Latin America and Latin America nephrology – a brief introduction

The part of the globe conventionally known as Latin America comprises an area of 19,197,000 km², with a population over 600 millions of inhabitants living in 21 countries, from Mexico to Uruguay. This vast geographic region is divided in four sections: North-America, Central-America, the Caribbean, and South-America. The ethnicity of this population is a complex mixture of Native Americans, Europeans, African and Asian people, likely making Latin America as one of the most diverse ethnic areas of the world. The two dominant languages spoken are Spanish (Mexico, Cuba, Dominican Republic, and Puerto Rico, and the majority of Central and South America) and Portuguese (Brazil).

Latin America has four megalopolis over 10 millions inhabitants (Mexico City, São Paulo, Buenos Aires and Rio de Janeiro) and areas almost inhabited, such as the Amazon forest, the Atacama Desert and Patagonia. Indeed, one of the main characteristics of Latin America is the profound socio-economic heterogeneity among countries, and even among areas of the same country. The gross domestic product per capita ranges from US$ 19,474 to 1,358 and the human development index from 0.819 to 0.456. As expected, these inequalities have an important impact on the pattern of diseases affecting the Latin America population, and in the way the national health services are organized and provided.

The nephrology medical community in Latin America is represented by the Latin American Society of Nephrology and Hypertension (SLANH), founded in 1970, which is composed by 22 National Societies from 20 countries (Mexico has three societies) representing over 5,000 nephrologists. The first SLANH president (1970-1972) was Professor R. Miattello, from Argentina, followed by 15 presidents from diverse countries. There have been already 16 Congress of the SLANH in the last 30 years (from 1972 to 2012), and Latin America has hosted three Congress of the International Society of Nephrology: 1972 in Mexico City, Mexico (2,650 participants); 1999 in Buenos Aires, Argentina (3,120 participants) and 2007 in Rio de Janeiro, Brazil (6,200 participants).

SLANH and the European Renal Association - European Dialysis and Transplant Association have developed solid scientific and educational links for a long time, and we hope to provide a glimpse on the Latin American nephrology for the readers of NDT.

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The first part of the South American Newsletter is available here.

The Argentine Health System: A Nephrologist Perspective

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Nephrology developed in Argentina almost simultaneously with the rest of the world. The Argentine Society of Nephrology (Sociedad Argentina de Nefrología) was established in 1960, shortly after the 1st International Congress of Nephrology was held in Evian, France. The first kidney transplantation in the country, which was also the first in Latin America, was performed in 1957. Since then, this therapeutic modality has achieved a
sustained development. The first hemodialysis session was performed by Alfonso Ruiz Guiñazú at the Instituto de Investigaciones Médicas. He used a home-made machine on a patient with post-transfusion acute renal failure who recovered within 21 days. In the same year, Carlos Gianantonio and his team successfully used peritoneal dialysis to treat a child with hemolytic-uremic syndrome, changing definitively the prognosis of this disease. The first renal nephrology and dialysis service was established in the Republic granting full coverage of chronic dialysis costs. As a natural corollary of this process, two federal laws were enacted to regulate renal replacement therapy (RRT):

1. The Dialysis Act Law No. 21,541, enacted in 1977, sets forth the conditions under which dialysis services are to be provided (physical structure, water treatment standards, staff training, dialyzer reuse, disposable needles and lines, etc.).

2. The Organ Transplantation Act – Law No. 24,541, created the CUCAI (Centro Único Coordinador de Ablación e Implante, Centralized Center on Organ Ablation and Implant), currently known as INCUCAI (Instituto Nacional Central Único Coordinador de Ablación e Implante, National Centralized Institute on Organ Ablation and Implant).

After these rules came into force in 1979, a solid deceased-donor kidney transplantation program was developed. The 1980s witnessed a great expansion of dialysis centers, and at present there are around 400 centers nationwide.

However, it was not until 1996 that full coverage for RRT was actually provided across the country, as a result of the implementation of the Mandatory Health Program (Programa Médico Obligatorio), which includes dialysis and transplantation among the medical practices that must be mandatorily covered by the health system. The role of nephrologists and the contributions of the Argentine Society of Nephrology have been pivotal for this process.

RRT has consistently evolved over time. Figure 1 shows an increase in the dialysis prevalence and incidence and kidney transplantation raw rates for 2000–2011. In 2011, the mean age of the incident dialysis population was 60 ± 17 years, with 44% ≥ 65 years of age. Diabetic nephropathy (36.4%) and nephroangiosclerosis (22.8%) were the main etiologies. If we add to these etiologies obstructive uropathy (8.3%), 67.5% of the causes for entry to dialysis would be potentially preventable with early diagnosis and treatment. Taking this into account, and adding the fact that 68% of incident patients begin dialysis with a temporary catheter, it is quite clear that patients are referred to the health system too late.1 Regarding renal transplantation, the rate of transplant and actual organ donors (15.1 pmp in 2011) has increased annually, and more than 75% of grafts come from deceased donors. However, this transplantation rate is not high enough to compensate for the number of patients on the waiting list.

There are no nationwide data on the prevalence of renal disease that does not require RRT. However, over the last few years, two national health surveys (conducted in 2005 and 2009) showed a high prevalence of risk factors for cardiovascular and renal disease in the general population (Table 1).

The increased awareness about the prevalence of CKD in the general population can be evidenced by important facts:

1. The Ministry of Health has included CKD in the non-communicable disease prevention programs.

2. The "Clinical Practice Guide on Prevention and Early Detection of Chronic Kidney Disease in Adults in the First Level of Care" 2 was established by all of the sectors involved (the Ministry of Health, academia, the Argentine Society of Nephrology and the health providers).

3. The Argentine Society of Nephrology together with the Argentine Biochemistry Foundation (Fundación Argentina de Bioquímica) and the Argentine Biochemistry Association (Asociación Argentina de Bioquímica) have made progress in promoting a better detection of CKD, developing expert guidelines and consensus documents for the determination of creatinine and proteinuria.

According to the last census, Argentina, considered a country with an upper-middle income level, has 40 117 086 inhabitants, distributed in 23 provinces and the Autonomous City of Buenos Aires (Ciudad Autónoma de Buenos Aires, CABA). The distribution of this population, predominantly concentrated in urban areas (93%), is not homogeneous: 46% are in the capital city (CABA) and one province, Buenos Aires. Therefore, population density is highly variable and ranges from 14 441 inhabitants/km2 in CABA to 0.1 in Tierra del Fuego, Antarctica and the South Atlantic Ocean Islands. This population is very heterogeneous, with disparity in the economic development among provinces, differences in poverty levels and persistence of pockets of disadvantaged populations, including indigenous peoples immersed in a process of forced trans-acculturation and epidemiological transition. The Argentine population is completing the late stages of the demographic transition process. Hence, the higher life expectancy at birth combined with the reductions of mortality and birth rates lead to an increase in the population age (10.2% older than 65 years, with a variation from 16.4% in CABA to 5.3% in Santa Cruz). In the same way, the causes of death are changing. Currently, the main causes of death are non-communicable chronic diseases, but at the same time, infectious diseases are still important as causes of death.

The Argentine health system operates in this complex socio-economic framework. It is composed of three independent, yet coexisting, subsystems: the Public System, the Social Security System and the Private System, comprising respectively 34.5%, 53% and 12.5% of the framework. These subsystems have significant differences in terms of structure, installed capacity, targeted population, services provided and resource sources.

The main problems do not seem to be dependent on health coverage or on the chances of getting treatment for ESRD, which is guaranteed for all diagnosed patients. Instead, the core issue lies with real and early access to prevention and early treatment programs for renal diseases affecting the general population. This requires community empowerment to drive changes in health care and lifestyles, which in turn promote changes in health-determining factors and lead to an improved quality of life for the population. Community education programs are necessary for this effect, and the state and scientific societies play a fundamental role in this process.

Bibliography


Table 1: Prevalence of cardiovascular and renal risk factors as per the National Risk Factor Survey (NRFS) for 2005 and 2009. Source: Argentine Ministry of Health.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>NRFS 2005 (%)</th>
<th>NRFS 2009 (%)</th>
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<tr>
<td>Sedentarism</td>
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<td>Smoking</td>
<td>29.7</td>
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<td>Hypertension</td>
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<td>34.8</td>
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<td>29.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.4</td>
<td>9.6</td>
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Information about nephrology research groups in Latin America
A new player in the pathophysiology of acute kidney injury and chronic kidney disease

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The classical role of aldosterone is increasing salt reabsorption and potassium secretion, actions exerted through binding to the intracellular mineralocorticoid receptor (MR) present in the tubular epithelium of the nephron. Now, it is well recognized that aldosterone performs other functions in other organs that possess MR in non-epithelial cells.

The Thomas Hostetter group showed for the first time in 1996 that aldosterone participated in the pathophysiology of chronic kidney disease (CKD) induced by 5/6 nephrectomy in the rat (1). Based on this study and several more, including some from our laboratory, it is known that MR antagonism with spironolactone or eplerenone is effective in reducing glomerular damage and tubulointerstitial fibrosis (TIF), as evidenced in several experimental models such as the hypertensive rat, cyclosporine nephropathy, unilateral ureteral obstruction and diabetic nephropathy type 1 and 2. Moreover, these experimental findings have supported the development of translational research and have shown the deleterious effects exerted by aldosterone in patients with chronic renal failure (for review see Ref. 2).

Our laboratory has also shown the involvement of aldosterone in the pathophysiology induced by ischemic processes, such as cyclosporine nephrotoxicity (CsA) or the renal damage induced by ischemia/reperfusion (I/R). In a first study, we observed that MR antagonism reduced the percentage of arteriolopathy and TIF in rats with chronic CsA nephropathy. A particularly interesting finding of this study was that animals receiving spironolactone did not show kidney dysfunction. In a subsequent study, we found that MR antagonism also prevented acute CsA nephrotoxicity characterized exclusively by renal vasoconstriction. This renoprotective effect was also observed in pre-established chronic CsA nephropathy. These results indicated that aldosterone modulates the tone of renal vasculature and contributes to renal vasoconstriction observed in this kind of nephropathy. Given the above, we inferred that aldosterone could also play an important role in acute kidney injury (AKI) induced by I/R. AKI is characterized by a transient decrease in blood flow and renal function together with tubulointerstitial damage. Despite advances in diagnosis and therapy, the morbidity and mortality associated with AKI is still very high (40 to 60 % in intensive care units) and has not improved considerably in the last four decades. Interestingly, we demonstrated that MR antagonism before or after renal I/R prevented functional and structural damage that is observed in this pathology (for review see Ref. 2). These findings allowed us to conduct translational research, where we found that although spironolactone did not improve renal function, there was a significant reduction of oxidative stress in renal transplant recipients (3).

Previously, it was speculated that patients recovering from an episode of AKI experienced no further consequences, however, recent evidence from epidemiological observations in patients suffering from AKI indicate that this is not the case, since a large percentage of these patients developed CKD. This also has been confirmed experimentally since we found that an ischemic episode is enough to produce CKD in the rat. Thus, CKD in these animals was characterized by renal dysfunction, proteinuria, glomerular and tubular hypertrophy, increased tubular cell proliferation and TIF. At the molecular level, the mechanisms responsible for the development of CKD were the activation of the TGF-β pathway, increased oxidative stress and a greater inflammatory response. Interestingly, we found that AKI prevention with spironolactone use avoided the development of CKD (4).

Therefore, our studies strongly suggest that 1) aldosterone plays a key role in mediating ischemic renal injury, 2) the beneficial effect of spironolactone is due to its ability to block the MR, 3) AKI prevention effectively avoids the development of CKD, and 4) MR antagonism can be used as a promising, safe, and low-cost strategy to protect against renal damage induced by ischemic processes and prevent the development of CKD.

References:

Our research group has been interested in studying the pathogenesis of essential hypertension and salt-sensitive hypertension in various experimental models. More specifically, we have focused on the role that immune cell-related inflammation plays in the development of hypertension in spontaneously hypertensive rats (SHR), in the hypertension that results from cellophane wrapping of the kidneys (Page kidney) and in the salt-sensitive hypertension (SSHTN) that follows transient inhibition of nitric oxide synthase and protein overload proteinuria. Investigations have shown that immunosuppression induced by mycophenolate mofetil (MMF) corrects the hypertension in SHR and in the Page kidney and prevents SSHTN. Correction of hypertension was also observed with inhibition of the pro-inflammatory transcription factor nuclear factor kappa B.

The pathogenesis of SSHTN includes impairment of the pressure-natriuresis relationship, which is related to the infiltration of immune competent cells in the renal tubulointerstitium with increment in the activity of renal angiotensin II; these events are corrected by immunosuppression. In recent investigations we have shown that autoimmunity, triggered by and directed to heat shock protein 70 (HSP70) plays a critical role in the pathogenesis of SSHTN and the induction of immune tolerance to HSP70, resulting in a regulatory T-cell response, prevents hypertension.

Patients with grade I essential hypertension that received MMF for 3 months as a treatment given for rheumatoid arthritis or psoriasis showed improvement in hypertension during treatment in association with a reduction in urinary excretion of proinflammatory cytokines. Taken together, these studies suggest the need to explore further the participation of autoimmunity in essential hypertension and raise the possibility of new treatment strategies in the treatment of essential hypertension.
protective and therapeutic effects of stem cells increases every year. Searching the ClinicalTrials.gov (August/2013), we found 4743 trials worldwide testing the potential therapeutic effects of stem cells. In Latin America, 58 trials are ongoing. However, stem cell trials in kidney diseases are only a small proportion; there are around 350 worldwide and none in Latin America. The Brazilian Network for Stem Cell Therapy (RNTC) aims to enhance clinical studies in this field in Brazil. RNTC is a consortium composed of eight cellular technology centers located in five Brazilian states and in 52 laboratories selected by the Brazilian National Research Council (CNPq) and the Science and Technology Department of the Ministry of Health. The main objective of RNTC is to integrate researchers of stem cells around the country and facilitate the exchange of information on stem cell research. The focus is on isolation and culture of different sources of stem cells, such as embryonic, pluripotent induced, mesenchymal, hematopoietic, neural and cardiac cells. The centers are working on projects to provide clinical-grade stem cells for cellular therapy, and the 52 laboratories are developing projects in different fields, most of them neuronal and cardiac-related. They are performing not only basic research (15 studies) but also pre-clinical (33 studies) and clinical (4 studies) projects. In the ClinicalTrials.gov, August/2013, 49 registered clinical trials from Brazil can be found. In Latin America, Argentina (seven trials), Chile (four trials) and Brazil (49 trials) are the principal centers researching stem cells.

One important concern about Brazilian stem cell research is that Brazilian researchers are involved in the vast majority of the projects, and therefore, more international cooperation is desirable and necessary. One program, which is sponsored by both the Brazilian and Argentine government, may help to build this collaboration.

Several pre-clinical projects have analyzed the beneficial properties of stem cells in kidney diseases, especially employing mesenchymal stem cells in acute and chronic kidney injury induced by nephrotoxins (1) and in 2/6 and 5/6 remnant models of chronic kidney disease (2). Additionally, many projects from our laboratory are focusing on the renoprotective effects of mesenchymal stem cells in the radiation-induced acute kidney injury model, as well as in the chronic kidney injury model of unilateral ureteral obstruction. We are also evaluating the effects of stem cells and physical exercise on the 5/6 nephrectomy and experimental diabetes mellitus chronic kidney disease models.

The Brazilian research in stem cells has not only confirmed the important findings demonstrated by American and European researchers, but most importantly has also published breakthroughs results, despite all of the challenges of performing basic research in our country, such as inadequate financial support, bureaucratic importation laws and scientific community mistrust. Different countries have studied the paracrine effect of mesenchymal stem cells, but our group has demonstrated the involvement of exosomes in the paracrine effect of mesenchymal stem cells (1).

Additionally, a new population of c-kit+cells derived from the neonatal kidney showing the characteristics of stem cells was found in the thick ascending limb of Henle’s loop. They exhibited clonogenicity, self-renewal and differentiation capacity (3).

In summary, despite the many local and regional problems, stem cell research in Brazil and in Latin America is clearly evolving.

References

This regional center began its activities in 1985, under the direction of Prof Sergio Mezzano in the city of Valdivia in southern Chile.

This university department, located at the Clinic Hospital of Valdivia, is involved in the clinical care of patients, undergraduate and postgraduate teaching activities and basic as well as clinical research. All their members have received training in prestigious centers in the USA and Europe.

This department is the reference center for renal transplantation and tissue typing for the entire southern part of this country and is affiliated with the Instituto Salud Pública Chile (ISP) and the Collaborative Transplant Study (CTS, Heidelberg). In addition, it is one of the three nephropathological reference centers in the country. In the area of postgraduate teaching, it collaborates with programs of specialization in pediatrics, internal medicine and pathology and has developed an attractive program in the specialization of clinical nephrology, having trained over 25 nephrologists working in Chile and South America.

Research activities characterize the group, where technicians, biochemists, nurses, PhD students and clinicians are integrated in a productive team. The main lines developed by our group are related to the immunopathogenesis of glomerular diseases, the mechanisms of progression of chronic kidney disease, fibrogenesis, diabetic nephropathy, renoprotection and salt sensitivity in relation with the kinin system. In the area of transplantation, tissue typing and pharmacokinetic studies have been relevant.

The most sophisticated methodological resources include advanced immunohistochemical and electron microscopy studies and transgenic models of renal diseases.

These efforts have been accomplished in collaboration with several important international groups including Fundación Jimenez Díaz, Madrid, Spain (Prof J. Egido); Universidad de Zulia, Maracaibo, Venezuela (Prof B. Rodriguez-Iturbe); University of Dublin, Ireland (Prof H. Brady); Institute Mario Negri, Bergamo, Italy (Prof G. Remuzzi); University of North Carolina, Chapel Hill, USA (Prof Ch. Jennette); University of Cambridge, UK (Prof C.M. Lockwood); University of Torino, Italy (Prof G. Camussi); University of Cincinnati, USA (Prof V. Pollak) and the Center of Scientific Studies CECS, Valdivia, Chile.

More than 120 manuscripts have been published from the results originating in this laboratory. Some of the most relevant are following: the symposium entitled "The role of the tubulointerstitium in hypertension and in the progression of renal disease" published as Suppl. 86: 2003, in Kidney Int.; our contribution in The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification, published in Kidney Int. 2009; and the manuscripts, "Expression of gremlin, a bone morphogenetic protein antagonist, in glomerular crescents of pauci-immune glomerulonephritis" (Nephrol Dial Transplant. 2007); "NF-kappa B activation and overexpression of regulated genes in human diabetic nephropathy" (Nephrol Dial Transplant. 2004); "Overexpression of chemokines, fibrogenic cytokines, and myofibroblasts in human membranous nephropathy" (Kidney Int. 2000); and "Podocyte-specific overexpression of wild type or mutant trpc6 in mice is sufficient to cause glomerular disease" (PLoS One 2010).