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EDITORIAL

What is the purpose of launching the *World Journal of Nephrology*?

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Abstract

The launch of the *World Journal of Nephrology* (*WJN*) has distinct purposes. Its main purpose is to incorporate the fields of diabetes, hypertension, urology, cardiology and neurology, which are related to kidney disease, and to make all of our readers, contributors and allied health professionals feel at home with the *WJN*. The *WJN* aims to rapidly report new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing skill in the field of nephrology. The *WJN* will cover diagnostic imaging, disorders of kidney development, renal obstruction, atrophy and regeneration, kidney tumors, renal pharmacology and therapy, renal replacement therapies including transplantation, and Chinese herbal medicine. The *WJN* issues will include an editorial, frontier, invited review of articles and commentaries in addition to original articles submitted. The *WJN* will solicit articles from investigators in areas of diabetes and hypertension, and high priority will be given to those articles with an emphasis on the prevention of dialysis. Final decision for publication will be based on the merit of the article, language and lucidity.

Figure 1 Editor-in-Chief of the *World Journal of Nephrology*. Anil K Mandal, MB, BS, Professor, Department of Medicine, University of Florida, Gainesville, Florida, Mandal Diabetes Research Foundation, 665 State Road 207, Suite 102, Saint Augustine, FL 32084, United States.

Key words: Nephrology; Biomedical sciences; Peer-reviewed; Open-access; Journal

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INTRODUCTION

I am Anil K Mandal, MB, BS, FACP, FCP, FASN, Professor form Medical Specialists of Northeast Florida, United States (Figure 1), together with Professor Josep M Campistol from the University of Barcelona, Spain, we will be the co-Editor-in-Chief of the *World Journal of Nephrology* (*World J Nephrol*, *WJN*, online ISSN 2220-6124, DOI: 10.5527). I am very pleased to announce that the

first issue of the *WJN,* on which preparation was initiated on February 14, 2011, is officially published on February 6, 2012. The *WJN* Editorial Board has now been established and consists of 103 distinguished experts from 30 countries. I feel obliged to convey my heart-felt appreciation to Professor Lian-Sheng Ma, President and Editor-in-Chief of the World Series of journals, and the members of the editorial board of *WJN* for bestowing this honor on me.

By virtue of the duties ascribed to this position, I have the arduous task of composing the inaugural editorial. At the outset, I ask an important question, "Why do we need another nephrology journal when there are already 30 in the market?" In answer, we can look at the focus of those other 30. Only four of them have a clinical focus[1] and only a few are produced independently. Most of the nephrology journals, like other journals, are produced by different societies. The aim of these journals is to offer its services as an efficient vehicle for the international dissemination of scientific information. In the narrowest sense, the term nephrology relates to the diagnosis and treatment of kidney diseases in man. Nevertheless, the art and science of nephrology are derived from a clinical mixture of information from several scientific disciplines, as well as experimental evidence whose immediate relevance in the practice of nephrology may have seemed less important at the time. According to Dr. RR Robinson, a nephrology journal should be multidisciplinary and sufficiently broad to be termed "kidney-oriented" at least. A commitment to accommodate a heterogeneous group of individuals with divergent interests, talents and research background poses a real challenge to the editor of any categorical journal; the clinical nephrologist, the clinical scientist and the basic scientist must be made to feel at home among its pages[2].

Thus, the intention of a society's journal is good but its fulfillment is imperfect. Pitifully, the delivery of the intention by the editor and the editorial board is often influenced by factors outside of the scientific merit of the work submitted for publication. There are often various types of bias at work in the decision making process. As a result, many good articles are not published while many mediocre articles are printed.

Great articles on renal physiology, pathophysiology, pathobiology or epidemiology, and pathophysiology of diabetes were published in the 1960s, 1970s and 1980s. These types of articles are relevant to improve our knowledge and understanding, thereby helping us to develop improved strategy and deliver better care to renal patients with a goal of prevention. Briggs and Hostetter have stated that, despite the impressive strengths of renal epidemiology, the evidence base for many of the important clinical questions that nephrologists face remains inadequate[3].

Over the years, the cost of publication has skyrocketed and thus many nephrology societies are taking the financial help of pharmaceutical companies to maintain their journal services. As a result, journal pages are crowded with clinical drug trials, almost completely replacing articles on water and electrolytes metabolism or acid base disorders which are far more common in the everyday practice of nephrology. Often, one third to one half of a journal's content is concerned with drug therapy rather than scientific findings of cause and / or prevention.

The opening editorial of the *Clinical Journal of the American Society of Nephrology* (*CJASN*) clearly states that much important work on the treatment of kidney disease is sponsored by the pharmaceutical industry. There is much work to be done and clearly a role to be played by the *CJASN*, but one hope for our new journal is that, by contributing to improvements in renal clinical trial methods, we can help to increase pharmaceutical interest beyond expensive drug therapies[3].

AIMS AND SCOPE

It is now my responsibility to reveal to our readers why this new journal has come to be. Our main purpose is not to compete head to head with other nephrology journals, but to incorporate the fields of diabetes, urology, cardiology and neurology, which are related to kidney disease, and to make all of our readers, contributors and allied health professionals feel at home with the *WJN*. While society members receive journals free of cost, the majority of allied health professionals must subscribe at a high price which limits the readership. The information readily available online also contributes to a rapidly vanishing need for books and journals. One important objective of the *WJN* will be to make our articles available online in an economical manner.

The *WJN* aims to rapidly report new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of nephrology. The *WJN* covers diagnostic imaging, disorders of kidney development, renal obstruction, atrophy and regeneration, kidney tumors, renal pharmacology, therapy of renal disease, hemodialysis, peritoneal dialysis, kidney transplantation, traditional medicine, integrated Chinese and Western medicine, evidence-based medicine, epidemiology and nursing. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to nephrology, such as immunology, physiopathology, cell biology, pharmacology, medical genetics and pharmacology of Chinese herbs.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJN* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of the *WJN* will include: (1) Editorial: to introduce and comment on major advances and developments in the field; (2) Frontier: to review representative achievements, comment on the state of current research and propose directions for future research; (3) Topic Highlight: this column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: to update the development of old and new questions, highlight unsolved problems and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: to provide guidelines for basic research; (6) Guidelines for Clinical Practice: to provide guidelines for clinical diagnosis and treatment; (7) Review: to review systematically progress and unresolved problems in the field, comment on the state of current research and make suggestions for future work; (8) Original Articles: to report innovative and original findings in nephrology; (9) Brief Articles: to briefly report novel and innovative findings in nephrology; (10) Case Report: to report a rare or typical case; (11) Letters to the Editor: to discuss and make reply to the contributions published in the *WJN*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: to introduce and comment on quality monographs of nephrology; and (13) Guidelines: to introduce consensuses and guidelines reached by international and national academic authorities worldwide on research nephrology.

CONCLUSION

A new horizon of the *WJN* is for articles on diabetes and hypertension control. Diabetes related nephropathy with acute or chronic renal failure constitutes a large part of nephrology practice throughout the world. The *WJN* will solicit articles from investigators in diabetes and hypertension management. High priority will be given to those articles dealing with prevention strategy of diabetic nephropathy with the aim of preventing patients from needing dialysis. All articles recommended for publication or rejection will be reviewed by the editor-in-chief for final decision. Prospective readers should know that, as editor-in-chief, I have no prejudice but a conviction for all or none and am resistant to a change of mind by outside influences. Final decision for publication will be based on the merit of the article, writing style, clarity of language, lucidity and succinctness.

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EDITORIAL

Cytoprotection behind heme oxygenase-1 in renal diseases

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Abstract

Renal insults are considered a public health problem and are linked to increased rates of morbidity and mortality worldwide. The heme oxygenase (HO) system consists of evolutionary specialized machinery that degrades free heme and produces carbon monoxide, biliverdin and free iron. In this sense, the inducible isoform HO-1 seems to develop an important role and is widely studied. The reaction involved with the HO-1 molecule provides protection to injured tissue, directly by reducing the toxic heme molecule and indirectly by the release of its byproducts. The up regulation of HO-1 enzyme has largely been described as providing antioxidant, antiapoptotic, anti-inflammatory and immunomodulatory properties. Several works have explored the importance of HO-1 in renal diseases and they have provided consistent evidence that its overexpression has beneficial effects in such injuries. So, in this review we will focus on the role of HO-1 in kidney insults, exploring the protective effects of its up regulation and the enhanced deleterious effects of its inhibition or gene deletion.

Key words: Heme oxigenase-1; Renal cytoprotection; Antioxidants; Anti-inflammatory; Renal diseases

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INTRODUCTION

Renal injuries can occur as a consequence of a number of factors, like hypoxia, nephrotoxicity, diabetes, renin-angiotensin system activation, among others. Most of these lesions are characterized by an increased amount of oxidative stress, inflammatory milieu and pro fibrotic stimuli. These factors lead to a breakdown of renal homeostasis and promote cell damage, with increased cell death and/or transdifferentiation. The ability of reducing this cellular damage could be crucial to a better outcome of the disease and, in this manner, the enzyme heme oxygenase (HO) could provide an important protective effect against renal insult[1].

Heme molecule (iron protoporphyrin IX) represents the prosthetic group of various proteins and enzymes, including hemoglobin, nitric oxide synthase, cytochrome P-450, cyclooxygenase, and catalase, among others. It is involved in critical functions, such as oxygen supply, mitochondrial respiratory burst and signal transduction[2,3]. In this sense, HO is the rate limiting enzyme responsible for heme degradation. HO cleaves to the heme ring in a reaction requiring oxygen and nicotinamide adenine dinucleotide phosphate and, as a result, biliverdin is produced, releasing iron and carbon monoxide (CO) in equimolar

quantities. Later, biliverdin is converted to bilirubin by the enzyme bilirubin reductase[4,5].

HO was previously described by Tenhunen *et al*[6] in 1968 and interest in it has increased every year. This information is based on the fact that, since its discovery, more than 10 000 publications have been reported, and in 2010 alone, almost 1000 papers were published with this theme.

The HO system consists of two distinct isoforms, HO-1 (inducible) and HO-2 (constitutive), which are products of different genes. HO-1 is localized in microsomes and is ubiquitously present in mammalian tissue. Moreover, in physiological conditions, its expression is relatively low. The only exception comes from the spleen, where HO-1 is important for recycling iron from senescent erythrocytes. Recent studies showed that HO-1 deficiency affects stress erythropoiesis and leads to reduced function and viability of erythrophagocytosing macrophages, resulting in tissue damage and iron redistribution[7,8].

On the other hand, HO-2 seems to work as a physiological regulator of cell function. It is present in mitochondria and generally expressed in brain, testis, endothelium, nephron distal segments, liver and the gastrointestinal tract[9]. It seems to share 40% of amino acid homology with HO-1. Finally, formerly known as an isoform, HO-3 now is recognized as a pseudogene[10].

PROTECTIVE EFFECTS OF HO-1

Of these two isoforms, HO-1 is the most studied and seems to provide higher cytoprotection; so, hereafter, we will mostly discuss this isoform. The protection beyond HO-1 is observed in a variety of processes and these will be discussed in more detail in the next paragraphs.

HO-1 acts as an antioxidant in a direct and indirect manner. Directly, the enzyme contributes withdrawal of excessive heme molecule, which is a pro oxidant agent[11]. Indirectly, the free iron released from the reaction stimulates the expression of ferritin, an intracellular iron reservoir, diminishing the generation of hydroxyl radicals[12]. Furthermore, the biliverdin and, consequently, bilirubin formation displays an important antioxidant effect, as both molecules are peroxyl radicals scavengers[13].

The antiproliferative effects are based mainly on vascular smooth muscle cells experiments. A recent study showed that rapamycin could induce HO-1 expression and this up regulation led to protection in a model of pulmonary disease. The same work showed that smooth muscle cells derived from deficient animals for HO-1 were not responsive to the antiproliferative or cell cycle inhibition actions of rapamycin[14]. Moreover, studies have shown that a possible mechanism related to inhibition of cell growth by HO-1 could be up regulation of inhibitory protein $p21^{cip}$. Interestingly, this pathway also contributes to an anti-apoptotic property of HO-1[15,16].

HO-1 can also act as an immunomodulatory enzyme, especially in T lymphocytes mediated diseases[17]. Burt *et al*[18] proposed that HO-1 contributes to T cells homeostasis, maintaining these lymphocytes in a nonactivated state, and the pharmacological inhibition of HO-1 leads to T cell activation and proliferation. The importance of HO-1 in Treg cells were described by a couple of works which stated that $CD4^+CD25^+$ Treg cells constitutively expressed HO-1 and that this enzyme could be induced after FoxP3 expression in $CD4^+CD25^-$ cells, conferring a regulatory phenotype to these[19,20]. Another study showed that, in a murine model of colitis, treatment with hemin, a HO-1 inducer, resulted in expansion of Treg cells and decreased the levels of Th17 related molecules. On the other hand, inhibition of HO-1 led to opposite effects and aggravated the disease[21]. Still, the immunomodulatory effect of HO-1 also influences the priming of T cells. Cheng *et al*[22] showed that deletion of HO-1 gene or use of small interfering RNA silence in dendritic cells promoted up regulation of major histocompatibility complex class Ⅱ, enhancing the alloantigen presentation to $CD4^+$ T lymphocytes.

Finally, the anti-inflammatory property of HO-1 could be due to the enzymatic degradation of the pro-inflammatory heme molecule, as well as the production of its byproducts, which have the capacity to suppress the inflammatory process. In the first case, free heme is a highly toxic compound and may cause oxidative stress. Furthermore, its presence led to increased influx of leukocytes into organs during an experimental inflammation[23]. In addition, heme is part of many pro-inflammatory enzymes, like cytochrome p450 mono-oxygenases, inducible nitric oxide synthase and cyclooxygenase[24]. So, once HO-1 removes excessive free heme, it will impair the optimal activity of those enzymes, attenuating the inflammation[25]. On the other hand, some studies have shown that the up regulation of HO-1 can directly inhibit the inflammatory process. A recent work indicated that when HO-1 is induced, there is a negative modulation of inflammation, with decreased gene expression and protein production of tumor necrosis factor α, interleukin (IL)-6 and IL-1β, with concomitant increased protein levels of the immunomodulatory cytokine IL-10[26]. One of the pathways involved in this suppression may be related to p38 mitogen activated protein kinase. Lee *et al*[27] have shown that when there is an inhibition of this kinase, HO-1 induction is diminished and, consequently, the protection on human proximal tubular epithelial cells is abrogated.

HO EXPRESSION IN THE KIDNEY

The first paper describing the role of HO in kidney was published by Pimstone *et al*[28] in 1971 and it provided evidence that HO induction could contribute to renal cytoprotection. As stated earlier, HO-2 is a constitutive enzyme, so its expression is important for maintenance of kidney functions. In this sense, a study published by Da Silva and colleagues documented that this isoform is present in vascular and tubular compartments[29]. More specifically, HO-2 was observed in the medullar thick

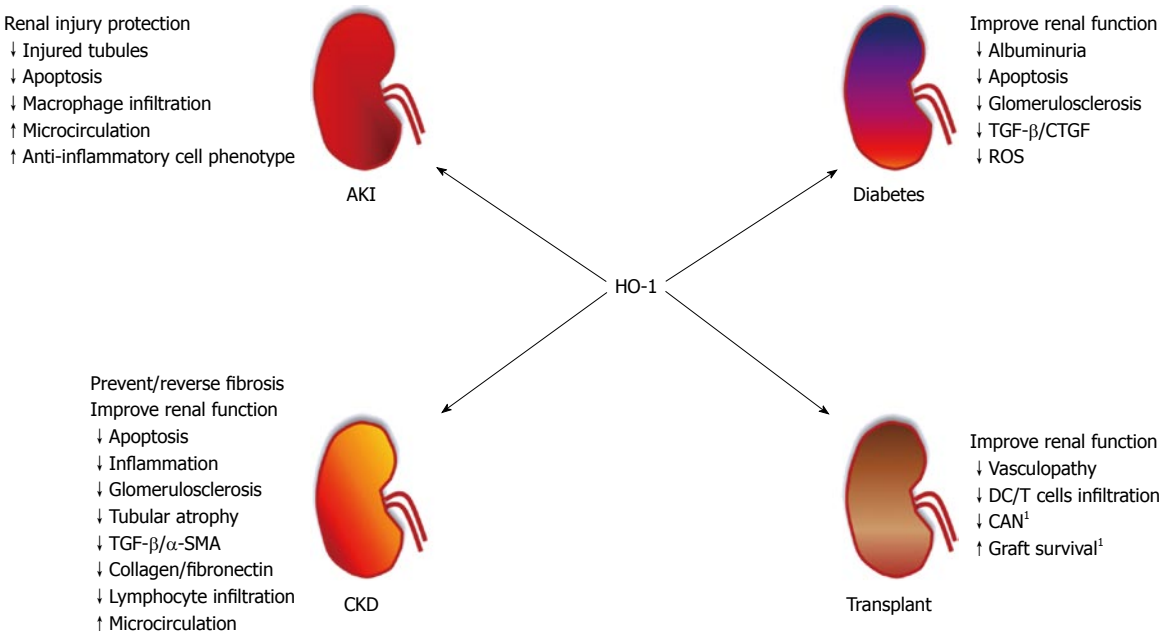

Figure 1 Overview of heme oxygenase-1 in renal diseases. Heme oxygenase (HO)-1 induction prevents renal damage in diverse renal diseases, such as acute kidney injury (AKI), chronic kidney disease (CKD), diabetic nephropathy (Diabetes) and renal Transplant. Arrows followed by text indicate increase (↑) or decrease (↓). [1]Requires further study. TGF: Transforming growth factor; SMA: Smooth muscle actin; CTGF: Connective tissue growth factor; CAN: Chronic allograft nephropathy.

ascending limb, distal convoluted tubule, connecting tubule segments, principal cells of the collecting duct, renal interlobar arteries and preglomerular arterioles in the kidney[29]. On the other hand, HO-1 is weakly expressed in the kidney under normal conditions. But, confirming its role as a stress induced enzyme, after an acute or chronic renal insult, it is rapidly expressed[30,31]. Immunolocalization of HO-1 in rat kidneys showed that this enzyme was identified on proximal and distal tubules, as well as in medullar collecting tubules and loops of Henle[29]. Still, in a model of streptozotocin-induced diabetic nephropathy, HO-1 was also expressed in glomeruli[9]. Moreover, according to Jarmi and Agarwal's work, HO-1 expression is also observed in human renal diseases, especially in proximal tubules[32]. Localization of HO-1 expression sites in different diseases could be important for development of specific therapeutic drugs.

Also, one of the main chemoattractant proteins is MCP-1, which can recruit leucocytes to the site of injury[5]. A recent study has shown that renal epithelial cells that constitutively overexpressed HO-1 presented decreased production of MCP-1 after stimulation with albumin[33]. Moreover, in HO-1 deficient mice, the basal levels of MCP-1 are significantly increased when compared to wild type animals and it becomes even higher after a stress condition[34]. Finally, as HO-1 is classified as a stress responsiveness enzyme, a recent work showed that urinary HO-1 could be useful and a sensitive biomarker for tubule interstitial inflammatory damage in renal diseases[35].

HO-1 AND RENAL INSULTS

In the following section, we will be discussing more about the protective effects of HO-1 in some renal diseases. For a better didactic comprehension, we divided it into four topics: acute kidney injury (AKI), diabetic nephropathy, renal transplantation and chronic kidney disease. Also, Figure 1 shows a summary of the role of HO-1 in these renal diseases.

AKI

AKI, previously called acute renal failure, is defined by a rapid decrease of renal function, resulting in retention of urea and creatinine levels in serum as well as changes in cellular volumes and electrolyte imbalance. AKI is associated with high mortality rates and ischemia and reperfusion injury (IRI)[36] is one of its causes.

IRI starts with the break of ionic homeostasis due to ATP depletion in proximal tubular cells, which lose polarity and undergo the cell death process. All this is accompanied by intense vasoconstriction, increase of adhesion molecules, reactive oxygen species, pro-inflammatory cytokines and chemokines[37]. This inflammatory process also comprises of cells from innate (macrophages, dendritic cells and neutrophils) and adaptive immune response (B cells, CD4+ and CD8+ T cells)[36]. As HO-1 was seen to modulate immune cells to a regulatory profile[38] and to favor anti-inflammatory response, it obviously questioned the role of HO-1 in AKI.

Shimizu *et al*[39] used an HO-1 inhibitor, tin mesoporphyrin, in the unilateral renal ischemia and reperfusion model and observed an increase in microsomal heme, which is toxic to the cell. Different from non-treated animals, levels of heme were sustained in tin treated rats and renal injury was exacerbated in this group. In the opposite way, tin chloride treatment, a HO-1 inducer, protected animals from IRI[39,40]. These results demonstrated

that HO-1 is associated with IRI protection. In the same direction, other HO-1 inducers led to protection in this model: hemin treatment improved microcirculation in an isogenic kidney transplantation model and also reduced IRI[41], and the use of Cobalt protoporphyrin (CoPPIX) in rapamycin-induced renal dysfunction after IRI increased HO-1 levels and eased renal injury[42]. Administration of cobalt chloride also protected rats from IRI, with an increase of hypoxia inducible factor (HIF)-1α, HO-1, erythropoietin, glucose transporter 1 and vascular endothelial growth factor, and diminished macrophage infiltration into the kidney[43]. More recently, Wu *et al*[44] showed that the induction of bardoxolone methyl increased HO-1 and nuclear factor erythroid 2-related factor 2 (Nrf2) expression, and protected mice from unilateral IRI. Ferenbach *et al*[45] produced macrophages that overexpressed HO-1, which presented an anti-inflammatory phenotype. Intravenous injection of these cells 20 min after IRI improved renal function outcome, suggesting a new tool to control injury in this model. The byproduct of HO-1, CO, was able by itself to protect animals from IRI with less injured tubules with the pre-administration of Tricarbonylchlor o(glycinato) ruthenium(II) ([Ru(CO)3Cl-(glycinate)], the CORM-3[46], indicating that HO-1 and its byproducts were able to protect kidney from ischemic AKI.

Other AKI models were also protected after HO-1 induction. Rhabdomyolysis is characterized by heme and myoglobin release from damaged muscle, which allows the excessive exposure of the kidney to these proteins and leads to AKI. Glycerol-induced rhabdomyolysis presented renal injury protection with hemoglobin injection, while exacerbated renal damage was observed when tin protoporphyrin, a HO-1 inhibitor, was administered[47]. HO-1 induction by granulocyte colony-stimulating factor also protected animals from rhabdomyolysis kidney injury accompanied by increased survival and diminished apoptosis[48]. The same model of AKI presented worse renal function and higher mortality when using HO-1 knockout mice[49], which reinforces the importance of HO-1 to diminish the toxic heme accumulation.

Nephrotoxic-induced AKI occurs mostly as a side-effect of chemotherapy and other treatment drugs. In the cyclosporine-renal injury model, the treatment with CoPPIX led to a kidney morphological pattern similar to control[50]. Similar results were observed in animals that received cisplatin, a chemotherapy drug, with the concomitant treatment of CORM-3, presenting renal injury protection[51]. These results demonstrated that HO-1 has a role in nephrotoxic-induced AKI and highlight the importance of CO, HO-1 byproduct, in kidney injury protection.

All these works show that HO-1 induction can improve the outcome in AKI and, although this subject needs further investigation, suggests that the HO-1 manipulation could be an interesting tool to diminish AKI related mortality.

Diabetic nephropathy

Diabetic nephropathy is the most common cause of end-stage renal failure in developed countries[52]. Although the beginning of the disease in type Ⅰ and type Ⅱ diabetes is distinct, the changes observed in renal physiology caused by excessive glucose are quite similar and usually lead to alterations in kidney architecture accompanied by renal failure[53]. The role of HO-1 system in diabetes has been widely reported and its upregulation has been proved to mediate insulin release by pancreatic cells, conferring a protective effect[54-57].

Specifically talking about renal involvement of high glucose levels, some studies have shown that treatment with HO-1 inducers provides a better renal function outcome. Ohtomo *et al*[58] used a model of obese, hypertensive and diabetes type Ⅱ rats (SHR/NDmcr-cp). These animals presented with severe proteinuria and renal histological changes. The up regulation of HO-1 with CoPPIX in such rats improved proteinuria levels and significantly decreased histological abnormalities. Moreover, the treatment also reduced the gene expression of pro-fibrotic molecules transforming growth factor (TGF)-β and CTGF.

Podocytes are important cells present in the glomerular compartment, being specialized in the good maintenance of the renal filtration[59]. A recent study showed that HO-1 inhibition promoted increased albuminuria and reduced podocyte numbers in diabetic rats. *In vitro* experiments showed that podocytes exposed to high glucose and to the HO-1 inhibitor ZnPP presented increased apoptosis. Induction of HO-1 protected these cells from pro apoptotic stimuli under diabetic conditions[60].

Finally, the most important antioxidant cellular regulator is Nrf2, which promotes expression of detoxifying and antioxidant enzymes that are a downstream Nrf2 gene, including HO-1[61]. Some recent studies have studied this pathway and its strict relationship with diabetic nephropathy. Li *et al*[62] showed that when streptozotocin-induced diabetic mice were treated with a Nrf2 activator, HO-1 gene and protein expressions were up regulated, with concomitant decreased levels of albuminuria, proteinuria and glomerulosclerosis index. Another study showed that mesangial cells submitted to high glucose levels presented increased reactive oxygen species production, proliferation and TGF-β production. When these cells were transfected with Nrf2-plasmid, HO-1 was induced and such parameters were ameliorated. On the other hand, when mesangial cells were exposed to Nrf2 specific siRNA, this protection was abrogated[63]. All these works provide support that one of the most important mechanisms of renal disease of diabetes, the pro-oxidant axis, can be attenuated by HO-1 induction.

Renal transplantation

Organ transplants are required in end state organ failure; however, in renal diseases, it might be the best treatment considering cost/benefit and quality of life, which encourages the increase of numbers in renal transplants. According to the World Health Organization, renal transplant comprises the majority of organ transplants

performed in 98 countries. In 2005, 66 000 kidneys were transplanted, while 21 000 livers and 6000 hearts were transplanted in the same year[64]. Although it seems easy and advisable to do, renal transplant comes with a series of complications. Delayed graft function (DGF) is one and frequently occurs after a kidney transplant in almost 50% of the cases[65]. Ischemia and reperfusion is associated with DGF once cadaveric organs undergo an ischemic period before transplant and the incidence of DGF is increased in this case. DGF is also involved in acute rejection and can leads to chronic allograft nephropathy (CAN) development and chronic rejection[65,66], which is why the search for new therapies is needed.

As HO-1 was seen to have a protective role in IRI, to induce an anti-inflammatory environment, it was thought to have the same role in renal transplants. Formerly known as a stress induced enzyme, HO-1 was observed when protein expression was analyzed in biopsies. An increase of HO-1 expression in kidney biopsies prior[67] and post-reperfusion[68] was associated with DGF. Moreover, Avihingsanon *et al*[69] demonstrated that nonrejecting grafts as well as chronic rejected grafts presented no expression of HO-1, while acute rejected grafts presented higher expression of the enzyme, suggesting that the increase of HO-1 in acute rejection is an attempt to maintain graft viability and function and limit tissue injury. On the other hand, Lemos *et al*[70] showed that cadaveric donor kidneys presented decreased expression of HO-1 and worse renal function compared to living donor kidneys, reinforcing the protective role of this enzyme. These inconsistencies might be explained by the different population analyzed in each study and the environmental conditions of the transplantation that may influence the outcome of the graft.

The consequence of genetic polymorphism has also been described in the literature. A polymorphism based on dinucleotide repeat (GT)n was identified in HO-1 gene promoter. The short (S)-allele (< 27) has increased transcription of HO-1 in comparison to the long (L)-allele (> 27)[71]. Studies about the influence of this polymorphism in renal transplant are controversial: improvement on graft survival was seen in S-allele, as well as less CAN[71] and better renal function[71-73], while different groups observed no influence of donors and/or recipient S-allele kidneys in graft survival and CAN[73,74].

Animal models at least minimize the conflict of genetic background. A HO-1 inducer, CoPPIX, was administered in recipient rats and prevented allograft rejection, presumably due to less vasculopathy[75]. Administration of CoPPIX in donor rats also reduced DC, T $CD4^+$ and T $CD8^+$ in the graft, indicating less immunogenicity[76]. Not only the induction of HO-1, but also the use of methylene chloride, a CO donor, was able to improve graft function[77], corroborating the idea of HO-1 as an immune modulator in favor of graft acceptance. Human studies require further investigation, but they suggest so far that HO-1 works as a biomarker for acute rejection and that it also has a role in kidney homeostasis, which might help the acceptance and the better outcome of the graft. Animal models contribute to the better understanding of the HO-1 role in renal transplant, confirming the protective and immune regulatory function that culminates in graft acceptance.

Chronic kidney disease

Renal fibrosis results from a complex process of extracellular matrix production that ultimately leads to end stage renal disease. In this sense, the fibrotic process in the tubule-interstitial compartment has been estimated as a value predictor of irreversible loss of renal function[78]. Some studies have addressed the role of HO-1 in this progressive renal disease and will be further discussed.

An important study, published by Kie and colleagues, highlighted the role of basal HO-1 expression in renal fibrosis. The authors performed the experimental model of unilateral ureter obstruction (UUO) in wild-type and HO-1 deficient mice. The latter exhibited increased fibrosis deposition, macrophage infiltration, extracellular matrix synthesis and TGF-β production. *In vitro* experiments using proximal tubular cells isolated from kidneys of both animals showed that, after TGF-β treatment, the HO-1 deficient mice derived cells presented increased epithelial-to-mesenchymal transition, a process that occurs in fibrotic states[79]. Such work confirmed the information that HO-1, acting as a stress induced enzyme, is up regulated after a renal insult[80] in an attempt by the injured tissue to attenuate the incipient damage.

If the basal levels of HO-1 are important for kidney homeostasis, its overexpression seems to have important cytoprotective effects on progressive renal disease. Iwai *et al*[81] described that rats pre-treated with CoPPIX and submitted to obstructive nephropathy had, when compared to untreated animals, less expression of fibrosis markers α smooth muscle actin, fibronectin and collagen. Furthermore, they presented decreased mRNA for TGF-β and lymphocyte infiltration. Interestingly, the treated group showed increased macrophage infiltration, but co-localization techniques evidenced that these cells were also positive for HO-1, which was not seen on untreated rats. Probably, such macrophages display an immune suppressor profile.

Another work addressed the role of HO-1 as an anti-apoptotic molecule. In this case, animals were treated with hemin 48 h prior to chronic renal disease surgical induction. The group that received HO-1 inducer presented less pro-apoptotic proteins Bad and cleaved caspase-3. In contrast, the protein expression of anti-apoptotic molecule Bcl-2 was enhanced in this group[82]. A previous work from our group described that modulation of the inflammatory process by HO-1 up regulation also provides protection on the UUO model. Our experiments support the idea that inflammation is an important mediator of the fibrotic process development. After the treatment of rats with hemin, the inflammatory pattern was reduced and, consequently, it promoted a better renal function outcome and decreased fibrosis deposition and

TGF-β production. A great finding in this work was that if the treatment with hemin was given after the effective establishment of the fibrosis, it could also reverse the progressive renal disease development[26].

Most of the studies that explored the role HO-1 in chronic kidney disease were performed using the UUO model. But, some work was also done in different experimental models. Desbuards *et al*[83] showed that induction of HO-1 in the remnant kidney model was able to improve systemic blood pressure and proteinuria, when compared to untreated animals. They also showed that the hemin-treated group had less glomerulosclerosis and tubular atrophy, which was accompanied by decreased TGF-β expression and increased BMP-7 levels (an anti fibrotic protein). Moreover, another work using this experimental model addressed the fact that induction of HO-1 with CoPPIX promotes a beneficial angiogenesis in renal tissue, with concomitant decrease of vimentin expression and tubular apoptosis[84]. Finally, Tanaka *et al*[85] demonstrated that HO-1 overexpression activates HIF-regulated genes and protects the hypoxic tubule interstitium compartment from injury in the nephrectomized Thy1 nephritis model.

Taken together, all these works support the idea that HO-1 up regulation can prevent and even reverse chronic kidney disease. The mechanism underlying this protection seems to be mainly by down regulating the inflammatory and apoptotic processes.

FINAL CONSIDERATIONS

In this review, we have explored the role of HO-1 in a variety of renal diseases. The cytoprotection behind it seems to be extremely relevant and provides an interesting feedback for future clinical trials. Nowadays, many studies have been performed to improve our knowledge upon HO-1 byproducts. The information that such studies are providing can be relevant for the development of specific drugs. We propose here that the HO-1 system plays an important role in the maintenance of renal homeostasis after an insult.

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OBSERVATION

Urinary stone disease and obesity: Different pathologies sharing common biochemical mechanisms

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Abstract

The prevalence of urolithiasis is increasing in parallel with the escalating rate of obesity worldwide. It has previously been speculated that obesity is a potential risk factor for urinary stone disease. The possibility that common biochemical mechanisms underlie both obesity and urolithiasis is remarkable. Better understanding of possible common mechanisms of these diseases could potentially lead to a better management of urinary stone prevention. The prevention of urinary stone formation gives clinicians an acceptable reason to encourage lifestyle modification and weight loss through a regular diet. In this review, the association of obesity with urinary stone disease, possible common biochemical mechanisms, effects of dietary habits and weight loss on stone formation, as well as difficulties in surgical management of obese individuals with urolithiasis are discussed.

Key words: Urinary stone disease; Obesity; Biochemical mechanism; Weight loss; Body mass index

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INTRODUCTION

The prevalence of urolithiasis requiring medical or surgical treatment is 5%-10% and increasing worldwide[1]. Urolithiasis is a multifactorial disease and it has previously been speculated that there is an association between urolithiasis and obesity[1-5]. Recently, a common pathophysiology has been advocated for both diseases, since several investigations have mentioned that the prevalence of urolithiasis has been increasing in parallel with obesity[2,3,6].

Various lithogenic risk factors, including increased body mass index (BMI), low urinary volume, hypercalciuria, hyperoxaluria and hyperinsulinemia, are associated with obesity[7]. A recent trial found that 98% of obese patients had at least one lithogenic risk factor in a-24 h urine sample and 80% had 3 or more factors[8]. As the possible biochemical mechanisms related with obesity and urinary stone disease are clearly identified, management will potentially be more effective.

In this review, the association of obesity with urinary stone disease, possible common biochemical mechanisms, effects of dietary habits and weight loss on urinary stone formation, as well as difficulties in surgical management of obese individuals with urinary stone disease will be discussed.

OBESITY AND URINARY STONE FORMATION

Little is known about the biochemical mechanisms that explain the association between obesity and urinary

stone disease. Recent investigations have mentioned that obesity is related with changes in the biochemical components of urine, including phosphate, oxalate, uric acid and citrate[2,3,5,9]. These biochemical changes may explain the association between obesity and urinary stone disease. In a recent study, uric acid and oxalate were found to be significantly higher in the urine samples of obese patients[5]. The authors demonstrated no significant increase in urinary calcium, magnesium and citrate levels. In another study, a positive relationship was observed between BMI and urinary excretion of oxalate, calcium, uric acid, citrate, sodium, phosphate and potassium[10]. The authors also observed a significant decrease in urinary pH level with increased BMI. Similarly Siener *et al*[11] found a positive relationship between BMI and urinary levels of sodium, ammonium, uric acid and phosphate, as well as an inverse relationship between urinary pH and BMI. In a retrospective study, it has been found that patients heavier than 120 kg with urolithiasis excreted more oxalate, calcium and uric acid in urine compared to patients weighing less than 100 kg[9]. In this trial, urine samples were observed to be more acidic in obese patients. Ekeruo *et al*[12] studied the effect of BMI on urine biochemistry and noted a significant association between increasing BMI and urinary levels of calcium, oxalate, sodium, phosphate and uric acid, as well as urinary pH. The authors also observed that protective factors, including urine volume and urinary citrate excretion, increased with an increasing BMI. Maalouf *et al*[13] have found that in urinary stone patients, urinary pH had a strong graded inverse association with BMI. In contrast, Nouvenne *et al*[14] demonstrated no significant change in urinary pH with increasing BMI for both patients with urolithiasis and a healthy control group.

Several studies including patients with urolithiasis showed that higher BMI is significantly associated with a lower urinary pH level[1,5,9,12]. The reasons for a progressive decline in urine pH with increasing BMI in urolithiasis patients are not well defined. Insulin resistance is one of the possible reasons[1]. Hyperinsulinemia and insulin resistance are more frequently observed in obese patients due to higher incidence of diabetes mellitus[3]. Insulin resistance may potentially result as a defect in ammonium production in the kidney and ability to excrete acid load, thus affecting urinary pH level[1,3]. It has previously been advocated that hyperinsulinemia could possibly lead to decreased urinary citrate level as well as increased lithogenic factors in urine, including calcium, uric acid and oxalate[1,3,15]. Another important factor causing a significant decrease in urinary pH level in obese patients might be increased risk of hyperuricosuria, resulting in increased uric acid excretion and thus acidic urine[1,3,15].

OBESITY AND URINARY STONE TYPES

The correlation between urinary stone type and increasing incidence of urolithiasis, as well as the biochemical mechanisms underlying this relationship, are not clear in obese individuals. In a recent study by Chou *et al*[3], the authors investigated if obesity was related to the formation of every kind of urinary stone. Although they demonstrated a higher risk of calcium oxalate and uric acid stone formation in obese patients, no significant increase was noted for calcium phosphate stones. There is increasing evidence that obese patients have a higher risk of uric acid stone formation[4,16]. Previously, it has been demonstrated that 63% of stones in obese patients were composed of uric acid compared to 11% in the non-obese group[12]. Increased urinary uric acid excretion is also a potential risk factor for calcium oxalate stone formation, since calcium oxalate stones may develop from heterogeneous nucleation of calcium oxalate in a hyperuricosuria environment[1,3]. Urinary pH decline in obese patients leads to a decrease in calcium phosphate crystal production, resulting in a relative increase in the formation of calcium oxalate stones[3].

It has previously been shown that although urinary excretion of oxalate and uric acid increased in obese patients, there was no significant change for calcium[5,17]. Chou *et al*[3] mentioned that the formation of calcium phosphate stones is frequently associated with metabolic factors, including hyperparathyroidism, and thus may explain why the incidence of calcium phosphate stones is not significantly higher in obese patients.

EFFECT OF DIETARY HABITS ON URINARY STONE FORMATION IN OBESE PATIENTS

High dietary sodium causes obese patients to be more susceptible to worsening calciuria due to natriuresis[4,5]. Obese patients' diet may possibly be deficient in potassium, magnesium and citrate, resulting in increased risk of calciuria[4]. Obese patients have urinary compositions reflecting a higher protein diet[10]. High dietary animal protein has been shown to be a risk factor for urinary stone disease, since this type of diet causes increased excretion of uric acid and calcium as well as decreased excretion of citrate, and a lower urinary pH level, thus making urine more lithogenic[4,18,19].

The effect of dietary intake of oxalate on urinary stone formation is controversial. In a previous study, Lemann *et al*[20] demonstrated that urinary oxalate excretion was significantly associated with BMI. In another retrospective study, Taylor *et al*[10] did not find an association between increased oxalate excretion and obesity. It has been advocated that adoption of a lower sodium diet with increased vegetables, fruits and foods including lower concentrations of fat might be useful to prevent urinary stone formation[4].

EFFECT OF WEIGHT LOSS ON URINARY STONE RECURRENCE

In a previous study, patients in both obese and non-obese

groups demonstrated a significant decrease in new stone formation rates following dietary and medical therapy[12]. In contrast, Curhan *et al*[21] noted no reduction in stone risk following weight loss. Natarajan *et al*[22] mentioned that the effects of long term weight loss are not as immediately apparent for urinary stone formation in obese patients. There are conflicting results for the effect of bariatric surgery on urinary stone formation in obese patients in the literature[23-26]. In a previous study, 35 morbidly obese patients who underwent biliopancreatic diversion surgery were included[23]. Authors found decreased urinary excretion rates of calcium and citrate as well as an increased urinary oxalate excretion 1 year postoperatively. In a further study, authors compared urine compositions of urolithiasis patients who underwent gastric banding or by-pass surgeries for weight reduction with other urinary stone formers who were not treated with bariatric surgeries[24]. Patients who were treated with surgical procedures for weight loss demonstrated a significantly increased incidence of hyperoxaluria. In another trial, Sinha *et al*[25] studied 60 patients who had urinary stones following a Roux-en-Y gastric bypass procedure and found a significantly increased calcium oxalate supersaturation with significantly decreased uric acid supersaturation. In contrast, in a similar study, no association was demonstrated between a Roux-en-Y gastric bypass procedure and risk of urolithiasis in a group of morbidly obese patients[26].

DIFFICULTIES IN SURGICAL MANAGEMENT OF OBESE PATIENTS WITH UROLITHIASIS

Extracorporeal shock wave lithotripsy may be a suboptimal treatment for obese patients since positioning of the patient for an optimal stone fragmentation is a limiting factor[7]. Most lithotripters have a maximum skin to stone distance of 12-14 cm for their focal point and thus can restrict the acquired distance for complete stone fragmentation in obese patients[7,27]. Similar difficulties may also decrease the success rate of a percutaneous nephrolithotomy (PCNL) procedure in an obese patient with nephrolithiasis due to difficulties in percutaneous access, as well as limitations in the use of normal sized instruments and higher risk of anesthetic complications in prone position[7]. In contrast, El-Assmy *et al*[28] showed that PCNL in obese patients is a safe method with similar success rates, morbidity and operative time.

Natalin *et al*[7] retrospectively compared stone free rates of ureteroscopic treatment between normal, overweight and obese patients with ureteral and renal stones. The authors concluded that flexible or semirigid ureteroscopy with holmium:yttrium-aluminum-garnet laser lithotripsy in obese and overweight patients is an acceptable treatment modality with success rates comparable to non-obese patients.

CONCLUSION

Obesity is associated with an increased risk of urinary stone disease. Further studies will better demonstrate the biochemical mechanisms connecting urinary stone disease and obesity. Given the significant association of obesity with urinary stone disease, clinicians should encourage obese patients with urolithiasis to reduce weight through a regular diet and recommend a dietician for further weight loss management. A balanced diet including moderately sized meals with more vegetables, fruits and less fat should be encouraged.

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Epidemiology, pathophysiology, clinical characteristics and management of childhood cardiorenal syndrome

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Abstract

Cardiorenal syndrome (CRS) is a new term recently introduced to describe the acute or chronic comorbid state of the heart and kidney that has been long known and frequently managed in very sick individuals. The tight and delicate coordination of physiological functions among organ systems in the human body makes dysfunction in one to lead to malfunction of one or more other organ systems. CRS is a universal very common morbidity in the critically ill, with a high mortality rate that has received very little research attention in children. Simultaneous management of heart and renal failures in CRS is quite challenging; the therapeutic choice made for one organ must not jeopardize the other. This paper reviews the epidemiology, pathophysiology, clinical characteristics and management of acute and chronic CRS in children.

Key words: Acute kidney injury; Congestive heart failure; Chronic kidney disease; Ultrafiltration

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INTRODUCTION

The tight and delicate coordination of physiological functions among organ systems in the human body is such that a dysfunction in one could lead to malfunction of one or more organ systems. Cardiorenal syndrome (CRS) is a new term recently introduced to describe the heart and kidney comorbid state that has been long known and frequently managed in very sick individuals. It is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction of the other[1,2]. The 7th Acute Dialysis Quality Initiative Workgroup recently standardized the classification of CRS into five distinct clinical types[1,2]. These are namely: Acute CRS (CRS Type 1 or CRS-1) - acute worsening of heart function leading to acute kidney injury (AKI) and/or dysfunction; chronic CRS (CRS Type 2 or CRS-2) - chronic abnormalities in heart function leading to kidney injury and/or dysfunction; acute renocardiac syndrome (CRS Type 3 or CRS-3) - acute worsening of kidney function leading to heart injury and/or dysfunction; chronic renocardiac syndrome (CRS Type 4 or CRS-4) - chronic kidney disease leading to heart injury, disease and/or dysfunction; and secondary CRS (CRS Type 5 or CRS-5) - systemic conditions leading to simultaneous acute or chronic injury and/or dysfunction of heart and kidney. Acute decompensated heart failure (ADHF), defined as new onset or acute exacerbation of heart failure (HF) with signs or symptoms requiring hos-

pitalization and inpatient treatment, has been associated with AKI in hospitalized children, prolonged hospitalization and in-hospital death, or the need for mechanical circulatory assistance[3]. Congestive HF (CHF) is a very serious morbidity that has been frequently associated with an increased need for acute dialysis and death in childhood AKI[4]. Children with mild or moderate chronic renal insufficiency (CRI) were associated with left ventricular hypertrophy (LVH) that progressed as renal function deteriorated[5]. Increased left ventricular mass index, indicating LVH, occurred in a third of children with mild to moderate CRI in some studies[6-8]. Risk factors for cardiovascular disease (CVD) in childhood chronic kidney disease (CKD) as reviewed by Mitsnefes *et al*[5] include: hypertension, anemia, dyslipidemia, hyperparathyroidism, hypoalbuminemia, increased C-reactive proteins level and hyperhomocysteinemia.

CRS is a very common disorder with a high mortality rate in children that has received very little original research attention[3,9]. This paper reviews the epidemiology, pathophysiology, clinical characteristics and management of acute and chronic CRS in children.

EPIDEMIOLOGY

Currently, the incidence of CRS in children is unknown as very little work has been done in this area, in spite of the fact that HF is a common comorbidity in renal failure. To date, there have been only three publications on childhood CRS in the medical literature. Two are original reports[3,9] while one is a review article[10]. A review of the various publications in which HF was a complication of acute or chronic renal dysfunction and vice versa revealed that CRS prevalence could range between 3.0% and 52.0%[3,4,9,11-19].

CRS-1

HF in children is a progressive clinical and pathophysiological syndrome caused by cardiovascular and non-cardiovascular abnormalities that result in characteristic signs and symptoms, including edema, respiratory distress, growth failure and exercise intolerance, and accompanied by circulatory, neurohormonal and molecular derangements[20]. The AKI in this CRS type may be a sequel to renal ischemia following low cardiac output or renal congestion as a result of volume overload HF. Classes Ⅲ and Ⅳ HF (based on modified Ross HF classification for children[20]) are more likely to be associated with renal dysfunction than classes I and Ⅱ HF. In a study by Price *et al*[3], the median age of children at admission was 10 years (0.1-20.3), while the male: female ratio was 1.3. Reports show that CHF leading to CRS-1 is a common complication of cardiopulmonary bypass (CPB) surgery. The prevalence rate of CRS-1 following CPB surgery ranged between 5% and 52% in various studies[12-14,19,21]. Congestive anemic HF was identified as a risk factor for hospital- acquired AKI in 30.43% of Nigerian children[22], while Price *et al*[3] showed that AKI, which they referred to as acute worsening of renal function (WRF), occurred in 35 of 73 (48%) American children hospitalized for ADHF. Dilated cardiomyopathy (52%), cyanotic congenital heart disease (14%), myocarditis (12%), acute graft rejection (12%) and ischemic cardiomyopathy (10%) caused ADHF that led to AKI in the American children. AKI was not only independently associated with in-hospital death or the need for mechanical circulatory support [odds ratio (OR) 10.2; 95% CI: 1.7- 61.2, $P = 0.011$], but it was also significantly associated with longer observed length of stay ($P < 0.03$). Fifteen of 35 (43%) patient hospitalizations in which AKI occurred resulted in death or the need for mechanical circulatory support[3]. HF was a significant risk factor for mortality among Thai children with CPB surgery associated AKI (OR, 8.7; 95% CI: 3.0-25.3, $P = 0.0001$). The mortality rate was 53.9%[13].

CRS-2

Although CRS-2 has rarely been reported in children, cardiac conditions capable of precipitating a CRS-2 in children include left-to-right shunting (due to ventricular septal defect and patent ductus arteriosus) and atrioventricular or semilunar valve insufficiency (due to aortic regurgitation in bi-commissural aortic valve or pulmonary regurgitation after repair of tetralogy of Fallot). All of these will cause CHF due to volume overload. On the other hand, CHF due to pressure overload may be secondary to severe aortic stenosis, aortic coarctation or severe pulmonary stenosis. The child with a structurally normal heart may also develop CHF following a primary dilated cardiomyopathy, ischemic, toxic, infectious, infiltrative or lupus cardiomyopathy. A number of causes of CHF in childhood CRS-1 may in fact become persistently progressive, leading to CRS-2. Postoperatively, transient or chronic CHF may complicate CPB surgery for a congenital heart disease in both children and adults[23-27]. Examples of the latter include right HF due to residual right ventricular outflow tract obstruction, volume overload from pulmonary insufficiency following repair of tetralogy of Fallot, and systemic ventricular dysfunction or elevated venous pressures in single ventricle physiology, leading to low cardiac output[28-32] and subsequent chronic renal dysfunction.

CRS-3

Acute HF following AKI typifies CRS-3. AKI is an abrupt clinical and/or laboratory manifestation of kidney dysfunction, usually within 48 h of bilateral kidney insult of any kind. Using serum creatinine (Scr) as a marker, the AKI network group used an increase in Scr level from the baseline within 48 h of bilateral kidney insult by at least 0.3 mg/dL (≥ 26.4 μmol/L) or a 50% (1.5-fold) increase or more as diagnostic of AKI[33]. Scr alone is an inadequate marker of AKI, as injury would have been far advanced before detection[22]. Chertow *et al*[34] showed a slight rise in Scr level as low as 0.3 mg/dL (26.5 μmol/L) to be significantly associated with kidney damage, high morbidity and mortality from AKI, indicating the need

Table 1 Some clinical and non-clinical features of cardiorenal syndrome

Heart failure	Renal failure
Difficulty in breathing; grunting respiration	Reduced daily urine output
Prolonged feeding time in infants	Facial puffiness
Tiredness	Acidotic breathing
Tachypnea	Drowsiness due to uremia
Tachycardia	Ascites/pitting bipedal edema
Raised jugular venous pressure	Pallor
Displaced apex beat	Hypertension when fluid overloaded or renal failure is due to either acute glomerulonephritis, Burkitt's lymphoma nephropathy or CKD
Heart murmurs	Bleeding diathesis
Galloping cardiac rhythm	Seizures
Bilateral basal crepitations	Failure-to-thrive in CKD
Tender hepatomegaly	Hyponatremia, hyperkalemia, metabolic acidosis, hypocalcemia, hyperhosphatemia, hyperuricemia, azotemia, hypercreatinemia, high fractional sodium excretion, reduced GFR; Ca × $PO4^{-3}$ product is elevated in late CKD stages and in those receiving calcium and vitamin D_3 supplements and regular dialysis
Pitting bipedal edema in older children with chronic heart failure; usually a late manifestation	Dyslipidemia and proteinuria especially in CKD; reduced plasma level of vitamin D_3; elevated parathyroid hormone. Low circulating level of erythropoietin
Increased cardiothoracic ratio on chest X-ray (> 60% in under fives and > 55% in older children)	Kidneys may be slightly enlarged in AKI or grossly enlarged in infantile polycystic kidney disease on ultrasound or shrunken in size in other forms of CKD. Radiological evidence of vascular calcification may be present
Electrocardiographical evidence of left ventricular hypertrophy	Biomarkers of kidney injury
	Plasma NGAL, plasma cystatin C, urine NGAL, urine interleukin-18, urine kidney injury molecule-1 and urine liver fatty acid-binding protein (rises within 4 h of injury) levels are elevated few hours after kidney injury
Echocardiographical evidence of heart failure like increased left ventricular mass index (> 38 g/$m^{2.7}$), reduced ejection fraction (normal: 64%-83%) and reduced shortening fraction (normal: > 30%)	
Biomarkers of cardiac injury	
Troponin, creatine kinase myocardial band and natriuretic peptides are elevated	

NGAL: Neutrophil gelatinase-associated lipocalin; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; AKI: Acute kidney injury.

for early diagnosis that is presently not possible with Scr. Early AKI diagnosis and treatment should be expected to prevent morbidity like CRS. Plasma and urinary biological markers of AKI[35,36] show some promise with regards to diagnosing AKI within few hours of bilateral kidney insult (Table 1). These are, however, still in their experimental and research stages. Usually, AKI is a reversible clinical state in which normal functions of both organs are expected to occur following treatment and recovery from the renal insult. CRS data from Nigeria in which the male to female ratio was 1.24, revealed the median age for both CRS-3 and CRS-5 to be 4.0 years (0.3-14.5) with 70.21% of the children being less than 6 years of age[9]. In that study, the CRS-3 prevalence rate was 21.3%. The etiologies were acute glomerulonephritis (AGN, 70.0%), captopril (10.0%), frusemide (10.0%) and hypovolemic shock due to gastroenteritis (10.0%). Bailey *et al*[11] reported that 45% of their AKI patients subsequently developed cardiac dysfunction or cardiac arrest as a complication. The overall mortality was 11 times higher in patients with than in those without AKI (27.3% *vs* 2.4%, $P < 0.001$)[11]. We had earlier reported a 25% prevalence rate for CHF in children with AKI. CHF was a major indication for acute dialysis in that report[4]. Similarly, CRS occurred in 31.03% of Nigerian children with AGN[17]. Recently, the cumulative mortality rate for CRS-3 in our unit was 87.5%[9]. This high mortality rate was attributed to AGN, which the majority of patients had. AGN was significantly associated with a very low survival rate in the study. CRS due to etiologies other than AGN was significantly less associated with mortality compared with CRS due to AGN (40.4% *vs* 78.6%; HR: 0.544; 95% CI: 0.322-0.919, $P = 0.023$). Figure 1 demonstrates the significance of etiology on CRS outcome as patients with CRS-5 survived well than those with CRS-3 (HR: 0.479, 95% CI: 0.299-0.768)[9].

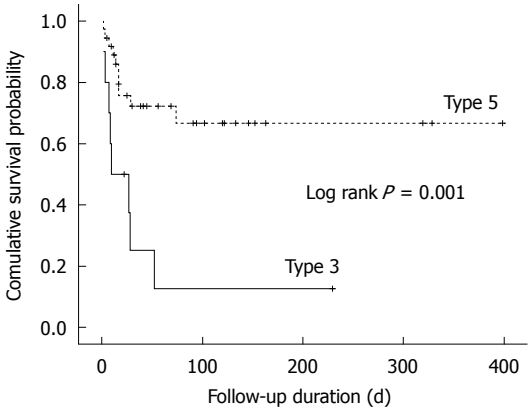

Figure 1 Kaplan -Meier survival curves showing significantly better survival in Type 5 compared to Type 3 cardiorenal syndrome (72.3% *vs* 12.5%). Figure reproduced from reference number 9 with permission.

CRS-4

This is a clinical syndrome in which a CKD, irrespective of etiology, leads to chronic HF or dysfunction. The National Kidney Foundation/Kidney Disease and Outcome Quality Initiative defined CKD as a bilateral kidney injury and/or impaired kidney function of at least 3 mo duration[37]. Kidney injury refers to the presence of microalbuminuria or overt proteinuria or abnormal urine sediment such as red blood cell (RBC), RBC casts, white blood cell (WBC), WBC casts, cellular casts, granular casts, oval fat bodies, fatty casts or free fats. Impaired kidney function is defined as a glomerular filtration rate (GFR) of 60 mL/min/1.73 m^2 or less[37]. Perturbed kidney function in CKD is frequently associated with multi-organ systems dysfunction which may occur sequentially or simultaneously as kidney function deteriorates progressively. Cardiovascular malfunction is a common comorbidity in CKD with a high prevalence of CVD associated deaths. Cardiac involvement in CKD is more often than not multi-factorial. Hypertension, malnutrition, uremia, sodium/water retention, regular dialysis, anemia, dyslipidemia and abnormal calcium-phosphorous metabolism are some of these factors. Both concentric and eccentric LVH consistent with the combined pressure and volume overload have been reported in children with mild to moderate chronic renal failure (CRF)[7,8]. Reduced left ventricular (LV) functional reserve during exercise has been observed in regularly dialyzing children with CRI, notwithstanding a normal resting LV function[7]. Concentric LVH occurs frequently because of left ventricular pressure overload caused by hypertension, arteriosclerosis and sometimes aortic stenosis, while eccentric LVH results from left ventricular volume overload associated with hypervolemia, arterio-venous fistula and anemia[38]. In patients starting dialysis, left ventricular growth occurs[39], although it regresses following renal transplantation[40]. While LVH can progress to left ventricular systolic dysfunction through progressive myocyte loss, LV diastolic dysfunction resulting from LVH frequently results in symptomatic pulmonary edema[41]. In Nigeria, cardiac dysfunction was found in 25% of pediatric patients with CRF[15] while 31% of incident pediatric patients in the US, who started chronic dialysis between 1991 and 1996, developed CVD[16]. Mortality from CKD associated CVD is very high, ranging between 23 and 45%[42-46]. Cerebrovascular accident (58%), CHF (15.4%), myocardial infarction (11.54%) and cardiac arrest (7.7%) were the most common causes of cardiac death among Dutch children with CKD[44]. The survival of children with CKD in the U.S. remains low; lifespan is 40-60 years less for children on dialysis and about 20-25 years less for transplant patients than that of an age and race-matched US population[47,48]. Development of accelerated ischemic heart disease and premature dilated cardiomyopathy were thought to be responsible for this. Similar analysis of long-term survival from the Australia and New Zealand Dialysis and Transplant Registry of all children and adolescents who were under 20 years of age when renal replacement therapy (RRT) commenced, showed mortality rates were 30 times higher than in the age-matched general population. CVD was the most common cause of death (45%)[46].

CRS-5

In CRS-5, acute or chronic failure or dysfunction of both the heart and the kidneys occur simultaneously as sequelae of a severe acute or chronic systemic illness. In an earlier report, simultaneous failure of both organs occurred in 36.4% of Nigerian children with systemic lupus erythematosus[18]. One of the two original publications to date on childhood CRS reported a 78.7% prevalence rate for CRS-5[9]. Malaria-associated hemoglobinuria (54.05%), septicemia (29.73%), lupus nephritis (8.11%), tumor lysis syndrome due to Burkitt's lymphoma (5.41%) and acute lymphoblastic leukemia (2.70%) were the etiologies in that study. Compared to CRS-3, children with CRS-5 survived better (HR: 0.479, 95% CI: 0.299-0.768, Figure 1). The better outcome in CRS-5 alluded to the majority of the patients having had malaria-associated hemoglobinuria that was significantly associated with the highest survival rate (81.4%), compared to CRS-3 in which majority of the patients had AGN that was significantly associated with a very low survival rate (21.4%, $P = 0.014$). A mortality rate of 27.7% was associated with CRS-5 in that study. The cumulative CRS-specific mortality rate for the study was 45.7% (CRS-3 and CRS-5 combined).

MECHANISMS, PATHOLOGY AND CLINICAL MANIFESTATIONS OF CRS

Acute CRS (CRS-1, CRS-3 and acute CRS-5)

A sudden decrease in cardiac stroke volume and cardiac output, regardless of whether symptomatic hypotension is present, can cause a decrease in renal arterial filling and perfusion, thus reducing the GFR. This reduction could cause AKI secondary to ischemic pre-renal acute tubular necrosis (CRS-1)[49,50]. Reduced renal perfusion activates the renin-angiotensin-aldosterone-system (RAAS). Upon RAAS activation, angiotensin Ⅱ (ANG Ⅱ) stimulates endothelin-1 (ET-1) expression in the kidney, a very strong pro-inflammatory and pro-fibrotic vasoconstrictor peptide. ET-1 reduces renal blood flow and GFR and, when over-expressed, might precipitate AKI and/or pre-renal ischemic acute tubular necrosis during acute heart dysfunction[51]. Irrespective of the etiology of AKI, impaired glomerular filtration (due to many factors) leads to circulatory congestion which, when associated with sodium and water retention and hypertension, as is often the case with AGN, could lead to CHF. As stated above, 70.0% of the cases of CRS-3 were caused by AGN[9].

Chronic CRS (CRS-2, CRS-4 and chronic CRS-5)

In CRS-2, chronic HF from any cause leads to persistently low cardiac output and circulatory blood volume with persistently reduced renal blood flow and resultant chronic renal damage brought about by the pro-

inflammatory and pro-fibrotic activity of activated RAAS, described in detail below for CRS-4. A number of pathological processes are involved in the development of CKD. Proteinuric kidney damage is one such pathological process. Proteinuria is an important marker of CKD that provokes intense and persistent inflammatory reaction through simultaneous vasoactive and pro-inflammatory signaling that ultimately causes irreversible kidney damage, leading to abnormal kidney function and serious morbidities in other organ systems such as CRS-4 when the CVS is involved.

Vasoactive signaling involves production of ANG Ⅱ, aldosterone and ET-1, leading to increased production of transforming growth factor-β (TGF-β), tissue inhibitor metalloproteinase-1 (TIMP-1) and -2 (TIMP-2) and plasminogen activator inhibitor-1 (PAI-1). Increased production of TGF-β results in increased fibroblast proliferation, collagen and matrix proteins formation with resultant tissue fibrosis both within the glomerulus and renal tubulointerstitium. TIMP-1, TIMP-2 and PAI-1 complicate the process further by inhibiting the tissue protease enzyme activity, thereby inhibiting matrix protein and collagen degradation, thus further promoting matrix deposition, fibrosis and kidney damage. ANG Ⅱ, aldosterone, and ET-1 are also independently associated with glomerular hypertrophy, hyperfiltration and intraglomerular hypertension, leading to proteinuria and further kidney damage[52].

Pro-inflammatory signaling similarly results in increased collagen and matrix protein formation, causing tissue fibrosis through increased production of the pro-inflammatory mediators, namely monocyte/macrophage chemoattractant protein-1, interleukin-8, nuclear factor κB and regulated upon activation, normal T-cell expressed and secreted; these pro - inflammatory mediators stimulate the production of TGF-β that enhances tissue fibrosis, as described earlier. The consequences of fibrosis are tubulointerstitial hypoxia and reduced nephron mass with intraglomerular hypertension; the latter results in increased glomerular filtration pressure and worsening of the proteinuria, as well as a vicious cycle of proteinuria and fibrosis[52].

The cardiovascular complications of chronic kidney damage include myocardial ischemia, hypertension, LVH and CHF. CKD-associated hypertension develops by a large variety of pathophysiological mechanisms. Fluid overload and RAAS activation have long been recognized as crucial pathophysiological pathways but sympathetic hyperactivation, endothelial dysfunction and chronic hyperparathyroidism have more recently been identified as important factors contributing to CKD-associated hypertension[53]. Two parallel processes are involved in the development of CVD in CKD patients. The first is cardiac remodeling leading to LVH as a response to either mechanical or hemodynamic overload. Two different patterns of LV remodeling can produce increase in LV mass (LVM). The patterns of sarcomere formation induced by pressure or volume overload are distinct. Pressure-induced concentric LVH is characterized by a parallel addition of sarcomeres, resulting in the increase of cross-sectional area and diameter of the myocytes. Increase in LVM in this case is obtained by a marked increase in wall thickness with a less evident increase in the LV cavity that yields an elevated relative wall thickness and concentric LVH. From the physiological view, increased systolic blood pressure and pulse pressure, due to increased peripheral resistance and arterial stiffness, are the principal factors opposing LV ejection and leading to an increased LV workload and concentric LVH[54]. An increase in LVM can also be obtained by an increase in the LV cavity with a symmetric increase in wall thickness to maintain the ratio between the wall thickness and normal LV transversal radius (relative wall thickness), producing eccentric LVH. In this case, the addition of sarcomeres occurs mainly in series resulting in longitudinal cell growth. In the transition to maladaptive LVH, LV dilatation becomes disproportional to wall thickness, with myocytes elongated without an increase in diameter[54]. In children, hypertension is one of the most common sequelae of CKD[55]. Anemia is also a highly prevalent comorbidity in both AKI[4,56-58] and CKD. It has been associated with increased severity of CHF, increased hospitalization, worse cardiac function and functional class, the need for higher doses of diuretics, progressive WRF and reduced quality of life[59]. Anemia occurred in 91.5% of our CRS patients with an anemia-specific mortality rate of 38.6%[9]. Anemia lowers the blood pressure as a result of peripheral vasodilatation due to anemia-associated tissue hypoxia. Reduced blood pressure stimulates increased sympathetic activity with attendant tachycardia and increased stroke volume. The latter leads to reduced renal blood flow, increased RAAS activity and anti-diuretic hormone production leading to salt and water retention. The effect of this is increased plasma volume, ventricular diameter and brain natriuretic peptide. The final outcome is ventricular dilation and hypertrophy with eventual myocardial cell death, fibrosis and CHF[60]. The child with CRS usually manifests with both features of heart and kidney failure, either sequentially depending on which organ was affected first or simultaneously when the two organs are injured at the same time, as it occurs in Type 5 CRS. These manifestations are summarized in Table 1.

THERAPEUTIC CONSIDERATIONS IN CRS

Simultaneous treatment of both heart and kidney failure, as is the case with CRS, requires sound understanding of the mechanisms, pathology and the hemodynamic changes that brought about the syndrome if unwanted complications associated with therapeutic indiscretion are to be avoided. This is not usually an easy task as many competing pathological factors must be considered for effective management and desired outcome. Treatment of HF requires that the myocardial contractility be increased, hyper-reninemia and associated sympathetic nervous system hyperactivity and the tachycardia be aborted

for a better outcome. Furthermore, there is the need for improved oxygenation of the cardiomyocytes for effective myocardial function. Digoxin is a popular positive inotropic agent that is used globally to achieve these objectives in pressure overload HF without any significant negative impact on kidney functions. It is rarely of any benefit in volume overload HF that requires a loop diuretic for rapid pulmonary and circulatory decongestion. Other positive inotropes that have been used in CRS with the objective of improving myocardial contraction in children hospitalized for ADHF include milrinone (78%), dopamine (38%), epinephrine (13%) and dobutamine (3%)[3]. Negative inotropes like β and calcium channel blockers are better avoided in CRS (with or without hypertension) because they are likely to do more harm than good.

Loop diuretics, namely frusemide, ethacrynic acid and bumetanide, are strongly plasma bound and are therefore actively secreted into the renal tubule by the organic anion transporter; they normally bind to the sodium potassium chloride co-transporter channel 2 (NKCC2) in the thick ascending limb of the loop of Henle where they inhibit sodium, potassium and chloride reabsorption, causing diuresis and loss of these electrolytes. Long-term use of these diuretics, however, may become counterproductive as the distal tubule becomes hypertrophied owing to the constant heavy load of solutes (sodium, potassium and chloride) delivered to it for reabsorption as result of the NKCC2 inhibition, causing sodium and water retention that was primarily meant to be prevented with the loop diuretics (loop diuretic resistance). Blocking the sodium chloride co-transporter (NCC) channel in the distal tubule using a thiazide diuretic (serial nephron blockade) may be beneficial if this situation arises. A small study reported significant improvements in urinary volume and sodium excretion following frusemide and metolazone (a thiazide-related diuretic) combination treatment in non-CRI children with frusemide-resistant edema[61]. Relieving congestion and volume overload, which is critical to survival in CHF and pulmonary edema, may be difficult to achieve alone with diuretics in the setting of severe CRS in which anyone of stage 3 AKI (severe oliguria or anuria), stage 4 CKD, end-stage renal disease (ESRD), class Ⅲ or Ⅳ HF is a component. It is in this clinical setting that ultrafiltration (UF) becomes the ultimate therapeutic goal if mortality is to be prevented. Studies have shown that UF could be performed safely in HF patients with significant relief of pulmonary congestion and volume overload[62-65]. In CRS patients with extremely low left ventricular shortening and ejection fractions, gradual removal of both fluid and solutes by continuous RRT (CRRT), like continuous venovenous hemofiltration or hemodialfiltration, becomes imperative if serious hemodynamic instability and death are to be avoided. Although CRRT is frequently indicated for AKI, it can also be used temporarily in patients with acute-on-chronic renal failure with pulmonary edema or severe CHF (class Ⅲ or Ⅳ HF) when hemodialysis (HD) cannot be tolerated. The functions the kidneys perform in 168 h/wk are what HD will do in 12 h/wk, thus imposing enormous stress on the heart leading to LVH over time or worsening of existing LVH and cardiac dysfunction. Patients treated with CRRT can be switched over to intracorporeal diffusive and convective therapy like continuous ambulatory or cycling peritoneal dialysis (CAPD/CCPD) when stable to protect the heart from the stress of HD. Some studies have shown improvements in altered cardiac geometry and functions as well as lack of progression of LVH in ESRD patients treated with CAPD[66,67], while others showed no improvement[68,69]. Lack of improvement in the latter was ascribed to high cardiac output[68] and inadequate control of hypertension in the patients[68, 69].

Adenosine is released endogenously from the macula densa in the injured kidney, causing vasoconstriction of the renal afferent arteriole *via* the adenosine A1-receptor as well as vasodilatation of the renal efferent arteriole *via* the adenosine A2-receptor. These actions lead to reduction in the renal blood flow and glomerular perfusion pressure, resulting in ischemic kidney injury[70]. Treatment with an adenosine A1-receptor antagonist like aminophylline may therefore be beneficial in CRS for the following reasons. One, it will improve breathing by dilating the bronchioles, thus increasing oxygen delivery to the lungs and ultimately to body tissues; two, it will promote diuresis by blocking the adenosine A1-receptor thereby reducing congestion and circulatory overload. Aminophylline therapy has been significantly associated with improved urine flow rate and decreased need for dialysis but not survival in children with acute oligoanuric AKI[71].

Studies have shown ANG Ⅱ[72] and aldosterone[73] to be independently associated with inflammatory kidney damage through promotion of adhesion molecules, pro-inflammatory mediator expression, cellular growth/proliferation, endothelial cell dysfunction, extracellular matrix and fibrosis. Clinical trials of angiotensin converting enzyme inhibitor (ACEi) and spironolactone (a mineralocorticoid receptor blocker or aldosterone antagonist) have been associated with clinical improvement and retardation of renal disease progression[72]. All of these pro-inflammatory properties of ANG Ⅱ and aldosterone are also active in the heart, causing progressive heart disease and HF. ACEi, ANG Ⅱ receptor-1 blocker (ARB) and spironolactone are now increasingly used in children to treat hypertension, altered cardiac geometry (LVH), HF, proteinuric and non-proteinuric CKD and to abort all of the inflammatory properties of escalated RAAS activity that are seen in both CHF and CKD[3,53,74-78]. It is, however, important to note that AKI may complicate ACEi therapy when renal perfusion is compromised[79]. In CHF, the renal perfusion pressure is low and the GFR is highly ANG Ⅱ driven; therefore, the use of ACEi/ARB when CHF is severe could further worsen the renal failure, thereby increasing morbidity and mortality from CRS. Therefore, in the clinical setting of CRS, patients treated with an ACEi or ARB should be carefully monitored for evidence of AKI by checking their urine output and Scr level regu-

larly. An acute rise in Scr by at least 0.3 mg/dL or 50% increase from baseline or a urine output < 0.5 mL/kg per hour for 6 or more hours should warrant immediate drug withdrawal. Serum potassium level should equally be monitored in such patients for early detection of hyperkalemia. Some conditions in which use of ACEi or ARB in CRS may not be advisable will include CRS: (1) with severe CHF (Class Ⅲ and Ⅳ HF); (2) with severe CHF on diuretics; (3) on non-steroidal anti-inflammatory drugs or calcineurin inhibitors (cyclosporine A or tarcrolimus), irrespective of CHF severity; and (4) with mean arterial pressure < 60 mmHg, irrespective of CHF class. In these conditions, treatment with spironolactone (for its anti-sodium/water retention, anti-renal and -myocardial fibrotic properties) in addition to loop diuretics, digoxin (in pressure overload CHF) and other safe therapeutic measures like CRRT may be helpful. However, in CRS patients with ESRD, it appears that drug treatment emphasis will shift to the HF while the ESRD is managed accordingly with regular dialysis until a kidney transplant is feasible. In the latter category of patients, there is no further fear of a worsening renal function. Treatment with either ACEi or ARB for better cardiovascular outcome should not, therefore, be inhibited unless they are reasonably contraindicated.

CONCLUSION

There is the need for collaborative work on childhood CRS between pediatric cardiologists and nephrologists to better understand the syndrome so that a well coordinated therapeutic program can be developed for universal application. Simultaneous management of heart and renal failure in CRS is quite challenging; the therapeutic choice made for one organ must not jeopardize the other.

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REVIEW

Arterial stiffness, vascular calcification and bone metabolism in chronic kidney disease

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Abstract

Patients with chronic kidney disease (CKD) have an extremely poor cardiovascular outcome. Arterial stiffness, a strong independent predictor of survival in CKD, is connected to arterial media calcification. A huge number of different factors contribute to the increased arterial calcification and stiffening in CKD, a process which is in parallel with impaired bone metabolism. This coincidence was demonstrated to be part of the direct inhibition of calcification in the vessels, which is a counterbalancing effect but also leads to low bone turnover. Due to the growing evidence, the definition of "CKD mineral bone disorder" was created recently, underlining the strong connection of the two phenomena. In this review, we aim to demonstrate the mechanisms leading to increased arterial stiffness and the up-to date data of the bone-vascular axis in CKD. We overview a list of the different factors, including inhibitors of bone metabolism like osteoprotegerin, fetuin-A, pyrophosphates, matrix Gla protein, osteopontin, fibroblast growth factor 23 and bone morphogenic protein, which seem to play role in the progression of vascular calcification and we evaluate their connection to impaired arterial stiffness in the mirror of recent scientific results.

Key words: Arterial stiffness; Vascular calcification; Bone metabolism; Chronic kidney disease

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ARTERIAL STIFFNESS IN CHRONIC KIDNEY DISEASE

Cardiovascular disease is the major cause of death in patients with chronic kidney disease (CKD)[1]. The cardiovascular mortality of patients on maintenance hemodialysis is more than 10-fold higher compared with the normal population[2].

In patients with CKD, increased aortic stiffness, measured as aortic pulse wave velocity (PWV), is a strong independent predictor of cardiovascular mortality[3]. A tendency for arterial stiffness to increase in parallel with the progression of decrease in kidney function is present in CKD. Wang *et al*[4] showed a stepwise increase in PWV (i.e. arterial stiffness) from CKD stage 1 to stage 5. Although there was a high prevalence of cardiovascular risk factors and cardiovascular disease in that patient population, estimated GFR and systolic BP were the major determinants of arterial stiffness in patients with CKD, independent of conventional risk factors for cardiovascular disease[4]. Later, the connection between the progression of CKD

and arterial stiffening was confirmed by another study, where the role of diabetes and CRP was also evaluated[5].

Many pathophysiological mechanisms are present, leading to increased arterial stiffness associated with CKD. To highlight the complexity of the question, we demonstrate some of these processes.

Alterations of the extracellular matrix (ECM) have been proven in subtotally nephrectomized rats, where the aortic wall thickness was significantly greater than in controls. ECM volume was increased, elastic fibers were smaller and collagen "islands" were evident[6]. The role of matrix metalloproteinases (MMPs) have been suggested as increased MMP production, present in CKD[7], enhances collagen and elastin turnover through enzymatic cross-link degradation, causing weakening of the ECM[8]. These data highlight the potential use of future therapeutic interventions with MMP inhibitors.

Accumulation of advanced glycation end-products (AGE) also result in arterial stiffening. Collagen modified with AGEs is stiffer and less susceptible to slow hydrolytic degradation and glycation can also cause arterial stiffening through generation of reactive oxygen species and nitric oxide deactivation[9]. Direct connection is present between the levels of circulating AGE and the serum creatinine in patients with CKD[10,11]. AGE cross-link breaker treatment can lead to significant reductions in arterial stiffness and endothelial dysfunction in hypertensive and older patients[12,13]. More data are needed but the future therapeutic use of AGE cross-link breakers to reduce arterial stiffness in CKD can also be possible.

Endothelial dysfunction is strongly associated with increased arterial stiffness in healthy individuals[14]. We previously demonstrated that endothelial dysfunction is remarkable in CKD, where both endothelium-dependent and -independent vasodilations are impaired[15]. This may reflect the high oxidative stress and the presence of risk factors like hypertension, diabetes and the reduced clearance of uremic toxins, such as asymmetrical dimethylarginin, an effective inhibitor of nitric oxide synthase[16,17]. A study of cultured endothelial cells *in vitro* showed that stiff arteries themselves further reduce nitric oxide bioavailability through diminished expression of endothelial nitric oxide synthase[18], suggesting that arterial stiffness can be a self-perpetuating process.

Endothelin, a powerful vasoconstrictor produced by endothelial cells is also implicated in the pathogenesis of several cardiovascular conditions and the progression of CKD[19]. Short-term administration of endothelin-receptor antagonist in non-diabetic CKD reduces proteinuria and arterial stiffness independently of blood-pressure lowering[20], data which suggest beneficial effects in the treatment of the vascular complications of CKD in the near future.

A clear association between chronic inflammation and arterial stiffness has been shown in different studies involving patients in a chronic inflammatory state, like rheumatoid arthritis and CKD[21,22], as well as studies of inflammatory markers and aortic PWV (aPWV) in healthy populations[23]. Accelerated arterial calcification has been shown in animal models due to inflammatory degradation of ECM elastin[24]. According to these data, the exploration of the role of immunosuppression and the inhibition of elastase enzymes as therapeutic possibilities in arterial stiffness reduction would be required[25].

The renin-angiotensin-aldosterone system (RAAS) is also involved in the process of arterial stiffening. Angiotensin Ⅱ stimulates vascular smooth muscle cells (VSMCs) to generate intracellular superoxides and inflammatory cytokines and induced vascular remodeling through VSMC hypertrophy and proliferation, increased collagen synthesis and increased production of MMP[26,27]. Inhibition of the RAAS with angiotensin converting enzyme inhibitors (ACEI) or angiotensin Ⅱ receptor blockers is associated with reduction of arterial stiffness, but it is accompanied with blood pressure reduction[28,29]. In hemodialyzed patients, treatment with ACEI blood pressure lowering combined with decreased aPWV was associated with reduced all-cause and cardiovascular mortality[30].

Aldosterone levels are correlated with arterial stiffness in hypertensive men, independent of blood pressure[31]. Aldosterone increases arterial stiffness independently of wall stress in subtotally nephrectomized rats given high-salt diets and these effects are inhibited by the mineralocorticoid receptor (MR) blocker eplerenone[32]. There are limited data demonstrating the influence of MR antagonism on arterial stiffness in human CKD. The addition of the MR inhibitor spironolactone to ACEI/ARB treatment in stage 2 and 3 CKD patients significantly reduced arterial stiffness and left ventricular mass, supporting the hypothesis that aldosterone is a major mediator of arterial stiffness and left ventricular hypertrophy in CKD[33].

High salt diets also have important role in the development of hypertension and arterial stiffness[34]. Dietary sodium promotes VSMC hypertrophy and increases VSMC tone; it also increases collagen cross-linking and facilitates aldosterone-induced oxidative stress and inflammation[34]. The restricting of dietary sodium in hypertensive patients can effectively reduce arterial stiffness[35]. The influence of accumulating dietary sodium and other dietary compounds, like bioavailable phosphate, AGEs and oxidants, on arterial stiffness in CKD is not totally understood and will be an area of future research.

VASCULAR CALCIFICATION IN CKD

The dramatically increased cardiovascular risk of death of uremic patients is directly associated with the magnitude of vascular calcification (VC)[36]. VC can either take place in the intima or in the media of the vessel wall. Calcification of the intima is a part of atherosclerosis, while medial calcification is the hallmark of arteriosclerosis. Both forms are prominent in CKD but arteriosclerosis primarily has an important role in the development of arterial stiffness[37].

A cross-sectional study assessed characteristics of dialysis patients with predominant intimal *vs* medial calcifi-

cations. Intimal calcification patients were about 20 years older and characterized by a history of traditional risk factors (e.g. smoking, dyslipidemia) prior to the start of dialysis, while medial calcification patients were characterized by a long history of dialysis and higher incidence of disturbances of calcium x phosphate metabolism, despite being younger[37]. Key risk factors associated with progressive cardiovascular calcification are age and diabetes, but many others are present in CKD and ESRD, like hyperphosphatemia, hypercalcemia, a high intake of calcium (by calcium-containing phosphate binders) and inflammation[38-41]. Amongst these risk factors, hyperphosphatemia is an especially strong and independent predictor of cardiovascular mortality in uremic patients[39]. Treatment of secondary hyperparathyroidism and hyperphosphatemia with calcimimetics might have beneficial effects for the vascular mineralization and mortality in CKD, an effect that can be at least be partly mediated through the reduction of arterial stiffness[42].

For many years, VC in CKD patients was thought to occur predominantly by unregulated, purely physiochemical mechanisms[43]. Recently, VC was hypothesized to be an active process in which vascular cells may acquire osteoblastic functions[44]. Indeed, an increasing body of evidence suggests that atherosclerotic calcification shares features with bone calcification.

CONNECTIONS BETWEEN VC AND BONE METABOLISM IN CKD

The first observations suggesting the existence of the bone-vascular axis were the frequent associations of osteoporosis and atherosclerotic VC observed in postmenopausal women[45-47]. Longitudinal population-based studies revealed a relationship between the progression of VC and bone demineralization, and others were identified between bone mineral density and aortic or central artery calcifications[46], or coronary arteries in type 2 diabetes[48].

A relationship between bone and vascular modifications was also observed in CKD and ESRD. In dialysis patients, coronary artery calcification score was found to be inversely correlated with vertebral bone mass[49,50]. High systemic calcification score combined with bone histomorphometry suggestive of low bone activity was observed in hemodialysis patients[51,52].

Disorders of the mineral metabolism associated with CKD were found to be key factors contributing to the excess mortality observed in this patient population[53,54]. Moreover, the skeletal remodeling disorders caused by CKD contribute directly to the disordered mineral metabolism and heterotopic mineralization, especially the VC in CKD[55]. Finally, CKD impairs skeletal anabolism, decreasing osteoblast function and bone formation[56]. Due to these pathophysiological discoveries, the term "CKD mineral bone disorder" (CKD-MBD) was created by the Kidney Disease Improving Global Outcomes Foundation (KDIGO)[57].

REGULATORS OF BONE METABOLISM WHICH HAVE AN ACTIVE ROLE IN VC AND THEIR ASSOCIATION WITH ARTERIAL STIFFNESS IN CKD

Osteoprotegerin

Osteoprotegerin (OPG) inhibits the activation of osteoclasts and promotes osteoclast apoptosis *in vitro*. The mechanism of this action is that OPG serves as a decoy receptor for the receptor activator of nuclear factor κB-ligand (RANKL) and thereby inhibits osteoclastogenesis and osteoclast activation by blocking RANK activation[58]. Mice deficient for OPG (OPG-/-) develop calcifications of the aorta and renal arteries, together with osteoporosis[59]. From these data, an inverse relationship between OPG levels and outcomes would have been expected; however, the opposite observations were made in clinical studies. In dialysis patients, serum OPG levels were independently associated with VC[60] and showed that OPG levels can, in part, explain the association between coronary artery calcification and CKD[61]. In our previous study, we found a significant positive relationship between serum OPG levels and aPWV in patients on hemodialysis and demonstrated an inter-relationship of these parameters on their effect on cardiovascular mortality[62]. These findings are compatible with the hypothesis that the prognostic significance of high OPG levels is, at least in part, mediated by higher PWV in these patients. Whether this relationship is dependent on the degree of aortic calcification and whether the same relationship also holds true in other populations needs further study.

Pyrophosphate

Pyrophosphate (PP), a ubiquitous small-molecule inhibitor of mineralization abundantly present in the extracellular environment, binds to calcium and mineral surfaces to inhibit crystal growth[63,64]. The local PP concentration depends on three regulatory factors: tissue nonspecific alkaline phosphatase (TNAP) degrades PP into phosphate ions, while ectonucleotide pyrophosphate phosphodiesterase (ENPP1) and the transporter protein ANK increases local PP concentration and thus facilitates a local defense against calcification in several tissues[65]. Idiopathic infantile arterial calcification, a severe syndrome causing deleterious calcifications in vessels of very young children, is caused by loss-of-function mutation of the ENPP1 gene[66].

Hemodialysis patients have reduced plasma PP levels; possibly these low molecular weight solutes are effectively removed by the dialysis procedure[67]. Low PP levels seem to be connected with increased arterial stiffness in patients with end-stage renal failure, as was found in a study by Eller *et al*[68], where patients heterozygous for ENPP1 K121Q polymorphism had higher coronary calcification scores and arterial stiffness. The impact of this mutation for the survival of CKD patients and the possible benefit of their intense treatment need further investigation.

Bisphosphonates share the chemical structure of PP and, especially the first generation of bisphosphonates, offer therapeutic hope for treatment of calciphilaxis and coronary calcification in dialysis patients[69,70]. However, bisphosphonate treatment may aggravate pre-existing hyperparathyroidism, so caution is advised in uncritical use in CKD[71]. The future solution may be direct supplementation of PP, as it was found in animal studies to reduce aortic calcification in experimental kidney failure[63], or the direct inhibition of TNAP[72], but further studies are needed before human use[64].

Matrix Gla protein

Among the ECM proteins that have been reported to regulate osteoblast-dependent mineralization, matrix Gla protein (MGP) is one of the most potent inhibitors of calcification[73,74]. MGP is a member of the N-terminal γ-carboxylated protein family. MGP requires vitamin K-dependent γ-carboxylation for biological activation. Mice deficient for MGP (MGP-/-) show severe medial calcification of the aorta and die a few weeks after birth because of the rupture of the bone-like aorta[74]. It has been shown that undercarboxylated MGP (ucMGP) is associated with intimal and medial calcification, indicating local or systemic vitamin K depletion is a potentially important confounder in the development of arterial calcification[75]. The potential clinical importance of vitamin K-dependent γ-carboxylation is underlined by a study by Koos *et al*[76], showing that patients on oral anticoagulant therapy had increased coronary and valvular calcifications compared to patients without anticoagulation treatment, presumably due to less active MGP. In the case of calciphylaxis, a severe disease of CKD patients characterized by extensive arteriolar calcifications, warfarin was shown to be a risk factor for the manifestation of this life-threatening disease[77].

Data about the association between MGP and arterial stiffness are controversial. Significantly lower ucMGP levels were found in dialysed patients compared to age-matched controls. In this dialyzed patient population, inverse correlation was found between augmentation index, an arterial stiffness parameter, and serum ucMGP levels, but no association was demonstrated with PWV. Besides, ucMGP had an inverse association with phosphate and positive association with fetuin-A levels, suggesting that low ucMGP can be a marker of active calcification and impaired arterial stiffness in dialysis[78]. This study was performed with SphygmoCor, one of the gold standard equipments of arterial stiffness measurements.

In contrast, in patients with CKD in stages 1-4, no correlation was found between serum MGP levels and arterial stiffness, although the stiffness was assessed by contour analysis of digital volume pulse, which is not a gold standard method[79]. In a recent study performed on renal transplant recipients, where arterial stiffness was measured with SphygmoCor, serum MGP level was not found to be predictor of carotid-femoral PWV[80].

Fetuin-A

Fetuin-A is a mineral carrier protein and a systemic inhibitor of pathological mineralization, complementing local inhibitors that act in a cell-restricted or tissue-restricted fashion. Fetuin-A deficiency is associated with soft tissue calcification in mice and humans[81]. The relevance of relative fetuin-A deficiency in humans was first demonstrated in a cohort of > 300 prevalent hemodialysis patients[82]. Patients within the lowest tertile of fetuin-A serum levels had a significantly increased all-cause and cardiovascular mortality. Sera from patients with low fetuin-A concentrations had a significantly impaired ability to inhibit calcium x phosphate precipitation compared to sera with normal fetuin-A concentrations[82]. Another study confirmed these data in incident dialysis patients, where hypoalbuminemia and CRP were strongly correlated to fetuin-A deficiency, suggesting an association with the malnutrition-inflammation-atherosclerosis (MIA) syndrome[83]. Patients on peritoneal dialysis with low fetuin-A levels showed a clear association with the MIA syndrome as well as with mortality and cardiovascular events[84].

Both coronary and aortic calcifications were found to be related to low fetuin-A levels and in patients with diabetic nephropathy, a positive association between fetuin-A levels and coronary calcification score was demonstrated[85-87].

The theory, that fetuin-A up-regulation may serve as a systemic defense mechanism to counteract early VCs, is supported by a study, where immunhistochemistry showed fetuin-A depositions around areas of VC, correlating well with the degree of calcification[85]. This calcification inhibitor effect of fetuin-A probably progressively fails with the development of uremia due to yet unidentified mechanisms[71].

Studies examining the role of fetuin-A in arterial stiffening in CKD have shown varied results. Among non-diabetic children receiving renal replacement therapy, fetuin-A was an independent predictor of baseline aortic PWV[88]. In a recent prospective observational study performed in peritoneal dialysis patients, inverse correlation was found between the serum fetuin-A concentration and heart-to-femoral PWV and fetuin-A was found to be an independent determinant of aortic stiffness[89]. However, in a study of elderly dialysis patients, the relationship between fetuin-A and arterial stiffness lost significance after correction for age, gender, mean arterial pressure and diabetic status[90]. Another study of heterogeneous CKD stage 4 and dialysis population found no association between fetuin-A and change in VC[91]. In contrast, low fetuin-A was shown to be an independent risk factor for change in arterial stiffness in non-diabetic patients with CKD stages 3 and 4[92]. The relationship between fetuin-A and arterial stiffening was found to be different in diabetic and non-diabetic patients, which underlines the concept that in diabetic CKD patients, arterial stiffening may be driven by different processes than in the non-diabetic population. These may include deposition of advanced glycation products, calcification of more exten-

sive atherosclerotic plaque or development of additional *de novo* atherosclerosis, processes yet to be proven[92].

Osteopontin

Osteopontin (OPN) is an acidic phosphoprotein normally found in mineralized tissues such as bones and teeth, and it is involved in regulation of mineralization by acting as an inhibitor of apatite crystal growth, as well as promoting osteoclast function through the $\alpha_v\beta_3$ integrin[93]. OPN is abundant at sites of calcification in human atherosclerotic plaques[94] and smooth muscle cells deficient for OPN display enhanced susceptibility to calcification *in vitro*[95]. In a study by Speer *et al*[96], OPN-null mice (OPN-/-) that have no overt vascular phenotype were bred to MGP-/- mice in which VC spontaneously develops. Mice deficient in both MGP and OPN (MGP-/-OPN-/-) showed accelerated and enhanced VC compared with mice deficient in MGP alone (MGP-/-OPN+/+).

Studies indicate that OPN is an inducible inhibitor of VC *in vivo* and may play an important role in the adaptive response of the body to injury and disease. In light of previous *in vitro* findings, part of the inhibition of arterial calcification in MGP-/- mice may be accounted for by the potent apatite inhibitory activity of phosphorylated OPN[97].

Elevated plasma OPN levels are found to be associated with CRP and increased arterial stiffness in patients with rheumatoid arthritis, suggesting that this protein might represent a bridge between inflammation and the consequent joint damage and cardiovascular risk in rheumatoid arthritis patients[98]. To date, there is no data about the connection between serum OPN levels and arterial stiffness in CKD.

Bone morphogenic proteins

Bone morphogenic proteins (BMPs) are members of the transforming growth factor β superfamily of cytokines and consist of a group of at least 15 morphogenes involved in intracellular messaging[99].

BMP-2 expression is up-regulated in human atherosclerotic plaques isolated from abdominal aorta and associated with specific immunostaining for MGP, osteocalcin and bone sialoprotein that are absent in normal aorta and early atherosclerotic lesions[100]. *In vitro* studies show that cultured cells isolated from aortic wall express BMP-2 and produce calcified nodules similar to those found in bone cell cultures[43]. Chen *et al*[43] reported a higher BMP-2 protein concentration in a pooled uremic serum than in normal human serum and demonstrated that BMP-2 could induce calcification of phosphate-treated bovine smooth muscle cells *via* up-regulation of Cbfa1[101]. The connection between BMP-2 and arterial stiffening has been proven recently, as Dalfino *et al*[102] found direct correlation between brachial-ankle PWV and BMP-2 in a population of 85 CKD (stage 2 or higher) patients.

BMP-7 is a crucial element for the development of kidneys, eyes and bones[103]. In the adult, BMP-7 maintains a role in osteoblast function, suggesting a hormonal role in bone metabolism. Interestingly, BMP-7 expression decreases early in the course of renal failure[104]. BMP-7 deficiency can have important consequences in the pathogenesis and treatment of chronic renal insufficiency[105], but is also very interesting in the pathogenesis and treatment of VCs. Indeed, BMP-7 maintains VSMC differentiation and prevents their transformation into cells with an osteoblastic phenotype[106,107]. Thus, the state of BMP-7 deficiency, characteristic of chronic renal failure, could favor VC, especially within the context of atherosclerotic lesions. The possible connection between BMP-7 and arterial stiffness still needs to be evaluated.

Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF-23) is a recently discovered regulator of phosphate and mineral metabolism. FGF-23 is a 251 amino acid protein that is predominantly synthesized and secreted by cells from an osteoblast lineage[108,109]. FGF induces phosphaturia by reducing the number of Na-P co-transporters on renal tubular cells, as well as mitigating the effects of calcitriol on intestinal absorption[110]. The biological effects of FGF-23 are exerted through activation of FGF receptors (FGF-R). Klotho is a trans-membrane protein originally described in mice with a phenotype of accelerated aging and atherosclerosis[109]. Klotho directly interacts with FGF-R, allowing it to bind FGF-23 with a higher affinity and increased specificity[111,112]. The activation of FGF-23 therefore occurs in a Klotho-dependent manner[112].

The main known physiological role of FGF-23 is to regulate urinary phosphate excretion and maintain a stable serum phosphate[113]. An important secondary role is the counter-regulation (against PTH) of vitamin D biosynthesis. The main stimuli for increased expression of FGF-23 are high dietary phosphate, calcitriol and persistent hyperphosphatemia[114-116]. In CKD, recently reported clinical studies support a phosphate-centric, FGF-23 mediated pathogenesis of secondary hyperparathyroidism and findings suggest that FGF-23 plays an active role in CKD-MBD[117].

A prospective cohort study of 219 dialysis patients demonstrated an association between FGF-23 levels and mortality, independent of serum phosphate[118]. In another study in dialyzed patients, FGF-23 levels were shown to predict 1 year mortality, also independent of phosphate levels[119]. Although FGF-23 levels in these two studies did not demonstrate additional prognostic information when compared with phosphate levels, the possibility of using FGF-23 as a biomarker in patients with CKD and normal phosphate levels is of interest and needs to be assessed.

There is also growing evidence about the association of cardiovascular disease and FGF-23 levels. In an observational study of 833 patients with early CKD and stable coronary artery disease, elevated FGF-23 was independently associated with mortality and cardiovascular events[120]. Association between arterial stiffness and

FGF-23 has also been demonstrated once in a cohort of 967 patients with early CKD, where arterial stiffness was measured with ShygmoCor[121].

FUTURE DIRECTIONS - NEW THERAPEUTIC PATHWAYS

With the growing amount of data about the pathophysiological role of bone metabolism regulators in VC, new possible therapeutic targets have emerged, such as denosumab, a human monoclonal antibody which binds RANKL with high specificity, mimicking the effect of endogenous OPG. In postmenopausal osteoporosis it decreases bone resorption but its effect on VC needs further studies[122]. Theoretically, the modification of the effects of FGF-23 could improve vitamin-D homeostasis[72]. Amongst the endogenous inhibitors, administration of fetuin-A and BMP-7 can have beneficial effects in the future[122]. Besides the direct supplementation of PP, as it was found to reduce aortic calcification in experimental kidney failure in animal studies[63], the inhibition of TNAP can also have perspectives in the increasing of PP levels and improvement of cardiovascular outcomes[72].

Certainly, the effect of these future interventions for arterial stiffening is an open question but there are already some results about present medications which are beneficial for arterial stiffness and that may partly act through the modification of the inhibitors of bone metabolism. The non-calcium-containing phosphate binder sevelamer has been linked to slowing the progression of aortic calcification in hemodialysis patients[123]. We demonstrated its beneficial effect for arterial stiffness parameters in dialysis patients previously[124]. A recent study in non-diabetic CKD patients demonstrated a significant increase in fetuin-A after treatment with sevelamer[125]. According to these results, sevelamer may attenuate the progression of arterial pathology in CKD, at least partly through the elevation of fetuin-A.

The AGE-cross-link breaker alagebrium did improve endothelial dysfunction and carotid augmentation index in patients with isolated systolic hypertension[13]. Its beneficial effect for the osteoporosis in patients with rheumatoid arthritis is hypothesized[126] but the influence of alagebrium on bone metabolism inhibitors has not been evaluated yet.

CONCLUSION

Increased arterial stiffness is associated with structural and functional changes of the vasculature and the poor cardiovascular outcome of patients with CKD. In these patients, a huge number of deleterious factors are present, like endothelial dysfunction, cumulation of AGEs, chronic inflammation, the impaired RAAS and processes leading to arterial media calcification. Recently, there is growing evidence about the active involvement of some of the bone and phosphate metabolism regulators in increased medial calcification and stiffening. Evaluation of their exact pathophysiological role and their correlation with mortality in CKD could lead to their use as biomarkers or new therapeutic targets, and may slow the progression of arterial stiffening and improve cardiovascular outcome.

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Events Calendar 2012

January 3-7, 2012
UK Renal Association-Advanced Nephrology Course
Corpus Christi College,
Oxford, United Kingdom

January 13-15, 2012
NATCO Symposium for Advanced Transplant Professional
Loews Miami Beach Hotel,
Miami, FL, United States

January 14-16, 2012
American Association of Tissue Banks (AATB) Tissue Donor Suitability Workshop
Ritz Carlton Tysons Corner
McLean, VA, United States

February 7-9, 2012
From Novice to Specialist-Empowering and Leading Families Donation Discussions
Gift of Life Institute
Philadelphia, PA, United States

February 13-15, 2012
Consensus Conference on Transplant Program Quality and Surveillance
Key Bridge Marriott
Arlington, VA, United States

February 14-17, 2012
17th Continuous Renal Replacement Therapies Conference
San Diego, CA, United States

February 17-19, 2012
Transplant Nursing Across the Lifespan...Sharing Best Practices
DoubleTree Atlanta Buckhead
Atlanta, GA, United States

February 26-28, 2012
32nd Annual Dialysis Conference (18th International Symposium on Hemodialysis-23rd Annual Symposium on Pediatric Dialysis)
Henry B. Gonzalez Convention Center,
San Antonio, TX, United States

March 7-8, 2012
Family Empowerment through Effective Advocacy: Averting and Overcoming Obstacles to Donation Today's Healthcare Environment
Gift of Life Institute,
Philadelphia, PA, United States

March 13, 2012
The Cutting Edge in Transplantation: New Insights
University Hotel,
Minneapolis, MN, United States

March 13-15, 2012
AOPO Quality Improvement Council
Embassy Suites San Diego Bay,
San Diego, CA, United States

March 15, 2012
Renal Physicians Association (RPA) East Coast Regional Nephrology Coding and Billing Seminar
Marriott Wardman Park,
Washington, DC, United States

March 15-18, 2012
2012 Renal Physicians Association (RPA) Annual Meeting
Marriott Wardman Park,
Washington, DC, United States

March 24-27, 2012
American Association of Tissue Banks (AATB) 16th Annual Spring Meeting
Caribe Hilton, San Juan, Puerto Rico

March 28-30, 2012
The Consensus Conference on Kidney Paired Donation (KPD)
Hyatt Dulles, Herndon, VA, United States

March 28-31, 2012
American Society of Extracorporeal Technology (AmSECT) 40th International Conference
Sheraton New Orleans,
New Orleans, LA, United States

April 13, 2012
Challenges and Innovations in Pediatric Transplantation
Boston Children Hospital - Folkman Auditorium,
Boston, MA, United States

April 26-29, 2012
American Association of Tissue Banks (AATB) CTBS Training & Review Course
Ritz Carlton Tysons Corner,
McLean, VA, United States

April 29-May 2, 2012
ANNA 43nd National Symposium
Walt Disney World Dolphin,
Orlando, FL, United States

May 2-3, 2012
Building Strong Hospital Partnerships: The Architecture of Strategic Hospital Development
Gift of Life Institute,
Philadelphia, PA, United States

May 4, 2012
Renal Physicians Association (RPA) West Coast Regional Nephrology Coding and Billing Seminar
The Wyndham Phoenix,
Phoenix, AZ, United States

May 9-11, 2012
Vascular Access for Hemodialysis XIII Symposium
Orlando, FL, United States

May 9-13, 2012
National Kidney Foundation (NKF) 2012 Spring Clinical Nephrology Meetings
Gaylord National,
Washington, DC, United States

May 20-24, 2012
Transplant Donation Global Leadership Symposium (GLS)
Gift of Life Institute,
L'Auberge Del Mar,
Del Mar, CA, United States

May 23-25, 2012
National Patient Safety Foundation (NPSF) 14th Annual Patient Safety Congress
Gaylord National Hotel and Conference Center,
Washington, DC, United States

May 24-27, 2012
IL ERA–EDTA Congress
Palais des Congrès, Paris, France

June 2-6, 2012
American Society of Nephrology (ASN) Kidney Week
Boston, MA, United States

June 6-9, 2012
40th Annual Renal Society of Australasia (RSA) Conference: Celebrating our Culture and Diversity in Renal Care
The Sebel Albert Park Melbourne,
Melbourne, Australia

June 15, 2012
Renal Physicians Association (RPA) MidWest Regional Nephrology Coding and Billing Seminar
Renaissance St. Louis Grand Hotel,
St. Louis, MO, United States

June 19-22, 2012
Association of Organ Procurement Organization (AOPO) Annual Meeting
Fairmont Chicago,
Chicago, IL, United States

July 11-13, 2012
Renal Physicians Association (RPA) 2012 Advanced Practitioner Conference
The Hilton Minneapolis,
Minneapolis, MN, United States

August 12-15, 2012
NATCO 37th Annual Meeting
Grand Hyatt Washington DC,
Washington, DC, United States

August 25-31, 2012
American Society of Nephrology (ASN) Review Course & Update
The Palace Hotel,
San Francisco, CA, United States

September 9-12, 2012
American Association of Tissue Banks (AATB) 36th Annual Meeting
Keystone Resort and Conference Center,
Keystone, CO, United States

September 9-12, 2012
14th Congress of the International Society of Peritoneal Dialysis
Kuala Lumpur, Malaysia

September 28, 2012
Renal Physicians Association (RPA) Southeast Regional Nephrology Coding and Billing Seminar,
Charlotte, NC, United States

October 4-5, 2012
National Learning Congress 2012
Gaylord Texan,
Grapevine, TX, United States

October 4-5, 2012
Central Manchester University Hospitals NHS Foundation Trust Hospital's 5th Annual Home Dialysis Conference
The Lowry Hotel, Dearmans Place,
Manchester, United Kingdom

October 4-7, 2012
International Association for the History of Nephrology 2012 Conference
8th Congress of the IAHN
Paestum, Salerno, Italy

October 30-November 4, 2012
American Society of Nephrology (ASN) Kidney Week 2012
San Diego Convention Center,
San Diego, CA, United States

November 7-8, 2012
Building Strong Hospital Partnerships: The Architecture of Strategic Hospital Development
Gift of Life Institute,
Philadelphia, PA, United States

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GENERAL INFORMATION

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The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

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The columns in the issues of *WJN* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in nephrology; (9) Brief Articles: To briefly report the novel and innovative findings in nephrology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJN*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of nephrology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research nephrology.

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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