Article published online: 2022-07-07

ABSTRACT BOOK

New Frontiers in the Management of Patients with Chronic Kidney Disease

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Published: 02 July 2013
Ibnosina J Med BS 2013,5(3):166-171
Received: 02 July 2013
Accepted: 02 July 2013
This article is available from: http://www.ijmbs.org

Abstract
New Frontiers in the management of patients with chronic kidney diseases was a the third in a series of one day symposium held in the Medical College of Ras Al-Khaimah University of Medicine and Health Sciences on the 16th of March 2013 to mark the world Kidney Day. Local, regional and international experts considered various diagnostic and management challenges in the areas of chronic kidney disease covering such wide spectrum of subjects ranging from pre-diabetes, diabetes kidney disease, glomerulonephritis, arterial hypertension and management of hypertension in patients with chronic kidney disease to mesenchymal stem cell therapy, pancreatic transplantation and gene polymorphism profiling in clinical practice. The concise abstracts of all the presentations are presented here to extend the benefit from the meeting to all those who did not attend the live event.

Key words: Chronic Kidney Disease, Diabetes, Dialysis, Glomerulonephritis, Hypertension, Renal Transplant, Pancreatic Transplant, Mesenchymal Stem Cells.

Introduction

Chronic kidney disease is a general term for heterogeneous disorders affecting the structure and function of the kidney. The variation in disease expression is related partly to cause and pathology, severity, and rate of progression. Modern clinical practice stresses on the early recognition, timely assessment and effective management of disease; emphasise guidelines and clinical trials; and address the challenges that are met in the association of chronic kidney disease with ageing and vascular disease, management of clinical trials, development of guidelines, and public health. We present the highlights of the "New Frontiers in the Management of Patients with Chronic Kidney Diseases". This was a the third in a series of one day symposium held in the Medical College of Ras Al-Khaimah University of Medicine and Health Sciences on the 16th of March 2013 to mark

the world Kidney Day. Local, regional and international experts considered various diagnostic and management challenges in the areas of chronic kidney disease covering such wide spectrum of subjects ranging from pre-diabetes, diabetes kidney disease, glomerulonephritis, atrial hypertension and management of hypertension in patients with chronic kidney disease to mesenchymal stem cell therapy and pancreatic transplantation and gene polymorphism profiling in clinical practice. The concise abstracts of all the presentations are presented here as they were submitted by the speakers to extend the benefit from the meeting to all those who did not attend the event.

Abstracts of Presentations

Management of Hypertension in patients with Chronic Kidney Disease: current status in 2013. Francois Berthoux. University Hospital of Saint-Etienne; Nephrology, Dialysis, and Renal Transplantation Department; 42055 Saint-Etienne cedex 2; France.

Arterial hypertension (HT) is a major risk factor associated with progression of CKD and occurrence of cardio-vascular (CV) events. Classical WHO definition remains for blood pressure (BP≥140/90), but the revised Working group-Joint National Committee (WG-JNC 7) focused also on CV risk factors, CV early markers, and on organ damage with isolation of 4 categories: Normal, Stage 1 (prehypertension), Stage 2 (HT + CV risk factors/organ damage), and Stage 3 (HT + CV events/organ damage). The perfect long-term control of BP is the cornerstone treatment of CKD together with the reduction of increased microalbuminuria and proteinuria. The management includes thorough evaluation of the CV risk and of the Absolute Renal Risk of Dialysis (1). HT treatment (2) should focus on diet, lifestyle corrections and pharmacological antiHT drugs. The target BP is usually ≤ 130/80 and in some situations ≤125/75. The choice of the antiHT drugs should integrate clinical tolerance, age, CV events/disease, amount of proteinuria, CKD staging, and native renal disease (diabetic, glomerulonephritis (3). Overall BP control is achieved in less than 50 % of the patients, but we will have to increase it in the future with better education and implication of the patient. This effective control is a very long-term goal during years and decades.

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3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int Suppl 2012; 2: 209-17.

2. KDIGO Clinical Practice Guideline for Glomerulonephritis- Immunoglobulin A nephropathy: Critical Analysis and Extended Applications.

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In 2012, the international foundation Kidney-Disease: Improving Global Outcome (KDIGO) published a clinical practice guideline for glomerulonephritis with chapter 10 devoted to IgA nephropathy, IgAN (1). It is composed of six sets of recommendations (Rec): Rec 1 is focused on initial evaluation and assessment of risk of progression; Rec 2 concerns anti-proteinuric and antihypertensive therapy; Rec 3 is dealing with corticosteroid therapy; Rec 4 focused on immunosuppressive agents; Rec 5 concerns other treatments including fish oil, anti-platelets agents, and the use of tonsillectomy; Rec 6 focused on atypical forms of IgAN including minimal change disease, acute kidney injury, and crescentic GN. For each recommendation, we have done a thorough analysis in the light of our large (up to 1000 cases) and long-lasting experience (more than 30 years). We have made several additional clarifications based mainly on the new concept of absolute renal risk (ARR) of Dialysis or Death (2,3) with integration of pathological data obtained on initial renal biopsy. Overall, this guideline on IgAN is too limited and restrictive and should integrate this ARR concept and the histo-pathological data (Oxford modified MEST score). We think that our suggestions are improving the applicability of this IgAN specific guideline.

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3. Current Concepts of Pancreas Transplantation

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Diabetes Mellitus (DM) is a devastating disease. It is number one etiology for kidney failure, blindness and amputations in the western countries. Diabetes is also a major contributor to cardiovascular events. Currently, there are two clinical therapeutic options to treat DM. The first one is insulin therapy and second option is to replace insulin-secreting B-cells by whole pancreas transplantation (PTX) or islet cell transplant. Although exogenous insulin therapy is effective at preventing acute metabolic decompensation and is life-saving for type 1 DM (T1DM), less than 40% of diabetic patients achieve recommended therapeutic goals. PTX is the only therapy that offers euglycemic status to the diabetic patients. Furthermore, successful PTX can halt or improve secondary complications of DM including neuropathy, nephropathy and opthalompathy. There are three types of PTX; simultaneous pancreas and kidney transplant (SPK), pancreas after kidney transplant (PAK) and pancreas transplant alone (PTA) in patients without renal failure. In has been shown that SPK has the best outcome compared to PAK or PTA. Also diabetic patients who receive a SPK has better patient and graft survival when compared to diabetic patients waiting for a pancreas transplant or diabetic patients who received only living donor (LD) or deceased donor (DD) kidney transplant. Furthermore, the kidney survival was superior in these patient compared to LD or DD kidney transplant alone. Initial experience with simultaneous SPKT in patients with Type 2 DM (T2DM) and end-stage renal disease (ESRD) suggested that increase of endogenous insulin production by PTX in patients with C-peptide-positive, insulin-dependent diabetes resulted in insulin independence, improved glucose counter-regulation, and enhanced quality of life. A number of single-center retrospective studies have documented equivalent outcomes in patients with either type 1 DM (T1DM) or T2DM undergoing predominantly SPKT, although clearly a selection bias exists for patients in the latter category. Selection criteria for SPKT in T2DM include patients less than 55–60 years of age with a BMI less than 30–32 kg/m^2, insulin-requiring for a minimum of 5 years with a total daily insulin requirement less than 1 u/kg/day, a fasting C-peptide level less than 10 ng/ml, absence of severe vascular disease or tobacco abuse, adequate cardiac function, and presence of complicated diabetes. Data from the International Pancreas Transplant Registry show that up to 7% of SPKT recipients are classified as having T2DM and that outcomes in these patients are comparable to those undergoing SPKT and classified as having T1DM. The most commonly used induction therapy is T-cell depleting agent and the most maintenance immunosuppression therapy currently used in USA is tacrolimus, mycophenolate mofetile and prednisone. The issue of steroid-free regimens remains controversial, although the data suggest that approximately 40% of pancreas transplant recipients are on regimens that avoid steroids. During the last decade the outcomes of PTX have improved significantly. The current report of SRTR shows that graft loss for all PTX types have been improving with current 5 years pancreas graft survival of 70% for SPK. Most graft loss occurred during the year. Rejection rate also reduced significantly and dropped to 16% at first 12 months for SPK patients. Due to significant improvements in surgical techniques and immunosuppression, we believe that pancreas transplant is a safe procedure and it should be offered to all T1DM and non-obese T2DM. The current data comparing the harm of immunosuppression and pancreas transplant surgery vs. remaining diabetics and on insulin therapy show that PTX is less harmful and more beneficiary to the patients with DM.

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4. Genetic Profiling in Organ Transplantation: Strengths and Weaknesses.

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Gene polymorphisms are the variations in the DNA, which could range from a single nucleotide base change to a thousand base pair changes in the DNA. The most common type of polymorphism is single nucleotide polymorphism, results from a single base mutation. Although most of gene polymorphism studies (GPS) has examined the association between the variations in the genes of Immunomodulatory molecules with acute renal allograft rejection, fewer focused on tailoring immunosuppression and on identifying patients at higher risk for chronic renal allograft dysfunction (CRAD). GPS have recently increasingly been reproached for their shortcomings. A main concern has been multiple-hypothesis testing, as many investigators search for associations using several genes but report on only positive results. On the other hand, a large number of studies are underpowered and the influence of donors' genotypes often has not been studied. Furthermore, most of the studies have attempted to investigate the influence of a "single gene" in a "single center". Like any "single-gene-single-center" studies, the results of these studies are hindered by improper patient stratification. Given a complex problem such as CARD, a need exists for multigenic consideration, as a single gene may not fully characterize an individual's risk of developing CARD. Despite these problems, GPS still remain attractive as the consideration of known antigen dependent and independent mechanisms in identifying risk factors for CRAD still does not account for the heterogeneity observed in allograft outcomes and that the genetic variability in the transplant population is most likely responsible for this diversity.

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5. Mesenchymal Stem Cell Therapy in Diseases.

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Mesenchymal stem cells (MSC) are adult stem cells which have potent immunomodulatory functions. MSC could be retrieved virtually from all adult tissues. The primary criteria currently used to characterize and identify MSC are the capacity for self-renewal, differentiation into tissues of mesodermal origin, and lack of expression of hematopoietic molecules but positive expression of MSC markers. Indeed, a battery of markers is used to characterize MSC. Although MSC developmental plasticity was the center of scientism attention, their immunomodulatory properties hold more immediate clinical applicability. Based on their immunomodulatory properties *in vitro* and in animal models and the lack of major complications in humans, MSC are currently used for the treatment of diseases in humans more frequently than any other cell therapy. Notably, recent clinical trials have focused more on the immunomodulatory capacities of MSC to target various inflammatory and immune-mediated diseases. Indeed, MSC are currently used for a wide variety of such conditions including renal transplantation, multiple sclerosis, type 1 diabetes, graft versus host disease, and Crohn's disease. Future plans are in place to use MSC for the treatment of other immune mediated diseases as well. Although the immunomodulatory effects of MSC make them particularly interesting candidate cells for immune mediated diseases, we need more of pre clinical studies to better understand the mechanisms of immunoregulation, their survival and function post injection to formulate the best MSC regimen.

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6. Prediabetes 2013: Where We Stand?

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Pre-diabetes is essentially a risk factor for developing diabetes that is defined by abnormal but not diabetic range fasting glucose, glucose tolerance or HbA1c. It represents about 35 % of U.S. adults ≥ 20 years and 50 % ≥ 65 years with estimation of 79 million Americans ≥ 20 in 2010. Prediabetes is not only and strongly predictive of diabetes, but also associated with cardiovascular disease (where Diabetes and coronary artery disease occur together more commonly than usually recognized, with the negative impact of dysglycemia apparent before diabetes) , neuropathy, retinopathy, nephropathy, cancer and mortality. Though risk increases with diabetes, the evidence suggests that early intervention may be beneficial on complications beyond diabetes. Diabetes prevention with lifestyle intervention has been shown in the U.S. Diabetes Prevention Program (DPP) ; the Finnish Diabetes Prevention Study , in which the intervention was most effective in the highest-risk group, with ongoing benefit for 4 years after the conclusion of the formal lifestyle intervention ; and in the Chinese Da Qing Diabetes Prevention Study, with separation between the control and intervention groups maintained for a 20-year period. Based on the differences reported in the DECODE analysis, it was suggested that treatment to reduce 2-h glucose by 2 mmol/l/l would reduce adverse outcomes by 20%. These early interventions in prediabetics could then be of great benefit, however, there are no available yet guidelines for management of prediabetes.

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7. Management of Hyperglycemia in Patients with Declining Renal Function.

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Patients with type 2 diabetes mellitus frequently have comorbidities that complicate the management of their disease. Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD), and one of the most prevalent microvascular complications of both type 1 and type 2 diabetes. Diabetes currently accounts for over 45% of cases of end-stage renal failure in patients undergoing hemodialysis. Management of hyperglycemia in chronic kidney disease (CKD) patients presents difficult challenges, partly due to the complexity involved in treating these patients, and partly due to lack of data supporting benefits of tight glycemic control (1-3). While hyperglycemia is central to the pathogenesis and management of diabetes, hypoglycemia and glucose variability also contribute to outcomes.

Multiple drugs with different mechanisms of action are now available; some can lower glucose levels without the risk of hypoglycemia. Physicians dealing with diabetes and CKD must have a sound understanding of metabolic changes present in kidney impairment/failure, contemporary views about glycemic goals, and treatment options for the diabetic patient with CKD. Clinicians, who manage these patients must deal with the challenge of adjusting multiple medications in the face of renal failure and cardiovascular disease as the disease progresses. Early on, the dose of Metformin may be halfed but this drug has no major role in diabetic management of patients with advanced kidney disease due to the increased risk of lactic acidosis. The main stay of the management is based on avoiding the risk of hypoglycemia, adjustment of the doses of drugs that are mainly or exclusively excreted via the kidneys (early generations of sulphonylureas), giving a priority to use newer medication which were shown to be safer by their inherently low risk of hyperglycaemia (incretin-based therapy) or short duration of action (Repaglinide). Adjusting the insulin therapy regimens to suit the dialysis (both peritoneal and haemodialysis) is also important. Many factors make improving glycemic control in patients on dialysis very challenging, including therapeutic difficulties with hypoglycemic agents, monitoring difficulties, dialysis strategies that exacerbate hyperglycemia or hypoglycemia, and possibly a degree of therapeutic nihilism or inertia on the part of clinical diabetologists and nephrologists (4). Classical drug therapy for hyperglycemia (eg, metformin) is clearly not possible in patients on dialysis. Thus, sulphonylureas and insulin have been the mainstay of treatment. Newer therapies for hyperglycemia, such as gliptins and glucagon-like peptide-1 analogues have become available, but until recently, renal failure has precluded their use (4). Newer gliptins have yet to be trialled in dialysis patients.

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