans, heparinoids and antagonists to variety of growth factors, including insulin like growth factor-I, transforming growth factor- β (TGF- β) and vascular endothelial growth factor. Antioxidants may be useful and intriguingly C-peptide is suggested as having renoprotective effects. There is also preliminary evidence that ligands of the peroxisome proliferators - activated receptors γ (thiazolidinediones) influence smooth muscle and mesangial cell function beneficially.

In cases of end-stage renal failure¹² the main problem of management is high mortality rate mainly from cardiovascular causes. Thus before going to renal replacement therapy cessation of smoking, optimal glycemic control²³, aggressive blood pressure lowering, ACE inhibitors,¹⁰ aggressive treatment of dyslipidemia, avoidance of malnutrition, and avoidance of severe anemia are crucial elements in the efforts to reduce not only the risk of

progression but also the cardiovascular risk of the diabetic patient in pre-dialysis phase²⁴ options for renal replacement therapy are hemodialysis (continuous ambulatory peritoneal dialysis or one of its modification i.e. intermittent peritoneal dialysis, continuous cycling peritoneal dialysis) and renal transplantation.

CAPD has a major advantage of avoidance of rapid fluid shifts and of intradialytic hypotension. No major differences in the patient survival between CAPD and hemodialysis are noted. A major long term problem with CAPD is inadequate fluid removal once residual divers diminished. In this case use of glargine insulin is proposed.

REFERENCES

1. Biesenbach F, Raml A, et al. decreased insulin requirement in relation to GFR in nephropathic type 1 and insulin-treated type 2 diabetic patients. *Diabetic Medicine* 2003;20:642-645.
2. Maaten JC, Voorburg A. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. *Clin Sci (Tolch)* 1957;92:51-58.
3. Stenvinkel, PJ, Bolinder J, Alverstand A Effect of insulin on renal hemodynamics and the proximal and distal tubular sodium handling in healthy subjects. *Diabetologia* 1992;35:1042-1049.
4. Pandey R, Srivastava RC, Rai M, Tripathi K. effect of insulin in hydraulic permeability. A new concept of insulin action on water reabsorption. *Novo Nordisk Diabetes Update* 1995 proceedings:185-188.
5. Gentil MA, Luna E, Osuna A, et al. Incidence of diabetes mellitus requiring insulin treatment after renal transplantation in patients with hepatitis C. *Nephrol Dial Transplant* 2002;17:887-891.
6. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. *Diab Res Clin Pract* 1995;28:103-117.
7. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853.
8. Tobe SW, McFarlane PA, Naimark DM. Microalbuminuria in diabetes mellitus. *Can Med Asso J* 2002;167:499-503.
9. Gerstein H, Mann JFE, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001;286:421-426.
10. Parving HH, Lehnert H, Brocher-Mortensen J, Gomis R, Andersen S, Arner P. The effects of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-878.
11. Bertani T, Gambara V, Remuzzi G. Structural basis of diabetic nephropathy in microalbuminuric NIDDM patients. A light microscopy study. *Diabetologia* 1996;39:1625-1628.
12. Ritz E, Rychlik I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions. *Am J Kidney Dis* 1999;34:795-808.
13. Tapia J, Tencer J, Ami P, Willner J, Torffvit O. Albuminuria, HbA_{1c} and LDL levels are associated with histopathological renal changes in type 2 diabetic patients with micro-macroalbuminuria. *Diab Res Clin Pract* 2000;50(suppl. 1),P 1089,S263.
14. Ole Torffvit, Carl-David Agardh. The impact of metabolic and blood pressure control on incidence and progression of nephropathy A 10-year study of 385 type 2 diabetic patients. *J Diab Complications* 2001;15: 307-313.
15. Torffvit O, Agardh CD. The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients. *J Diab complications* 2001;15:307-313.

16. Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: Origin and development of ideas. *Diabetologia* 1999;42:263-285.
17. Herbst KL, Hirsh IB. Insulin strategies for primary care providers. *Clin Diab* 2002;20:11-17.
18. Wolf G, Ziyadeh FN. The role of angiotensin II in diabetic nephropathy: Emphasis on nonhemodynamic mechanisms. *Am J Kidney Dis* 1997;29: 153-163.
19. Yokoyama H, Tomonaga O, Hirayama, M, Ishii, A, Takeda M, Babazono T, Ujihara U, Takahashi C, Omori Y. Predictors of the progression of diabetic nephropathy and the beneficial effect of angiotensin-converting enzyme inhibitors in NIDDM patients. *Diabetologia* 1997;40:405-411.
20. Zubair M, Karim S, Hussain S. Isradipine in Asian patient with hypertension *Drugs* 1990;40:26-29.
21. Chowdhury SGM, Alon Mal. A selective alpha receptor antagonist doxazosin in the treatment of essential hypertension. *Bangladesh Med J* 1991;20:85-88.
22. Chia BL. A comparison between once daily and twice daily administration of metoprolol in the treatment of hypertension. *Curr Med Res* 1980;7: 85-90.
23. Morioka T, Emoto M, Tabata T, Shoj T, Thara H, Kishimoto H. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. *Diabetes Care* 2001; 24:909-913.
24. Wu MS, Yu CC, Yang CW, Wu CH, Haung JY, Hong JJ, Fan Chian CY, Hunag CC, Leu ML. Poor pre-dialysis glycaemic maintenance haemodialysis. *Nephrol Dial Transplant* 1997;12:2105-2110.
25. Saltiel AR. New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. *Cell* 2001;104:517-529.